Trends in Food Science & Technology 115 (2021) 147–254

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

Moroccan antidiabetic medicinal plants: Ethnobotanical studies, phytochemical bioactive compounds, preclinical investigations, toxicological validations and clinical evidences; challenges, guidance and perspectives for future management of diabetes worldwide

Abdelhakim Bouyahya[a,*], Nasreddine El Omari[b], Naoual Elmenyiy[c], Fatima-Ezzahrae Guaouguaou[d], Abdelaali Balahbib[e], Omar Belmehdi[f], Najoua Salhi[g], Hamada Imtara[h], Hanae Naceiri Mrabti[i], Mohamed El-Shazly[j,k], Youssef Bakri[a]

[a] Laboratory of Human Pathologies Biology, Department of Biology, Faculty of Sciences, Genomic Center of Human Pathologies, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, Morocco
[b] Laboratory of Histology, Embryology and Cytogenetic, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, Morocco
[c] Laboratory of Physiology, Pharmacology & Environmental Health, Faculty of Science, University Sidi Mohamed Ben Abdellah, Fez, Morocco
[d] Mohammed V University in Rabat, LPCMIO, Materials Science Center (MSC), Ecole Normale Supérieure de Rabat, Morocco
[e] Laboratory of Zoology and General Biology, Faculty of Sciences, Mohammed V University in Rabat, Rabat, Morocco
[f] Biology and Health Laboratory, Department of Biology, Faculty of Science, Abdelmalek Essaadi University, Tetouan, Morocco
[g] Laboratory of Pharmacology and Toxicology, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, Morocco
[h] Faculty of Arts and Sciences, Arab American University Palestine, Jenin 240, Palestine
[i] Laboratory of Pharmacology and Toxicology, Bio Pharmaceutical and Toxicological Analysis Research Team, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, BP 6203, Rabat, Morocco
[j] Department of Pharmacognosy, Faculty of Pharmacy, Ain-Shams University, Cairo, 11566, Egypt
[k] Department of Pharmaceutical Biology, Faculty of Pharmacy and Biotechnology, German University in Cairo, Cairo, 11835, Egypt

ARTICLE INFO

Keywords:
Medicinal plants
Secondary metabolites
Bioactive compounds
Mechanism insights
Therapeutic applications
Nutritional value

ABSTRACT

Background: Moroccan flora is rich with medicinal plants that are widely used in traditional medicine for the treatment of various diseases including diabetes. These plants possess several classes of bioactive molecules, which belong to different chemical families such as phenolic acids, flavonoids, terpenoids and alkaloids.
Scope and approach: This review highlights the published reports on the antidiabetic properties of Moroccan medicinal plants. The mechanism of action of these plants and their secondary metabolites were discussed in detail. Clinical trials on the antidiabetic active constituents were summarized demonstrating the potential application of these natural treasures to be developed as potent antidiabetic agents.
Key findings and conclusions: were reported to be used in the treatment of diabetes in Morocco. Among these medicinal plants, the antidiabetic activity was evaluated for 15 species *in vitro* and 30 species *in vivo*. The *in vitro* studies showed significant inhibition of enzymes involved in the intestinal metabolism of carbohydrates. The *in vivo* reports revealed that the extracts and essential oils of these plants exhibited several antidiabetic effects such as a decrease of blood glucose and an increase of insulin secretion. Phytochemical analysis of the active plants revealed the presence of 148 secondary metabolites. These compounds belong to different chemical classes such as terpenoids, flavonoids, alkaloids, phenolic acids, and fatty acids. Among the identified compounds, 95 were evaluated for their antidiabetic activity. The results showed that these compounds manage diabetes by several mechanisms such as enzymatic inhibition, interference with glucose and lipid metabolism signaling pathways, and the inhibition and/or the activation of gene expression involved in glucose homeostasis. Eighteen active compounds reached clinical trials and showed impressive results in controlling diabetes and its manifestations.

* Corresponding author.
E-mail address: boyahyaa-90@hotmail.fr (A. Bouyahya).

https://doi.org/10.1016/j.tifs.2021.03.032
Received 15 September 2020; Received in revised form 28 January 2021; Accepted 18 March 2021
Available online 11 June 2021
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1. Introduction

Diabetes is a multifactorial complex disease that is developed in response to several risk factors. This disease is classified into several types including insulin-dependent diabetes (type 1 diabetes), insulin-dependent diabetes (type 2 diabetes) and moody diabetes (type 3 diabetes). Type 1 diabetes and moody diabetes result from genetic and/or epigenetic predisposition factors (Rosik, Szostak, Machaj, & Pawlik, 2019; Yahaya and Salisu, 2020). Type 2 is developed due to several triggering factors especially those linked to our daily diet (Aune, Mahamat-Saleh, Norat, & Riboli, 2020). Epidemiological studies demonstrated that the world's population with type 2 diabetes is increasing due to the dramatic changes in the eating habits and life style in the last 70 years following the second world war (Aune, Mahamat-Saleh, Norat, & Riboli, 2020). In Morocco, like other countries in the world, the incidence of type 2 diabetes is much higher than other types of diabetes. The physiopathology of type 2 is quite complicated and several theories were developed to explain the diabetogenesis of type 2 (Blair, 2016). Insulin-resistance, obesity and the chronic burden of fat mass are suggested as major triggers for type 2 diabetes (Biessels et al., 2006). The contribution of other factors especially the negative balance between food intake and physical activity increases the incidence of diabetes. Anti-diabetic treatments are primarily aimed at decreasing blood glucose concentration and thus prevent the serious complications associated with diabetes.

Diabetes has been known for more than 3000 years and remained a redoubtable disease until the beginning of the century. It is a very common disease globally and especially in the Middle East countries such as Morocco. It represents a huge social and economic burden with serious consequences in terms of morbidity and mortality. Currently, there are more than two million people aged 18 and over suffer from diabetes in Morocco and 50% of those patients do not know that they have this disease (MS, 2013a). More than 350,000 patients are treated by insulin and the number of diabetic children is estimated to be more than 15,000 (MS, 2016). This disease is behind more than 12,000 deaths per year and the indirectly related to an additional 32,000 deaths (WHO, 2016). The WHO in the latest national figures (2016) estimated that the percentage of Moroccan citizens with diabetes exceeded 12.4% of the whole population (WHO, 2016). This prevalence was significantly higher in urban areas (9%) than in rural areas (4.4%) according to a national survey carried out in 2000 (Tazi et al., 2003). Field research carried out in different regions of the country showed different prevalence, for example, the prevalence of type 2 in the southern region was 11.9% in 2001–2002 (Rguibi and Belahsen, 2004), 19% in the Meknes region and northern Morocco (El Boukhrissi et al., 2017), and in eastern Morocco was 10.2% (Ramdani et al., 2012). A study of Moroccan immigrants indicated a prevalence of 8% (Ujcic-Voortman et al., 2009). About 80% of diabetes cases are type 2 and they are closely linked to obesity and lifestyle. In Morocco, 55.1% of the population is overweight and 21.7% is obese (Mrabi, 2016). Diabetes is the number one cause of blindness, end-stage renal disease (FID, 2015) and lower extremity amputations (MS, 2015a; MS, 2015b). Another common complication of diabetics in Morocco are retinopathy, diabetic neuropathy (Hammoudi et al., 2018), nephropathy and heart disease (Selihi et al., 2015). Several factors promote the increase in the rate of diabetes in Morocco such as the transition from a rural and traditional way of life to a modern and urban way of life, changes in eating habits and lifestyle (Belahsen et al., 2005; Dinar and Belahsen, 2014).

The diabetes bill alone absorbs a tenth (10.2%) of the health coverage for chronic non-communicable diseases (ANAM, 2014). Morocco provides basic medical coverage to 62% of its population and the government aims to reach 90% of the population by 2020, in order to achieve Universal Health Coverage recommended by the World Health Organization convention in 2005 and the United Nations assembly meeting in 2012 (Errajraji et al., 2010). Morocco launched a national plan for the prevention and control of diabetes between 2010-2015 aiming to reduce the burden of morbidity and mortality linked to diabetes and its complications. The plan targets diabetics and people at high risk including pregnant women, hypertensive patients, women with a history of gestational diabetes, tuberculosis patients, 1[st]degree familial diabetes (MS, 2013b). The use of oral antidiabetic agents is often associated with undesirable effects. In certain patients, the undesirable effects may become severe and require the discontinuation of these drugs resulting in uncontrolled diabetes and serious complications (Ajdi et al., 2009). The recent development of herbal medicine offers an opportunity to find natural molecules capable of exerting beneficial effects on the regulation of carbohydrate metabolism while avoiding the side effects of synthetic therapeutic agents.

The reduction of carbohydrates absorption from the intestinal tract is one of the hallmarks in the fight against diabetes (Godos et al., 2020). Acarbose has been used for years as an antidiabetic drug that inhibits the intestinal absorption of sugars. Its pharmacological mechanisms are essentially based on the inhibition of the main enzymes (α-amylase and α-glucosidase) involved in the catabolism of carbohydrates and thus reduces their absorption (Chen et al., 2020).Several other drugs target the regulation of glucose metabolism such as metformin. Balanced diet is one of the important approaches to reduce the excessive intake of sugars (Brown et al., 2019).

Since antiquity, Moroccan people have used medicinal plants to treat several diseases including diabetes. Numerous species have been used in Moroccan traditional medicine against diabetes. Traditional healers by trial and error selected the richest organs in each plant with active constituents producing the most potent activity. They also developed interesting simple formulation to deliver the plant material to the consumers. Scientific studies proved the antidiabetic effect of the organic extracts and essential oils of many of these medicinal plants using *in vitro* and *in vivo* models. The antidiabetic effect was found to be related to the inhibition of enzymes implicated in intestinal carbohydrates metabolism and the reduction of the glucose level in blood. These plants are rich in bioactive secondary metabolites such as terpenoids, flavonoids, alkaloids, phenolic acids, and tannins that proved effective in managing diabetes and its manifestation in preclinical and clinical trials. Several compounds emerged as potential drug leads to be developed as antidiabetic agents with potent activity and more favorable safety profile.

In this review, we critically analyzed previous reports on Moroccan medicinal plants as source of antidiabetic agents. The traditional use, *in vitro*, and *in vivo* studies of Moroccan antidiabetic medicinal plants were highlighted. Phytochemical contents of these plants were summarized, their biological activity and mechanisms of action were discussed. Moreover, toxicological reports on Moroccan antidiabetic medicinal plants as well as the clinical trials of their bioactive compounds were critically presented.

2. Diabetes epidemiology in Morocco

Diabetes has been known for more than 3000 years and remained a redoubtable disease until the beginning of the century. It is a very common disease in Morocco and globally. It constitutes a real social scourge whose consequences in terms of morbidity and mortality are severe. Currently, around two million people aged 18 and over suffer from diabetes in Morocco and 50% of those patients do not know their disease (MS, 2013a). More than 350,000 patients are treated by insulin and the number of diabetic children is estimated to be more than 15,000 (MS, 2016). This disease is behind more than 12,000 deaths per year and the indirectly related to an additional 32,000 deaths (WHO, 2016). The WHO in the latest national figures (2016) estimated that the percentage of Moroccan citizens exceeded 12.4% of the whole population (WHO, 2016). This prevalence was significantly higher in urban areas (9%) than in rural areas (4.4%) according to a national survey carried out in 2000 [are the new sentences scientifically correct, are these numbers belong to Morocco?] (Tazi et al., 2003). Research carried out in different regions of the country showed different prevalence, for example, the

prevalence of T2DM in the southern region was 11.9% in 2001–2002 (Rguibi and Belahsen, 2004), 19% in the Meknes region and northern Morocco (El Boukhrissi et al., 2017), and the percentage of T2DMin eastern Morocco was 10.2% (Ramdani et al., 2012). A study of Moroccan immigrants indicated a prevalence of 8% (Ujcic-Voortman et al., 2009). About 80% of diabetes cases are type 2 and they are closely linked to obesity and lifestyle. In Morocco, 55.1% of the population is overweight and 21.7% is obese (Mrabi, 2016). Diabetes is the number one cause of blindness, end-stage renal disease (FID, 2015) and lower extremity amputations (MS, 2015a; MS, 2015b). Another common complication of diabetics in Morocco are retinopathy, diabetic neuropathy (Hammoudi et al., 2018), nephropathy and heart disease (Selihi et al., 2015). Several factors promote the increase in the rate of diabetes in Morocco such as the transition from a rural and traditional way of life to a modern and urban way of life, changes in eating habits and lifestyle (Belahsen et al., 2005; Dinar and Belahsen, 2014).

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3. Research methodology

The information collected about Moroccan antidiabetic medicinal plants included their ethnobotanical use, phytochemical content, *in vitro* and *in vivo* evaluation of their biological activity. Literature on the antidiabetic properties of bioactive compounds identified in these plants were also summarized. Certain scientific search engines were used to collect the relevant information including Web of Science, Medline, Scopus, Science-Direct, and Google-Scholars. In the first part of our research, we have summarized Moroccan ethnobotanical studies to identify species used to treat diabetes. A literature search on the *in vitro* and *in vivo* antidiabetic effects of Moroccan medicinal plants was carried using different key words such as "antidiabetic effects of Moroccan medicinal plants"and "Moroccan antidiabetic plants". The collected manuscripts were identified and examined for relevance based on their titles and abstracts. Information on the preclinical evaluation and clinical trials of the reported bioactive compounds from Moroccan antidiabetic plants were also collected. References lists of the retrieved papers were also examined to identify further relevant papers. Chemical structures were drawn using Chem Draw Pro 8.0 software. PubChem database was used to check the IUPAC names of phytochemicals reported from each plant.

4. Ethnopharmacological use of Moroccan antidiabetic medicinal plants

Medicinal plants have been used for a long time in folk medicine to treat several diseases. Several plants have been used to treat diabetes in Morocco. Plants belonging to sixty-five families were reported in the literature as traditional antidiabetic agents. The parts used and the mode of preparation vary from a region to another.

The Asteraceae family is one of the most common families in Moroccan traditional medicine as a source of antidiabetic plants. Twenty-three species were reported as antidiabetic remedies in the literature including *Anvillea radiata*, *Artemisia absinthium*, *Achillea odorata*, *Artemisia absinthium*, *Artemisia arborescens*, *Artemisia herba-alba*, *Artemisia campestris*, *Artemisia mesatlantica*, *Bubonium graveolens*, *Calendula arvensis*, *Cynara cardunculus*, *Cichorium intybus*, *Cynara scolymus*, *Echinops spinosissimus*, *Helianthus annuus*, *Ormenisafricana, Ormenis scariosa*, *Launaea arborescens, Matricaria chamomilla, Scorzonera undulata*, *Taraxacum officinale*, *Tanacetum vulgare*, and *Warionasa harae*. Different parts of these plants are used such as leaves, flowers, roots, seeds, latex, stem, and sometimes the whole aerial part. The mode of preparation varies from a region to another, but the decoction is the most used form (Table 1) (Barkaoui et al., 2017; Bellakhdar, 1997; Benchaabane and Abbad, 1994; Benlamdini et al., 2014; Chaachouay et al., 2019; Eddouks et al., 2017a; El Rhaffari and Zaid, 2002; Fakchich and Elachouri, 2014; Hachi et al., 2015; Hmamouchi, 1999; Kahouadji, 1995; Orch et al., 2015; Sijelmassi, 1993; Tahraoui et al., 2007).

Plants from the Lamiaceae family are also commonly used as antidiabetic remedies in Morocco. Several species have been known by their extensive use against diabetes such as *Ajuga iva, Allium cepa, Calamintha alpina, Lavandula dentata, Lavandula officinalis, Lavandula stoechas, Lavandula x abrialis, Marrubium vulgare, Marrubium deserti, Mentha pulegium, Mentha absinthium, Mentha suaveolens, Origanum compactum, Rosmarinus officinalis, Salvia officinalis, Salvia phlomoides, Sideritis subatlantica, Teucrium polium, Thymus broussonetii, Thymus ciliatus, Thymus munbyanus, Thymus satureioides,* and *Thymus satureioides* (Table 1). Different parts of these plants are used, and the preparation methods vary from a region to another. Plants of this family are used in all regions of Morocco because of their effectiveness as antidiabetic remedies (Barkaoui et al., 2017; Bellakhdar, 1997; Bouyahya et al., 2017; Eddouks et al., 2002, 2017a; El Rhaffari and Zaid, 2002; Fakchich and Elachouri, 2014; Ghourri et al., 2013; Kahouadji, 1995; Orch et al., 2015; Skalli et al., 2019; Tahraoui et al., 2007; Ziyyat et al., 1997).

Rosaceae family has been reported as rich source of antidiabetic plants used in Moroccan traditional medicine. Species used include *Crataegus laevigata, Crataegus oxyacantha, Cydonia oblonga, Eriobotrya japonica, Malus domestica, Prunus dulcis*syn *Prunus amygdalus,* and *Rosa fruticosus.* Different parts are used such as fruits, leaves, nuts, and seeds. The used form varies according to the region (Barkaoui et al., 2017; Bellakhdar, 1997; Bellakhdar et al., 1991; Benlamdini et al., 2014; Chaachouay et al., 2019; Eddouks et al., 2002; El Rhaffari and Zaid, 2002; El-Hilaly et al., 2003; Fakchich and Elachouri, 2014; Ghourri et al., 2013; Hmamouchi, 1999; Orch et al., 2015; Sijelmassi, 1993; Skalli et al., 2019; Tahraoui et al., 2007; Ziyyat et al., 1997). Another important family used in Moroccan traditional medicine as a source of antidiabetic remedies is Rutaceae. The species reported from this family include *Citrus aurantium, Citrus bigaradia, Citrus amara, Ruta montana,* and *Ruta chalepensis.* The aerial parts of these species including the leaves and flowers are prepared mainly by infusion and decoction in order to treat diabetic patients (Benkhnigue et al., 2014; Eddouks et al., 2002; Fakchich and Elachouri, 2014; Orch et al., 2015; Tahraoui et al., 2007; Teixidor-Toneu et al., 2016; Ziyyat et al., 1997).

Plants belonging to Amaryllidaceae family have been alsoused in Moroccan traditional medicine as antidiabetic remedies. Three species of this family were reported in literature including *Allium ampeloprasum*, *Allium cepa*, and *Allium sativum*. For the mode of use, the stem of *A. ampeloprasum* are crushed and ingested with water (Skalli et al., 2019), and for *A. cepa* and *A. sativum* the bulb is used as raw material (Barkaoui et al., 2017; Benkhnigue et al., 2014; Bouyahya et al., 2017; Eddouks et al., 2002, 2017a; Fakchich and Elachouri, 2014; Hachi et al., 2015; Hmamouchi, 1999; Orch et al., 2015; Tahraoui et al., 2007; Ziyyat et al., 1997). Six species of Amaranthaceae family were described as antidiabetic plants in traditional medicine of Morocco. The part used and the mode of preparation differ from a region to another. Different

Table 1
Moroccan medicinal plants used in traditional medicine against diabetes.

Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
Aloeaceae	*Aloe socotrina*Lamk.,	Sibrsidqi Sabr	Leaves Juice	Powder Dry juice	Oriental Morocco	Kahouadji (1995)
	*Aloe socotrina*Lamk.,	Sibrsidqi Sabr	Leaves Juice	Powder Dry juice	Morocco	Bellakhdar et al. (1991)
	*Aloe socotrina*Lamk.,	Sibrsidqi Sabr	Leaves Juice	Powder Dry juice	Morocco	Bellakhdar (1997)
	*Aloe succotrina*Lam.,	Sibr	Nd	Nd	South east region	Eddouks et al. (2002)
Amaranthaceae	*Chenopodiumambrosoides*L.,	Mkhinza	Leaves	Nd	High Atlas	Teixidor-Toneu et al. (2016)
	*Anabasisaretiodes*Moq.,&Coss.,	Sallaa	Nd		South east region	Eddouks et al. (2002)
	*Anabasisaretioides*Moq.,&Coss.,	Salla	Nd	Nd	DaraaTafilalet region	Eddouks et al. (2017a)
	Chenopodiumambrosioides L.	Mkhinza	Nd	Nd	Oriental Morocco	Ziyyat et al. (1997)
	Chenopodiumambrosioides L.,	Mkhinza	Leaves Flowers	Infusion Fresh juice	Oriental Morocco	Ziyyat et al. (1997)
	Chenopodiumambrosioides L.,	Mkhinza	Nd	Decoction Powder Infusion	DaraaTafilalet region	Eddouks et al. (2017a)
	Fredolia aretioides Coss. & Dur.,	Shejrali Idihacherrih Sella	Aerial parts	Powder	Morocco	Bellakhdar (1997)
	Fredolea arelioïdes Coss. &Dur.,	Sellaâ/Sellah/ Akennoud/Achennoud	Aerial parts	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	Haloxylonscoparium Pomel.,	âkenoud Rremt, âssây	Whole plant	Infusion Powder	Morocco	Bellakhdar (1997)
	*Hammadascoparia*Pomel.,	Assay	Seeds	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	*Hammadascoporia*Pomel.,	Rremt/TassaytAssay	Latex Leaves	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	*Suaedamollis*Dest.,	Adeghmous	Ariel parts	In meals	Tafilalet	El Rhaffari and Zaid (2002)
Amaryllidaceae	*Allium ampeloprasum* L.,	Leborrou	Stems	Crushed and ingested with water	Rabat	Skalli et al. (2019)
	Allium cepa L.,	Al'Bassla, Azlim Azalim	Bulbs	Raw		Hmamouchi (1999)
	Allium cepa L.,	Al'Bassla	Bulbs	Raw	South eastern Morocco	Tahraoui et al. (2007)
	Allium cepa L.,	Al'Bassla	Nd	Nd	South east region	Eddouks et al. (2002)
	Allium cepa L.,	Al'Bassla	Bulbs	Nd	North of Morocco	Orch et al. (2015)
	Allium cepa L.,	Al'Bassla	Bulbs	Juice	HaousRhamnaregion	Benkhnigue et al. (2014)
	Allium sativum L.,		Nd	Nd	South east region	Eddouks et al. (2002)
	Allium sativum L.,	Toum, Touma Tiskert	Bulbs	Raw	Oriental Morocco	Ziyyat et al. (1997)
	Allium sativum L.,	Tiskert Touma	Bulbs	Raw	Western Anti Atlas	Barkaoui et al. (2017)
	Allium sativum L.,		Nd	Decoction, infusion, and powder	DaraaTafilalet region	Eddouks et al. (2017a)
	Allium sativum L.,	Touma	Bulbs	Cultivated	HaousRhamnaregion	Benkhnigue et al. (2014)
Anacardiaceae	*Pistacia atlantica* Desf.,	Btem Igg Drou	Fruits	Decoction	Khenifra	Hachi et al. (2015)
	*Pistacia lentiscus*L.,	Trou	Leaves	Decoction	North West	Bouyahya et al. (2017)
	*Pistacia lentiscus*L.,	Lentisque/Trou	Latex Leaves	Nd	Khenifra	Hachi et al. (2015)
	*Pistacia lentiscus*L,	Adru	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	*Pistacia lentiscus*L.,	Adru	Leaves	Decoction Infusion	North of Morocco	Orch et al. (2015)
Apiaceae	*Ammi visnaga*L., (Lam.)	Bachnikha	Fruits	Decoction	Oriental Morocco	Kahouadji (1995)
	*Ammi visnaga*L., (Lam.)	Bachnikha	Fruits	Decoction	Morocco	Bellakhdar (1997)
	*Ammi visnaga*L., (Lam.)	Bachnikha	Fruits	Decoction	Morocco	Bellakhdar et al. (1991)
	*Ammi visnaga*L., (Lam.)	Bachnikha	Fruits	Decoction	Oriental Morocco	Ziyyat et al. (1997)
	*Ammi visnaga*L., (Lam.)	Bachnikha	Nd	Nd	South east region	Eddouks et al. (2002)
	*Ammi visnaga*L., (Lam.)	Tabechnikht/Khella	Seeds	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	*Ammi visnaga*L., (Lam.)	Bachnikha	Fruits	Decoction	North of Morocco	Orch et al. (2015)
	*Ammivisnaga*L., (Lam.)	Bachnikha	Seeds Stems	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	*Ammi visnaga*L., (Lam.)	Bachnikha	Seeds Stems Fruits	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	Carum carvi L.,	El-qarwiya	Seeds	Decoction	Northern Morocco	El-Hilaly et al. (2003)

(continued on next page)

Table 1 (*continued*)

Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Carum carvi L.,	El-qarwiya	Seeds	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	Carum carvi L.,		Nd	Nd	DaraaTafilalet region	Eddouks et al. (2017a)
	Carum carvi L.,	El-qarwiya	Seeds	Decoction, maceration infusion and powder	Western Anti Atlas	Barkaoui et al. (2017)
	Carum carvi L.,	El-qarwiya	Seeds	Decoction Infusion Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Coriandrum sativum L.,	Coriandre	Seeds	Powder, infusion	HaousRhamnaregion	Benkhnigue et al. (2014)
	Coriandrum sativum L.,	Kasbour	Seeds and leaves	Infusion with water teaspoon	Rabat	Skalli et al. (2019)
	Coriandrum sativum L.,	Qasbur	Seeds and leaves	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	Cuminum cyminum L.,	Kammun	Seeds	Cooking	North West	Bouyahya et al. (2017)
	Eryngium ilicifolium Lam.,	Tasnant/Iglifin	Stems and leaves	Decoction and powder	Western Anti Atlas	Barkaoui et al. (2017)
	Ferula asafetida L.,	Hantit	Resin	Decoction	Morocco	Sijelmassi (1993)
	Ferula communis L.,	Klarh, nard	Nd	Fumigation,	Oriental Morocco	Kahouadji (1995)
	Ferula communis L.,		Resin	external use	Moroccan Rif	Merzouki et al. (2000)
	Foeniculum vulgare Mill.,	Nafaa	Seeds	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Foeniculum vulgare Mill.,	Nafas	Seeds	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Foeniculum vulgare Mill.,	Nafas	Seeds	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	Foeniculum vulgare Gaertn.,	Nafas	Nd		South east region	Eddouks et al. (2002)
	Foeniculum vulgare Mill.,	Uamsa	Fruits Leaves Roots		High Atlas	Teixidor-Toneu et al. (2016)
	Foeniculumdulce Dc.,	Nafa, besbas, Wamsa, Oumasa	Seeds Roots Leaves	Decoction, inhalation	Morocco	Sijelmassi (1993)
	Pastinaca sativa L.,	Leftlmahfour	Roots	Raw	Western Anti Atlas	Barkaoui et al. (2017)
	*Pimpinella anisum*L.,	Habbathlawa	Seeds	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	*Pimpinella anisum*L.,	Hebbathlaoua	Seeds	Infusion handful	Rabat	Skalli et al. (2019)
	Pimpinella anisum L.,	Habathlawa	Seeds	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Ridolfia segetum (L.) Moris.,	Slilo	Leaves	Cooked	Moroccan Rif	Chaachouay et al. (2019)
Apocinaceae	*Apteranthes europaea* (Guss.) Murb.,	Oukaniddan	Stems	Decoction, infusion, and raw	Western Anti Atlas	Barkaoui et al. (2017)
	Caralluma europaea L.,	Daghmoûss	Leaves	Juice	Khenifra	Hachi et al. (2015)
	Caralluma europaea L.,	Daghmoûss	Racket	Juice, powder Decoction	HaousRhamnaregion	Benkhnigue et al. (2014)
	*Nerium oleander*L.,	Dafla	Leaves	Infusion	North West	Bouyahya et al. (2017)
	*Nerium oleander*L.,	Dafla	Leaves	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Nerium oleander L.,	Dafla	Nd	Nd	South east region	Eddouks et al. (2002)
	Nerium oleander L.,	Laurier -rose/DeflaAlili	Leaves	Infusion	Eastern High Atlas	Benlamdini et al. (2014)
	Nerium oleander L.,	Defla	Leaves	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	Nerium oleander L.,	Defla Allili	Whole plant		Khenifra	Hachi et al. (2015)
	*Nerium oleander*L.,	Laurier rose	Leaves	Decoction	Moroccan Sahara	Ghourri et al. (2013)
	Nerium oleander L.,	Laurier rose	Leaves Roots	Decocotion	HaousRhamnaregion	Benkhnigue et al. (2014)
	Nerium oleander L.,	Defla/Alili	Leaves	Fumigation	Western Anti Atlas	Barkaoui et al. (2017)
	Periploca angustifolia L., abill.,	Asllif	Fruits	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Ptychotis verticillata L.,	Nûnkha	Aerial parts	Fumigation Infusion	Oriental Morocco	Ziyyat et al. (1997)
Apparaceae	*Capparis spinosa* L.,	Kebbar	Fruits	Decoction	Oriental Morocco	Kahouadji (1995)
	Capparis spinosa L.,	Kebbar	Seeds	Powder	Oriental Morocco	Ziyyat et al. (1997)
Aristolochiaceae	*Aristolochia longa*L.,	Aristoloche	Rhizomes	Powder Decoction	Moroccan Sahara	Ghourri et al. (2013)
	Aristolochi alonga L.,	Berztam	Rhizomes	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
Asparagaceae	*Asparagus albus* L.,	Zkoum	Roots	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
Asteraceae	*Anvillea radiata* (Coss et Dur).,	Ajri/Gijou/Anderoual	Leaves	Infusion	Tafilalet	El Rhaffari and Zaid (2002)
	Artemisia absinctium L.,	Chiba	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)

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Table 1 (*continued*)

Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Achillea odorata L.,	Korte	Leaves Flowers	Decoction	Oriental Morocco	Kahouadji (1995)
	Artemisia absinthium L.,	Chiba Chibat al-ajûj	Aerial parts	Infusion	Morocco	Bellakhdar (1997)
	Artemisia absinthium L.,	Chiba			South east region	Eddouks et al. (2002)
	Artemisia arborescens L.,	Chiba Chibat al-ajûj	Aerial parts	Infusion	Morocco	Bellakhdar (1997)
	Artemisia arborescens L.,	Chiba Chibat al-ajûj	Aerial parts	Infusion	Oriental Morocco	Ziyyat et al. (1997)
	Artemisia absinthium L.,	Chıba	Leaves Aerial part	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	Artemisia herba-alba Asso.,	Chih	Leaves Roots	Powder	South eastern Morocco	Tahraoui et al. (2007)
	Artemisia herba alba Assac.,	Chih	Leaves Aerial parts	Poudre Decoction Infusion	North of Morocco	Orch et al. (2015)
	Artemisia herba alba Asso.,	Chih	Nd	Nd	South east region	Eddouks et al. (2002)
	*Artemisia herba alba*Asso.,	Izri/Chih	Steam Leaves Roots	Decoction Infusion	Western Anti Atlas	Barkaoui et al. (2017)
	Atemisia herba-alba Asso.,	Chih	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Artemisia herba alba Asso.,				DaraaTafilalet region	Eddouks et al. (2017a)
	Artemisia herba-alba Asso.,	Armoise blanche	Aerial parts	Decoction	HaousRhamnaregion	Benkhnigue et al. (2014)
	Artemisia herba-alba Asso.,	Chih Izri	Aerial parts	Decoction	Eastern High Atlas	Benlamdini et al. (2014)
	Artemisia herba-alba Asso.,	Shih, Ifsî Fessî	Leaves and roots	Nd	Morocco	Bellakhdar (1997)
	Artemisia herba-alba Asso.,	Shih, Ifsî Fessî	Leaves and roots	Nd	Oriental Morocco	Ziyyat et al. (1997)
	Artemisia herba-alba Asso.,	Shih Ifsî Fessî	Leaves and roots	Nd	Morocco	Bellakhdar et al. (1991)
	*Artemisia absinthium*L.,	Nd	Nd	Nd	South East Region	Eddouks et al. (2002)
	Artemisia campestris L.,	Allal	Flowers Leaves	Decoction		Hmamouchi (1999)
	Artemisia campestris L.,	Allal	Flowers Leaves	Decoction	Morocco	Sijelmassi (1993)
	Artemisia mesatlantica Maire.,	Chih Ifsi	Aerial parts	Decoction	Eastern High Atlas	Benlamdini et al. (2014)
	Artemisia mesatlantica Maire.,	Chih Ifsi	Aerial parts	Decoction	Eastern High Atlas	Benlamdini et al. (2014)
	Bubaniumgraveolen Forsk.,	Ngoud	Aerial parts	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	*Calendula arvensis*Bieb.,	Jemra Azwiwel	Flowers	Infusion	Moroccan Rif	Chaachouay et al. (2019)
	Cynara cardunculus L.,	Kharchouf	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	*Cynara cardunculus*L.,	Kharchouf	Root and rib	Decoction, Infusion	HaousRhamna region	Benkhnigue et al. (2014)
	Cichorium intybus L.,	Bouaggad, timerzuga	Roots	Infusion	Marakech Region	Benchaabane and Abbad (1994)
	Cynara scolymus L.,	Kharchouf Tagemmut Amazzûgh	Roots, Capitules	Decoction	Morocco	Sijelmassi (1993)
	Cynara scolymus L.,	Kharchouf Tagemmut Amazzûgh	Roots Capitules	Decoction	Morocco	Bellakhdar (1997)
	Cynara scolymus L.,	Kharchouf Tagemmut Amazzûgh	Roots Capitules	Decoction	Morocco	Bellakhdar et al. (1991)
	Cynara scolymus L.,	Kharchouf Tagemmut Amazzûgh	Roots Capitules	Decoction	Eastern High Atlas	Benlamdini et al. (2014)
	Cynara scolymus L.,	Kharchouf Tagemmut Amazzûgh	Roots Capitules	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Echinops spinosus L.,	Tassekra L-kherchouf Chouk Al-himar	Leaves	Infusion	Oriental Morocco	Kahouadji (1995)

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Table 1 (*continued*)

Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Helianthus annuus L.,	Nouaratchamess	Roots	Powder	Khenifra	Hachi et al. (2015)
	Ormenis africana (Jord. & Four)	Îrzgi Gartôfa	Latex	Decoction	Oriental Morocco	Kahouadji (1995)
	Ormeniss cariosa Ball., (lit.& Maire)	Îrzgi, Gartôfa	Latex Roots	Decoction	Oriental Morocco	Kahouadji (1995)
	Laune aarborescens (Batt.) Maire.,	Sekkûm, Mmû-lbeyna	Seeds	Infusion Extract	Morocco	Bellakhdar (1997)
	Launaea arborescens (Batt.) Murb.,	Iferskel/Mo ulbina	Stems Leaves Flowers	Decoction and Infusion	Western Anti Atlas	Barkaoui et al. (2017)
	Matricaria chamomilla L.,	Mansania	Leaves and flowers	Decoction Infusion	North of Morocco	Orch et al. (2015)
	Scorzonera undulata Vahl.,	Tamtla	Flower	Raw	Western Anti Atlas	Barkaoui et al. (2017)
	Taraxacum officinale L.,	Chlada and handaba	Leaves Roots	Decoction Powder	Morocco	Sijelmassi (1993)
	Tanacetum vulgare L.,	Lbalssem	Leaves	Infusion	Moroccan Rif	Chaachouay et al. (2019)
	Tanacetum vulgare L.,	Tanaisie	Leaves	Infusion	Haous Rhamnaregion	Benkhnigue et al. (2014)
	Warione asaharae L.,	Tanaisie	Leaves	Infusion	Daraa Tafilalet region	Eddouks et al. (2017a)
Berberidaceae	*Berberis hispanica* Boiss & Reut.,	Aghris	Cortex	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
Brassicaceae	*Brassica rapa* L.,	Leffet	Leaves	Decoction	Eastern High Atlas	Benlamdini et al. (2014)
	Lepidium sativum L.,	Habber sad Rchad Lhurf	Seeds	Decoction		Hmamouchi (1999)
	Lepidium sativum L.,	Habber sad Rchad Lhurf	Seeds	Powder	Oriental Morocco	Kahouadji (1995)
	Lepidium sativum L.,	Habber sad Rchad Lhurf	Seeds	Powder	South east region	Eddouks et al. (2002)
	Lepidium sativum L.,	Habber sad Rchad Lhurf	Seeds	Powder	HaousRhamnaregion	Benkhnigue et al. (2014)
	Lepidium sativum L.,	Hebb rechad	Seeds	Decoction Powder	South eastern Morocco	Tahraoui et al. (2007)
	Lepidium sativum L.,	Heberechad Leharf	Seeds	Ground powder withmilk	Rabat	Skalli et al. (2019)
	Raphanus sativus L.,	Lfjel	Roots	Raw	Western Anti Atlas	Barkaoui et al. (2017)
Burseraceae	*Boswelia carteii* Bridw.,	Loubanedacare	Resin	Infusion	Oriental Morocco	Kahouadji (1995)
	Boswelia sp.,	Salabane	Resin	Decoction	Oriental Morocco	Kahouadji (1995)
Cactaceae	*Opuntia ficus-indica* Mill.,	Hindiya	Flowers Fruits	Powder	South eastern Morocco	Tahraoui et al. (2007)
	Capparis spinosa L.,	Lkebar	Flowers Fruits	Maceration	South eastern Morocco	Tahraoui et al. (2007)
	Opuntia ficusindica L., Mill.	Lhndia Aknari	Stems Flowers	Decoction and powder	Western Anti Atlas	Barkaoui et al. (2017)
Capparaceae	*Capparis spinosa* L.,	Al'Kabbar	Seeds	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Capparis spinosa L.,	L-kebbar Taylalout Tayloulout	Leaves	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	Capparis spinosa L.,	Al'Kabbar	Aerial parts Fruits	Decoction	North of Morocco	Orch et al. (2015)
	Capparis spinosa L.,	Al'Kabbar			South east region	Eddouks et al. (2002)
Caryophyllaceae	*Hernaria hirsuta* L.,	Hrastlahjar	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
Cistaceae	*Cistus ladaniferus* L.,	Taouzla	Leaves	Infusion Decoction	Oriental Morocco	Kahouadji (1995)
	Cistus libanotis L.,	Yazirlahmir	Leaves	Decoction	Oriental Morocco	Kahouadji (1995)
	Cistus creticus L.,	Irgel	Leaves	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Cistus salviifolius L.,	Tirgelt	Leaves	Decoct ion	Western Anti Atlas	Barkaoui et al. (2017)
Cucurbitaceae	*Citrullus colocynthis* L., (Schrad.)	TaFerzizt Lehdej	Seeds	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	Citrullus colocynthis L., (Schrad.)	Hantel Hadjaja	Fruits	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Citrullus colocynthis L., (Schrad.)	Hantel Hadjaja	Fruits	Decoction	South east region	Orch et al. (2015)
	Citrullus colocynthis L., (Schrad.)	Lhdej Taferzizte	Seeds	Infusion	Moroccan Rif	Chaachouay et al. (2019)
	Citrullus colocynthis L., (Schrad.)	Aferziz	Seeds	Decoction and powder	Western Anti Atlas	Barkaoui et al. (2017)

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Table 1 (*continued*)

Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Citrullus colocynthis L., (Schrad.)	Coloquinte	Fruits Seeds	Maceration	HaousRhamna region	Benkhnigue et al. (2014)
	Citrullus colocynthis L., (Schrad.)	Hdej	Fruits	Cutaneous application Once a day during three days	Rabat	Skalli et al. (2019)
Cucurbitaceae	*Cucumis sativus* L.,	Lkhiar	Fruits	Raw	Western Anti Atlas	Barkaoui et al. (2017)
Compositae	*Launea arborescens* L.,	Malbina	Whole plant	decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Brocchia cinera Del.,	Kartoufa	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Lactuca sativa L.,	Khouss			South east region	Eddouks et al. (2002)
	Cichorium intybus.,	Alokif	Whole plant	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Insula viscose L.,	Trklan	Flowers	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Anvillea radiata Coss & Dur.,	Nkad	Roots	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Anacyclus Pyrethrum L.,	Takntist	Leaves	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
Cucurbitaceae	*Citrullus colocynthis* L., (Schrad.)	Handal Hdejja Tijjelt	Fruits Pulps	Crud maceration external use	Morocco	Bellakhdar (1997)
	Citrullus colocynthis L., (Schrad.)	Handal Hdejja Tijjelt	Fruits Pulps	Crud maceration external use	Morocco	Bellakhdar et al. (1991)
	Citrullus colocynthis L., (Schrad.)	Handal Hdejja Tijjelt	Fruits Pulps	Crud maceration External use	Oriental Morocco	Ziyyat et al. (1997)
Cupressaceae	*Juniperus phoenicea* L.,	Lôarôar Adeghmam	Root	Infusion	Tafilalet	El Rhaffari and Zaid (2002)
	Juniperus phoenicea L.,	Arâar,	Cones Leaves	Powder Decoction	Morocco	Bellakhdar (1997)
	Juniperu sphoenicea L.,	Arâar,	Leaves Aerial parts Cones	Maceration Decoction	HaousRhamna region	Benkhnigue et al. (2014)
	Juniperu sphoenicea L.,	ArarFiniqi	Leaves	Decoction	Moroccan Rif	Chaachouay et al. (2019)
	Juniperus thuri L., (Fera var; Fricana)	L-ôarôar Taoualt		Infusion		
	Tetraclinis articulate (Vahl) Mast L.,	Azuka	Leaves Fruits		High Atlas	Teixidor-Toneu et al. (2016)
	Tetraclinis articulata Benth L.,	Arâar Azuka Imijjed	Aril	Maceration Powder	Oriental Morocco	Ziyyat et al. (1997)
	Tetraclinis articulata Masters L.,	El-sarsar	Leaves Aerial part	Maceration and powder	South estern Morocco	Tahraoui et al. (2007)
	Tetraclinis articulata Benth.,	Araar			South east region	Eddouks et al. (2002)
	Tetraclinis articulata.,	Thuya Ar'ar	Leaves Young branch		Khenifra	Hachi et al. (2015)
Dracaenaceae	*Dracaena draco* subsp.,	Ajgal	Stem leaves	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
Ephedraceae	*Ephedra altissima* Desf.,	Tougelargan	Stems Leaves Whole plant	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Euphorbia officinarum L.,	Tikiout Dag hmouss	Stem and leaves	Powder	Western Anti Atlas	Barkaoui et al. (2017)
	Ephedra alata Decne.,	Laâlenda Chdida/Amater	–	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	Euphorbia officinarum subsp. echinus (Hook. f. &Coss.).,	Tikiout Dag hmouss	Stem and leaves	Powder	Western Anti Atlas	Barkaoui et al. (2017)
Ericaceae	*Arbutus unedo* L.,	Sasnou El-lenj, unnîs	Leaves and roots	Decoction	Oriental Morocco	Ziyyat et al. (1997)
	Juniperus phoenicea., L.,	–	Leaves	Powder Decoction	Moroccan Sahara	Ghourri et al. (2013)
	Arbutus unedo L.,	*Sasnou*	Leaves	Decoction	North of Morocco	Orch et al. (2015)
Fabaceae	*Cassia Senna* L.,	Snaa	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Ceratonia siliqua L.,	Kharoub	Fruits	Nd	Rabat	Skalli et al. (2019)
	Ceratoni a siliqua L.,	Tikida Lkharoub	Leaves Seeds	Decoction and powder	Western Anti Atlas	Barkaoui et al. (2017)
	Glycine max L., (Merr)	Soja	Seeds	Maceration and raw	Western Anti Atlas	Barkaoui et al. (2017)
	Glycine max L., (Merr)	Soja, A'ssoja	Seeds and fruits	Fried seed	South eastern Morocco	Tahraoui et al. (2007)
	Glycine max L., (Merr)	A'ssoja	Seeds	Decoction	Morocco	Sijelmassi (1993)
	Glycine max L., (Merr)	A'ssoja	Seeds	Decoction	Morocco	Bellakhdar et al. (1991)

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Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Glycine max L., (Merr)	A'ssoja	Seeds	Decoction	Morocco	Bellakhdar (1997)
		Termas, Semqâlabeyda	Seeds	Decoction and powder	Morocco	Bellakhdar (1997)
Fabaceae	*Glycyrrhiza glabra* L.,	Ark souss	Bark	Infusion of the roots	Rabat	Skalli et al. (2019)
	Glycyrrhiza glabra L.,	Arqsouss	Fruits Roots	Decoction		Hmamouchi (1999)
	Foenum graecum L.,	Helba	Seeds	Maceration	Rabat	Skalli et al. (2019)
	Lupinusalbus L.	Tarmas	Seeds	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Lupinusalbus L., (sensuLato),	*Lfoulmessri*	nd	Nd	South east region	Eddouks et al. (2002)
	Lupinusaugustifolius, L.,	kîkel, fwila	nd	Nd	Moroccan Rif	Merzouki et al. (2000)
	Lupinushirsutus L.,	Semqala	nd	Powder	Moroccan Rif	Merzouki et al. (2000)
	Lupinus luteus, L.,	Rjel Ed-djaja	nd	Nd	Moroccan Rif	Merzouki et al. (2000)
	Lupinuspilosus L.,	Îbaûnwijjan	nd	Decoction	Moroccan Rif	Merzouki et al. (2000)
	Lupinuspilosus L.,	RjelDjaja	Seeds	Infusion	Morocco	
	Lupanusalbus.,	Lupin blanc	Seeds	Powder, maceration and infusion	Moroccan Sahara	Ghourri et al. (2013)
	Lupinusalbus L.,	Lupin blanc	Seeds		HaousRhamna region	Benkhnigue et al. (2014)
Fabaceae	*Perseaamericana* Mill.,	Avocat	Fruits core	Ingested with milk	Rabat	Skalli et al. (2019)
	Retamasphaerocarpa L., (Boiss.)	Rtem	Roots	Decocction	South eastern Morocco	Tahraoui et al. (2007)
	Trigonellafoenum graecum L.,	Helba	Seeds	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Trigonellafoenum- graecum L.,	Tefedas	Seeds		High Atlas	Teixidor-Toneu et al. (2016)
	Trigonellafoenum-graecum L.,	Al'Houlba	Seeds	Decoction Powder Maceration	North of Morocco	Orch et al. (2015)
	Trigonellafoenum graecum L.,	Nd	Nd	Nd	DaraaTafilalet region	Eddouks et al. (2017a)
	Trigonellafoenum-graecum L.,	Halba Tifidas	Seeds	Decoction	Moroccan Rif	Merzouki et al. (2000)
	Trigonellafoenum-graecum L.,	Halba Tifidas	Seeds	Maceration	Oriental Morocco	Ziyyat et al. (1997)
	Trigonellafoenum-graecum L.,	Halba Tifidas	Seeds	Maceration	Morocco	Bellakhdar et al. (1991)
	Trigonellafoenum-graecum L.,	Halba Tifidas	Seeds	Decoction	Morocco	Bellakhdar (1997)
	Trigonellafoenum graecum L.,		Nd	Decoction Infusion Maceration and powder	DaraaTafilalet region	Eddouks et al. (2017a)
	Trigonellafoenum-graecum L.,	Halfa	Seeds	Maceration	Northern Morocco	El-Hilaly et al. (2003)
	Trigonellafoeniculum-graecum L.,	Halba	Nd	Nd	South east region	Eddouks et al. (2002)
	Trigonellafoenum-graecum L.,	el-halba	Seeds	Decoction, maceration and Powder	South eastern Morocco	Tahraoui et al. (2007)
	Trigonellafoenum graecum L.,	Fenugrec	Seeds	Powder, maceration and infusion	Moroccan Sahara	Ghourri et al. (2013)
	Trigonellafoenum graecum L.,	Fenugrec	Seeds	Maceration	HaousRhamna region	Benkhnigue et al. (2014)
Fagaceae	*Vigna sinensis* End.,	Foul gnawa	Seeds	Maceration	Moroccan Rif	Merzouki et al. (2000)
	Quercus faginea Lam.,	L'aâssaf	Gall	Powder	Moroccan Rif	Merzouki et al. (2000)
Gentianaceae	*Centaurium erythraea* Rafn.,	Gosset l-hayat Merrâret Lehnes	Aerial parts	Infusion	Morocco	Bellakhdar (1997)
	Centaurium erythraea Rafn.,		Nd	Nd	Morocco	Bellakhdar et al. (1991)
	Centaurium erythraea Rafn.,	Mrartlhanch	Whole plant	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Centaurium erythraea Rafn.,	Al'Hayya	Aerial parts	Decoction and infusion	North of Morocco	Orch et al. (2015)
Geraniaceae	*Centaurium spicatum* L., (Fritsch.)	Gosset l-hayat Merrâret Lehnes	Aerial parts	Infusion	Morocco	Bellakhdar (1997)
	Centaurium spicatum L., (Fritsch.)	Gosset l-hayat Merrâret Lehnes	Aerial parts	Infusion	Morocco	Bellakhdar et al. (1991)
	Geranium robertianum L.,	Laatarcha	Leaves Flowers Stems	Infusion	Oriental Morocco	Kahouadji (1995)

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Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
Globulariaceae	*Globularia alypum* L.,	Ain larnab	Leaves	Infusion	HaousRhamna region	Benkhnigue et al. (2014)
	Globularia alypum L.,	Ain larnab	Leaves	Infusion and decoction	Morocco	Bellakhdar (1997)
	Globularia alypum L.,	Ain larnab	Leaves	Infusion and decoction	Morocco	Bellakhdar et al. (1991)
	Globularia alypum L.,	Ain larnab	Leaves	Infusion and decoction	Oriental Morocco	Ziyyat et al. (1997)
	*Globularia alypum*L.,	Âinlemeb Taselgha	Leaves	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	Globularia alypum L.,	Ain larnab	Leaves	Decoction	South east region	Eddouks et al. (2002)
	Globularia alypum L.,	Ain larnab	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
Gramineae	*Cynodon dactylon* L., (Pers.)	Til, njem, affie, tagamait	Rhizome and whole plant	Decoction		Hmamouchi (1999)
	Panicum miliaceum L.,	Anili, illane, tafsût	Seeds	Boiled powder	Morocco	Sijelmassi (1993)
	Panicum miliaceum L.,	Anili, illane, tafsût	Seeds	Boiled powder?	Oriental Morocco	Ziyyat et al. (1997)
	Phlaris paradoxa L.,	Zuan	Seeds	Powder	Northern Morocco	El-Hilaly et al. (2003)
	Phalaris canariensis L.,	Bachna	Seeds	Powder	Oriental Morocco	Kahouadji (1995)
	Sorghum vulgare L.,	*Bachna, tafsût*	Seeds	Boiled powder	Oriental Morocco	Ziyyat et al. (1997)
Juglandaceae	*Juglans regia* L.,	Guergae, gûz, sswak	Fruitsleaves, and cortex	Infusion and decoction		Hmamouchi (1999)
	Juglans regia L.,	Guergae, gûz, sswak	Fruits, leaves, and cortex	Infusion and decoction	Morocco	Bellakhdar (1997)
	Juglans regia L.,	Guergae, gûz, sswak	Fruits, leaves, and cortex	Infusion and decoction	Morocco	Sijelmassi (1993)
	Juglans regia L.,	Noyer	Leaves	Infusion and decoction	HaousRhamna region	Benkhnigue et al. (2014)
	Juglans regia.,	Noyer	Nuts	Maceration	Moroccan Sahara	Ghourri et al. (2013)
Lamiaceae	*Ajuga iva* L.,	Chendgora	Aerial parts	Decoction Powder	Morocco	Bellakhdar (1997)
	Ajuga iva L.,	Chendgora	Nd	Nd	Oriental Morocco	Ziyyat et al. (1997)
	Ajuga iva.,	Ivette musquée	Leaves	Powder Decoction	Moroccan Sahara	Ghourri et al. (2013)
	Ajuga iva (L.,) Schreb.,	Chendgora	Aerial partss	Decoction	North of Morocco	Orch et al. (2015)
	Ajuga iva (L.,) Schreb.,	Bugle	Aerial parts	Decoction	Haous Rhamna region	Benkhnigue et al. (2014)
	Ajuga iva (L.)	Touf-Telba/Chendgoura	Aerial parts	Tisane,	Tafilalet	El Rhaffari and Zaid (2002)
	Ajuga iva (L.,) Schreb.,	s̆endgora	Leaves, stems, Aerial parts	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	Ajuga iva L.,	Chendgoura	Stems Leaves	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Ajuga iva (L.) Schreb.,	Timernanzenkhad/ Chndkoura	Stem and leaves	Powder	Western Anti Atlas	Barkaoui et al. (2017)
	Allium cepa L., *(ALLCE)*.,	Bessela	Bulb	Bulb	Rabat	Skalli et al. (2019)
	Calamintha alpina L.,	Fliyyo dial berr	Leaves	Decoction	Rabat	Skalli et al. (2019)
	Lavandula dentata L.,	Timzeria	Stems and leaves	Decoction, infusion and raw	Western Anti Atlas	Barkaoui et al. (2017)
	Lavandula dentata L.,	Lkhzama	Nd	Nd	South east region	Eddouks et al. (2002)
	Lavandula dentata L.,	Lakhzama	Aerial parts	Powder		Orch et al. (2015)
	Lavandula dentata L.,.	Timzurri	Leaves and inflorescences		Higt Atlas	Teixidor-Toneu et al. (2016)
	Lavandula dentata L.,	Khzama, Taymerza	Flowers and whole plant	Infusion, decoction, powder	Moroccan Rif	Merzouki et al. (2000)
	Lavandula officinalis L.,	hzama	Leaves and whole plant	Decoction/ Infusion	South eastern Morocco	Tahraoui et al. (2007)
	Lavandula stoechas L.,	Imzeria/Tikenkert	Leaves	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Lavandula stoechas L.,	El-halhal	Flowers and leaves		South easternMorocco	Tahraoui et al. (2007)
	Lavandula stoechas L.,	Halhal	Flowering tops	Decoction	North West	Bouyahya et al. (2017)
	Lavandula stoechas L.,	Lhalhal	Leavs	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Lavandula x abrialis L.,	Lakhzama	Flowers	Infusion	Morocco	Bellakhdar (1997)
	Lavandula x abrialis L.,	Lakhzama	Flowers	Infusion	Oriental Morocco	Ziyyat et al. (1997)
	Lavandula x abrialis L.,	Lakhzama	Flowers	Infusion	Morocco	Bellakhdar et al. (1991)
	Marrubium vulgare L.,	Marrube blanc	Leaves	Powder Decoction	Moroccan Sahara	Ghourri et al. (2013)
	Marrubium vulgare L.,	Merriwa	Leaves stems, andaerial parts	Decoction	South eastern Morocco	Tahraoui et al. (2007)

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Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Morrubium desertii (DeNoe).,	Jâayda/Jcôdo	Leaves	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	Marrubium vulgare (L.,)	Merriout/lfzi/Merrau/ Iffegh/Imourine	Aerial parts	Tisane	Tafilalet	El Rhaffari and Zaid (2002)
	Marrubium vulgare L.	Mriwt/Ifzi	Leaves	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Marrubium vulgare L.,	Merriwet	Leaves and stems	Infusion handful	Rabat	Skalli et al. (2019)
	Marrubium vulgare L.,	Merriwa, Merriwta	Nd	Nd	South east region	Eddouks et al. (2002)
	Mentha pulegium L.,	Fliou	Aerial parts	Infusion	Oriental Morocco	Ziyyat et al. (1997)
	Mentha absinthium L.,	Chiba	Leaves	Decoction	North West	Bouyahya et al. (2017)
	Mentha suaveolens Her.,	Timrssad	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Mentha suaveolens L.,	Mchehtro	Leaves	Decoction	North West	Bouyahya et al. (2017)
	Mentha suaveolens.,	Timja	Leaves	Nd	High Atlas	Teixidor-Toneu et al. (2016)
	Mentha pulegium L.,	Fliyyo dial mae	Leaves	Infusion	Rabat	Skalli et al. (2019)
	Mentha pulegium L.,	Fliou	Nd	Nd	South east region	Eddouks et al. (2002)
	Mentha suaveolens Ehr.,	Marseta	Leaves	Leavesinfusion	Rabat	Skalli et al. (2019)
	Origanum compactum Benth.,	Zaâtar			South east region	Eddouks et al. (2002)
	Origanum compactum Benth.,	Zaâtar	Leaves and flowering top		North West	Bouyahya et al. (2017)
	Origanum compactum Benth.,	Origan	Flowers Leafy stem	Powder infusion	Haous Rhamna region	Benkhnigue et al. (2014)
Lamiaceae	*Origanum compactum Benth*.,	Zâtar	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Origanum compactum Benth.,	Zâtar	Leaves	Infusion	Morocco	Sijelmassi (1993)
	Origanum compactum Benth.,	Zâtar	Leaves	Infusion	Oriental Morocco	Ziyyat et al. (1997)
	Rosmarinus officinalis L.,			Decoction, infusion, powder and mask	DaraaTafilalet region	Eddouks et al. (2017a)
	Rosmarinus officinalis L.,	Azır	Leaves and aerial parts	Decoction/ Infusion	South eastern Morocco	Tahraoui et al. (2007)
	Rosmarinus officinalis L.,	Azir	Leaves	Decoction	North of Morocco	Orch et al. (2015)
	Rosmarinus officinalis L.,	Azir			South east region	Eddouks et al. (2002)
	Rosmarinus officinalis L.,	Azir	Leaves and stems	Infusion/ Decoction Maceration	Rabat	Skalli et al. (2019)
	Rosmarinus officinalis L.,	Azir	Leaves	Infusion	North West	Bouyahya et al. (2017)
	Rosmarinus officinalis L.,	Azir, yazir, barkella	Aerial parts	Infusion and decoction	Oriental Morocco	Kahouadji (1995)
	Salvia officinalis L.,	Salmia	Leaves	Decoction and infusion	Western Anti Atlas	Barkaoui et al. (2017)
	Salvia officinalis L.,	Assalmiya	Leaves	Infusion	North of Morocco	Orch et al. (2015)
	Salvia officinalis L.,			Decoction, infusion and powder	DaraaTafilalet region	Eddouks et al. (2017a)
	Salvia officinalis L.,	Saugeofficinale	Leaves	Infusion	HaousRhamna region	Benkhnigue et al. (2014)
	Salvia officinalis L.,	Saugeofficinale/Salmiya	Whole plant and Flower		Khenifra	Hachi et al. (2015)
	Salvia officinalis L.,	Salmia	Leaves	Infusion leaves	Rabat	Skalli et al. (2019)
	*Salvia officinalis*L.,	Salmia	Leaves	Infusion	Oriental Morocco	Fakchich and Elachouri (2014)
	Salvia officinalis L.,	Salmia, tilsas, tamazzût	Leaves	Infusion	Oriental Morocco	Kahouadji (1995)
	Salvia phlomoides Asso.,	Bouftache	Leaves and seeds		Oriental Morocco	Kahouadji (1995)
	Sideritis subatlantica Doum.,	Garn el kabch	Leaves and stems	Decoction		
	Teucrium polium L.,	Tawerart/Fl you lbour	Leaves	Decoction and Powder	Western Anti Atlas	Barkaoui et al. (2017)
	Teucrium polium L.,	Tawerart/Fl you lbour	Leaves	Decoction and Powder	Western Anti Atlas	Barkaoui et al. (2017)
	Thymus broussonetii Boiss.,	Zietra	Leaves and stems	Infusion and Maceration Handful	Rabat	Skalli et al. (2019)
	Thymus ciliatus (Desf.) Benth.,	Zatar, zîtra, âzukenni	Leaves	Decoction Powder	Rabat	Skalli et al. (2019)
	Thymus munbyanus Boiss. &Reut.,	Touchna	Flowers Leaves	Infusion	Rabat	Skalli et al. (2019)
	Thymus satureioides Cosson&Balam.,	Touwichant	Leaves and flowers		Rabat	Skalli et al. (2019)
	Thymus satureioides Cosson.&Balam.,	Azoukni	Leaves and flower	Decoction	South eastern Morocco	Tahraoui et al. (2007)

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Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Thymus saturejoides Coss.,	Azukni	Leaves and inflorescences		High Atlas	Teixidor-Toneu et al. (2016)
	Thymus saturejoides Coss.,	Asserkna	Leaves	Infusion, powder, and Maceration	Western Anti Atlas	Barkaoui et al. (2017)
Lythraceae	*Punica granatum* L.,	Rman	Pericarp	Decoction, infusion, and powder	Western Anti Atlas	Barkaoui et al. (2017)
Lauraceae	*Cinnamum cassia* Blume.,	Kerfa	cortex;	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Cinnamomum verum Presl.,	Kerfa	Bark	Infusion and decoction Maceration Tablespoons	Rabat	Skalli et al. (2019)
	Cinamomum cassia.,	Kerfa	Nd		South east region	Eddouks et al. (2002)
Liliaceae	*Androcymbium garmineum* (cav.) Mc Bride.,	Ssgêatlerneb, lawzatlehjel,	Extract	Infusion	Oriental Morocco	Kahouadji (1995)
	Androcymbium garmineum (cav.) Mc Bride.,	Ssgêatlerneb, lawzatlehjel,	Extract	Infusion	Morocco	Bellakhdar (1997)
	Androcymbium garmineum (cav.) Mc Bride.,	Ssgêatlerneb, lawzatlehjel,	Extract	Infusion	Morocco	Bellakhdar et al. (1991)
	Aintermedium Gatt. & Maire.,	gerga'atleghrab	Juice Bulbs	Extract	Oriental Morocco	Kahouadji (1995)
	A. intermedium Gatt. & Maire.,	gerga'atleghrab	Juice Bulbs	Extract	Morocco	Bellakhdar et al. (1991)
	A. intermedium Gatt. & Maire.,	gerga'atleghrab	Juice Bulbs	Extract	Morocco	Bellakhdar (1997)
	Androcymbium pundalum (Schlet) Cavan.,	Ssgaiôa	Bulbs	Infusion	Morocco	Bellakhdar (1997)
Linaceae	*Linum usitatissimum* L., *(angustifoliumHuds).*,	zreat el katan	Nd	Nd	South east region	Eddouks et al. (2002)
	Linum usitatissimum L.,	Kattan, beri, zreat el katan, el atal	Seeds	Infusion		Hmamouchi (1999)
	Linum usitatissimum L.,	Lin cultivé/Ziaat al kettane	Seeds	Nd	Khenifra	Hachi et al. (2015)
	Linum usitatissimum L.,	Lekattan	Seeds	Ground seeds with water	Rabat	Skalli et al. (2019)
Lythraceae	*Lawsonia inermis*.,	Hanna	Nd	Nd	South east region	Eddouks et al. (2002)
	Lapa communis L.,	Bardane, arkitoun	Roots Leaves Flowers	Decoction and infusion Leaves	Morocco	Hmamouchi (1999)
	Lapa communis L.,	Bardane, arkitoun	Roots, leaves flowers	Decoction Infusion	Morocco	Sijelmassi (1993)
Malvaceae	*Abelmoschus esculentus* L.,	Mloukhia	Fruits	Maceration	Rabat	Skalli et al. (2019)
Mimosaceae	*Acacia gummifera* Willd.,	Amrad Telh	Fruits	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
	Acacia ehrenbergiana Hay.,	Tifzet Amrad Telh	Seeds	Decoction	Tafilalet	El Rhaffari and Zaid (2002)
Moraceae	*Ficus carica* L.,	Karma kermôs Chriha Tin Bakûr Dukkar	Fruits and leaves	Powder extract	Oriental Morocco	Ziyyat et al. (1997)
	Ficus carica L.,	Karmous Chriha	Leaves	Infusion	Moroccan Rif	Chaachouay et al. (2019)
	Ficus abelii Miq.,	Karmous Chriha	Leaves	Decoction	Moroccan Rif	Chaachouay et al. (2019)
	Ficus carica L.,	Tazart Lkarmous	Fruits	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Ficus carica L.,	El-baku¯r	Fruits Leaves	Powder	South eastern Morocco	Tahraoui et al. (2007)
	Morus alba L.,	Ettout	Leaves	Infusion	Moroccan Rif	Chaachouay et al. (2019)
	Morus nigra L.,	Tout	Fruits Leaves	Infusion, Decoction	Morocco	Hmamouchi (1999)
	Morus nigra L.,	Tout	Fruits Leaves	Infusion, Decoction	Oriental Morocco	Kahouadji (1995)
	Morus nigra L.,	Tout	Fruits, Leaves	Infusion, Decoction	Morocco	Sijelmassi (1993)
Musaceae	*Musa* sp.,	Banan	Roots	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
Myristicaceae	*Myristica fragrans* Houtt.,	Lgouza	Seed	Powder	Western Anti Atlas	Barkaoui et al. (2017)
Myrtaceae	*Eucalyptus globulus* Labill (sp.).,	Al' Kalitouss	Leaves Fruits	Decoction	North of Morocco	Orch et al. (2015)

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Table 1 (*continued*)

Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Eucalyptus globulus L.,	Kelitto	Stemsand leaves	Nd	North West	Bouyahya et al. (2017)
	Eucalyptus globulus Labill.,	Kalitûs Kallitû	Flowers and leaves	Infusion, decoction, and powder	Oriental Morocco	Ziyyat et al. (1997)
	Eucalyptus globulus Labill (sp.).,	Kalitous		Nd	South east region	Eddouks et al. (2002)
	Eucalyptus spp.,	Kalitu¯se	Leaves	Decoction and infusion	South eastern Morocco	Tahraoui et al. (2007)
	Eugenia caryophyllata.,	Qronfel	Leaves	Decoction, powder and maceration	North of Morocco	Orch et al. (2015)
	Myrtus communis L.,	Rihàn	Leaf	Powder	North West	Bouyahya et al. (2017)
	Myrtus communis L.,	Rihan	Leaves and fruits	Decoction and infusion	South easternMorocco	Tahraoui et al. (2007)
	Myrtus communis L.,	Arraihan	Leaves and fruits	Decoction and infusion	North of Morocco	Orch et al. (2015)
	Myrtus communis L.,	Arraihan	Leaves and fruits	Decoction and infusion	South east region	Eddouks et al. (2002)
	Myrtus communis L.,	Arraihan	Leaves	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Myrtus communis L.,	Raihane Tarîhant Moqqô	Leaves and fruits	Infusion and decoction	Oriental Morocco	Ziyyat et al. (1997)
	Syzigium aromaticum (L.) Merr.& Perry.	Qrûnfûl	Fruits and leaves	Decoction and powder	Morocco	Bellakhdar (1997)
	Syzygium aromaticum (L.) Merr.& Perry/	Kronfel Oud newwar	Seeds	Powder	Rabat	Skalli et al. (2019)
Oleaceae	*Fraxinus augustifolia* Vahl.,	Touzalt, lisântir	Fruits and leaves	Powder	Morocco	Bellakhdar (1997)
	Olea europea L., (*var. oleaster*)	Zitoun zebbouj	Leaves	Decoction	Oriental Morocco	Ziyyat et al. (1997)
	Olea europea L., (*var. oleaster*)	Zitoun zebbouj	Leaves	Decoction	HaousRhamna region	Benkhnigue et al. (2014)
	Olea europea L., (var. sativa.)	Zitoun zebbouj	Leaves	Decoction and infusion	HaousRhamna region	Benkhnigue et al. (2014)
	Olea europaea L., (var. sativa.)	Zitoun zebbouj			South east region	Eddouks et al. (2002)
	Olea europaea L., (var. sativa.)	Zitoun Zabbouj	Leaves and fruits	Decoction, infusion, and oil	North of Morocco	Orch et al. (2015)
	Olea europaea L., (*var. oleaster*)	El-berri, zebu¯j	Leaves	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	*Olea europaea*L., (var. sativa.)	Zaytoun	Nd		DaraaTafilalet region	Eddouks et al. (2017a)
	Olea europaea L., (var. sativa.)	Zaytoun	Leaves	Decoction	South eastern Morocco	Tahraoui et al. (2007)
	Olea europaea L., (var. sativa.)	Jbouj Azmour Zitoun	Leaves	Decoction, maceration and powder	Western Anti Atlas	Barkaoui et al. (2017)
	Olea europaea L.,	Zaytoun	Fruits	Oil	Oriental Morocco	Fakchich and Elachouri (2014)
	Olea europea L.,(var. sativa.)	Zaytoun	Leaves	Powder	Northern Morocco	El-Hilaly et al. (2003)
	Olea europea., (var. sativa.)	Zaytoun	Leaves	Infusion	North West	Bouyahya et al. (2017)
	Olea europaea.,	Olivier	Leaves and fruits	Powder and decoction	Moroccan Sahara	Ghourri et al. (2013)
	Olea europaea L.,subsp. europaea var. sylvestris (Mill.)	Zaytoun	Leaves	Infusion decoction leaves	Rabat	Skalli et al. (2019)
	Olea europaea L.,	Zeet	Leaves, oil, seeds, and wood		High Atlas	Teixidor-Toneu et al. (2016)
	Olea europaea L.,	Olivier/Zitoune	Leaves		Khenifra	Hachi et al. (2015)
Palmaceae	*Chamaerops humilis* L.,	Doum	Leaves and fruits	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Chamaerops humilis L.,	Doum	Resin	Infusion	North West	Bouyahya et al. (2017)
	Chamaerops humilis L.,	Doum	Rhizome			
	Phoenix dactylifera L.,	Nakhla tayniyût Tazdâyt Tmer El-bluh	Fruits and seeds	Infusion, powder, pulp	Oriental Morocco	Ziyyat et al. (1997)
	Phoenix dactylifera L.,	Palmier dattier	Seeds	Powder and decoction	Haous Rhamna region	Benkhnigue et al. (2014)

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Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Phoenix dactylifera L.,	Tmar, Nkhil	Leaves, fruits and pulps	Infusion, powder, and pulp	South eastern Morocco	Tahraoui et al. (2007)
Papaveraceae	*Papaver rhoeas* L.,	Belaaman	Seeds	Powder	Western Anti Atlas	Barkaoui et al. (2017)
Pedaliaceae	*Sesamum indicum* Dc.,	Jenjlan	Seeds	Infusion and powder	North of Morocco	Orch et al. (2015)
	Sesamum indicum Dc.,	Jenjlan	Seeds	Infusion and powder	South east region	Eddouks et al. (2002)
	Sesamum indicum L.,	Jenjlan	Seeds	Decoction		
Plantaginaceae	*Globularia alypum* L.,	Turbith	Stem	Powder	Moroccan Sahara	Ghourri et al. (2013)
Poaceae	*Hordeum vulgare* L.,	Chaair	Seeds	Powder and maceration	Moroccan Sahara	Ghourri et al. (2013)
	Hordeum vulgare L.,	Chaair	Seeds	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Hordeum vulgare L.,	Chaâi	Seeds	Powder	North West	Bouyahya et al. (2017)
	Phalaris paradoxa L.,	Zwaan	Seeds	Powder	South eastern Morocco	Tahraoui et al. (2007)
	Phalaris canariensis L.,	Zwân	Fruits	Decoction and infusion	North of Morocco	Orch et al. (2015)
	Stipa tenacissima L.,	Lhalfa	Whole plant	Decoction	Oriental Morocco	Fakchich and Elachouri (2014)
	Triticum aestivum L.,	Lkamh	Cortex	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Zea mays L.,	LahyatAdra	Stigma of flowers	Powder, decoction and infusion	North of Morocco	Orch et al. (2015)
Portulacaceae	*Portulaca oleracea* L.,	Rejla, Baqla l-hamqâ, Agertîntazelluzt	Whole plant and seeds	Decoction	Morocco	Bellakhdar (1997)
	Portulaca oleracea L.,	Rejla	Whole plant	Raw	Tafilalet	El Rhaffari and Zaid (2002)
Polygonaceae	*Polygonum aviculare* L.,	Wadmu, lbetbat	Leaves and roots	External use and fumigation	Oriental Morocco	Kahouadji (1995)
Punicaceae	*Punica granatum* L.,	Romman	Cortex	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Punica granatum L.,	Qchourromman	Pericarp	Decoction and powder	Morocco	Bellakhdar et al. (1991)
	Punica granatum L.,	Romman	Peel of fruits	Crushed	South east region	Eddouks et al. (2002)
	Punica granatum L.,	Romman	Peel of fruits	Crushed	Northern Morocco	El-Hilaly et al. (2003)
	Punica granatum.,	Romman	Barks	Decoction	North West	Bouyahya et al. (2017)
	Punica granatum L.,	Reman	Pericarp	Decoction and powder	South eastern Morocco	Tahraoui et al. (2007)
Ranunculaceae	*Nigella sativa* L.,	Sanouj	Seeds	Powder		Hmamouchi (1999)
	Nigella sativa L.,	Sanouj	Seeds	Powder	Oriental Morocco	Ziyyat et al. (1997)
	Nigella sativa L.,	Nigelle	Seeds	Decoction	HaousRhamna region	Benkhnigue et al. (2014)
	Nigella sativa	Nigelle	Seeds	Nd	DaraaTafilalet region	Eddouks et al. (2017a)
	Nigella sativa L.,	Sanouj	Seeds	Nd	South east region	Eddouks et al. (2002)
	Nigella sativa L.,	Sanouj- Habatsaouda	Seeds	Ground powder with water	Rabat	Skalli et al. (2019)
Ranunculaceae	*Nigella sativa* L.,	Assanouj	Seeds	Decoction and powder	North of Morocco	Orch et al. (2015)
Rhamnaceae	*Ziziphus lotus*(L.) Lam.	Jujubier	Fruits and leaves	Powder and decoction	Moroccan Sahara	Ghourri et al. (2013)
	Zizyphus lotus (L.) Lam.	Sadra, nnbeg, âzar, âmezmemMzah	Leaves and fruits	Powder and decoction	Nd	Hmamouchi (1999)
	Zizyphus lotus (L.) Lam.	Sadra, nnbeg, âzar, âmezmemMzah	Leaves and fruits	Powder and decoction	Oriental Morocco	Ziyyat et al. (1997)
	Ziziphus lotus (L.) Lam.	Sedra	Leaves Roots	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Ziziphus lotus (L.) Lam.	Nbeg/Azougga	Leaves	Decoction and powder	Western Anti Atlas	Barkaoui et al. (2017)
	Ziziphus lotus (L.) Lam.	Nbek	Fruits and leaves	Decoction and powder	South easternMorocco	Tahraoui et al. (2007)
Rosaceae	*Crataegus laevigatus* L.,	Ademmam	Leaves	Infusion	Tafilalet	El Rhaffari and Zaid (2002)
	Crataegus oxyacantha L.,	Saarour chaik Admam Mesnagen	Leaves Flowers	Infusion		Hmamouchi (1999)
	Cydonia oblonga Mill.,	Sferjel	Fruits	Raw and cooked	South eastern Morocco	Tahraoui et al. (2007)
	Eriobotrya japonica Thunb., Lindl.		Leaves	Decoction	Oriental Morocco	Ziyyat et al. (1997)

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Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	*Eriobotriajaponica*Thunb., Lindl.	Mzah	Leaves	Decoction	Northern Morocco	El-Hilaly et al. (2003)
	Malus domestica Borkh.,	Teffâh	Fruits	Juice	Eastern High Atlas	Benlamdini et al. (2014)
	Malus domestica Borkh.,	Tûffah	Fruits	Decoction	Moroccan Rif	Chaachouay et al. (2019)
	Prunus amygdalus Stokes., (var. amara)	Louz	Fruits	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Prunus amygdalus Stokes., (var. amara)	Louz lhar		Nd	South east region	Eddouks et al. (2002)
	Prunus amygdalus Stokes., (var. amara)	Louz lhar	Fruits	Nd	Morocco	Bellakhdar (1997)
	Prunus amygdalus Stokes., (var. amara)	Louz lhar	Fruits	Nd	Oriental Morocco	Ziyyat et al. (1997)
	Prunus amygdalus Stokes., (var. amara)	Louz lhar	Fruits	Nd	Morocco	Bellakhdar et al. (1991)
	Prunus amygdalus Stokes., (var. amara)	Louz lhar	Fruits	Powder	Moroccan Sahara	Ghourri et al. (2013)
	Prunus amygdalus Stokes., (var. amara)	Louz mar Louz harr	Seeds	Extract	Morocco	Sijelmassi (1993)
	Prunus dulcis (Mill.) Webb.	Louz imrzig	Seeds	Raw	Western Anti Atlas	Barkaoui et al. (2017)
	Prunus dulcis (Mill.) Webb.	Louz	Fruits	Fruits	Rabat	Skalli et al. (2019)
	Rosa fructicosus L.,	Toute chaouki	Leaves and fruit	Decoction and infusion	North of Morocco	Orch et al. (2015)
Rutaceae	*Cardamine amara* L.,	Louz Morr	Seed	Decoction and infusion	North of Morocco	Orch et al. (2015)
	Citrus aurantium L.,(var. amara Link)	Tranj	Leaves and fruits	Decoction, infusion and Raw	South eastern Morocco	Tahraoui et al. (2007)
	Citrus aurantium L.,	Larenj	Flowers	Infusion	Oriental Morocco	Fakchich and Elachouri (2014)
	Citrus bigaradia Riss.,	Larenj	Leaves and flowers	Decoction and infusion	North of Morocco	Orch et al. (2015)
	Citrus aurantium L.,(var. amara Link)	Tranj	Leaves and fruits	Decoction and infusion Raw	South eastern Morocco	Tahraoui et al. (2007)
	Citrus bigaradia Riss.,	L-ronge	–	–	South east region	Eddouks et al. (2002)
	Citrus amara L.,	Laymon	Fruits	Jus	Haous Rhamna region	Benkhnigue et al. (2014)
	Ruta montana L.,	Fidjel	Aerial parts	Infusion and decoction Powder and fumigation	Oriental Morocco	Ziyyat et al. (1997)
	Ruta montana L.,	Fijel Awermi	Aerial parts	Decoction and infusion Powder	South eastern Morocco	Tahraoui et al. (2007)
	Ruta montana L.,	Al'Fijel	Aerial parts	Decoction, infusion and powder	North of Morocco	Orch et al. (2015)
	Ruta chalepensis L.,	Aurmi	All aerialparts and roots	Nd	High Atlas	Teixidor-Toneu et al. (2016)
Santalaceae	*Santalum album* L.,	A'sandal	Resin	Mixed with Honey	Moroccan Rif	Merzouki et al. (2000)
Salicaceae	*Salix alba* L.,	Ud el-mâ	Leaves	Decoction	Eastern High Atlas	Benlamdini et al. (2014)
	Salix alba L.,	Ud el-mâ	Leaves	Decoction	North West	Bouyahya et al. (2017)
Sapotaceae	*Argania spinosa* L.,	Argane	Almond fruits	Crushed teaspoon	Rabat	Skalli et al. (2019)
	Argania spinosa (L.) Skeels.	Argan	Seeds	Raw	Western Anti Atlas	Barkaoui et al. (2017)
	Camellia sinensis L.,(Kuntze)	Attay	Leaves	Infusion	Western Anti Atlas	Barkaoui et al. (2017)
	Capsicum frutenscens L.,	Piment enrage	Fruits	Decoction	Moroccan Sahara	Ghourri et al. (2013)
Thymelaeaceae	*Daphne gnidium* L.,	Mathnane, lazaz, înif	Leaves and stembark	Infusion	Oriental Morocco	Ziyyat et al. (1997)
	Thymelaea tartonraira L.,	Talazazt	Leaves	Decoction	South eastern Morocco	Tahraoui et al. (2007)
Urticaceae	*Urtica dioica* L.,	Harrigua	Leaves	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Urtica dioica L.,	Taznagt Tig zenin Lhriga	Stem and leaves	Decoction	Western Anti Atlas	Barkaoui et al. (2017)
	Urtica dioïca L.,	Lhourriga Taslekhte	Leaves	Tisan	Tafilalet	El Rhaffari and Zaid (2002)
	Urtica dioica L.,	Harrigua Tikzinin Tizmekt Timezrit	Aerial parts	Infusion and decoction	Morocco	Hmamouchi (1999)
	Urtica dioica L.,	Harrigua Tikzinin Tizmekt Timezrit	Aerial parts	Infusion and decoction	Oriental Morocco	Ziyyat et al. (1997)

(*continued on next page*)

Table 1 (*continued*)

Family	Scientific name	Vernacular name	Used parts	Preparation	Region	References
	Urtica urens L.,	Harrigua Karas Takznt Timezrit	Aerial parts	Infusion	Morocco	Hmamouchi (1999)
Verbenaceae	*Verbena officinalis* L.,	Louiza	Leaves	Decoction	Rabat	Skalli et al. (2019)
	Lippia citriodora (Palau.) Kunth.			Decoction, infusion, maceration and powder	Daraa Tafilalet region	Eddouks et al. (2017a)
Vitaceae	*Vitis vinifera* L.,	Adilite	Leaves	Decoction	South eastern Morocco	Tahraoui et al. (2007)
Zingiberaceae	*Zingiber officinae* Roscoe.,	Zanjabil, skinjbir	Rhizome	Powder		Hmamouchi (1999)
	Curcuma longa L.,	Al-kharkoum	Rhizomes	Infusion	Rabat	Skalli et al. (2019)
	Zingiber officinale Roscoe.,	Skenjbir	Rhizomes	Maceration	Rabat	Skalli et al. (2019)
Zygophyllaceae	*Peganum harmala* L.,	Harmel	Seed	Infusion and powder	South eastern Morocco	Tahraoui et al. (2007)
	Zygophyllum gaetulum (Emb. & Maire).	Harmel			South east region	Eddouks et al. (2002)
	Peganum harmala L.,	Harmel El madjnouna			South east region	Eddouks et al. (2002)
	Zygophyllum gaetulum (Emb. & Maire).	Aggaya	Leaves	Powder	Oriental Morocco	Fakchich and Elachouri (2014)
	Zygophyllum gaetulum (Emb. & Maire).	Aggaya	Leaves andstems	Decoction and infusion	South eastern Morocco	Tahraoui et al. (2007)
	Peganum harmala L.,	Harmal	Seeds	Powder and infusion		Hmamouchi (1999)
	Peganum harmala L.,	Harmal	Seeds	Powder and infusion	Oriental Morocco	Ziyyat et al. (1997)
	Zygophyllum gaetulum (Emb. & Maire).	Tirta Tirremt	Stems	Decoction and powder		Hmamouchi (1999)
	Zygophyllum gaetulum (Emb. & Maire).	Tirta Tirremt	Stems	Decoction and powder	Oriental Morocco	Kahouadji (1995)
	Zygophyllum gaetulum (Emb. & Maire).	Tirta Tirremt	Stems	Decoction and powder	Morocco	Bellakhdar (1997)
	Zygophyllum gaetulum (Emb. & Maire).	Tirta Tirremt	Stems	Decoction and powder	Morocco	Bellakhdar et al. (1991)
	Zygophyllum album L., ssp.	Aggaya,l-barrâya Tazzlost,	Leaves	Infusion		
	Zygophyllum gaetulum (Emb. & Maire).	tirta, tirremt	Stem	Decoction and powder	Oriental Morocco	Ziyyat et al. (1997)
	Zygophyllum gaetulum L.,	tirta, tirremt	Whole plant	Powder and decoction	Moroccan Sahara	Ghourri et al. (2013)

parts have been used such as leaves, flowers, aerial part, seeds, latex, and the whole plant in some cases. The mode of preparation also varies, but in most cases, decoction and infusion are the most used forms (Barkaoui et al., 2017; Bellakhdar, 1997; Eddouks et al., 2002, 2017a; El Rhaffari and Zaid, 2002; Hmamouchi, 1999; Teixidor-Toneu et al., 2016; Ziyyat et al., 1997). Moreover, plants of Anacardiaceaehave been used as antidiabetic agents in different Moroccan regions. Two species we reported as antidiabetic including *Pistacia atlantica* and *Pistacia lentiscus*. Different parts were used to treat diabetic patients such as fruit, leaves, and the latex in some cases. The mode of preparation is decoction (Bouyahya et al., 2017; Fakchich and Elachouri, 2014; Hachi et al., 2015).

Apiaceae family is another example of a plant family used as a source of antidiabetic agents in Moroccan folk medicine. It has been used in all regions of Morocco. Eleven species have been reported in the literature as antidiabetic. The part used are seeds, root, leaves, fruits, resin, and stem. In some studies, the part used has not been determined (Barkaoui et al., 2017; Bellakhdar, 1997; Bellakhdar et al., 1991; Benkhnigue et al., 2014; Bouyahya et al., 2017; Chaachouay et al., 2019; Eddouks et al., 2002, 2017a; El Rhaffari and Zaid, 2002; El-Hilaly et al., 2003; Fakchich and Elachouri, 2014; Kahouadji, 1995; Merzouki et al., 2000; Orch et al., 2015; Sijelmassi, 1993; Skalli et al., 2019; Tahraoui et al., 2007; Teixidor-Toneu et al., 2016; Ziyyat et al., 1997). Apocynaceae plants have been also used as antidiabetic agents in traditional medicine in Morocco. It was used in different regions, but the part used, and the mode of preparation vary from a region to another. Five species including *Apteranthes europaea*, *Caralluma europaea*, *Nerium oleander*, *Periplocaan gustifolia*, and *Ptychotis verticillata* were described in the literature as antidiabetic remedies. Different parts have been used such as stems, leaves, roots, and the whole plants in some regions. The mode of preparation varies from a region to region (Barkaoui et al., 2017; Benkhnigue et al., 2014; Benlamdini et al., 2014; Bouyahya et al., 2017; Eddouks et al., 2002; El-Hilaly et al., 2003; Ghourri et al., 2013; Hachi et al., 2015; Tahraoui et al., 2007; Ziyyat et al., 1997).

Zygophyllaceae family is also an important source of antidiabetic plants in Morocco. *Peganum harmala, Zygophyllum gaetulum,* and *Zygophyllum album* are the main species used against diabetes. The parts used differ according to the regions. In some regions, the leaves are prepared as decoction and infusion, while in another areas the stem and seeds are used as powder (Bellakhdar et al., 1991; Kahouadji, 1995; Ziyyat et al., 1997; Bellakhdar, 1997; Hmamouchi, 1999; Eddouks et al., 2002; Tahraoui et al., 2007; Ghourri et al., 2013; Fakchich and Elachouri, 2014). Species of the Myrtaceae family have been widely used by Moroccan diabetic patients. *Eucalyptus globulus, Eugenia caryophyllata, Myrtus communis,* and *Syzygium aromaticum* are reported in the literature as antidiabetic in traditional medicine in Morocco. Leaves, fruits, and seeds are prepared by decoction and infusion and sometimes the powder of this parts are taken dry by diabetic patients (Table 1) (Bellakhdar, 1997; Bouyahya et al., 2017; Eddouks et al., 2002; Fakchich and Elachouri, 2014; Orch et al., 2015; Skalli et al., 2019; Tahraoui et al., 2007; Ziyyat et al., 1997).

Plants of Oleaceae have been used in different Moroccan regions to

treat diabetes. *Fraxinus angustifolia* and *Olea europaea*are the two species of this family that are described in the literature as antidiabetic plants. The parts used are the leaves which are prepared as decoction infusion or served as dry powder (Barkaoui et al., 2017; Bellakhdar, 1997; Benkhnigue et al., 2014; Bouyahya et al., 2017; Eddouks et al., 2002; Eddouks et al., 2002, 2002, 2017a; El-Hilaly et al., 2003; Fakchich and Elachouri, 2014; Ghourri et al., 2013; Hachi et al., 2015; Skalli et al., 2019; Tahraoui et al., 2007; Teixidor-Toneu et al., 2016; Ziyyat et al., 1997). Palmae family has been also reported as a source of antidiabetic plants in Moroccan herbal literature. *Chamaerops humilis* and *Phoenix dactylifera* are the two species that are popular in Moroccan traditional medicine. The leaves, fruits, seeds, and the resin are prepared as decoction, infusion or used directly as dry powder to treat diabetic patients (Benkhnigue et al., 2014; Bouyahya et al., 2017; El-Hilaly et al., 2003; Tahraoui et al., 2007; Ziyyat et al., 1997). Plants from Cupressaceae have been used as antidiabetic in several regions in Morocco. *Juniperus phoenicea, Juniperus thuri,* and *Tetraclinis articulate* were reported in the literature as antidiabetic species. Different parts are used such as the leaves, fruits, and aerial parts. The mode of preparation is mostly maceration (Bellakhdar, 1997; Benkhnigue et al., 2014; Chaachouay et al., 2019; Eddouks et al., 2002; El Rhaffari and Zaid, 2002; Hachi et al., 2015; Tahraoui et al., 2007; Teixidor-Toneu et al., 2016; Ziyyat et al., 1997).

Plants of Liliaceae have been also popularized among Moroccan inhabitants to treat diabetes. Three species including *Androcymbium gramineum, Androcymbium intermedium,* and *Androcymbium pundalum* were showed antidiabetic effect in traditional medicine. People use *Androcymbium gramineum* as infusion and the two other species their bulb juice is used (Bellakhdar, 1997; Bellakhdar et al., 1991; Kahouadji, 1995). Plants of Gramineae have been also used in folk medicine in Morocco against diabetes. Five species are known as antidiabetic remedies including *Cynodondactylon, Panicum miliaceum, Phalaris paradoxa, Phalaris canariensis,* and *Sorghum vulgare.* For *Cynodon dactylon,* the rhizome and the whole plant are prepared as decoction, while for the other species the seeds are used after preparation by grinding or boiling (El-Hilaly et al., 2003; Hmamouchi, 1999; Kahouadji, 1995; Sijelmassi, 1993; Ziyyat et al., 1997). Four species of the Cistaceae family including *Cistus ladanifer, Cistus libanotis, Cistus criticus,* and *Cistus salviifolius* have been used as antidiabetic remedies in Morocco. The leaves of these plants are prepared as infusion or decoction (Barkaoui et al., 2017; Kahouadji, 1995).

Plants from Moraceae family have been used for a long time in Morocco to treat diabetes. Four species are described in the literature to treat diabetes which are *Ficus carica, Ficus abelii, Morus alba,* and *Morus nigra*. The parts used are the leaves and fruits prepared as decoction or infusion (Sijelmassi, 1993; Kahouadji, 1995; Ziyyat et al., 1997; Hmamouchi, 1999; Tahraoui et al., 2007; Barkaoui et al., 2017; Chaachouay et al., 2019). Species of Cucurbitaceae family such as *Citrullus colocynthis* and *Cucumis sativus* are also used as antidiabetic remedies in folk medicine in Morocco. The fruits and seeds from these plants are prepared mostly as decoction in order to treat diabetic patients (El Rhaffari and Zaid, 2002; Fakchich and Elachouri, 2014; Benkhnigue et al., 2014; Barkaoui et al., 2017; Chaachouay et al., 2019; Skalli et al., 2019). Plants from the Poaceae family have been known to be used in folk medicine in Morocco to treat diabetes. The species described as antidiabetic are mentioned in Table 1. The parts used are mostly the seeds, which are used as powder or after decoction depending on the region (Bouyahya et al., 2017; Fakchich and Elachouri, 2014; Ghourri et al., 2013; Orch et al., 2015; Tahraoui et al., 2007).

Brassicaceae family has been also used as a source of antidiabetic plants in different Moroccan regions. The species used are *Brassica rapa, Lepidium sativum,* and *Raphanus sativus.* Leaves, seeds, and root are used as powder or after decoction (Barkaoui et al., 2017; Benkhnigue et al., 2014; Benlamdini et al., 2014; Eddouks et al., 2002; Hmamouchi, 1999; Kahouadji, 1995; Skalli et al., 2019; Tahraoui et al., 2007). Species of Ericaceae family are used by the people of Morocco to treat diabetes. Two species are described as antidiabetic in traditional medicine. *Arbutus unedo* is used in the North region of Morocco, while *Juniperus phoenicea*is used only at Moroccan Sahara. The parts used are mostly the leaves prepared as decoction (Ghourri et al., 2013; Orch et al., 2015; Ziyyat et al., 1997). Urticaceae family has been also described as antidiabetic rich family in Moroccan traditional medicine. Two species have been reported to be used by diabetic patients which are *Urtica dioica* and *Urtica urens.* The parts used differ according to the regions which are mostly the aerial part, leaves, and the stem. They are served as decoction and infusion (Barkaoui et al., 2017; El Rhaffari and Zaid, 2002; Fakchich and Elachouri, 2014; Hmamouchi, 1999; Ziyyat et al., 1997).

Lythraceaeplants have been reported in the literature as antidiabetic remedies in Moroccan folk medicine. Two species from this family are used by Moroccan people including *Lawsoniainermis* and *Lapsana communis*. The part used are the leaves, fruits and roots and the preparation is done as decoction and infusion (Eddouks et al., 2002; Hmamouchi, 1999; Sijelmassi, 1993). *Acacia ehrenbergiana* and *Acacia gummifera* are the two species of the Mimosaceae family, that are known to be used by Moroccan inhabitants as antidiabetic plants. For *A. ehrenbergiana* the seeds are used, while in the case of *A. gummifera* the fruits are used. The mode of preparation for the two species is the decoction (El Rhaffari and Zaid, 2002). Two species of the Fabaceae family are used in folk medicine against diabetes in Morocco including *Vigna sinensis* and *Quercus faginea*. These plants are used only at the level of Moroccan Rif. The seeds powder is macerated and used by diabetic patients (Merzouki et al., 2000).

Plants of Geraniaceae have been used traditionally in Morocco against diabetes. Two species are described in the literature as antidiabetic including *Centaurium spicatum* and *Geranium robertianum.* The aerial parts of these plants is prepared by infusion in order to treat diabetic patients (Bellakhdar, 1997; Bellakhdar et al., 1991; Kahouadji, 1995). Four species of Ephedraceae are used to treat diabetes including *Ephedra altissima, Euphorbia officinarum, Ephedra alata,* and *Euphorbia officinarum*. People on the western Anti-Atlas of Morocco and Tafilalet regions use the leaves and stems, and sometimes the whole plants after grinding as a decoction (Barkaoui et al., 2017; El Rhaffari and Zaid, 2002).

Furthermore, some species of the Sapotaceae family, are also reported to be used as antidiabetic plants in Moroccan folk medicine. Three species are used, *Argania spinosa, Camellia sinensis,* and *Capsicum frutescens.* The parts used are mostly the leaves, fruits, and seeds (Barkaoui et al., 2017; Ghourri et al., 2013; Skalli et al., 2019). Thymelaeaceae family has been used in the South eastern part of Morocco as a source of antidiabetic plants. *Daphne gnidium,* and *Thymelaea tartonraira* are the two species of this family that are reported to be used to treat diabetes. The leaves of these plants are prepared as infusion or decoction (Tahraoui et al., 2007; Ziyyat et al., 1997). *Lippia citriodora* and *Verbena officinalis*, Verbenaceae family, are highly consumed by Moroccan people for the treatment of diabetes. To be used, the leaves of these plants are prepared as a decoction or maceration (Eddouks et al., 2017a; Skalli et al., 2019).

Zingiberaceae contains many plants which are used antidiabetic agents in Morocco. Two species (*Zingiber officinale* and *Curcuma longa*) were reported in the literature that are used to treat diabetic patients. The rhizomes of these plants are served as infusion or used as a powder (Hmamouchi, 1999; Skalli et al., 2019). Burseraceae plants (*Boswellia carterii* and *Boswellia* spp.) have been used in folk medicine in Morocco to treat diabetes. The resin of these plants is prepared by infusion or decoction and used by patients. It has been used only on the oriental Morocco (Kahouadji, 1995). Plants of Cactaceae (*Capparis spinosa* and *Opuntia ficus-indica*) are used in traditional medicine in Morocco. The flowers, fruits, and stems are prepared by maceration or grinding and used to treat diabetes disease (Tahraoui et al., 2007). Two species (*Cinnamomum cassia* and *Cinnamomum verum)* of the Lauraceae family have been reported to be used as antidiabetic agents in traditional medicine in Morocco. The bark and the cortex are prepared by

maceration, decoction or infusion (Eddouks et al., 2002; Fakchich and Elachouri, 2014; Skalli et al., 2019). The seeds of *Papaver rhoeas* and *Sesamum indicum* belonging to the Papaveraceae and Pedaliaceae families, respectively, have been used by Moroccan people in traditional medicine against diabetes (Barkaoui et al., 2017; Ghourri et al., 2013).

Several families are represented only by one species. *Punica granatum* (Punicaceae), has been used in Moroccan traditional medicine against a variety of diseases including diabetes. Different parts of this plants are used such as the bark, peel fruit, the cortex, and the pericarp. The cortex and the pericarp are used as powder after grinding, the bark after decoction, while the peel fruits are crushed (Bellakhdar et al., 1991; Bouyahya et al., 2017; Eddouks et al., 2002; El-Hilaly et al., 2003; Fakchich and Elachouri, 2014; Tahraoui et al., 2007). *Nigella sativa,* (Ranunculaceae) has been used in folk medicine in different Moroccan region. The seeds of this plant are prepared as decoction or powder and used to treat diabetic patients (Benkhnigue et al., 2014; Eddouks et al., 2002, 2017b; Hmamouchi, 1999; Orch et al., 2015; Skalli et al., 2019; Ziyyat et al., 1997). *Ziziphus lotus* (Rhamnaceae) has been also reported as antidiabetic agent from Moroccan flora. Different parts of this plant have been ingested by diabetic patients such as the fruits, leaves as well as the roots. People use this plant as a powder or after decoction (Barkaoui et al., 2017; El-Hilaly et al., 2003; Ghourri et al., 2013; Hmamouchi, 1999; Tahraoui et al., 2007; Ziyyat et al., 1997).

The Apparaceae family has been used against diabetes only at the oriental Morocco. One species of this family was described in the literature as antidiabetic, *Capparis spinosa*. The parts used were the fruits prepared by decoction or as dry powder of the seeds (Kahouadji, 1995; Ziyyat et al., 1997). The fruit pulp of *Citrullus colocynthis* (Cucurbitaceae) are used as antidiabetic drug in tradition medicine in Morocco. The mode of preparation is mostly by maceration (Bellakhdar, 1997; Bellakhdar et al., 1991; Ziyyat et al., 1997). On the Western Anti-Atals of Morocco, *Dracaena draco* (Dracaenaceae) is used to treat diabetic patients. People in this region collect the plant (leaves and stems) and prepare it by decoction in order to extract the antidiabetic compounds (Barkaoui et al., 2017). The aerial parts, and sometimes the whole plant of *Centaurium erythraea* (Gentianaceae) are used by people in Morocco to treat diabetes. The plant is prepared by infusion or decoction based on the region (Bellakhdar, 1997; Bellakhdar et al., 1991; Fakchich and Elachouri, 2014; Orch et al., 2015).

Globularia alypum (Globulariaceae) is reported as a famous antidiabetic plant in traditional medicine in Morocco. Only the leaves of this plant are prepared by infusion or decoction (according to the region) and used by diabetic patients (Bellakhdar, 1997; Bellakhdar et al., 1991; Benkhnigue et al., 2014; Eddouks et al., 2002; El Rhaffari and Zaid, 2002; Fakchich and Elachouri, 2014; Ziyyat et al., 1997). *Juglans regia* (Juglandaceae) is also used to treat diabetic patients in Morocco. People in Sahara prepare this plant by maceration using its nut, while in other regions they prepare it by infusion and decoction using leaves, fruits, or the cortex (Bellakhdar, 1997; Benkhnigue et al., 2014; Ghourri et al., 2013; Hmamouchi, 1999; Sijelmassi, 1993). *Aloe socotrina*, is the only species of Aloeaceae that was reported to be used in folk medicine in Morocco against diabetes (Bellakhdar, 1997; Bellakhdar et al., 1991; Eddouks et al., 2002; Kahouadji, 1995). These studies reported that the leaves juice of this plant is dried and used as powder to treat diabetic patients.

Capparaceae family, especially *Capparis spinosa*, is used against diabetes in traditional medicine in Morocco. Leaves, fruits, seeds, and the aerial parts are used to treat diabetes. The mode of preparation is mostly by decoction (El Rhaffari and Zaid, 2002; Eddouks et al., 2002; Fakchich and Elachouri, 2014; Orch et al., 2015). *Punica granatum* (Lythraceae) is used at the level of Western Anti Atlas of Morocco to treat people suffering from diabetes diseases. The pericarp of this plant is prepared by infusion, decoction oras dry powder (Barkaoui et al., 2017). *Aristolochia longa* is the only species of Aristolochiaceae that is used as antidiabetic agent in Moroccan traditional medicine. The plant rhizomes are used to treat diabetes (Fakchich and Elachouri, 2014; Ghourri et al., 2013). The family of Asparagaceae, especially *Asparagus albus* has been used in the oriental Morocco to treat diabetes. The patients use the roots after decoction (Fakchich and Elachouri, 2014).

Berberidaceae family represented by *Berberis hispanica* have been used as antidiabetic agentat the oriental Morocco. The powder of this plant is used to tread diabetic patients (Fakchich and Elachouri, 2014). *Herniaria hirsute* (Caryophyllaceae) has been used at the oriental Morocco as an antidiabetic drug. The leaves of this plant are prepared by decoction and used to treat diabetic patients (Fakchich and Elachouri, 2014). The seeds of *Linum usitatissimum* (Linaceae)are prepared by infusion and grinding and used to treat diabetic people in Morocco (Eddouks et al., 2002; Hachi et al., 2015; Hmamouchi, 1999; Skalli et al., 2019). *Abelmoschus esculentus* (Malvaceae) has been known as antidiabetic remedy in Morocco. People use the fruits of this plant after maceration (Skalli et al., 2019). *Musa* sp. (Musaceae) has been used in the oriental Morocco against diabetes. The roots of this plant are prepared by decoction and used to treat diabetic patients (Fakchich and Elachouri, 2014). *Myristica fragrans* (Myristicaceae) has been used in the Western Anti Atlas of Morocco as an antidiabetic plant. The powder of seeds is used by diabetic patients in this region (Barkaoui et al., 2017).

Portulaca oleracea (Portulacaceae) has been used in traditional medicine in Morocco against diabetes. The whole plant is prepared by decoction in order to treat the diabetic patients (Bellakhdar, 1997; El Rhaffari and Zaid, 2002). *Polygonum aviculare* (Polygonaceae) is used in the Oriental Morocco as an antidiabetic plant. People use the leaves and the roots of this plants after fumigation (Kahouadji, 1995). *Santalum album* is the only species of Santalaceae that has been used in Morocco, especially in the Rif region, to treat diabetic patients. The resin of this plant is used in therapeutic mixtures with honey (Merzouki et al., 2000). *Salix alba* (Salicaceae), has been used in the north west and in the eastern high Atlas of Morocco as an antidiabetic plant. The parts used are the leaves prepared by decoction (Benlamdini et al., 2014; Bouyahya et al., 2017). *Vitis vinifera* (Vitaceae) is also used as antidiabetic in Morocco. The leaves of this species are prepared by decoction and used against debates disease (Tahraoui et al., 2007).

5. Antidiabetic properties of Moroccan medicinal plants

5.1. In vitro antidiabetic effects

The degradation of hydrocarbons in the intestine plays a decisive role in the increase of glucose in the blood. This degradation is under the control of enzymes involved in intestinal digestion such as α-amylase, α-glucosidase and β-glucosidase. The inhibition of these enzymes is an important therapeutic strategy to decrease blood glucose level and to contribute to the management of diabetes type 2. Some drugs such as acarbose have been used to manage diabetes acting as anti-α-amylase and anti-α-glucosidase agents. However, acarbose has shown numerous side effects and toxicities (Nakhaee and Sanjari, 2013). It provokes diarrhea in by the excessive inhibition of α-amylase (Kast, 2002). In the colon, the excessive inhibition of pancreatic α-amylase can lead to abnormal bacterial fermentation of carbohydrate foods which may lead to adverse digestive disorders (Apostolidis et al., 2007; Kast, 2002). Acarbose has been also reported to exaggerate hepatitis (Andrade et al., 1998; Fujimoto et al., 1998) and to increase liver enzyme levels (Gentile et al., 1999). Several studies were conducted to identify natural alternative substances to treat type 2 diabetes. Medicinal plants secondary metabolites such as alkaloids, flavonoids, phenolic acids and terpenoids constitute the best candidate drugs. Several studies demonstrated that medicinal plants and their bioactive compounds exhibit important *in vitro* antidiabetic *via* the inhibition of α-amylase, α-glucosidase and β-glucosidase (Malviya et al., 2010; Salehi et al., 2019).

Some Moroccan medicinal plants were tested for their *in vitro* antidiabetic effects against α-amylase, α-glucosidase, and β-glucosidase by numerous researchers (Abid et al., 2014; Bouabid et al., 2018; Marmouzi et al., 2017b, 2019; Mrabti et al., 2018a, 2018b; Ouassou et al., 2018;

Sayah, Marmouzi, Naceiri Mrabti, Cherrah, & Faouzi, 2017). A total of 15 Moroccan medicinal plants (*Ajuga iva, Mentha viridis, Anabasis aretioides, Thymelaea hirsuta, Cistus salviifolius, Cistus monspeliensis, Atractylis gummifera, Calendula arvensis, Scolymus hispanicus, Caralluma europaea, Avena sativa, Aristolochia longa, Arbutus unedo, Ziziphus Lotus,* and *Centaurium erythraea*) belonging to 11 botanical families (Lamiaceae, Chenopodiaceae, Thymelaeaceae, Cistaceae, Asteraceae, Asclepiadaceae, Poaceae, Aristolochiaceae, Ericaceae, Rhamnaceae, Gentillaceae) have been tested for their anti-diabetic activities *in vitro*. The results are shown in Table 2. For the 15 plants tested *in vitro*, only the activity of five species was evaluated *in vivo*.

5.1.1. Asteraceae family

Three Moroccan medicinal plants (*Atractylis gummifera, Scolymus hispanicus, Calendula arvensis*) belonging to Asteraceae family were tested for their *in vitro* antidiabetic effects. *Atractylis gummifera* organic extracts was tested by (Bouabid et al., 2018) for their capacities to inhibit α-amylase, β-galactosidase and α-glycosidase. The authors tested several extracts (methanolic extract, macerated methanol, chloroform extract, ethyl acetate extract, petroleum ether extract, aqueous extract, infused extract, and decocted extract). They showed that all extracts exhibited potent enzymatic inhibitory activity, especially the macerated methanol extract which inhibited α-amylase, and α-glycosidase, at $IC_{50} = 557 \pm 0.013$ μg/mL, $IC_{50} = 743 \pm 0.017$ μg/mL, respectively. Moreover, the aqueous extract showed inhibition of β-galactosidase ($IC_{50} = 2230 \pm 0.012$ μg/mL), this inhibition is a very weak inhibition, unless we compare it with the positive control (Bouabid et al., 2018). The methanolic extract of several parts (roots, stems, leaves, flowers) from *Scolymus hispanicus* were tested for their anti-α-amylase and anti-α-glucosidase inhibitory activity (Marmouzi et al., 2017a). All parts demonstrated enzymatic inhibitory activity with some variability. The authors attributed this difference to the phenolic compounds present in each part of the plant. Abudunia et al., 2019 tested the *in vitro* antidiabetic effect of the methanolic, *n*-hexane and aqueous extracts of *Calendula arvensis* collected from the region of Khmisset (Abudunia et al., 2019). All tested extracts exhibited enzymatic inhibitory effects on α-amylase, α-glucosidase and β-glucosidase with some variability. The methanolic extract exhibited the most potent activity against α-amylase ($IC_{50} = 573.37 \pm 36.85$ μg/mL) and α-glucosidase ($IC_{50} = 848.83 \pm 49.93$ μg/mL).

5.1.2. Lamiaceae family

Although Moroccan medicinal flora is very rich in medicinal plants belonging to Lamiaceae, only two of them (*Ajuga iva* and *Mentha viridis)* were tested for their *in vitro* antidiabetic effect. *Ajuga iva* is known by its antidiabetic effect in Moroccan traditional medicine and was recently tested by Fettach et al. (2019a,b). The authors showed that the aqueous and methanolic extract of *A. iva*inhibitedα-amylase ($IC_{50} = 0.210 \pm 0.003$ and $IC_{50} = 0.180 \pm 0.005$ μg/mL, respectively), and α-glycosidase ($IC_{50} = 0.172 \pm 0.012$ and $IC_{50} = 0.130 \pm 0.008$ μg/mL, respectively). They suggested that these effects are related to the phenolic compounds present in plant extracts. Moreover, the acute toxicity evaluation on rats showed that these extracts are nontoxic (Fettach et al., 2019a,b). Recently, Bouyahya and collaborators tested the inhibitory effect of *Mentha viridis* essential oils on the enzymatic activity of α-amylase and α-glucosidase (Bouyahya et al., 2020). The essential oil showed potent inhibition of both enzymes with IC_{50} values of 101.72 ± 1.86 μg/mL and 86.93 ± 2.43 μg/mL, respectively.

5.1.3. Cistaceae family

The antidiabetic effect of Moroccan Cistaceae medicinal species was evaluated for two species (*Cistus salviifolius* and *Cistus monspeliensis*). Sayah, Marmouzi, Naceiri Mrabti, Cherrah, & Faouzi, 2017 studied the inhibitory effects of *Cistus salviifolius* and *Cistus monspeliensis* aqueous and methanolic extracts against α-amylase and α-glucosidase. The results showed that *Cistus salviifolius* methanolic extract exhibited the highest inhibition of α-amylase ($IC_{50} = 217.10 \pm 0.15$ mg/mL) and α-glucosidase ($IC_{50} = 0.95 \pm 0.14$ mg/mL) (Sayah, Marmouzi, Naceiri Mrabti, Cherrah, & Faouzi, 2017).

5.1.4. Gentillaceae family

Centurium erythraea is the only species from Gentillaceae that has been tested *in vitro* for its antidiabetic effect. This plant is mainly used in Moroccan traditional medicine to treat several diseases including diabetes. Bouyahya et al. (2019) evaluated the *in vitro* antidiabetic effect of *Centurium erythraea* essential oils collected at three phenological stages. *Centurium erythraea* essential oils inhibited α-amylase and α-glycosidase compared with acarbose. At the post-flowering stages, *Centurium erythraea* essential oils showed important inhibited α-amylase ($IC_{50} = 31.91 \pm 0.336$) and α-glycosidase ($IC_{50} = 31.91 \pm 0.336$) (Bouyahya et al., 2019). At flowering and post-flowering stages it showed interesting anti-α-glucosidase activity by inhibition with $IC_{50} = 87.18 \pm 0.422$ and $IC_{50} = 71.83 \pm 0.72$ μg/mL, respectively. The authors attributed these effects to the oxygenated monoterpenes present in *Centurium erythraea* essential oils, including carvacrol, menthol, and tricosane (Bouyahya et al., 2019).

5.1.5. Ericaceae family

The root aqueous extract of *Arbutus unedo* revealed important enzyme inhibitory of α-amylase and α-glucosidase (Mrabti et al., 2018b). The inhibitory effect was significantly potent against α-glucosidase ($IC_{50} = 94.81 \pm 5.99$ mg/mL). This result led Naceiri Mrabti and collaborators to fractionate the root aqueous extract of *Arbutus unedo* and to isolate its major compounds. One of the major compounds, catechin was tested for its inhibitory effect onα-glucosidase (Mrabti et al., 2018a). The inhibitory activity of α-glucosidase was higher for catechin ($IC_{50} = 87.55 \pm 2.23$ mg/mL), compared with the inhibitory activity of the aqueous extract (Mrabti et al., 2018b).

5.1.6. Other families

Abid et al. (2014) tested the inhibitory effect on α-glucosidase of various fractions of *Thymelaea hirsuta* (Thymelaeaceae) from its aerial parts extract. The results showed that the methanolic fraction was the most active fraction; which inhibited 79.3 ± 8.5% of enzyme activity at 165 μg/mL. The action of methanol fraction on α-glucosidase revealed a non-competitive inhibition (Abid et al., 2014). In another study carried out by Marmouzi et al. (2019), the methanolic extracts of the leaves and fruits of Ziziphus *lotus* (Rhamnaceae)inhibited α-amylase and α-glucosidase at low concentration with some variabilities between the fruits and leaves extracts. The leaves extract revealed the highest inhibitory activity as anti-α-amylase and anti-α-glucosidase compared with the fruits extract with $IC_{50} = 20.40 \pm 1.30$ and $IC_{50} = 8.66 \pm 0.62$, respectively (Marmouzi et al., 2019). Berrani and its collaborators tested the inhibitory effect of *Anabasis aretioides* (Chenopodiaceae) methanolic extract of theatrical parts, roots and seeds. The authors revealed potent inhibitory activity ofα-amylase and α-glucosidase, especially with the roots extract. The chemical analysis of the extracts showed the presence of several phenolic compounds (chlorogenic, vanillic, gallic and *p*-hydroxybenzoic acids), which could be responsible for these activities (Berrani et al., 2018).

5.2. In vivo antidiabetic effect

Diabetes is an endogenous disease expressed by a disorder of glucose concentration in the blood. The *in vivo* anti-diabetic activity is expressed by the capacity of anti-diabetic molecules to decrease the concentration of glucose in the blood, to increase insulin secretion, to protect the β-pancreatic cells, and to stimulate glycogen biosynthesis. The *in vivo* anti-diabetic activity of medicinal plants in Morocco was investigated in 54 manuscripts (Table 3). In total, 32 Moroccan medicinal plants (*Ajuga iva, Origanum vulgare, Calamintha officinalis, Carum carvi, Ammoides pusilla, Ammi visnaga, Coriandrum sativum, Thymelaea hirsuta, Silybum*

Table 2
In vitro antidiabetic effects.

Family	Species	Part	Extract/compound	Experimental method	Key results	References
Thymelaeaceae	*Thymelaea hirsuta*	Aerial parts	Hexane, dichloromethane, ethyl acetate, methanol anddistilled water fraction.	α-Glucosidase	All fractions induced significant inhibition ofα-glucosidase. The ethyl acetate fraction had high activity and its inhibition mode was non-competitive.	Abid et al. (2014a)
Asteraceae	*Atractylis gummifera*	Roots and rhizome	Methanolic extract	*α*-Amylase	IC_{50} = 924 ± 0.067 μg/mL	Bouabid et al. (2018)
				α-Glucosidase	IC_{50} = 1236 ± 0.089 μg/mL	
				β-Galactosidase	IC_{50} = 4558 ± 0.052 μg/mL	
			Macerated methanol	*α*-Amylase	IC_{50} = 557 ± 0.013 μg/mL	
				α-Glucosidase	IC_{50} = 743 ± 0.017 μg/mL	
				β-Galactosidase	IC_{50} = 2443 ± 0.071 μg/mL	
			Chloroform extract	*α*-Amylase	IC_{50} = 1256 ± 0.029 μg/mL	
				α-Glucosidase	IC_{50} = 1674 ± 0.039 μg/mL	
				β-Galactosidase	IC_{50} = 3300 ± 0.068 μg/mL	
			Ethyl acetate extract	*α*-Amylase	IC_{50} = 1397 ± 0.010 μg/mL	
				α-Glucosidase	IC_{50} = 1863 ± 0.013 μg/mL	
				β-Galactosidase	IC_{50} = 2549 ± 0.204 μg/mL	
			Petroleum ether extract	*α*-Amylase	IC_{50} = 1605 ± 0.005 μg/mL	
				α-Glucosidase	IC_{50} = 1509 ± 0.011 μg/mL	
				β-Galactosidase	IC_{50} = 4440 ± 0.131 μg/mL	
			Decocted extract	*α*-Amylase	IC_{50} = 1352 ± 0.060 μg/mL	
				α-Glucosidase	IC_{50} = 1802 ± 0.080 μg/mL	
				β-Galactosidase	IC_{50} = 4337 ± 0.160 μg/mL	
			Infused extract	*α*-Amylase	IC_{50} = 852 ± 0.128 μg/mL	
				α-Glucosidase	IC_{50} = 1133 ± 0.171 μg/mL	
				β-Galactosidase	IC_{50} = 3239 ± 0.163 μg/mL	
			Aqueous extract	*α*-Amylase	IC_{50} = 1000 ± 0.055 μg/mL	
				α-Glucosidase	IC_{50} = 1461 ± 0.047 μg/mL	
				β-Galactosidase	IC_{50} = 2230 ± 0.012 μg/mL	
	Calendula arvensis	Flowers	Aqueous extract	*α*-Amylase	IC_{50} = 1368.27 ± 9.14 μg/mL	Abudunia et al. (2019)
				α-Glucosidase	IC_{50} = 1121.10 ± 6.42 μg/mL	
				β-Galactosidase	IC_{50} = 2116.82 ± 17.6 μg/mL	
			Methanol extract	*α*-Amylase	IC_{50} = 573.37 ± 36.85 μg/mL	
				α-Glucosidase	IC_{50} = 848.83 ± 49.93 μg/mL	
				β-Galactosidase	IC_{50} = 1422.66 ± 260.9 μg/mL	
			Hexane extract	*α*-Amylase	IC_{50} = 1955 ± 28.13 μg/mL	
				α-Glucosidase	IC_{50} = 1722.59 ± 22.42 μg/mL	
				β-Galactosidase	IC_{50} = 3156.98 ± 58.17 μg/mL	
	Scolymus hispanicus	Roots	Methanolic extract	*α*-Amylase	IC_{50} = 1299.75 μg/mL	Marmouzi et al. (2017a)
				α-Glucosidase	IC_{50} = 2088.11 μg/mL	
		Stems	Methanolic extract	*α*-Amylase	IC_{50} = 1538.46 μg/mL	
				α-Glucosidase	IC_{50} = 1267.90 μg/mL	
		Leaves	Methanolic extract	*α*-Amylase	IC_{50} = 1640.35 μg/mL	
				α-Glucosidase	IC_{50} = 2388.34 μg/mL	
		Flowers	Methanolic extract	*α*-Amylase	IC_{50} = 1632.65 μg/mL	
				α-Glucosidase	IC_{50} = 1271.45 μg/mL	
Asclepiadaceae	Caralluma europaea	Stems	Ethyl acetate fraction	*α*-Glucosidase	Inhibition of 66% at a dose of 328 μg/mL. The inhibition mode was competitive	Ouassou et al. (2018a)
Poaceae	Avena sativa	Grain	Methanolic	*α*-Amylase	IC_{50} = 723.9 μg/mL	Marmouzi et al. (2017b)
				α-Glucosidase	IC_{50} = 1543.12 μg/mL	
Thymelaeaceae	*Thymelaea hirsuta*	Aerial parts	Hexane, dichloromethane, methanol and ethyl acetate extracts	*α*-Glucosidase	At 165 μg/mL, the methanol fraction appeared to be the most active. It showed a 79.3 ± 8.5% inhibitory activity; followedby ethyl acetate, dichloromethane, aqueous, and hexane fraction.	Abid et al. (2014a)
Cistaceae	*Cistus salviifolius*	Aerial parts	Aqueous extract	*α*-Amylase	IC_{50} = 217.10 ± 0.15 μg/mL	Sayah, Marmouzi, Naceiri Mrabti, Cherrah, & Faouzi, 2017
				α-Glucosidase	IC_{50} = 0.95 ± 0.14 μg/mL	
			Methanolic extract	*α*-Amylase	IC_{50} = 597.10 ± 0.26 μg/mL	
				α-Glucosidase	IC_{50} = 8.47 ± 0.58 μg/mL	
	Cistus monspeliensis	Aerial Parts	Aqueous extract	*α*-Amylase	IC_{50} = 886.10 ± 0.10 μg/mL	
				α-Glucosidase	IC_{50} = 14.58 ± 1.26 μg/mL	
			Methanolic extract	*α*-Amylase	IC_{50} = 706.50 ± 0.17 μg/mL	
				α-Glucosidase	IC_{50} = 2.67 ± 0.50 μg/mL	
Chenopodiaceae	*Anabasis aretioides*	Aerial parts	Methanolic extract	*α*-Amylase	IC_{50} = 3148.07 ± 124.45 μg/Ml	Berrani et al. (2018a)
				α-Glucosidase	IC_{50} = 2940.59 ± 110.32 μg/mL	
		Roots	Methanolic extract	*α*-Amylase	IC_{50} = 2440.20 ± 84.90 μg/mL	

(*continued on next page*)

Table 2 (*continued*)

Family	Species	Part	Extract/compound	Experimental method	Key results	References
Thymelaeaceae	*Thymelaea hirsuta*	Aerial parts	Hexane, dichloromethane, ethyl acetate, methanol anddistillated water fraction.	α-Glucosidase	All fractions induced significant inhibition ofα-glucosidase. The ethyl acetate fraction had high activity and its inhibition mode was non-competitive.	Abid et al. (2014a)
				α-Glucosidase	IC_{50} = 3521.81 ± 145.67 μg/mL	
		Seeds	Methanolic extract	α-Amylase	IC_{50} = 3395.71 ± 98.22 μg/mL	
				α-Glucosidase	IC_{50} = 3393.83 ± 129.89 μg/mL	
Ericaceae	*Arbutus unedo*	Roots	Aqueous extract	α-Amylase	IC_{50} = 730.15 ± 0.25 μg/mL	Mrabti et al. (2018b)
				α-Glucosidase	IC_{50} = 94.81 ± 5.99 μg/mL	
		Roots	Catechin	α-Glucosidase	IC_{50} = 87.55 ± 2.23 μg/mL	Mrabti et al. (2018a)
Rhamnaceae	*Ziziphus Lotus*	Fruits	Methanolic extract	α-Amylase	IC_{50} = 31.91 ± 1.53 μg/mL	Marmouzi et al. (2019)
				α-Glucosidase	IC_{50} = 27.95 ± 2.45 μg/mL	
		Leaves	Methanolic extract	α-Amylase	IC_{50} = 20.40 ± 1.30 μg/mL	
				α-Glucosidase	IC_{50} = 8.66 ± 0.62 μg/mL	
Gentillaceae	*Centauruim erythraea*	Aerial parts	Essential oils at vegetative stage	α-Amylase	IC_{50} = 31.91 ± 0.336 μg/mL	Bouyahya et al. (2019)
				α-Glucosidase	IC_{50} = 56.77 ± 1.02 μg/mL	
			Essential oils at vegetative stage	α-Amylase	IC_{50} = 168.62 ± 0.636 μg/mL	
				α-Glucosidase	IC_{50} = 87.18 ± 0.422 μg/mL	
			Essential oils at vegetative stage	α-Amylase	IC_{50} = 94.99 ± 1.263 μg/mL	
				α-Glucosidase	IC_{50} = 71.83 ± 0.72 μg/mL	
Aristolochiaceae	*Aristolochia longa*	Roots	Methanolic fraction	α-Glucosidase	IC_{50} = 2.378 ± 0.037 μg/mL	El Omari et al. (2019)
				β-Galactosidase	IC_{50} > 5	
			Ethyl acetate fraction	α-Glucosidase	IC_{50} = 1.112 ± 0.026 μg/mL	
				β-Galactosidase	IC_{50} > 5	
			Aqueous fraction	α-Glucosidase	IC_{50} > 5	
				β-Galactosidase	IC_{50} > 5	
			Aqueous extract	α-Glucosidase	IC_{50} > 5	
				β-Galactosidase	IC_{50} > 5	
Lamiaceae	*Ajuga iva*	Aerial parts	Aqueous extract	α-Amylase	IC_{50} = 0.210 ± 0.003 μg/mL	Fettach et al., (2019a,b)
				α-Glucosidase	IC_{50} = 0.180 ± 0.005 μg/mL	
			Methanolic extract	α-Amylase	IC_{50} = 0.172 ± 0.012 μg/mL	
				α-Glucosidase	IC_{50} = 0.130 ± 0.008 μg/mL	
	Mentha viridis	Leaves	EOs	α-Amylase	IC_{50} = 101.72 ± 1.86 μg/mL	Bouyahya et al. (2020)
				α-Glucosidase	IC_{50} = 86.93 ± 2.43 μg/mL	

marianum, Chamaemelum nobile, Caralluma europaea, Avena sativa, Triticum repens, Rubus fruticosus, Crataegus oxyacantha, Centaurium erythraea, Suaedafruticosa, Lepidium sativum, Chamaerops humilis, Capparis spinosa, Spergularia purpurea, Opuntia ficus-indica, Arbutus unedo, Eucalyptus globulus, Zygophyllum gaetulum, Retama raetam, Crocus sativus, Fraxinus excelsior, Globularia alypum, Nigella sativa, Argania spinosa, Urtica dioica) belonging to 21 botanical families (*Lamiaceae, Apiaceae, Asteraceae, Rosaceae, Amaranthaceae, Brassicaceae, Arecaceae, Capparaceae, Caryophyllaceae, Cactaceae, Ericaceae, Myrtaceae, Zygophyllaceae, Fabaceae, Iridaceae, Oleaceae, Plantaginaceae, Ranunculaceae, Sapotaceae*) were tested for their anti-diabetic activity *in vivo*. The results are shown in Table 3. Among the 32 species evaluated *in vivo*, only have been evaluated in *vitro* while 25 have not been tested *in vitro* so far (see Table 4).

5.2.1. *Asteraceae family*

Silybum marianum and *Chamaemelum nobile* are two species of Moroccan Asteraceae which were tested for their *in vivo* antidiabetic effect. Maghrani et al. (2004a) studied the hypoglycemic effect of *Silybum marianum* aerial parts aqueous extract using normal and streptozotocin-induced diabetic rats (STZ diabetic rats). The administration of a dose of 20 mg/kg for 15 days significantly reduced the blood glucose levels in both normal and STZ-induced diabetic rats. No changes were observed in the basal plasma insulin concentrations after treatment in either normal or STZ-induced diabetic rats indicating that these plants exert their pharmacological activity without affecting insulin secretion (Maghrani et al., 2004a). Using the same methodology, Eddouks and collaborators tested the *in vivo* antidiabetic effect of *Chamaemelum nobile* (Eddouks et al., 2005a). It was revealed that *Chamaemelum nobile* aqueous extract reduced blood glucose levels from 6.0 ± 0.3 mmol/L to 4.9 ± 0.09 mmol/L 6h after the administration in normal rats and from 21.1 ± 1.3 mmol/L to 14.5 ± 0.9 mmol/L in STZ-induced diabetic rats (Eddouks et al., 2005a).

5.2.2. *Apiaceae family*

The species belonging to Apiaceae that were studied *in vivo* for their antidiabetic action are *Carum carvi, Ammoides pusilla, Ammi visnaga,* and *Coriandrum sativum*. The hypoglycemic effect of *Ammoides pusilla*aerial parts aqueous extract was tested by Bnouham et al. (2007) and (Bnouham et al., 2010). In 2007, the authors used two methods including oral glucose tolerance test and intravenous glucose tolerance test and showed that the administration of the extract at 250 mg/kg p.o. significantly decreased hyperglycemia suggesting a significant inhibition of glucose absorption. Using oral glucose tolerance test on normal and streptozotocin-induced diabetic rats demonstrated that the same extract decreased plasma glucose levels to 27.4% (Bnouham et al., 2010). *Carum carvi*is, another medicinal species of Apiaceae family that was tested *in vivo* for its antidiabetic activity. The aqueous extract of its fruits was administrated orally at 20 mg/kg revealed a potent antidiabetic effect in streptozotocin-induced diabetic rats. The extract significantly decreased blood glucose levels in STZ-diabetic rats without affecting basal plasma insulin concentrations. No significant changes in blood glucose levels were observed in normal rats (Eddouks et al., 2004b). Jouad et al. (2002a) investigated the hypoglycemic effect of the aqueous extract of the aerial part of *Ammi visnaga* in normal and streptozotocin-induced diabetic rats. The results showed that the oral

Table 3
In vivo antidiabetic of Moroccan Medicinal plants example of Moroccan plant extracts tested for their antihyperglycemic activity.

Family	Species	Part used	Extracts	Dose/rote of administration	Model	Key results	References
Lamiaceae	*Origanum vulgare*	Leaves	Aqueous extract	20 mg/kg Orally	Normal and STZ-induced diabetic rats	Significant antidiabetic effect without affecting basal plasma insulin concentrations	A Lemhadri et al. (2004)
	Ajuga iva	Whole plant	Aqueous extract	10 mg/kg Orally	Normal and STZ-induced diabetic rats	Strong hypoglycemic effect in diabetic rats by significantly decreasing in plasma glucose.	Hilaly and Lyoussi (2002)
	Ajuga iva	Whole plant	Aqueous extract	10 mg/kg; Orally	Normal and STZ-induced diabetic rats	Hypolipidemic and hypoglycemic activity in diabetic rats	El-Hilaly et al. (2006)
	Calamintha officinalis	Aerial parts	Aqueous extract	100 mg/kg, during 3 weeks Orally	Diabetes mellitus model of mouse (high fat diet orally)	Anti-diabetic activity with a loss of weight as well as glucoseconcentrations Decrease in the free fatty acid plasmatic concentrations	(M. Eddouks et al., 2017)
	Calamintha officinalis	Aerial parts	Aqueous extract	20 mg/kg Single or daily oral	Normal and STZ-induced diabetic rats	Significant hypoglycemic effect without affecting basal plasma insulin concentrations.	(A. Lemhadri et al., 2004)
Asclepiadaceae	*Caralluma europaea*	Stems	Aqueous extract	50 mg/kg Orally	Normal and STZ-induced diabetic rats Alloxan induced hyperglycemia Oral sucrose tolerance test (OSucTT) in normal and diabetic rats. Oral glucose tolerance test in normal and diabetic rats	Reduced the postprandial hyperglycemia after sucrose and glucose loading in normal and diabetic rats. Decreased intestinal glucose absorption.	Ouassou et al. (2018b)
Amaranthaceae	*Suaeda fruticose*	Aerial part	Aqueous extract	192 mg/kg Intravenously	Normal and STZ-diabetic rats	Decreased blood glucose and plasma cholesterol levels in both normal and diabetic rats.	Benwahhoud et al. (2001)
Asteraceae	*Silybum marianum*	Aerial part	Aqueous extract	Single or daily oral dose (20 mg/kg) for 15 days Orally	Normal and STZ-diabetic rats	Hypoglycemic activity, without affecting basal plasma insulin concentrations.	(M Maghrani et al., 2004a)
	Chamaemelum nobile	Aerial part	Aqueous extract	Single or 15 day of treatment at dose of 20 mg/kg. Orally	Normal and STZ-diabetic rats	Significant decreasein blood glucose levels in normal and STZ diabetic rats without affecting basal plasma insulin concentrations	Eddouks et al. (2005a)
F/Apiaceae	*Carum carvi*	Fruits	Aqueous extract	Single oral dose (20 mg/kg) or 14 daily doses Orally	Normal and STZ-diabetic rats	Significant decrease on blood glucose levels in STZ diabetic rats without affecting basal plasma insulin concentrations but no changes in blood glucose levels were observed in normal rats.	Eddouks et al. (2004)
F/Apiaceae	*Ammoides pusilla*	Aerial part	Aqueous extract	250 mg/kg Orally	Oral glucose tolerance test (OGTT) Intravenous glucose tolerance test (IVGTT)	Significant inhibition of glucose absorption. In combination with insulin potentiate its activity and enhance the utilization of glucose.	Bnouham et al. (2007a)
	Ammoides pusilla	Aerial part	Aqueous extract	400 mg/L in STZ-induced diabetic rats (Orally) 150 mg/kg OGTT (Intraperitoneally)	Oral glucose tolerancetest Normal and STZ-diabetic rats	Decrease plasma glucose levels at 27.4%. In oral glucose tolerance, extract showed significant reduction glycemia in rats	Bnouham et al. (2010)
F/Apiaceae	*Ammi visnaga*	Aerial part	Aqueous extract	Single and repeated dose of 20 mg/kg Orally	Normal and STZ-induced diabetic rats	Extract possessedsignificant hypoglycemic effect in both normal and STZ diabetic rats.	Jouad et al. (2002a)
F/Apiaceae	*Coriandrum sativum*	Seeds	Aqueous extract	Single and chronic dose of 20 mg/kg Orally	Normal and obese–hyperglycemic–hyperlipidemic (OHH) Meriones shawi rats	A single dose of CS-extract suppressed hyperglycemia in OHH Meriones shawi rats. Sub-chronic administration of CS-extract in OHH Meriones	Aissaoui et al. (2011)

(*continued on next page*)

Table 3 (*continued*)

Family	Species	Part used	Extracts	Dose/rote of administration	Model	Key results	References
						shawi rats normalized glycemia and decreased the elevated levels of insulin, LDL-cholesterol and TG.	
Zygophyllaceae	*Zygophyllum gaetulum*	Aerial part	Water infusion	1 g/10 mL per kg body weight Orally	Alloxan-induced diabetic rats	Continuous reduction of blood glucose levels.	Jaouhari et al. (2000)
Fabaceae	*Retama raetam*	Leaves	Aqueous extract	Single and repeated oral administration (2 mg/kg) Intraperitoneally	Normal and STZ-induced diabetic rats)	Reduction of the blood glucose in normal rats. This hypoglycemic effect caused the inhibition of renal glucose reabsorption. The aqueous extract of RR had no effect on basal plasma insulin levels indicating that the underlying mechanism of RR activity is extra-pancreatic.	Maghrani et al. (2003)
Fabaceae	*Retama raetam*	Whole plant	Aqueous extract	Single and repeated oral administration (2 mg/kg) Intraperitoneally	Normal and STZ diabetic rats)	Significant decrease of plasma triglycerides and cholesterol levels after a single and repeated oral administration. Aqueous extract caused a significant decrease of body weight one week after repeated oral treatment in diabetic rats. Extract exhibited lipid and body weight lowering activities in both normal and severe hyperglycemic rats	(M. Maghrani et al., 2004a)
Fabaceae	*Retama raetam*	Whole plant	Aqueous extract	Single dose of 10 mg/kg/h Orally	Normal and STZ-diabetic rats	AE produced a significant decrease in blood glucose levels in normal and an even more marked in diabetic rats. AE caused a potent increase of glycosuria both in normal and diabetic rats.	Maghrani et al. (2005)
Iridaceae	*Crocus sativus*	Stigmas	Aqueous extract	120 mg/kg Orally	Tartrazine induced diabetic male rats	Saffron has curative (antidiabetic) and protective (antidiabetogenic)effect against diabetes induced by Tartrazine *via* reducing blood glucose level and creatinine	Lahmass et al. (2018)
Iridaceae	Crocus sativus	Stigmas	Aqueous extract	120 mg/kg Orally	Tartrazine induced diabetic male rats	Treatment with saffron did not affect body weights, metabolic parameters but changed the blood glucose levels.	Lahmass et al. (2017)
Gentianaceae	*Centaurium erythrea*	Leaves	Aqueous extract	200 mg/kg bw/day Orally	Pancreas β-cells' Normal and STZ-induced diabetic rats	CE extract caused a significant reduction in blood glucose and MDA levels in STZ treated rats. Showed a significantdecrease in glucose levels CE extract increased the activities of both enzymatic and non-enzymatic antioxidants diabetic rats. Minimized to near normal morphology the degenerative changes of pancreatic β-cells in STZ.	Sefi et al. (2011)
Brassicaceae	*Lepidium sativum*	Aerial part	Aqueous extract	Single dose (20 mg/kg) or chronic 15	Normal and STZ- induced diabetic rats	Aqueous extract of LS exhibits a potent	Eddouks et al. (2005c)

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Table 3 (*continued*)

Family	Species	Part used	Extracts	Dose/rote of administration	Model	Key results	References
				daily repeat administration Orally		hypoglycemic activity in rats without affecting basal plasma insulinconcentrations.	
Brassicaceae	*Lepidium sativum*	Aerial part	Aqueous extract	10 mg/kg/h Intravenouslyand orally	Normal and STZ- induced diabetic rats	Extract reduced blood glucose levels both in normal and diabetic rats. Oral administration of LS for 15 days normalized glycaemia enhanced glycosuria and decreased the amount of urinary TGF-β 1 in diabetic rats. Extract caused a potent inhibition of renal glucose reabsorption whichin turn reduced blood sugar.	Eddouks and Maghrani (2008)
Arecaceae	*Chamaerops humilis*	Leaves	Aqueous extract	Single and chronic dose (10 mg/kg)	Normal and obese–hyperglycemic–hyperlipidemic (OHH) Meriones shawi rats	Plant-extract decreased plasma glucose levels	Gaamoussi et al. (2010)
Capparidaceae	*Capparis spinosa*	Fruits	Aqueous extract	20 mg/kg Orally	Normal and STZ-induced diabetic rats)	Significant antihyperglycemic activity in STZ rats without affecting basal plasma insulin concentrations	Eddouks et al. (2004)
Capparidaceae	*Capparis spinosa*	Aerial part	Aqueous extract	100 mg/kg, during 3 weeks Orally	Diabetes mellitus model of mouse (high fat diet orally)	Anti-diabetic activity, a loss of weight as well as adecrease in the free fatty acid plasmatic concentrations	(M. Eddouks et al., 2017)
Caryophyllaceae	*Spergularia purpurea*	Whole plant	Aqueous extract	10 mg/kg Orally and intravenously	Normal and STZ-induced diabetic rats	Water extractdecreased significantly the plasma glucose levels in normal and streptozotocin-induced diabetic rats. Water extractexhibiteda cholesterol and body weight-lowering activities in both normal and severe hyperglycemic rats.	Jouad et al. (2000a)
Caryophyllaceae	*Spergularia purpurea*	Whole plant	Aqueous extract	10 mg/kg orally and intravenously	Normal and STZ-induced diabetic rats	Aqueous extract of SP exhibiteda cholesterol and body weight-lowering activities. The repeated oral administration of SP aqueous extract caused a significant decrease of body weight after 2 weeks of treatment.	
Caryophyllaceae	*Spergularia purpurea*	Whole plant	Aqueous extract	10 mg/kgorally and intravenously	Normal and STZ-induced diabetic rats	Asignificant decrease in blood glucose levels in normal rats ($P < 0.05$), and even more in diabetic rats ($P < 0.001$)	Eddouks et al. (2003)
Cactaceae	*Opuntia ficus-indica*	Seeds	Oil	1 mL/kg orally	Normal and STZ diabetic rats	CPSO (p.o.) decreased postprandial hyperglycemia (60 min after glucose loading),40.33% and 16.01%, in healthy and STZ-diabetic glucose-loaded rats, respectively. CPSO, also, significantly decreased intestinal glucose absorption by 25.42%.	Berraaouan et al. (2014)
Cactaceae	*Opuntia ficus-indica*	Seeds	Oil	2 mL/kg, per os	Alloxan-induced diabetic rats.	CPSO (2 mL/kg) significantly attenuated alloxan-induced death and hyperglycemia ($P < 0.001$) in treated mice. Morphometric study of pancreas revealed that CPSO significantly	Berraaouan et al. (2015)

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Table 3 (*continued*)

Family	Species	Part used	Extracts	Dose/rote of administration	Model	Key results	References
						protected islets of Langerhans against alloxan induced-tissue alterations.	
Ericaceae	*Arbutus unedo*	Aerial part	Aqueous extract	500 mg/kg oral	Glucose Tolerance Test (OGTT) Intravenous Glucose Tolerance Test (IVGTT)	Significant inhibition of glucose absorption. In combination with insulin potentiated its activity and enhanced the utilization of glucose.	Bnouham et al. (2007a)
Ericaceae	*Arbutus unedo*	Roots	Aqueous extract	500 mg/kg orally	Normal and STZ-induced diabetic rats	The extract produced a significant decrease in blood glucose level in diabetic mice	Mrabti et al. (2018b)
Ericaceae	*Arbutus unedo*	Roots	Aqueous extract	400 mg/L in chronic treatment of streptozotocin-induced diabetic rats (Intraperitoneally) 150 mg/kg, in oral glucose tolerance test (orally)	Oral Glucose Tolerance Test Normal and STZ-induced diabetic rats	Decreasedin plasma glucose levels at 31.6%.	Bnouham et al. (2010)
Myrtaceae	*Eucalyptus globulus*	Leaves	Aqueous extract	150 and 300 mg/kg, body weight and intraperitoneally	Single and repeated oral STZ-induced diabetic rats	Exhibited a significant, dose-dependent hypoglycemic effectin streptozotocin diabetic rats. Extract significantly increased the basal plasma insulin concentrations	Jouad et al. (2004)
Oleaceae	*Fraxinus excelsior*	Seeds	Aqueous extract	Single or daily oral dose (20 mg/kg), orally	Normal and STZ-induced diabetic rats	Hypoglycemic activity, without affecting basal plasma insulin concentrations.	(M Maghrani et al., 2004b)
Oleaceae	*Fraxinus excelsior*	Seeds	Aqueous extract	10 mg/kg/h, orally	Normal and STZ-induced diabetic rats	Produced a significant decrease in blood glucose levels in normal rats ($P < 0.001$)and even more in diabetic rats ($P < 0.001$). This hypoglycemic effect might be due to an extra-pancreatic action of the aqueous extract ofFE, since the basal plasma insulin concentrations were unchanged after FE treatment. Caused a potent inhibition of renal glucose reabsorption.	Eddouks and Maghrani (2004)
Plantaginaceae	*Globularia alypum*	Leaves	Aqueous extract	Not reported	Normal and STZ-induced diabetic rats	Significant decrease of blood glucose levels and the mechanism(s) by which this plant decrease blood glucose levels is extra-pancreatic.	Jouad et al. (2002b)
Poaceae	*Triticum repens*	Rhizome	Aqueous extract	20 mg/kg, orally	Normal and STZ diabetic rats	Significant decrease of plasma glucose levels in STZ-induced diabetic rats. TR exhibiteda potent hypoglycemic activity in STZ rats without affecting basal plasma insulin concentrations.	Eddouks et al. (2005b)
Poaceae	*Triticum repens*	Rhizome	Aqueous extract	Single and oral administration at dose of (20 mg/kg)	Normal and STZ diabetic rats	Aqueous extract of TR exhibits lipid and body weight lowering activities in severe hyperglycemic rats after repeatedoral administration	(M. Maghrani et al., 2004b)
Poaceae	*Avena sativa*	Grain		2000 mg/kg, orally	STZ-induced diabetic rats Oral Glucose Tolerance Test	Oat extract (2000 mg/kg) ameliorated the glucose tolerance, decreased fasting blood glucose (FBG) and oxidative stress markers, including superoxide dismutase	Marmouzi et al. (2017b)

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Table 3 (*continued*)

Family	Species	Part used	Extracts	Dose/rote of administration	Model	Key results	References
						(SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione (GSH) and malondialdehyde (MDA) in rat liver and kidney.	
Rosaceae	*Rubus fructicosis*	Leaves	Aqueous extract	Single and repeated oral administration	STZ-induced diabetic rats	Significant decrease of blood glucose levels and the mechanism(s) by which this plant decrease blood glucose levels is extra-pancreatic.	Jouad et al. (2002b)
Rosaceae	*Crataegus oxyacantha*	Leaves	Aqueous extract	150 or 300 mg/kg, orally	STZ-induced diabetic rats	Aqueous extract produced a significant and dose-dependent decrease on blood glucose levels in STZ diabetic rats without any change in basal plasma insulin concentrations.	Jouad et al. (2003a)
Ranunculaceae	*Nigella sativa*	Seeds	Aqueous extract	2 g/kg/day, orally	Short-circuit current technique Oral Glucose Tolerance Test	Inhibited the electrogenic intestinal absorption of glucose *in vitro* chronic treatment improved glucose tolerance in rats also reduced body weight without any toxic effect.	Meddah et al. (2009)
Ranunculaceae	*Nigella sativa*	Seeds	Petroleum ether extract	2 g/kg/day for four weeks, intragastric gavage	STZ-induced diabetic rats	The petroleum ether extract exertedan insulin-sensitizing action by enhancing the activity of the two major intracellular signal transduction pathways of the hormone's receptor.	Le et al. (2004a)
Ranunculaceae	*Nigella sativa*	Seeds	Ethanol extract	2 g/kg/day forfour weeks, intragastric gavage	Oral Glucose Tolerance Test on *Meriones shawi*	Hypoglycemic and hypolipidemic activity	Benhaddou-Andaloussi et al. (2011)
Thymelaeaceae	*Thymelaeahirsuta*	Aerial part	Aqueous extract	250 mg/kg, oral	Oral Glucose Tolerance Test Intravenous Glucose Tolerance Test (IVGTT)	Significant inhibition of glucose absorption after combination with insulin potentiate its activity and enhance the utilization of glucose.	Bnouham et al. (2007a)
Thymelaeaceae	*Thymelaea hirsuta*	Aerial part	Aqueous extract	Intraperitoneally, 400 mg/Lin chronic treatment of streptozotocin-induced diabetic rats. 150 mg/kg in oral glucose tolerance test	Oral Glucose Tolerance Test STZ-induced diabetic rats	Decreasedin plasma glucose levels at 31.6%.	Bnouham et al. (2010)
Thymelaeaceae	*Thymelaea hirsuta*	Aerial part	Polyphenol-rich fraction	Single and sub-chronic administration of 2 mL⁄Kg per day, orally	STZ-induced diabetic L-nitroarginine methylester (L-NAME) hypertensive rats	Increased significantly hepatic glycogen levels and reduced the amount of glucose absorbed.	Bnouham et al. (2012)
Thymelaeaceae	*Thymelaea hirsuta*	Aerial part	Ethyl acetate	50 mg/kg, orally	STZ-induced diabetic rats	Decreased significantly *in vivo*, the postprandial hyperglycemia after sucrose loading in normal and diabetic mice. Decreased intestinal glucose uptake, *in situ*, in rats.	Abid et al. (2014b)
Sapotaceae	*Argania spinosa*	Fruits	Oil	Single and sub-chronic administration of 2 mL/Kg, orally	Alloxan-induced diabetic rats	VAO, on subchronic treatment, prevented the body mass loss, induced a significant reduction ofblood glucose and a significant increase of hepatic glycogen level.	Bellahcen et al. (2012)
Sapotaceae	*Argania spinosa*	Fruits	Oil	Single and sub-chronic	Oral Glucose Tolerance Test STZ-induced diabetic rats	Induceda significant reduction of glycemia in the OGTT test.	Bnouham et al. (2008)

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Table 3 (*continued*)

Family	Species	Part used	Extracts	Dose/rote of administration	Model	Key results	References
				administration of 2 ml/Kg		In the subchronic, showed a significant improvement of body mass and a significant reduction of the glycemia and the amount of absorbed glucose.	
Sapotaceae	*Argania spinosa*	Fruits	Oil	Single and sub-chronic administration of 2 ml/Kg/day, orally	STZ-induced diabetic L-Nitroarginine methylester (L-NAME)hypertensive rats	Decreased hyperglycemia and caused a significant increase of hepatic glycogen levels.	Bellahcen et al. (2013)
Sapotaceae	*Argania spinosa*	Fruits	Oil	Single and sub-chronic administration of 1 mL/100 g, orally	Normal and obese–hyperglycemic–hyperlipidemic (OHH) Meriones shawi rats	Reduced blood lipoproteins, total cholesterol, lipoprotein (LDL)-cholesterol, triglycerides, and body weight.	Berrougui et al. (2003)
Urticaceae	*Urtica dioica*	Aerial part	Aqueous extract	250 mg/kg	Oral glucose tolerance test (OGTT) at dose 250 mg/Kg in normal and alloxan-induced diabetic rats.	Strong glucose lowering effect in normal rats and no effect in alloxan-induced diabetic rats	Bnouham et al. (2003a)
Urticaceae	*Urtica dioica*	Aerial part	Aqueous extract	Intraperitoneally, 400 mg/l in chronic treatment of streptozotocin-induced diabetic rats. 150 mg/kg in oral glucose tolerance test	Oral glucose tolerance test STZ-induced diabetic rats	Decreased in plasma glucose levels at 31.6. Significant reduction in glycemia in oral glucose tolerance.	Bnouham et al. (2010)

administration of repeated dose of this extract at 20 mg/kg decreased blood glucose in normal and streptozotocin (STZ) diabetic. The aqueous extract of *Coriandrum sativum* seeds was tested on normal and obese, hyperglycemic, and hyperlipidemic Meriones shawi rats (Aissaoui et al., 2011). The results demonstrated that the single and long-term administration of this extract at a dose of 20 mg/kg significantly suppressed hyperglycemia. The sub-chronic administration of this extract in Meriones shawi rats normalized glycemia, decreased the elevated levels of insulin and LDL-cholesterol and triglycerides (Aissaoui et al., 2011).

5.2.3. Lamiaceae family

Lamiaceae family is rich in medicinal plants with valuable activities against several ailments. In Morocco, several species from this family were used traditionally to treat diabetes. The *in vivo* studies showed that only three species (*Origanum vulgare*, *Calamintha officinalis, Ajuga iva*) were investigated for their *in vivo* antidiabetic effect. Lemhadri et al. (2004a) and Lemhadri et al. (2004b) revealed the oral administration of *Origanum vulgare* leaves aqueous extract at a dose of 20 mg/kg was administered to streptozotocin (STZ)-induced diabetic rats showed important antidiabetic effect without affecting basal plasma insulin concentrations. The aqueous extract of *Ajuga iva* whole plant was tested for its antidiabetic effect in normal and streptozotocin diabetic rats (El-Hilaly et al., 2006; Hilaly and Lyoussi, 2002). Hilaly and Lyoussi (2002) showed that the oral administration of *Ajuga iva* aqueous extract at a dose of 10 mg/kg significantly reduced plasma glucose level in diabetic rats. At the same concentration, the hypoglycemic effect was also accompanied by a hypolipidemic action in a study carried out by (El-Hilaly et al., 2006). *Calamintha officinallis*is another Moroccan antidiabetic medicinal plant which belong to Lamiaceae. The oral administration of the aqueous extract of this plant at 20 mg/kg in normal and streptozotocin-induced diabetic rats revealed an important decrease of plasma glucose level without affecting basal plasma insulin concentrations (Lemhadri et al., 2004b). Furthermore, using 100 mg/kg for three weeks of the same extract (Eddouks et al., 2017a), showed an anti-diabetic effect, a loss of weight as well as a decrease in the free fatty acid plasma concentrations.

5.2.4. Poaceae family

Triticum repens and *Avena sativa* which belong to the Poaceae family were investigated for their antidiabetic effect in animal model. The aqueous extract of *Triticum repens* was tested in normal and streptozotocin-induced diabetic rats with a dose of 20 mg/kg. The extract did not show any changes in the basal plasma insulin concentrations after treatment in either normal or STZ-diabetic rats (Eddouks et al., 2005b). The authors suggested that the pharmacological activity of this extract appeared to be independent of insulin secretion. Using the same animal model (Maghrani et al., 2004c), showed that this extract exhibits significant lipid and body weight lowering activities in severe hyperglycemic rats after repeated oral administration. Recently, *Avena sativa*, another plant which belong to Poaceae, was tested by Marmouzi et al. (2017b) using normal and STZ-induced diabetic rats and oral glucose tolerance test. The authors showed that the oral administration of *A. sativa* extract at 2000 mg/kg ameliorated the glucose tolerance, decreased fasting blood glucose and oxidative stress markers such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione (GSH), and malondialdehyde (MDA) in rat liver and kidney (Marmouzi et al., 2017b).

5.2.5. Ericaceae family

Arbutus unedo (*Ericaceae*) is a Moroccan medicinal plant used mainly to treat several diseases including diabetes. The aqueous extract of its aerial parts administrated orally at 500 mg/kg showed potent inhibition of glucose absorption. Its combination with insulin significantly potentiated the hypoglycemic effect and enhanced the utilization of glucose (Bnouham et al., 2007). In 2010, the same authors evaluated the *in vivo* antidiabetic activity of *Arbutus unedo* roots aqueous extract using oral glucose tolerance on normal and streptozotocin-induced diabetic rats (Bnouham et al., 2010). The results revealed a significant decrease in plasma glucose levels to 31.6%. In a recent work, Mrabti et al. (2018b) showed the *in vivo* antidiabetic effect of *Arbutus unedo* roots aqueous extract in normal and streptozotocin-induced diabetic rats.

5.2.6. Thymelaeaceae family

Thymelaea hirsuta is the only species of Thymelaeaceae family which was investigated in Morocco for its *in vivo* antidiabetic effect. Using glucose tolerance test and intravenous glucose tolerance test, Bnouham et al. (2007) showed thatthe administration of aqueous extracts at 250 mg/kg significantly decreased glycemia after glucose loading. Moreover, a significant inhibition of jejunal glucose absorption at 40.5% was observed. In 2010, the same authors reported a decrease in plasma glucose levels at 31.6% after administering 400 mg/L i.p.in long term treatment of STZ diabetic rats and 150 mg/kg in oral glucose tolerance test of aqueous extracts (Bnouham et al., 2010). This decrease of plasma glucose was explained by Bnouham et al. (2012) when they investigated the effect of polyphenol-rich fraction from *Thymelaea hirsuta* aerial partson STZ diabetic L-nitroarginine methylester (L-NAME). The results of this study showed a significant increase of hepatic glycogen levels and reduced the amount of the glucose absorbed extracts (Bnouham et al., 2012). Another study was carried out by Abid et al. (2014) who indicated that the use of ethyl acetate at 50 mg/kg p.o. significantly decreased postprandial hyperglycemia after sucrose loading in normal and diabetic mice as well as intestinal glucose uptake, *in situ*, in rats.

5.2.7. Sapotaceae family

In Morocco, four studies investigated the *in vivo* antidiabetic effect of *Argania spinosa* (Sapotaceae) (Bellahcen et al., 2012, 2013; Berrougui et al., 2003; Bnouham et al., 2008). Vegetable oil from *Argania spinosa* fruits exhibited potent antidiabetic effect on alloxan-induced diabetic rats (2 mL/kg p.o.) by its ability to prevent the body mass loss, and to induce a significant reduction of blood glucose and as well as a significant increase of hepatic glycogen level (Bellahcen et al., 2012). Using STZ diabetic rats test (Bnouham et al., 2008), revealed that this oil induced a significant improvement of body mass and a significant reduction of the glycemia and the amount of absorbed glucose. In another study, it was shown that *Argania spinosa* vegetable oil decreased plasma glucose by significantly increasing hepatic glycogen levels (Bellahcen et al., 2013). Another mechanism ofthe antidiabetic effect of *Argania spinosa* vegetable oil was suggested using obese–hyperglycemic–hyperlipidemic Meriones shawi rats (Berrougui et al., 2003). The authors concluded that this effect was associated with a significant reduction of blood lipoproteins, total cholesterol, lipoprotein (LDL)-cholesterol, triglycerides and body weight (Berrougui et al., 2003).

5.2.8. Other families

The leaves and the whole plants of *Retama raetam* (Fabaceae) were effective as antidiabetic in normal and STZ-induced diabetic rats. It was demonstrated that the aqueous extract of the leaves and whole plant administered intraperitoneally and orally at 2 mg/kg exhibited potent reduction in blood glucose in normal rats and induced significant inhibition of renal glucose reabsorption. The extracts did not show any effect on the basal plasma insulin levels indicating that its antidiabetic effect is related to extra-pancreatic mechanisms (Maghrani et al., 2003). Increasing the dose to10 mg/kg of the whole plant aqueous extract in STZ-induced diabetic rats led to a significant decrease in plasma triglycerides and cholesterol levels. A significant decrease of body weight one week after repeated oral treatment was also noted (Maghrani et al., 2004b). The antidiabetic effect of *Crocus sativus* (saffron) stigmas aqueous extracts was evaluated using tartrazine induced diabetic male rats model showing a reduction in blood glucose and creatinine levels (Lahmass et al., 2017, 2018). The administration of 120 mg/kg p.o. showed curative antidiabetic effect and a protective effect (antidiabetogenic) of saffron extract. Saffron extract changed blood glucose levels but did not affect body weights and metabolic parameters (Lahmass et al., 2018). Sefi et al. (2011) investigated the *in vivo* antidiabetic properties of *Centaurium erythraea* (Gentianaceae) using pancreas β-cells, and normal and STZ-induced diabetic rats. The authors revealed, after oral administration of the aqueous extract at 200 mg/kg b.w./day, *Centaurium erythraea* significantly reduced blood glucose in STZ-treated rats. The degenerative changes of pancreatic β-cells in STZ were significantly minimized (Sefi et al., 2011). The administration of *Zygophyllum gaetulum* aerial part extract (1 g/10 mL per kg body weight) showed potent reduction of glucose levels using orally alloxan-induced diabetic rats (Jaouhari et al., 2000). Eddouks et al. (2005c) reported that *Lepidium sativum* aerial parts aqueous extract (Brassicaceae) administrated orally at 20 mg/kg exhibited a potent hypoglycemic effect without affecting basal plasma insulin. However, the oral and intravenous administration of the same extract at 10 mg/kg/h in normal and STZ-induced diabetic rats, caused significant reduction of blood glucose levels in both, normal and diabetic rats. This extract normalized glycemia, enhanced glycosuria, and decreased the amount of urinary TGF-β 1 in diabetic rats. These findings suggested that plant extract demonstrated a potent inhibition of renal glucose reabsorption resulting in a reduction of blood glucose (Eddouks and Maghrani, 2008). Gaamoussi et al. (2010) showed that the oral administration of the leaves aqueous extracts of *Chamaerops humilis* (Arecaceae) at 10 mg/kg decreased plasma glucose levels in normal and obese–hyperglycemic–hyperlipidemic (OHH) Meriones shawi rats. In STZ-induced diabetic rats, the oral and intravenous administration of the whole plant aqueous extract of *Spergularia purpurea (*Caryophyllaceae)significantly decreased the plasma glucose levels and exhibited a cholesterol and body weight-lowering activities in both, normal and severe hyperglycemicrats (Eddouks et al., 2003; Jouad et al., 2000, 2003a).The oral administration of *Opuntia ficus-indica* (Cactaceae) seeds oil (1 mL/kg per kg body weight) significantly decreased postprandial hyperglycemia (60 min after glucose loading) and intestinal glucose absorption by 25.42%in normal and STZ-induced diabetic rats (Berraaouan et al., 2014). Using a dose of 2 mL/kg, of the same oil significantly attenuated hyperglycemia in treated mice and protected islets of Langerhans against alloxan induced-tissue alterations (Berraaouan et al., 2015).

The antidiabetic effect of *Eucalyptus globulus* (Myrtaceae) was investigated using normal and STZ-induced diabetic. The results revealed that the intraperitoneal administration of 150 and 300 mg/kg body weight of the leaves aqueous extract of this plant exhibited a significant, dose-dependent hypoglycemic effect and increased the basal plasma insulin concentrations in diabetic rats (Jouad et al., 2004). The aqueous extract of *Fraxinus excelsior* (Oleaceae) seeds administered orally at 10 mg/kg in normal and STZ-induced diabetic rats also caused hypoglycemic effect without affecting the basal plasma insulin concentrations (Maghrani et al., 2004a). At the dose of 20 mg/kg, the hypoglycemia effect was also accompanied by a potent inhibition of renal glucose reabsorption in a study carried out by Eddouks and Maghrani, (2004). The oral administration of the leaves aqueous extract of *Globularia alypum* (Plantaginaceae) revealed a significant decrease of blood glucose levels in normal and streptozotocin-induced diabetic rats (Jouad et al., 2002b). Using STZ-induced diabetic rats (Jouad et al., 2002b), showed that the oral administration of the leaves aqueous extracts of *Rubus fruticosus*(Rosaceae)significantly decreased blood glucose levels.

The antidiabetic effect of *Nigella sativa* (Ranunculaceae) was investigated by three studies *in vivo* and *in vitro* (Benhaddou-Andaloussi et al., 2011; Le et al., 2004; Meddah et al., 2009). Using the oral glucose tolerance test, seeds aqueous and ethanolic extract of *Nigella sativa* (2 g/kg/day) caused hypoglycemic and hypolipidemic activities, and reduced body weight without any toxic effect (Benhaddou-Andaloussi et al., 2011; Meddah et al., 2009). An *in vitro* study using short-circuit current technique revealed that the aqueous extract of *Nigella sativa* caused a potent inhibition of the electrogenic intestinal absorption of glucose (Meddah et al., 2009). In another study, Le et al. (2004) investigated the antidiabetic effect of *Nigella sativa* (Ranunculaceae) using STZ-induced diabetic rats. The results showed that the oral administration of the seeds petroleum ether extract at a dose of 2 g/kg/day during four weeks caused an insulin-sensitizing action by enhancing the activity of the two major intracellular signal transduction pathways of

the hormone's receptor. Bnouham et al. (2003) studied the hypoglycemic effect of the aerial part aqueous extracts of *Urtica dioica* (Urticaceae) using oral glucose tolerance test (OGTT) at a dose of 250 mg/kg in normal and alloxan-induced diabetic rats. The results showed a strong glucose lowering effect in normal rats and no effect in alloxan-induced diabetic rats. In another work, the intraperitoneal administration of aerial parts aqueous extracts of this plant at a dose of 400 mg/L in the chronic treatment of streptozotocin-induced diabetic rats and 150 mg/kg in oral glucose tolerance test caused a significant reduction of glycaemia in oral glucose tolerance and plasma glucose levels (Bnouham et al., 2010).

6. Toxicological evidence

The use of plants for therapeutic purposes is a very ancient practice reported in ancient Arabic, Chinese, Egyptian, Hindu, Greek and Roman literature (Satapathy et al., 2009). Today despite the spectacular development of modern medicine, medicinal plants still find their therapeutic indications in the treatment of a many ailments and diseases in different societies and cultures. Even in developed countries, the world has witnessed renaissance in the use of medicinal plants due the failure and serious side effects of some conventional pharmaceutical treatments, especially in the case of chronic diseases. One important example of this movement is the shift of diabetic patients to herbal treatment hoping to find effective remedies that are better tolerated by the body and more accessible given the huge plant biodiversity in different contents and their richness in bioactive metabolites (Eddouks et al., 2007).

A renewed interest in phytotherapy in recent years made it possible to expand the analysis of the therapeutic efficacy of medicinal plants and understand their toxicological aspects (De Smet, 1993). Studying the toxicological aspects of medicinal plants is still in its infantile stage because of the general misleading belief that anything natural is safe and well tolerated without side effects. The toxicity of medicinal plants can be linked to the presence of mixtures of active compounds from different classes such as terpenes, alkaloids, glycosides, coumarins, and saponins. These active compounds are responsible for the activity and side effects due to their synergistic or antagonistic effects (Saad et al., 2006). Depending on the duration, frequency and quantity of toxic products to which an individual is exposed, there are several types of toxicity (Alain, 2002). Several studies were carried out on traditional herbal treatments reported serious cases of toxicity or drug-herbal, herbal-herbal or herbal food interactions that could cause therapeutic failures or accidents (Hmamouchi, 1998). Conventionally, in the presence of an unknown substance, the first step in the search for pharmacological activity begins with the study of toxicity especially the evaluation of the lethal dose 50 (LD_{50}) (Rolland, 1988).

Many anti-diabetic herbs can cause a sudden drop in blood sugar with hypoglycemic discomfort, even coma similar to insulin and other hypoglycemic drugs. The sides effects are intensified especially if these plants are associated with an already existing antidiabetic treatment. The induced hypoglycemia is sometimes accompanied by a β-blocking adrenergic effect and hepatotoxicity (Marles, 1994). The acute and chronic oral toxicity test carried out on rats revealed that the extracts of *Ammodaucus leucotrichus*, *Petroselinum sativum*, *Chamaemelum nobile*, *Rosmarinus officinalis*, *Lavandula officinalis*, *Ajuga iva*, *Arbutus unedo*, *Caralluma europaea*, *Oat cultivars* and *Scolymus hispanicus*at (Table 4) different doses of 2000 mg/kg showed no deaths, no signs of toxicity and no adverse effects. The LD_{50} can be classified in class 5 following the OECD guideline 423 (Fettach et al., 2019a,b; Marmouzi et al., 2017a; Marmouzi et al., 2017a, 2017a; Mrabti et al., 2018b; Ouassou et al., 2018).

Studies focusing on the effect of the aqueous extract of *Caralluma europaea* on the biochemical, hematological and histopathological parameters in rats, showed that the repeated administration of the extract resulted in serious renal and hepatic damage for doses higher than 2.5 and 5 g/kg (Issiki et al., 2017). The acute treatment of the aqueous extract of the root of *Atractylis gummifera* showed that the lethal concentration for the fresh roots was 1 g/kg of the body weight while that of the dried roots was 5 g/kg of the body weight (Errai et al., 2017).Prolonged oral toxicity was carried out on rats using the aqueous extract of *Aristolochia longa*rhizomes. The extract caused an atypical locomotion and significant toxicity to the liver, intestine and kidney (Benzakour et al., 2011). Jouad et al. (2004) showed that the LD_{50} of the aqueous extract of *Eucalyptus globules* leaves was greater than 4000 g/kg body weight ($LD_{50} = 4.5$ g/kg) in case of a sub-chronic toxicity.

Toxicological studies indicated that the hypoglycemic activity is dose-dependent and strongly affect the mortality rate. The acute toxicity study on the aqueous extracts of the leaves of *Crataegus oxyacantha*, *Rubus fruticosus*, and *Globularia alypum* as well as the fruits of *Ammi visnaga* and *Spergularia purpurea* revealed that the median lethal doses (LD_{50}) were 13.5 g/kg, 8.1 g/kg, 14.5 g/kg, 10.1 g/kg and 10.75 g/kg body weight, respectively. The lethal doses were dose dependent influencing the animal mortality rate (Jouad et al., 2000b; Jouad et al., 2002a, 2002b, 2003a). These studies validated the safety of some plants tested against diabetes. Toxicological work brings a certain credibility to the enthnopharmacological practices of using certain plants in the treatment of diabetes.

7. Chemistry of anti-diabetic Moroccan medicinal plants

Secondary metabolites of medicinal plants contain various bioactive compounds belonging to several chemical families such as terpenes, phenolic acids, flavonoids, and alkaloids. These bioactive compounds were investigated for their antidiabetic effect and the results demonstrated that they have specific targets against diabetes. In this section, we summarize the secondary metabolites content of Moroccan antidiabetic medicinal plants.

7.1. Terpenoids

The terpenoids are volatile and semivolatile compounds synthetized and secreted by aromatic plants. They form the main part of essential oils and possess a huge diversity in chemical structures. Structurally, terpenoids are derived from the coupling of at least two isoprene (5-carbon subunit). Depending on the number of isoprene units, terpenes are classified into monoterpenes (10-carbons, $C_{10}H_{16}$), sesquiterpenes (15-carbons, $C_{15}H_{24}$), and diterpenes (20-carbons, $C_{20}H_{32}$). Monoterpenes and sesquiterpenes are mainly found in the essential oils of plants in the form of acyclic, monocyclic or bicyclic compounds carrying numerous functionalized molecules such as alcohols, aldehyde, ketones, esters, ethers, and peroxides (Table 5).

Several Moroccan medicinal plants with anti diabetic effect were found to contain terpenoids (Fig. 1) such as *Nigella sativa, Caralluma europaea, Cistus monspeliensis, Cistus ladanifer, Myrtuscommunis, Avena sativa, Centaurium erythraea,* and *Mentha viridis.* These species contain volatile compounds with some variability depending on various factors. Khan et al. (1999) identified five terpenoids (*p*-cymene, α-pinene, thymol, (R)-limonene, (R)-carvone) in steam distillated oil of *Nigella sativa* seeds. Using the hydro-distillation and supercritical CO_2 extraction, Venkatachallam et al. (2010) identified pimaradiene, thymoquinone, γ-terpinene, thymol,2,4,(10)-thujadiene, α-terpinene, pinocarvone, ocimenone, carvacrol, and β-caryophyllene in *Nigella sativa* seeds. Another study was conducted in 2016 that revealed the presence of various volatile compounds in *Nigella sativa* essential oils such as*p*-cymene, α-thujene, γ-terpinene, α-pinene, sabinene, β-pinene, myrcene, α-terpinene, limonene, γ-terpinen-4-ol, and thymoquinone (Khalid et al., 2016). The differences between these results were attributed to the method used, the phenological stages of plant, and the plant part used. Moreover, the geographical origin of *Nigella sativa* also influences the expression of secondary metabolites.

Cistus ladaniferand Cistus monspeliensis are two Moroccan antidiabetic

species of Cactaceae which contain terpenoids. Viuda-Martos et al. (2011) studied the chemical composition of the two species using GC-MS analysis. They identified 1,8-cineole, α-pinene, verbenene, sabinene, γ-terpinene, hexanal, camphor, pinocarvone, myrtenol, and bornyl acetate as the main compounds in *Cistus monspeliensis.* However, *Cistus ladanifer* essential oil was rich in1,8-cineole, camphene, α-terpinene, *p*-cymene, γ-terpinene, *trans*-pinocarveol, borneol, terpinen-4-ol, geraniol and carvacrol (Viuda-Martos et al., 2011).

Argania spinosa is a medicinal plant used mainly by Moroccan population against several illnesses exhibited *in vivo* antidiabetic effect. Kamal et al. (2019) revealed that the vegetable oil of this species contained four terpenoid compounds including α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol. Essential oils of *Caralluma europaea* contained various terpenoids compounds including widdrene, (*Z*)-α-bisabolene, spathulenol, β-eudesmol, valerenol and (*Z*)-phytol (Zito et al., 2010). Essential oils from *Centaurium erythraea* showed *in vitro* antidiabetic activity and were found to contain carvacrol, menthol, tricosane, β-thujone, linalool, camphor, menthone, borneol, terpinen-4-ol, pulegone, and thymol.

7.2. Phenolic acids

Phenolic acids are compounds that possess a basic skeleton of fifteen carbon atoms. They consist of two aromatic rings and a pyran-type central heterocycle, forming a C_6–C_3–C_6 structure. Moroccan medicinal species (*Avena sativa, Scolymus hispanicus, Anabasis aretioides*) with antidiabetic effect contain some important phenolic acids (Fig. 2). *Avena sativa* grain aqueous extracts contain numerous phenolic compounds including gallic acid, chlorogenic acid, *p*-hydroxybenzoic acid, caffeic acid, syringic acid, *p*-coumaric acid, ferulic acid, sinapic acid, and salicylic acid (Marmouzi et al., 2017b). The same author identified various phenolic compounds in the roots and aerial parts aqueous extracts of *Scolymus hispanicus* including gallic acid, pyrogallol, chlorogenic acid, *p*-hydroxybenzoic acid, vanillic acid, caffeic acid, syringic acid, *p*-coumaric acid, ferulic acid, sinapic acid, salicylic acid, and rosmarinic acid. Different phenolic compounds including gallic acid, chlorogenic acid, vanillic acid, caffeic acid, syringic acid, *p*-hydroxybenzoic acid, coumaric acid, salicylic acid, catechol, pyrogallol, ferulic acid, 3-hydroxycinnamic acid, 4-hydroxycinnamic acid, 3,4-dihydroxybenzoïc acid, 3-hydroxybenzoic acid were also identified from *Anabasis aretioides* methanolic extract (Berrani et al., 2018). Other phenolic compounds such as dicaffeoylquinic shikimic acid, chlorogenic acid, and galloyl quinic acid were identified in the methanolic extract of the leaves and yellow and red fruits of *Arbutus unedo* (Maldini et al., 2019). The fruits and leaves aqueous extracts of *Ziziphus lotus* are rich in various phenolic compounds including gallic acid, chlorogenic acid, *p*-hydroxybenzoic acid, caffeic acid, vanillic acid, syringic acid, *p*-coumaric acid, 3-hydroxycinnamic acid, ferulic acid, sinapic acid, salicylic acid, rosmarinic acid, pyrogallol and catechol (Marmouzi et al., 2019).

7.3. Flavonoids

Flavonoids represent a class of secondary metabolites widely distributed in the plant kingdom. They are almost universal pigments of plants which are partly responsible for the coloring of the flowers, fruits and sometimes the leaves. They are found dissolved in the cell vacuoles in the state of heterosides or as constituents of plastids such as chromoplasts (Guignard, 1974). The term flavonoid includes a very wide range of natural polyphenolic compounds. There are nearly 6500 flavonoids divided into 12 classes (Stöckigt et al., 2002) and their number is constantly increasing. By definition, flavonoids are compounds which have in common the structure of diphenylpropane (C6–C3–C6). Three carbons serve as a junction between two benzene rings denoted A and B generally form an oxygenated heterocycle C (De Rijke et al., 2006). There are different structures of flavonoids such as flavones, flavonols, flavanones, flavanonols, flavans, flavan-3-ols, flavylium, chalcones, aurones, isoflavones, isoflavonols, isoflavanes, pterocarpanes, coumaronochromones, 3-arylcoumarins, coumestanes, rotenoids.

Moroccan medicinal species (*Calendula arvensis*, *Ziziphus lotus*, *Argania spinosa*, *Arbutus unedo, Anabasis aretioides, Scolymus hispanicus, Myrtus communis, Cistus ladanifer*) with anti-diabetic effects contain various flavonoids (Fig. 3). The aqueous extract of the fruits and leaves of *Ziziphus lotus* contains many flavonoids including naringin, quercetin, rutin, resveratrol, catechin and epicatechin (Marmouzi et al., 2019). The same author identified various flavonoids in the methanolic extract from the aerial parts, roots and seeds of *Anabasis aretioides* including catechin, rutin, quercetin, epicatechin, naringin, hesperidin, quercitrin, luteolin, naringenin, and hesperetin (Marmouzi et al., 2019). Three flavonoids (resveratrol, catechin, and rutin) were also identified in the ethanolic extract of *Scolymus hispanicus* (Marmouzi et al., 2017a). The methanolic extract of the leaves, yellow and red fruits of *Arbutus unedo* are rich in various flavonoids including catechin/epicatechin, strict ininellagitannin, arbutin, myricetin glucoside, myricetin pentoside, quercetin galloylhexoside isomer, myricetin rhamnoside, quercetin pentoside, quercetin galloylhexoside isomer, isoquercitrin, quercitrin, and kaempferol pentoside, and kaempferol-rhamnoside (Maldini et al., 2019).

Another study was conducted in 2019 and revealed the presence of various flavonoids in the aqueous and methanolic extract of *Calendula arvensis* flowers such as catechin, rutin, epicatechin, quercetin, and resveratrol (Abudunia et al., 2019). On the other hand, the analysis of the vegetable oil from the seeds of *Argania spinosa* demonstrated the presence of quercetin and epicatechin (Kamal et al., 2019). The methanolic extract of the leaves and berries of *Myrtus communis* contains many flavonoids such as myricetin-3-*O*-galactoside, myricetin-3-*O*--rhamnoside, myricetin-3-*O*-arabinoside, quercetin-3-*O*-glucoside, delphinidin-3-*O*-glucoside, cyanidin-3-*O*-glucoside, petunidin-3-*O*-gluco side, peonidin-3-*O*-glucoside, malvidin-3-*O* glucoside (Viuda-Martos et al., 2011). The same author identified various flavonoids in the methanolic extracts *Cistus ladanifer* and *Cistus monspeliensis* leaves including apigenin, 4′-*O*-methyl-apigenin, 7′-*O*-methyl-apigenin, 3-*O*-methyl-Kaempferol, 3,4′-di-*O*-methyl kaempferol, 3,7′-di-*O*-methyl-Kaempferol, and 3,7,4′-di-*O*-methyl-kaempferol (Viuda-Martos et al., 2011).

7.4. Fatty acids

Fatty acids are the basic constituents of lipids. They are either esterified to a glycerol skeleton or free (Peter, 2008). They are only composed of carbon, hydrogen and oxygen atoms (Léger, 2010). They are weak organic acids formed from a hydrocarbon chain ending on one side with a methyl group and from the other side with a carboxyl group. They differ from each other by the number of carbons forming the chain (Peter, 2008), generally between 4 and 30 carbons (Gornay, 2006), the number of unsaturated double bonds and the positions of these double bonds (Peter, 2008).

In Morocco, several medicinal plants tested against diabetes contain fatty acids such as *Argania spinosa*, *Caralluma europaea* and *Nigella sativa* (Fig. 4). These species are rich in fatty acids with some variation. Kamal et al. (2019) and (Harhar et al., 2019) identified several fatty acids (lauric, myristic, palmitic, palmitoleic, stearic, oleic, linoleic, linolenic, arachidic, and erucic acids in the fruits seeds and oil of *Argania spinosa*.

Other studies carried out in 1999 and 2007 revealed the presence of various fatty acids in the seeds and oil of *Nigella sativa* such as myristic, myristoleic, palmitic, palmitoleic, margaric, margaroleic, stearic, oleic, linoleic, linolenic, arachidic, eicosenoic, behenic, lignoceric acid, dihomo-linoleic acid, oleic, palmitic, stearic, oleoyldilinoleoyl, palmitoyldilinoleoyl, palmitoyloleoyllinoleoyl, dioleoyllinoleoyl, monogalactosyl diglyceride, digalactosyldiglyceride, acylated, sterylgalacto side, sterylgalactoside, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, candiolipin, and phosphatidylglycerol (Cheikh-Rouhou et al., 2007; Khan, 1999). The phytochemical analysis

Table 4
Toxicological investigations.

Family	Species	Part	Extracts	Doses	Route of administration	Model	Effects	References
Apiaceae	*Ammodaucus leucotrichus*	Seeds	Aqueous extracts	300, 500 and 2000 mg/kg	Orally	Acute toxicity	No mortality was conducted during the 15 days of acute administrationof extracts	Chebaibi et al. (2019)
Apiaceae	*Petroselinum sativum*	Stem and leaves						
Asteraceae	*Chamaemelum Nobile*	Flowers						
Lamiaceae	*Rosmarinus officinalis*	Leaves						
Lamiaceae	*Lavandula officinalis*	Stem and leaves						
Lamiaceae	*Ajuga iva*	Aerial part	Aqueous extracts Methanol extract	2000 mg/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Fettach et al., (2019a,b)
Ericaceae	*Arbutus unedo* L	Roots	Aqueous extracts	0.5 and 2 g/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Mrabti et al. (2018b)
Apocynaceae	*Caralluma europaea*	Stems	Aqueous extract Ethyl acetate	1, 2, 3, 4, 6, and 8 g/kg 100, 300, 500, and 700 mg/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Ouassou et al. (2018a)
Poaceae	*Oat Cultivars*	Grain	Aqueous extract	2000 mg/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Marmouzi et al. (2017b)
Asteraceae	*Scolymus hispanicus*	Roots, stems, leaves and flowers	Ethanol extracts	2000 mg/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Marmouzi et al. (2017a)
Apocynaceae	*Caralluma europaea*	Aerial parts	Aqueous Extract	5 g/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Issiki et al. (2017)
				1, 2.5 and 5 g/kg	Orally	Subchronic toxicity	Serious kidney and liver injury for the higher doses 2.5 and 5 g/kg	
Apocynaceae	*Caralluma europaea*	Aerial parts	Methanol extract	200, 500, 1000, 2000 mg/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Dra et al. (2019)
Asteraceae	*Atractylis gummifera*	Root	Aqueous extract	0.01, 0.1, 1, 5 and 10 g/kg	Orally	Acute Toxicity	Lethal concentration for fresh root was 1 g/kg BW while that of dried root was 5 g/kg BW	Errai et al. (2017)
Thymelaeaceae	*Thymelaea hirsuta*	Aerial parts	Aqueous extract	5 mg/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Azza et al. (2012)
				0, 0.5, 1 and 2 g/kg	Orally	Sub-chronic toxicity	No death and no observed signs of toxicity. No significant change of the blood parameters of the treated animals. Histopathological examination of the different organ did not reveal any extract induced significant changes.	
Aristolochiaceae	*Aristolochia longa* L	Rhizomes	Aqueous extract	2.5 g/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Benzakour et al. (2011)
				1.25 and 2.5 g/kg	Orally	Sub-chronic toxicity	Induced atypical locomotion and a significant toxicity on the liver, intestine and kidney	
Gentianaceae	*Centaurium erythraea*	whole plant	Aqueous extract	0–15 g/kg	Orally andintraperitoneally	Acute toxicity	No death and no observed signs of toxicity	Tahraoui et al. (2010)
				0, 100, 600 and 1200 mg/kg	Orally	Subchronic toxicity	Not significant change of the blood parameters of the treated animals. Histopathological examination of the different organ did not reveal any extract induced significant changes.	
Ericaceae	*Arbutus unedo*	Roots	Aqueous extract	Different doses	Intraperitoneally	Acute toxicity	No death and no observed signs of toxicity	Bnouham et al. (2007b)
Apiaceae	*Ammoides pusilla*	Whole plant	Aqueous extract					
Thymelaeaceae	*Thymelaea hirsuta*	Whole plant	Aqueous extract					
Ranunculaceae	*Nigella sativa*	Seeds	Petroleum ether extract	2 g/kg	Orally	Acute toxicity	No death and no observed signs of toxicity	Le et al. (2004b)
Myrtaceae		Leaves			Orally			

(continued on next page)

Table 4 (*continued*)

Family	Species	Part	Extracts	Doses	Route of administration	Model	Effects	References
	Eucalyptus globulus		Aqueous Extract	0, 1, 1.5, 2, 2.5, 3, 3.5, 4.5, 5, 7.5, 8, 10, 14, 15 and 20 g/kg		Acute toxicity	Death rate is dose dependenthypo-activity, and death of the animals (LD_{50} = 4.5 g/kg)	Jouad et al. (2004)
Urticaceae	*Urtica dioica*	Aerial part	Aqueous extract	250 mg/kg	Intraperitoneally	Acute toxicity	Low toxicity (LD_{50} = 3.5 g/kg)	Bnouham et al. (2003b)
Rosaceae	*Crataegus oxyacantha*	Leaves	Aqueous extract	0, 5, 7.5, 10, 11.75, 12, 12.5, 13, 14, 15 and 20 g/kg	Orally	Acute toxicity	Death rate is dose dependenthypo-activity, and death of the animals (LD_{50} = 13.5 g/kg)	Jouad et al. (2003b)
Rosaceae	*Rubus fruticosusL*	Leaves	Aqueous extract	0, 2.5, 5, 6, 7, 8, 9, 10, 12, and 14 g/kg	Orally	Acute toxicity	Moderate toxicity for high doses (LD_{50} = 8.1 g/kg)	(Jouad et al., 2002c)
Globulariaceae	*Globularia alypum L.*	Leaves	Aqueous extract	0, 2.5, 5, 6, 7, 8, 9, 10, 12, and 14 g/kg	Orally	Acute toxicity	Moderate toxicity for high doses (LD_{50} = 14.5 g/kg)	(Jouad et al., 2002c)
Apiaceae	*Ammi visnaga*	Fruits	Aqueous extract	0, 2, 4, 8, 10, 12, 16, and 20 g/kg	Orally	Acute toxicity	Death rate is dose dependenthypo-activity, and death of the animals (LD_{50} = 10.1 g/kg)	Jouad et al. (2002b)
				0, 1, 2, 3, 3.5, 4, 4.5, 5, and 10 g/kg	Intraperitoneally	Acute toxicity	Death rate is dose dependant Hypo-activity, and death of the animals (LD_{50} = 3.6 g/kg)	
Caryophyllaceae	*Spergularia purpurea*	Whole plant	Aqueous extract	0, 2.5, 5, 7.5, 10, 11, 11.5 and 12 g/kg	Orally	Acute toxicity	Low toxicity (LD_{50} = 10.75 g/Kg)	Jouad et al. (2000b)
Sapotaceae	*Argania spinosa*	Whole plant	Aqueous extract	100 and 200 mg/kg	Orally	Acute toxicity Chronic toxicity	No death and no observed signs of toxicity Not significant changes of the blood parameters of the treated animals	Alaoui et al. (1998)

of the essential oils of *Caralluma europaea* showed the presence of two fatty acids, tetradecanoic and hexadecanoic acids (Zito et al., 2010).

7.5. Steroids

Steroids are a group of lipids derived from triterpenoids (lipids with 30 carbon atoms), mainly squalene. They are characterized by a partially or fully hydrogenated hydrophobic cyclopentanophenanthrenenucleus. Steroids also include lipids whose cyclopentanophenanthrene nucleus is modified by splitting a bond and adding or deleting a carbon. In medicine the term "steroids" refers to steroid hormones. In a sporting context, the term "steroids" is usually used to designate anabolic steroids. Moroccan medicinal species (*Argania spinosa* and *Caralluma europaea*) with anti-diabetic effects contain various steroids (Fig. 5). The vegetable oils of *Argania spinosa* and *Caralluma europaea* contain several steroids namely cholesterol, campesterol, Δ7-avenasterol, schottenol and spinasterol (Kamal et al., 2019; Zito et al., 2010).

7.6. Tannins

The tannin term is derived from the tanning capacity of animal skin by transforming it into leather. It is a group of high molecular weight polyphenols. Tannins are highly hydroxylated molecules that can form insoluble complexes when combined with carbohydrates, proteins and digestive enzymes and thus reduce the digestibility of food. They can be linked to cellulose and numerous mineral elements (Ref'at et al., 2008). They are classified into hydrolysable and condensed tannins. Hydrolysable tannins are dimers of gallic acid condensed with carbohydrates. They include gallic acid and the condensation products of its dimer, hexahydroxydiphenic acid. Condensed tannins are also known as proanthocyanidins or procyanidins. They result from the auto-oxidation or enzymatic polymerization of the flavan-3,4-diol units mainly linked by the C4–C8 bonds (sometimes C4–C6) of the adjacent units (Dykes and Rooney, 2006). Among Moroccan medicinal species studied against diabetes is *Scolymus hispanicus*, which was found to contain tannins (Fig. 6). The ethanolic extracts of the stems, flowers, leaves and roots contain tannic acid (Marmouzi et al., 2017a).

7.7. Alkane

Alkanes are saturated hydrocarbons. They consist of carbon and hydrogen atoms and do not have a C=C or C≡C multiple bonds. The acyclic alkanes have the crude formula $C_nH_{2n}+2$. They are very abundant in Nature such and can be found in deposits of natural gas, petroleum or bituminous shales, which come from the slow fossilization of vegetable organic matter. Despite the intensive exploitation of these fossil materials, no synthesis process is still economically viable compared to the extraction of natural oil. *Caralluma europaea,* one of the Moroccan medicinal species tested for its diabetic activity, was found to contain alkanes (Fig. 7). The essential oils of *Caralluma europaea* the stems contain heneicosane, tricosane, pentacosane, heptacosane, hentriacontane (Zito et al., 2010).

8. Preclinical investigation insights of the antidiabetic bioactive compounds from Moroccan medicinal plants

8.1. Antidiabetic properties of terpenoids

8.1.1. Thymoquinone

Thymoquinone (TQ) is an active ingredient isolated from *Nigella sativa*, and more than 20 studies (Table 6) evaluated its anti-diabetic activity (Hawsawi et al., 2001; Fararh et al., 2005; Chandra et al., 2009; Pari and Sankaranarayanan, 2009; Abdelmeguid et al., 2010;

Table 5
Chemical compounds of antidiabetic Moroccan medicinal plants.

Species	Part	Extracts/essential oils	Compounds groups	Compounds	Reference
Mentha viridis	Leaves	Essential oil	Terpenoids	-Carvone −1,8-cineole -Terpinen-4-ol -Limonene -Camphor -*α*-Terpineol - *β*-Caryophyllene - *p*-Cymene - Pulegone - Borneol - Linalol - Myrcene	Bouyahya et al. (2020)
Calendula arvensis	Flowers	Aqueous and Methanolic extract	Phenolic Acids	- Gallic acid - Chlorogenic acid - Vanillic acid - Caffeic acid - Syringic acid - *p*-Hydroxybenzoic acid - Rosmarinic acid - Sinapic acid - *p*-Coumaric acid - Salicylic acid - Catechol - Pyrogallol - Ferulic acid	Abudunia et al. (2019)
			Flavonoids	- Catechin - Rutin - Epicatechin - Quercetin - Resveratrol	
Ziziphus lotus	Fruits and Leaves	Aqueous extract	Phenolic Acids	- Gallic acid - Chlorogenic acid - *p*-Hydroxybenzoic acid - Caffeic acid - Vanillic acid - Syringic acid - *p*-Coumaric acid - 3-Hydroxycinnamic acid - Ferulic acid - Sinapic acid - Salicylic acid - Rosmarinic acid - Pyrogallol - Catechol	Marmouzi et al. (2019)
			Flavonoids	- Naringin - Quercetin - Rutin - Resveratrol - Catechin - Epicatechin	
Centaurium erythraea		Essential oil	Terpenoids	Carvacrol Menthol Tricosane *β*-Thujone Linalool Camphor Menthone Borneol Terpinen-4-ol Pulegone Thymol Linoleic acid	Bouyahya et al. (2019b)
Argania spinosa L.	Seeds	Vegetable oil	Fatty acids	- Monounsaturated fatty acids - Polyunsaturated fatty acids - Saturated fatty acids	Kamal et al. (2019)
			Phenolic Acids	- Caffeic acid - Syringic acid - *p*-Coumaric acid - Ferulic acid - Sinapic acid - Gallic acid - *p*-Hydroxybenzoic acid - Vanillic acid	

(*continued on next page*)

Table 5 (*continued*)

Species	Part	Extracts/essential oils	Compounds groups	Compounds	Reference
			Flavonoids	- Epicatechin - Quercetin α-Tocopherol β-Tocopherol γ-Tocopherol δ-Tocopherol	
			Steroids	- Cholesterol - Campesterol - Δ7-Avenasterol - Schottenol - Spinasterol	
Arbutus unedo	Leaves	Methanolic extract	Phenolic Acids	- Galloyl quinic acid - Chlorogenic acid - Digalloylquinic shikimic acid	Maldini et al. (2019)
			Flavonoids	- Catechin/epicatechin - Strictinin ellagitannin - Arbutin - Myricetin glucoside - Myricetin pentoside - Quercetin galloylhexoside - Myricetin rhamnoside - Quercetin pentoside - Quercetin galloylhexoside isomer - Isoquercitrin - Quercitrin - Kaempferol pentoside - Kaempferol-rhamnoside	
Arbutus unedo	Yellow fruits	Methanolic extract	Phenolic Acids	- Galloyl quinic acid - Digalloylquinic shikimic acid	Maldini et al. (2019)
			Flavonoids	- Catechin/epicatechin - Arbutin - Quercetin pentoside - Quercetin galloylhexoside isomer - Quercitrin - Kaempferol-rhamnoside	
Arbutus unedo	Red fruits	Methanolic extract	Phenolic Acids	- Galloyl quinic acid - Chlorogenic acid - Digalloylquinic shikimic acid	Maldini et al. (2019)
			Flavonoids	- Catechin/epicatechin - Strictinin ellagitannin - Arbutin - Myricetin glucoside - Myricetin pentoside - Quercetin galloylhexoside - Myricetin rhamnoside - Quercetin pentoside - Quercetin galloylhexoside isomer - Isoquercitrin - Quercitrin - Kaempferol pentoside - Kaempferol-rhamnoside	
Argania spinosa (L.)	Fruit pulp	Oil	Fatty acids	- Lauric C12:0 - Myristic C14:0 - Palmitic C16:0 - Palmitoleic C16:1 - Stearic C18:0 - Oleic C18:1 - Linoleic C18:2 - Linolenic C18:3 - Arachidic C20:0 - Erucic C22:1	Harhar et al. (2019)
Arbutus unedo L	Roots	Aqueous extract	Flavonoids	Catechin	Mrabti et al. (2018a)
Anabasis aretioidesCoss. &Moq.	Aerial part Roots Seeds	Methanolic extract	Phenolic Acids	- Gallic acid - Chlorogenic acid - Vanillic acid - Caffeic acid - Syringic acid - *p*-Hydroxybenzoïc acid - Coumaric acid - Salicylic acid - Catechol - Pyrogallol	Berrani et al. (2018b)

(continued on next page)

Table 5 (*continued*)

Species	Part	Extracts/essential oils	Compounds groups	Compounds	Reference
				- Ferulic acid - 3-Hydroxycinnamic acid - 4-Hydroxycinnamic acid – 3,4-Ddihydroxybenzoïc acid - 3-Hydroxybenzoïc acid	
			Flavonoids	- Catechin - Rutin - Quercetin - Epicatechin - Naringin - Hesperidin - Quercitrin - Luteolin - Naringenin - Hesperetin	
Scolymus hispanicus(Golden Thistle)	Roots	Ethanolic extracts	Phenolic Acids	- Gallic acid - Pyrogallol - Chlorogenic acid - *p*-Hydroxybenzoic acid - Vanillic acid - Caffeic acid - Syringic acid - *p*-Coumaric acid - Ferulic acid - Sinapic acid - Salicylic acid - Rosmarinic acid	Marmouzi et al. (2017b)
			Flavonoids	- Resveratrol - Catechin - Rutin	
			Tannins	Tannic acid	
Scolymus hispanicus (Golden Thistle)	Stems Flowers Leaves	Ethanolic extracts	Phenolic Acids	- Gallic acid - Pyrogallol - Chlorogenic acid - *p*-Hydroxybenzoic acid - Vanillic acid - Caffeic acid - Syringic acid - *p*-Coumaric acid - Ferulic acid - Sinapic acid - Salicylic acid - Rosmarinic acid	Marmouzi et al. (2017b)
			Flavonoids	- Resveratrol - Catechin - Rutin	
			Tannins	Tannic acid	
Avena sativa	Grain	Aqueous extracts	Phenolic Acids	- Gallic acid - Chlorogenic acid - *p*-Hydroxybenzoic acid - Caffeic acid - Syringic acid - *p*-Coumaric acid - Ferulic acid - Sinapic acid - Salicylic acid	Marmouzi et al. (2017b)
			Terpenoids	*α*-Tocopherol	
Nigella sativa L	Seeds	Essential oil	Terpenoids	- *p*-Cymene - *α*-Thujene - *γ*-Terpinene - *α*-Pinene - Sabinene - *β*-Pinene - Myrcene - *α*-Terpinene - Limonene - *γ*-Terpinen-4-ol - Thymoquinone - Carvacrol	Khalid and Shedeed (2016)
Myrtus communis L	Leaves Barry	Essential oil	Terpenoids	-1,8-Cineole - *α*-pinene - Myrtenyl acetate - *α*-terpineol - Camphene - *β*-pinene	Viuda-Martos et al. (2011)

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Table 5 (*continued*)

Species	Part	Extracts/essential oils	Compounds groups	Compounds	Reference
				- Terpinolene - Linalool - Terpinen-4-ol - Myrtenol - Geraniol	
Cistus ladanifer L.	Leaves	Essential oil	Terpenoids	-1,8-Cineole - Camphene - *α*-Terpinene - *p*-Cymene - γ-Terpinene, - *trans*-Pinocarveol - Borneol - Terpinen-4-ol - Geraniol - Carvacrol	Viuda-Martos et al. (2011)
Cistus monspeliensis L.	Leaves	Essential oil	Terpenoids	-1,8-Cineole - *α*-Pinene - Verbenene - Sabinene - *γ*-Terpinene - Hexanal - Camphor - Pinocarvone - Myrtenol - Bornyl acetate	Viuda-Martos et al. (2011)
Myrtus communis L	Leaves Berry	Methanolic extract	Flavonoids	- Myricetin-3-*O*-galactoside - Myricetin-3-*O*-rhamnoside - Myricetin-3-*O*-arabinoside - Quercetin-3-*O*-glucoside - Delphinidin-3-*O*-glucoside - Cyanidin-3-*O*-glucoside - Petunidin-3-*O*-glucoside - Peonidin-3-*O*-glucoside - Malvidin-3-*O*-glucoside	Viuda-Martos et al. (2011)
Cistus ladanifer L.	Leaves	Methanolic extract	Flavonoids	- Apigenin -4′-*O*-Methyl-apigenin -7′-*O*-Methyl-apigenin - 3-*O*-Methyl-Kaempferol -3,4′-Di-*O*-methyl-Kaempferol -3,7′-Di-*O*-methyl-Kaempferol -3,7,4′-Di-*O*-methyl-Kaempferol	Viuda-Martos et al. (2011)
Cistus monspeliensis L.	Leaves	Methanolic extract	Flavonoids	- Apigenin – 4′-*O*-Methyl-apigenin – 7′-*O*-Methyl-apigenin - 3-*O*-Methyl-Kaempferol -3,4′-Di-*O*-methyl-Kaempferol -3,7′-Di-*O*-methyl-Kaempferol -3,7,4′-Di-*O*-methyl-Kaempferol	Viuda-Martos et al. (2011)
Carallumaeuropaea	Stems	Essential Oil	Terpenoids	- Widdrene - (*Z*)-*α*-Bisabolene - Spathulenol - *β*-Eudesmol - Valerenol - (Z)-Phytol	Zito et al. (2010)
			Alkane	- Heneicosane - Tricosane - Pentacosane - Heptacosane - Hentriacontane	
Caralluma europaea	Fruits		Fatty acids	- Tetradecanoic acid - Hexadecenoic acid	
			Steroids	- Cholesterol - Campesterol - Δ7-Avenasterol - Schottenol - Spinasterol	
Nigella sativa L.	Seed	Hydro-distillation and Supercritical CO_2 extraction	Terpenoids	- Thymoquinone - γ-Terpinene - Thymol, – 2,4,(10)-Thujadiene - α-Terpinene - Pinocarvone - Ocimenone - Carvacrol - *β*-Caryophyllene	(Tiruppur Venkatachallam et al., 2010)

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Table 5 (*continued*)

Species	Part	Extracts/essential oils	Compounds groups	Compounds	Reference
				- Pimaradiene	
Nigella sativa L.	Seed	Oil (hexane)	Fatty acids	- Myristic C14:0	Cheikh-Rouhou et al. (2007)
				- Myristoleic C14:1	
				- Palmitic C16:0	
				- Palmitoleic C16:1	
				- Margaric C17:0	
				- Margaroleic C17:1	
				- Stearic C18:0	
				- Oleic C18:1	
				- Linoleic C18:2	
				- Linolenic C18:3	
				- Arachidic C20:0	
				- Eicosenoic C20:1	
				- Behenic C22:0	
				- Lignoceric C24:0	
Nigella sativa L.	Seed	Fixed oil (steam distillation)	Fatty acids	- Dihomo-linoleic acid	Khan (1999)
				- Linoleic	
				- Oleic	
				- Palmitic	
				- Stearic	
				- Trilinoleoyl	
				- Oleoyldilinoleoyl	
				- Palmitoyldilinoleoyl	
				- Palmitoyloleoyllinoleoyl	
				- Dioleoyllinoleoyl	
				- Monogalactosyl diglyceride	
				- Digalactosyldiglyceride	
				- Acylated-sterylgalactoside	
				- Sterylgalactoside	
				- Phosphatidylcholine	
				- Phosphatidylethanolamine	
				- Phosphatidylinositol,	
				- Candiolipin	
				- Phosphatidylglycerol	
			Terpenoids	- *p*-Cymene	
				- α-Pinene	
				- (R)-Limonene	
				- (R)-Carvone	
				- Thymol	

Fararh et al., 2010; Abdelmeguid et al., 2011; Sankaranarayanan and Pari, 2011; Al Wafai, 2013; BacakGüllü & Avci, 2013; Al-Sa'aidi et al., 2014; Ashour, 2015; Bashandy et al., 2015; Sangi et al., 2015; Abduallah, 2017; Aarag et al., 2017; El-Shemi et al., 2018; Karandrea et al., 2017; Salahshoor et al., 2017; Abdelrazek et al., 2018; Rani et al., 2018). Hawsawi et al. (2001) was among the first researchers to carry out these studies. They found a decrease in blood glucose level in normal albino rats in response to thymoquinone treatment. Whereas in STZ-induced diabetic hamsters, Fararh et al. (2005) measured blood glucose and HbA_{1c} levels, and estimated hepatic glucose production after the oral administration of thymoquinone (50 mg/kg b.w.) per day for 30 days. At the end of the treatment, the authors noted a normalization of all the parameters studied. The anti-diabetic activity of this monoterpene was linked to the increase in insulin secretion.Chandra et al. (2009) confirmed this effect using INS-1 cells as a model for regulation of insulin secretion, and the ELISA method to quantify insulin levels. Another study was conducted to assess the antihyperglycemic potential of this compound (Pari and Sankaranarayanan, 2009), by intragastric administration of three increasing doses to STZ-nicotinamide (NA) induced diabetic rats for 45 days. The levels of blood glucose, insulin, and HbA_{1c} were measured. The activities of hexokinase, G6Pase, FBPase, and glucose 6-phosphate dehydrogenase were analyzed. As a result, TQ treatment, depending on the dose, improved glycemic status, carbohydrate metabolism as well as insulin and HbA_{1c} levels. Abdelmeguid et al. (2010) injected (i.p.) this monoterpene (3 mg/mL) 6 days a week for 30 days to a model of diabetes mellitus in rats and determined the biochemical parameters and a analyzed histologically the pancreatic tissues. They noticed potent therapeutic effect such as restoring serum glucose and insulin levels, and protective effects such as preserving the integrity of pancreatic β-cells. They explained these effects by improving the ultrastructure of β-cells and reducing oxidative stress, respectively. As already cited in their previous study conducted in 2005, Fararh et al. (2010) further confirmed the hypoglycemic potential of the tested compound; using another animal model with the determination of plasma glucose and insulin concentrations. Abdelmeguid et al. (2011) carried out a second study in which they induced cellular damage in the pancreatic islets of rats by STZ, and they found that treatment with TQ (5 mg/kg) improved the harmful effects of this substance on pancreatic β-cells. This prevention was attributed to the antioxidant properties of this monoterpene. This protective activity of TQ was also observed by Sankaranarayanan and Pari, (2011) when they induced diabetes in rats by estimating their blood glucose, their pancreatic and plasma insulin levels. This protection was accompanied by an improvement in the aforementioned parameters. These results corroborated those obtained by Al Wafai, (2013), in STZ-induced diabetic rats, where they investigated the effect of TQ on mRNA expression of the intercellular adhesion molecule-1 (ICAM-1), cyclooxygenase-2 (COX-2) (detected by RT-PCR), and oxidative stress in pancreatic tissue. There was inhibition of COX-2 mRNA expression and normalization of SOD levels confirming the potential of TQ in improving inflammation and oxidative stress accompanying diabetes. In the same year, a Turkish research team treated rats, fed a fatty diet, with TQ (50 mg/kg b.w./day). Blood glucose and plasma insulin were measured (BacakGüllü & Avci, 2013). However, the results were not in agreement with those found by previous studies. These researchers reported an increase in plasma glucose level and a decrease in plasma insulin. This decrease was attributed to the loss of body weight

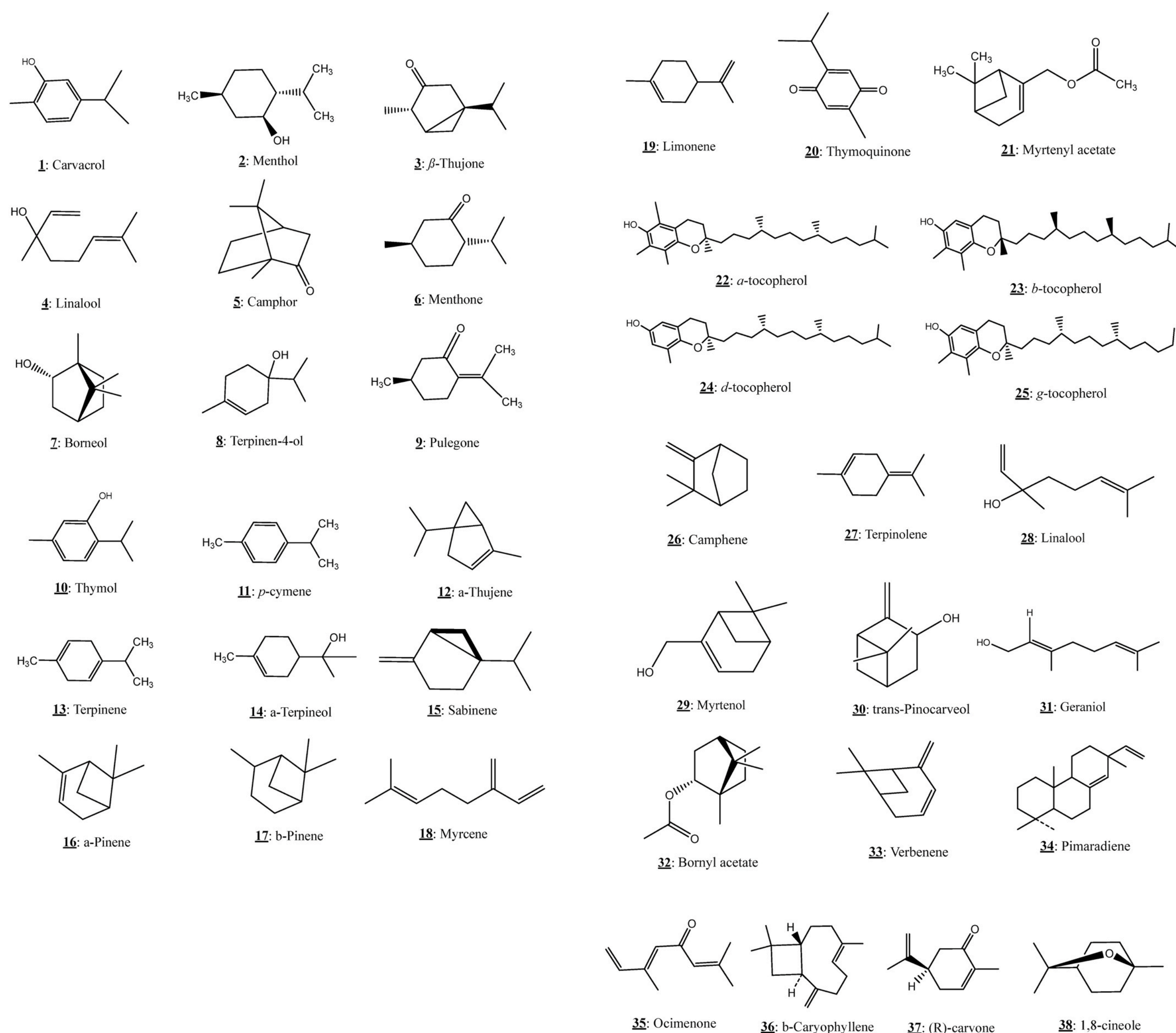

Fig. 1. Chemical structures of terpenoids identified from antidiabetic Moroccan medicinal plants (structures designed by ChemDraw).

observed because TQ could reduce food intake. The plasma insulin level was significantly reduced and lead to an increase in plasma glucose. Additionally, this increase may be explained by the fact that high-fat diets induce hyperinsulinemia and hyperglycemia (Amin et al., 2009). The short period of this study may not be enough to notice this hyperinsulinemia. Moreover, the glucose rise did not reach hyperglycemic thresholds (300 mg/dl) (Buettner et al., 2007).

The following year, Al-Sa'aidi and colleagues estimated the blood glucose and insulin concentrations in experimentally induced diabetic male rats (Al-Sa'aidi et al., 2014), receiving 42-day TQ treatment (50 and 100 mg/kg, b.w.). The authors noted a significant decrease in the measured concentrations (glucose/insulin) during the studied period. These data were supported by Ashour, (2015) who selected a rat model of STZ-induced diabetes to test the antihyperglycemic activity of TQ after determining several parameters such as blood glucose, serum insulin, and HbA_{1c}. TQ improved the above parameters and protected the pancreatic islets of Langerhans from damage caused by STZ injection. Likewise, these results were confirmed by Bashandy et al. (2015) who administered TQ (40 mg/kg b.w.) by gastric gavage to diabetic rats for 21 days. After dividing the animals into 3 groups, blood samples were taken to determine the plasma insulin and glucose levels. Diabetic rats treated with TQ showed at the third week a decrease in inflammatory markers (TNF-α and IL6) and plasma glucose levels (45%) with an increase in insulin level and a reduction in lipid peroxidation in the pancreas. In the same way, other authors injected (i.p.) TQ (3 and 5 mg/kg) into diabetic rats induced by STZ for 56 days (Sangi et al., 2015). At the end of each period (1, 4, and 8 weeks), they determined blood glucose level and observed the status/number of *β* islets of Langerhans. Using the same experimental protocol (Abduallah, 2017), treated the animals with TQ (5 and 10 mg/kg b.w.). At the end of the experiment, the glucose and insulin concentrations of different groups were evaluated. The therapeutic effect of this molecule revealed a decrease in blood glucose concentration values and an increase in those of insulin, in a dose-dependent manner. These effects may be linked to a reduction in hepatic gluconeogenesis.

Combinatorial therapy was tested to assess the ability of this monoterpene to normalize parameters related to hyperglycemia. Aarag et al. (2017) tested the effect of the oral administration of TQ alone and/or in combination with metformin on STZ-induced diabetic rats and they estimated glucose and HbA_{1c} levels. Treating these animals with

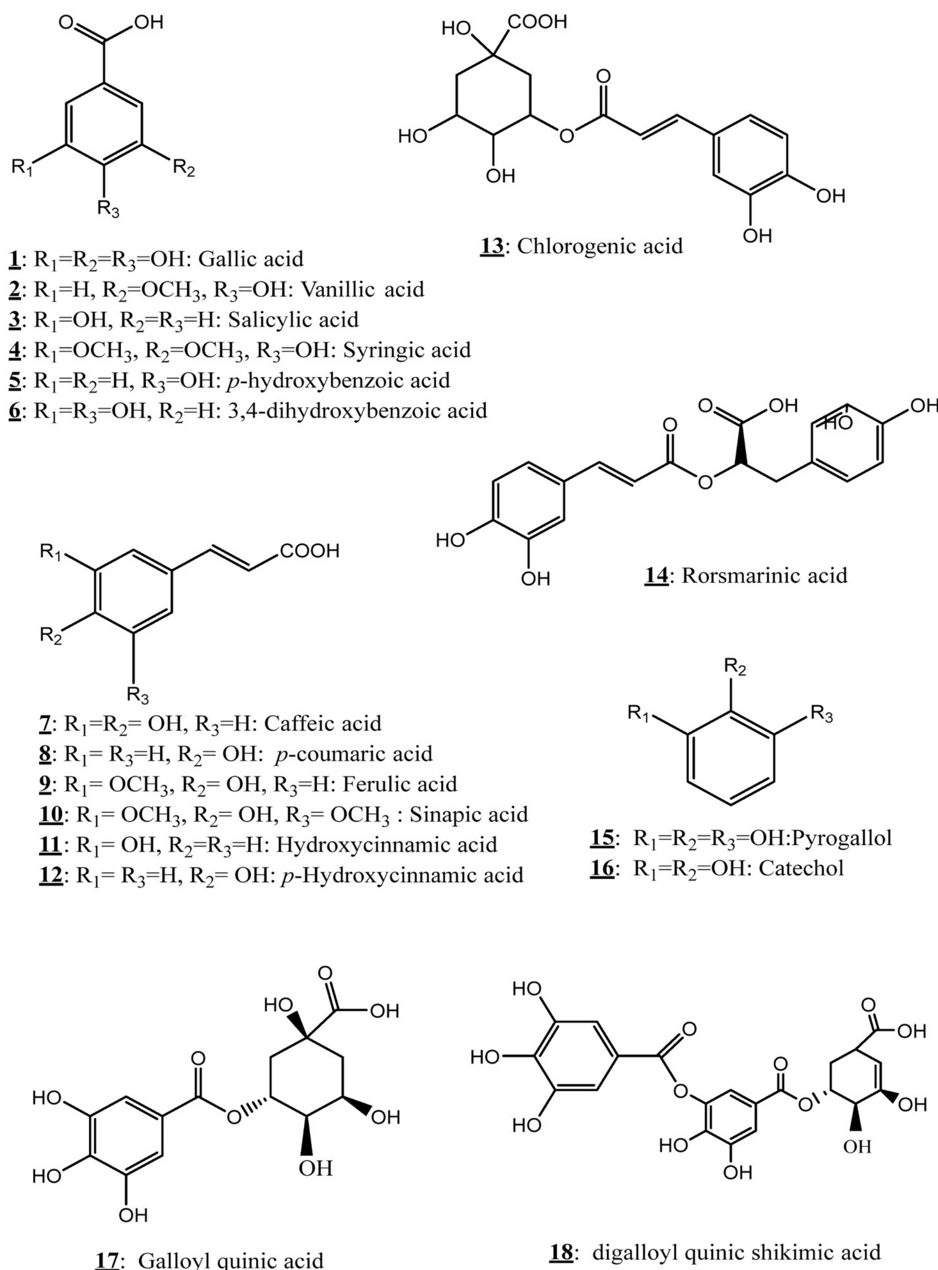

Fig. 2. Chemical structures of phenolic acids identified from antidiabetic Moroccan medicinal plants (structures designed by ChemDraw).

these two compounds for 7 weeks reduced the elevation of glucose and HbA_{1c} levels and increased the expression of Glut-2 and the insulin receptor. The latter is a transmembrane receptor activated by insulin (Breen et al., 2009) and its suppression can lead to type 2 diabetes (Xavier et al., 2012). A study by El-Shemi et al. (2018) explored the mechanisms linked to the antidiabetic activity of TQ (35 mg/kg/day) in diabetic rats for 5 weeks by assessing FBG, serum insulin, and HbA_{1c} levels, measuring insulin sensitivity (HOMA-IR and ISI) and examining pancreatic tissue. TQ corrected the diabetic phenotype and increased peripheral sensitivity to insulin, with a protective/regenerative action on pancreatic β-cells. These findings confirmed the antidiabetic potential of this monoterpene as an antidiabetic agent having a protective effect on the pancreas against inflammation and oxidative stress. These antidiabetic findings were supported *in vivo* and *in vitro* by Karandrea et al. (2017) who administered TQ to diet-induced obesity mice. Insulin sensitivity was assessed by the insulin resistant HepG2 cell line. TQ (20 mg/kg/day) reduced FBG and fasting insulin levels, and improved insulin sensitivity and glucose tolerance (ITT and OGTT). Additionally, TQ increased insulin sensitivity *in vitro* via SIRT-1 dependent pathways. As indicated in the above-mentioned research, TQ exhibited a protective action on the pancreas against toxic substances. Within the same roam (Salahshoor et al., 2017), induced pancreatic lesions by morphine in mice to confirm the protective effect of TQ. The effect was tested by histological examination and morphometric measurement of pancreas, and measurement of blood glucose and hormonal insulin. It seems that injecting increasing doses of TQ (4.5, 9 and 18 mg/kg i.p.) for 3 days improved pancreas and reduced the damage; which were mediated by an increase in the pancreas weight, number and diameter of the islets, and a significant increase in serum insulin levels with a reduction in glucose levels. Consistent with these results, a recent study evaluated the protective effect of this monoterpene on the pancreas of diabetic rats by immunohistochemistry and histological examination of the pancreas, and by measuring pancreatic islets size (Abdelrazek et al., 2018). The authors revealed an improvement in the histopathological picture, an

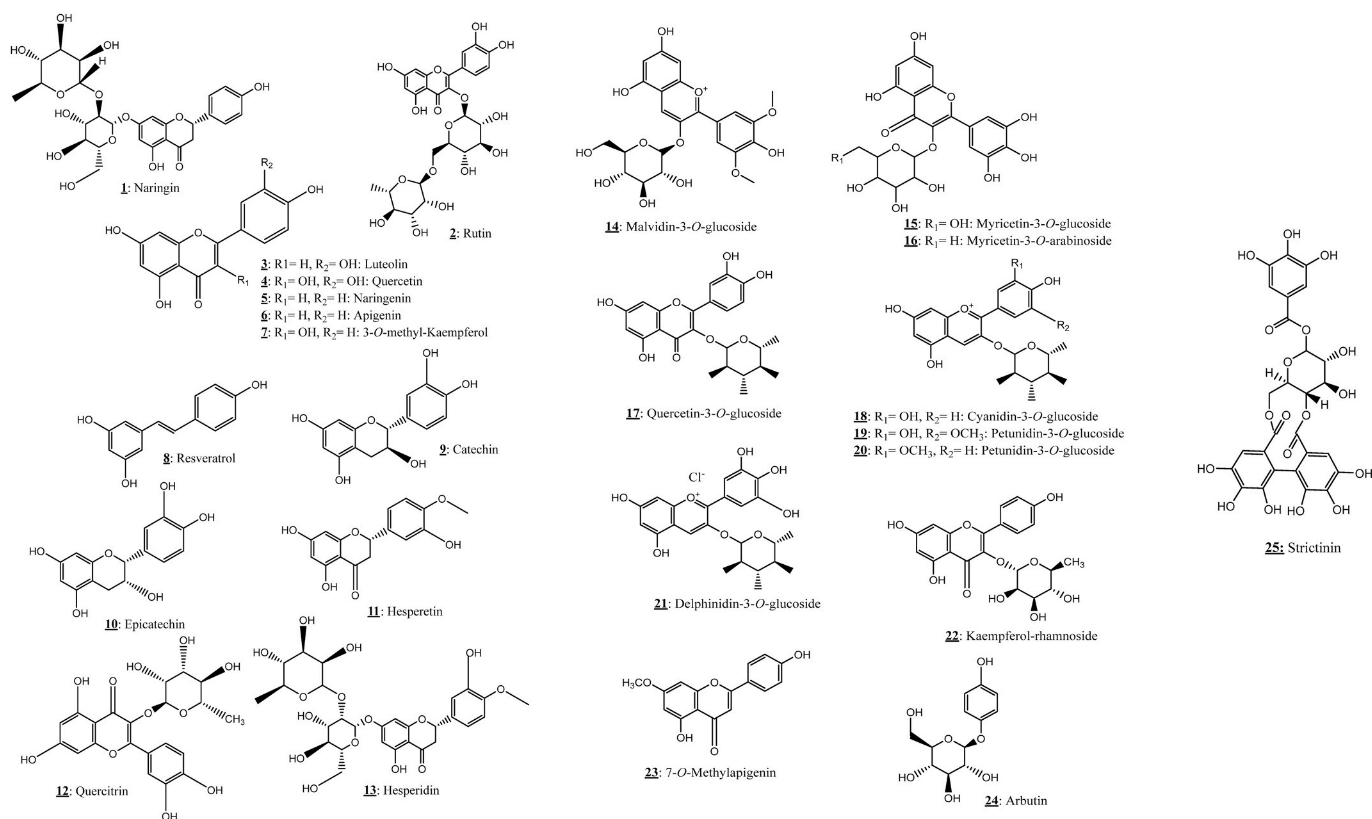

Fig. 3. Chemical structures of phenolic acids identified from antidiabetic Moroccan medicinal plants (structures designed by ChemDraw).

increase in the hepatic glycogen content and the insulin level and a decrease in hyperglycemia. Rani and colleagues recently confirmed that TQ is a potent medicinal agent in the management of type-2 diabetes (Rani et al., 2018). They observed a dose-dependent decrease in HbA_{1c} and blood glucose levels in type-2 diabetic rats treated with 20, 40 and 80 mg/kg b.w. of TQ.

8.1.2. Carvacrol

Since 2013, several reports evaluated the anti-diabetic properties of carvacrol. Woon et al. (2013) evaluated insulin resistance *via* a specific indicator (HOMA-IR index) in HFD-induced diabetic C57BL/6J mice. This monoterpene phenol reduced the blood glucose and insulin levels, lowered (HOMA-IR) index, decreased the expression of the mRNA of gluconeogenic genes, PEPCK and G6Pase. In 2014, the same animal model was used by Ezhumalai et al. (2014) and the authors evaluated several with biochemical markers and assesses the histopathological changes of the pancreas. They found that the combination of this molecule with rosiglitazone (recommended in the treatment of complications of type 2 diabetes) reduced plasma glucose, insulin and HbA_{1c}, decreased in G6Pase and FBPase activities. It also promoted the activities of glucokinase and glucose-6-phosphate dehydrogenase in the liver and protected pancreatic islets. Two studies that have been conducted in 2015 (Bakır et al., 2016; Kılıç et al., 2016) showed that this compound causes AP and hepatic complications revealed by the perturbation of pancreatic enzymes, in particular amylase and lipase. The authors found that the studied molecule reduced the levels of the tested enzymes and attenuated the glycogen content of hepatocytes. The effects observed in this work were attributed to carvacrol protective action of pancreatic islets and to an increase in the endogenous antioxidant defense mechanisms. Recently, Stojanović et al. (2018) found an increase in the weight of pancreatic tissue, an improvement in α-amylase and lipase activity in response to carvacrol treatment. However, it altered pancreatic tissue in high doses, but at lower doses it prevented L-arginine-induced pancreatic damage. Finally, the determination of glycemia in STZ-induced diabetic mice, revealed that, unlike the previous results, the oral administration of this compound did not change blood glycemia levels (Vujicic et al., 2018).

Several researchers evaluated the antidiabetic effect of carvacrol *in vitro* through examining its effect on digestive enzymes. This monoterpene inhibited the activity of α-amylase ($IC_{50} = 152.3 \pm 1.21$ μg/mL), α-glucosidase ($IC_{50} = 94.02 \pm 0.78$ μg/mL) (Govindaraju and Arulselvi, 2018), and β-galactosidase in combination with cinnamaldehyde and thymol (Wang et al., 2017c). Stojanović and coworkers (Stojanović et al., 2018, 2019) induced pancreatic damage by L-arginine in rats and measured serum α-amylase and lipase activities as well as evaluated histological changes of pancreatic tissues. Stojanović et al. (2018) noted an increase in serum α-amylase activity, followed by inflammatory cell infiltration and the prevention of oxidative damage by attenuating cellular oxidative mechanisms.

8.1.3. Caryophyllene

Many studies investigated the anti-diabetic properties of caryophyllene. Basha and Sankaranarayanan, (2014) administered this natural sesquiterpene orally to diabetic rats and determining certain parameters such as oral glucose tolerance, gluconeogenic enzyme activities, glycogen content, glycogen synthase and glycogen phosphorylase activities. They showed that this compound stimulated the release of insulin and promoted glucose homeostasis by regulating the activities of carbohydrate metabolic enzymes. In the same year (Suijun et al., 2014), showed that *trans*-caryophyllene regulated glucose-stimulated insulin secretion (GSIS) in pancreatic β-cells in a dose-dependent manner and this effect depended on the activation of the cannabinoid type 2 receptor (CB2R). In 2016, Basha and Sankaranarayanan, (2016) also treated diabetic animals with β-caryophyllene (BCP) by protecting pancreatic β-cells and reducing the concentration of blood glucose and increasing that of insulin plasma. The effect was mediated by the

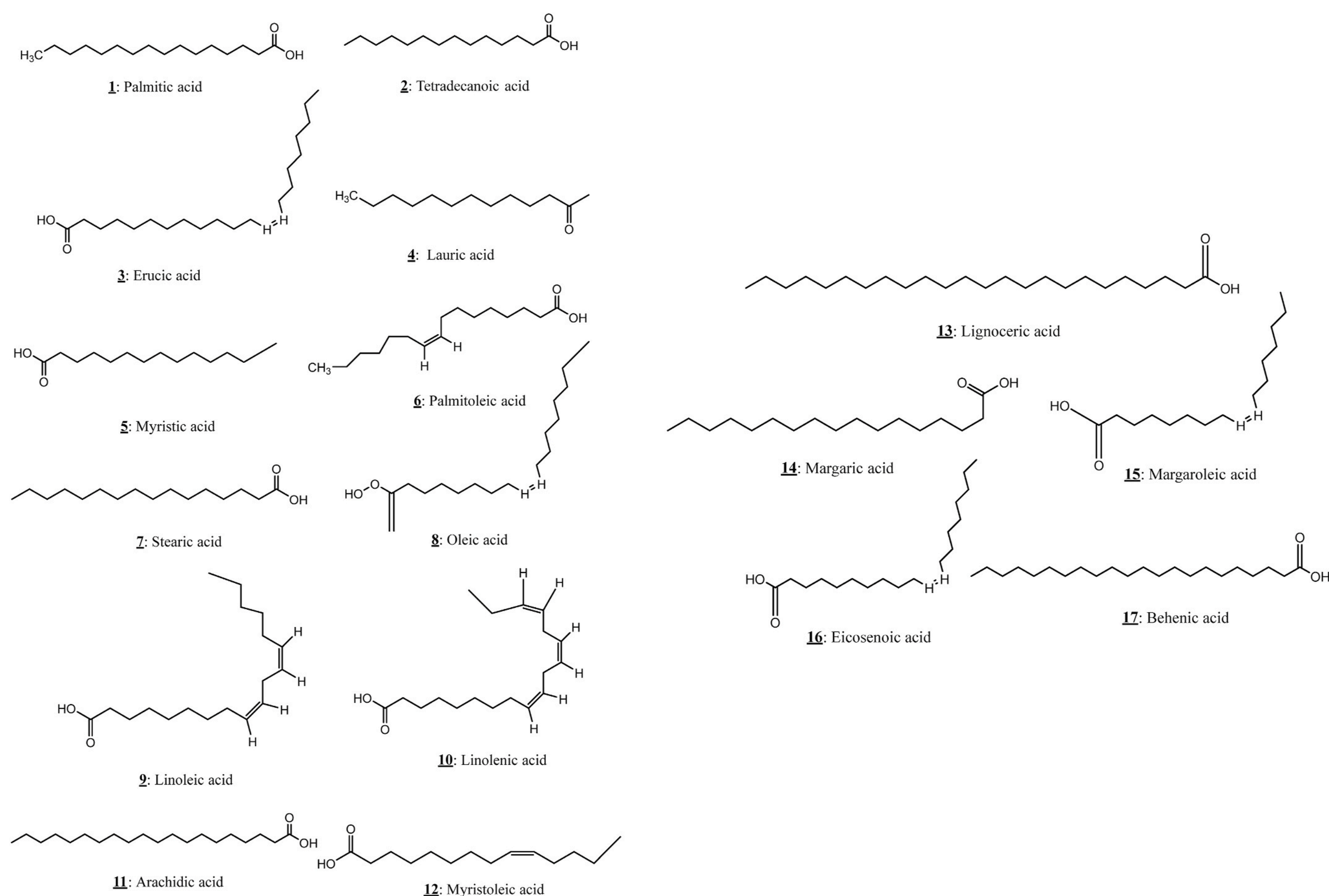

Fig. 4. Chemical structures of fatty acids identified from antidiabetic Moroccan medicinal plants (structures designed by ChemDraw).

decrease in the pro-inflammatory cytokines such as TNF-α and IL-6.

AMP-activated protein kinase (AMPK) is among the therapeutic targets for diabetes, whose activation causes insulin sensitization effects (Coughlan et al., 2014). BCP induces AMPK phosphorylation, which is attributed to the activation of CB2R in human HepG2 hepatocytes (Kamikubo et al., 2016). The combinatorial therapy of this monoterpene was tested by (Kaur et al., 2018). They evaluated the *in vitro* anti-diabetic activity (*α*-glucosidase inhibition assay) of BCP alone and in combination with L-arginine. This combination revealed a greater synergistic effect than the individual agent by inhibiting the activity of *α*-glucosidase (53.28%). No histological abnormalities of the pancreatic tissue were noted. Other meroterpene-like compounds derived from BCP demonstrated potent inhibitory activity against *α*-glucosidase in a non-competitive manner (Ma et al., 2018). Aguilar-Ávila et al. (2019) studied the effect of BCP on mice induced DM using OGTT and they assessed the levels of insulin and pro-inflammatory cytokines. The chronic oral administration of BCP (10 mg/kg/60 μL) reduced hyperglycemia, TNF-*α* and IL-6. In the same year, a study on *trans*-*β*-caryophyllene measured glucose uptake *in vitro* with the GLUT4 translocation analysis (Geddo et al., 2019). The results showed an improvement in glucose absorption in C2C12 myotubes and in glucose transporter type 4 (GLUT4).

8.1.4. Limonene

Several studies focused on the evaluation of the anti-diabetic properties of this monocyclic monoterpene. Murali and Saravanan, (2012) administered increasing doses (50, 100 and 200 mg/kg b.w.) of limonene daily for 45 days in STZ-induced diabetic rats. The results showed an increase in liver glycogen with a decrease in plasma glucose and HbA1c levels along with a suppression in the activities of gluconeogenic enzymes (G6Pase and FBPase). These results were consistent with those found by Victor Antony Santiago et al. (2012), who administered 2% D-limonene orally to rats fed a high-fat diet with L-NG-Nitro Arginine Methyl Ester (L-NAME). The authors evaluated the insulin resistance and examined pancreatic tissues. There was an improvement in insulin resistance and a restoration of pancreatic altered features.The following year, Jing et al. (2013) measured the glucose in blood samples taken from obese mice given an intraperitoneal injection of glucose (1 g/kg), and found that *D*-limonene reduced the FBG level and glucose tolerance along with the activation of PPAR-α signaling. The hypoglycemic effect of D-limonene was attributed to this activation. Murali et al. (2013) published another work confirming the results of the above reports showing a decrease in the glucose level (by 56.77%) and an increase in the insulin level (by 52.49%). The combinatorial therapy approach caught the attention of More and collaborators for better diabetes management (More et al., 2014). Treating diabetic rats (per oral) with a combination of limonene and linalool resulted in a drop in hyperglycemia to 126 mg/dl in 45 days. This decrease was also noted by Bacanlı et al. (2017) with an increase in insulin levels following a treatment of diabetic animals with D-limonene (50 mg/kg b.w.) for 4 weeks. Paarakh, 2018) used another experimental model to assess the anti-diabetic activity of natural limonene; by the *in-silico* docking approach with a molecular target (glutamine). Docking studies showed that limonene, isolated from the fruits of *Coriandrum sativum*, is a good inhibitor of the target protein. In 2018, Soundharrajan and coworkers tested the glucose uptake in two different cell lines, C2C12 skeletal muscle cells (Soundharrajan et al., 2018b) and 3T3-L1 preadipocytes (Soundharrajan et al., 2018a). Both studies reported an improvement in glucose absorption. The effect was attributed to the increased phosphorylation of activated protein kinase B (Akt) (Soundharrajan et al., 2018a) as well as the

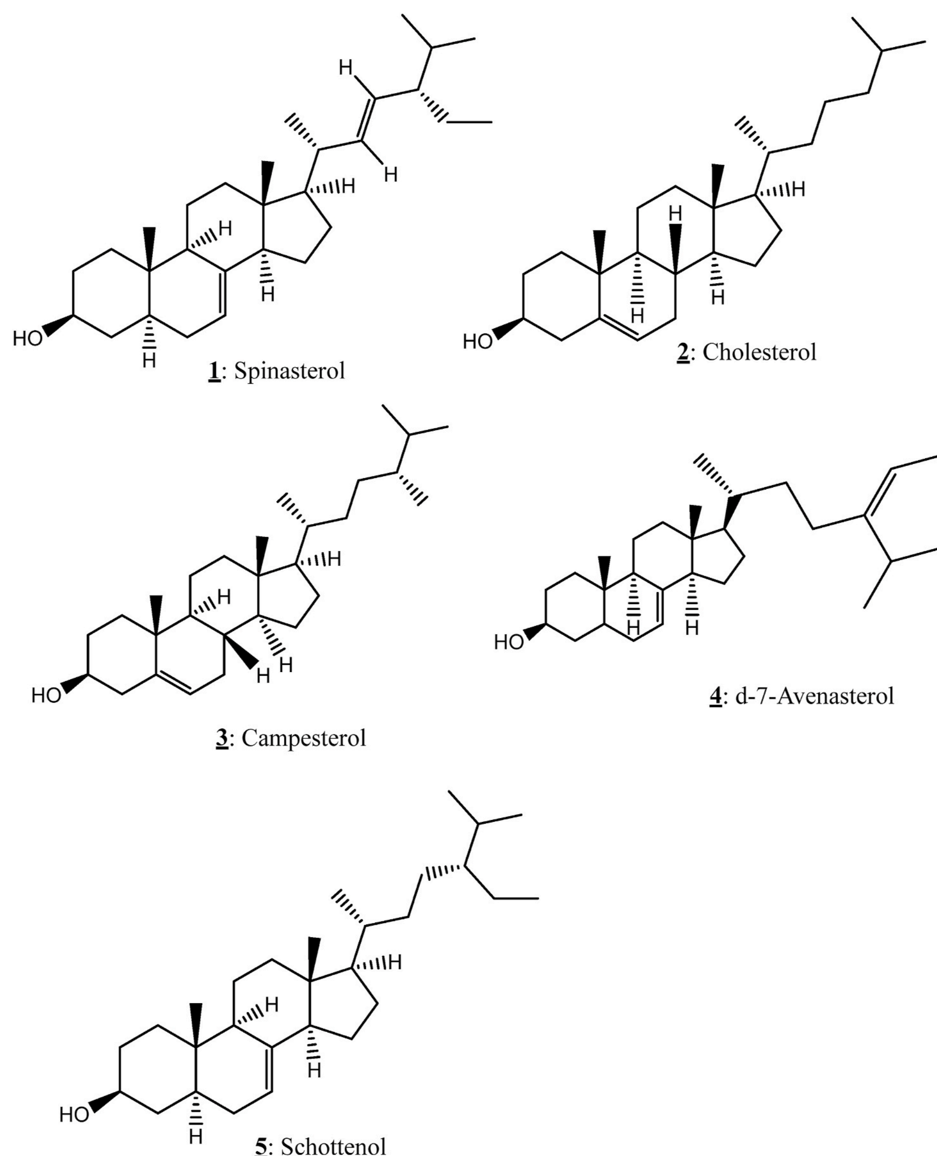

Fig. 5. Chemical structures of steroids identified from antidiabetic Moroccan medicinal plants (structures designed by ChemDraw).

promotion of p38 mitogen activated protein kinase (p38MAPK). However, a Turkish research team found no anti-diabetic effect in alloxan-induced diabetic mice, treated intraperitoneally with limonene (0.15 mL/kg b.w.) (Sever Yılmaz and Özbek, 2018).

8.1.5. Myrtenol

Several methods were implied to investigate the anti-diabetic effect of myrtenol. Immunoblot analysis showed an up-regulation of the TNF-α protein expression (Hari Babu et al., 2012), involved in the development of insulin resistance (SSwaroop et al., 2012). An *in vivo* method was applied in the same year by Lingaiah et al. (2013) to evaluate the antidiabetic effect of myrtenol by determining biochemical parameters using RT-PCR technique. This method revealed an improvement in the modified enzymes of carbohydrate metabolism, the tumor suppressor protein p53 and the mitochondrial and lysosomal enzymes. Another *in vivo* method was used by Rathinam et al. (2014) who fed myrtenol (20, 40, or 80 mg/kg b.w.) to diabetic rats for 28 days, and measured glucose and insulin levels, as well as carbohydrate metabolic enzymes and biochemical parameters. At the end of the experiment, the pancreases of the animals were removed for histological examination. This natural monoterpene resulted in a significant reduction in plasma glucose levels, an improvement in insulin secretion and glycogen content, and normalization of the parameters studied, as well as protection of pancreatic β-cells. Two years later, Ayyasamy and Leelavinothan, (2016) administered 80 mg/kg of myrtenol to diabetic animals for 28 days leading to a decrease in hyperglycemia and an improvement in pancreatic insulin levels. This experimental protocol was taken up by Pari, (2016) using the same treatment dose. However, there was an increase in plasma glucose levels, tissues and plasma glycoproteins with an increase in plasma insulin levels. From this study it can be deduced that myrtenol exhibited an anti-diabetic effect due to the increase in insulin secretion. Rathinam and Pari, (2016) also adopted the above protocol in addition to Western blot analysis and the histological assessment of pancreas. Myrtenol improved symptoms associated with diabetes such as glucose uptake, insulin and glucose levels, and up-regulation of Akt, IRS2 and GLUT2 in the liver and Akt, IRS2 and GLUT4 protein expression in the skeletal muscle, and ultimately protected pancreatic tissue. These findings suggest that this monoterpene exhibited an anti-hyperglycemic effect by enhancing GLUT2 by Akt pathway in the liver and skeletal muscle of diabetic animals. Recently, this research team observed a decrease in the levels of pro-inflammatory cytokines (TNF-α and IL-6) and NF-κB p65 following the administration of

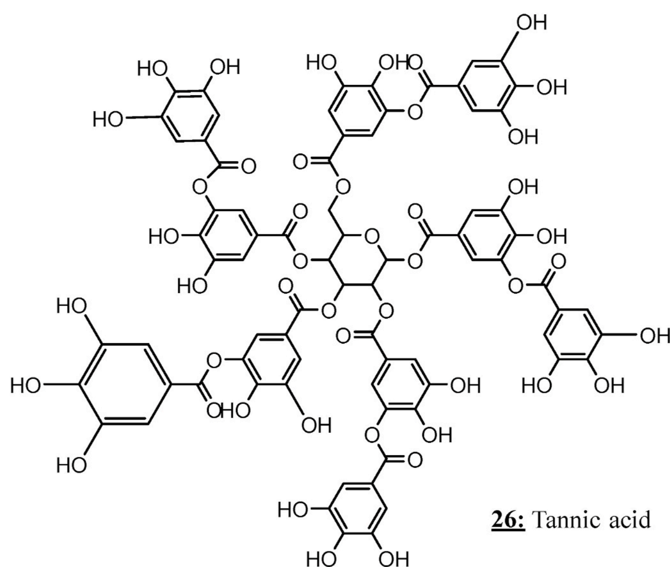

Fig. 6. Chemical structures of tannic acid identified from antidiabetic Moroccan medicinal plants (structures designed by ChemDraw).

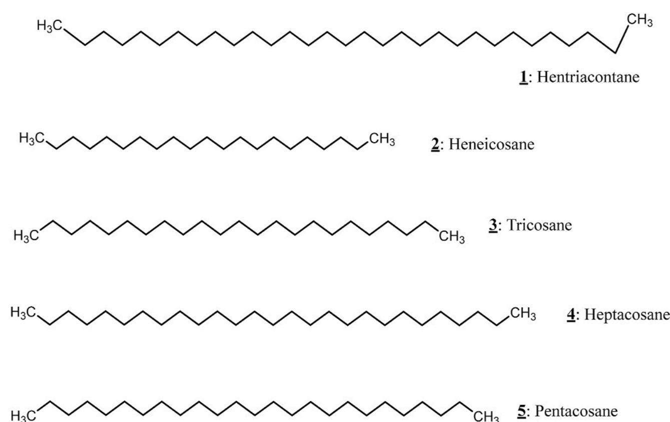

Fig. 7. Chemical structures of alkanes identified from antidiabetic Moroccan medicinal plants (structures designed by ChemDraw).

myrtenol (80 mg/kg b.w.) to diabetic rats (Rathinam et al., 2019). It can be deduced that this compound possesses a potent antioxidant and anti-inflammatory effects and thus can be used in the management of diabetes.

8.1.6. Geraniol

This monoterpene is also an unsaturated terpene alcohol, which attracted attention due to its effect in the treatment of diabetes. Several authors highlighted the anti-diabetic effect of this compound on fructose fed rats, by measuring glucose clearance (IPGTT) and evaluating FBG and insulin along with the use of other tests (HOMA-IR, QUICKI, McAuley Index, and HbA_{1c}) (Ibrahim et al., 2015). It was found that this monoterpene, alone and in combination with pioglitazone, reduced FBG, suppressed HbA_{1c} and improved insulin sensitivity. Another study subsequently was carried out on STZ-induced diabetic rats using the previous methods in addition to a histopathological examination of the pancreas, showed similar results with an improvement in the content of hepatic glycogen and a preservation of the general structure of β-cells (Babukumar et al., 2017). In another work performed using the same experimental model, geraniol significantly reduced hyperglycemia (El-Bassossy et al., 2017). Recently in 2019, an Indian research team treated experimental diabetes with the same molecule and evaluated its effect on the intestinal absorption of glucose, on renal glycogen, and on the inhibition of GLUT2 as well as glucose tolerance test (Kamble et al., 2020). They observed an inhibition in the release of hepatic glucose, an increase in the content of renal glycogen, an increase in the production of renal glucose, an improvement in the levels of HbA_{1c} and an inhibition of the overexpression of GLUT2. From these findings, we can consider geraniol as an interesting monoterpene in the management of diabetes and the prevention of its complications.

8.1.7. Linalool

The first study evaluating the hypoglycemic effect of this compound was carried out in 1998 by Afifi et al. (1998), which showed a significant hypoglycemic effect in diabetic rats induced by STZ. In another study, linalool (25 mg/kg b.w.) was administered to hyperglycemic rats for 45 days. The authors determined blood glucose (mmol/L) against time (min) and the biochemical markers (Deepa and Anuradha, 2011). The results showed a marked decrease in the area blood glucose, HbA_{1c}, fructosamine, IL-6 and TNF-α as well as a marked reduction was observed for the area under the curve of ($AUC_{glucose}$) glucose value. Insulin level was also increased. These results were in line with (More et al., 2014) who followed the same experimental protocol, with a measurement of glucose uptake *in vitro*, which was increased in a dose-dependent manner. The combination of linalool and limonene showed a decrease in blood sugar within 45 days (More et al., 2014).

8.1.8. Phytol

All studies concerning phytol evaluated its anti-diabetic effect *in vivo*. Elmazar et al. (2013) administered glucose (i.p) with and without insulin injection to diabetic insulin-resistant rats, as carried out a molecular docking study on retinoid X receptor (RXRα)/PPARγ heterodimer. The results revealed a decrease in TNF-α, an improvement in glucose homeostasis, a heterodimerization of RXRα structure with PPARγ, and an activation of nuclear receptors. In another study, a Chinese research team administered phytol to mice fed high-fat and high fructose diet by administering glucose (OGTT) and injecting insulin (ITT) (Wang et al., 2017a). This team tested the glucose uptake by 3T3-L1 preadipocytes. The *in vivo* results showed an improvement in glucose tolerance, an increase in glucose absorption (GLUT4) and in the expression of PPARγ. These data were in agreement with the *in vitro* experiments, which confirmed the glucose uptake in 3T3-L1. This effect was attributed to the activation of PI3K/Akt signaling pathway. The following year, another Chinese research team treated HFD-fed mice with phytol revealed an activation of AMP-activated protein kinase (AMPK)-α, this activation may be an interesting finding in the fight against type 2 diabetes (Zhang Ai et al., 2018; Zhang, Zhang et al., 2018).

8.1.9. Pinene

Acute pancreatitis (AP) is a painful disease that is characterized by the rapid inflammation of the pancreas and several natural products were tested aiming to treat this ailment. Several studies were carried out to assess the protective effect of alpha-pinene against acute pancreatitis. South Korean authors injected alpha-pinene intraperitoneally in mice with cerulein-induced AP (Bae et al., 2012), and evaluated the histopathology of pancreas. The results showed an attenuation of the production of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) and an inhibition of apoptosis and cytokine production (*in vitro*) in acinar pancreatic cells. In another study, AP was induced by L-arginine to test the protective effect of α-pinene (Biradar and B, 2014). The results of this work confirmed the protective effect of α-pinene, by reducing pancreatic enzymes (amylase and lipase) and pancreatic edema ordamage. Recently, Özbek and Yılmaz, (2017) injected 0.25 mL/kg i.p. of α-pinene to alloxan-induced diabetic mice and they showed a decrease in FBG levels.

8.1.10. Thymol

Saravanan and colleagues were interested in evaluating the anti-

Table 6
Terpenoids.

Compounds	Methods	Keys results	References
1,8-Cineole	Induced acute pancreatitis in mice. Histological analysis of pancreas tissues.	Reduced the histological damage, pancreatic edema and NF-κB expression. Enhanced anti-inflammatory IL-10 cytokine level.	Lima et al. (2013)
	α-Amylase inhibition assay.	Inhibition of α-amylase activity with $IC_{50} = 0.78 \pm 0.05$ mg/mL.	Paul and Bhattacharjee (2018)
Bisabolene	Protein tyrosine phosphatase 1B (PTP1B).	Inhibited PTP1B activity ($IC_{50} = 1.9$ μM). Enhanced the insulin-stimulated phosphorylation levels of Akt in Huh-7 cells.	Abdjul et al. (2016)
Borneol	STZ-induced diabetic rats. Estimation of FBG, HbA_{1c}, and liver glycogen. Estimation of plasma insulin-ELISA. Homeostatic model assessment for β-cell function index (HOMA-% B). Histology of pancreas. Total count of β-CELL number.	Decreased FBG concentration and HbA_{1c}. Increased plasma insulin, HOMA-β-cell functioning index, and glycogen. Protective effect on pancreatic β-cells.	Madhuri and Naik (2017)
Camphene	HFD-fed mice. Measurement of blood glucose and insulin levels.	Reduced FBG level and blood insulin level. Improved insulin resistance in the liver tissue. Reduced the expression of cytokines (TNF-α or IL-6) activating inflammation.	Park (2012)
	HFD-Fed mice. Measurement of blood glucose and insulin levels.	Reduced FBG level and blood insulin level. Improved insulin resistance in the liver tissue. Reduced the expression of cytokines (TNF-αor IL-6) activating inflammation.	Park (2013)
	HFD-Induced insulin resistance in mice. IPGTT. Western blot analysis.	Lowered blood glucose levels. Lowered area under the glucose concentration–time curve. Attenuated the elevation in plasma glucose (−30%) and insulin levels (−37%). Increased AMPK activation. Increased insulin-signaling molecules activation and stimulated GLUT2 translocation to the plasma membrane in the liver.	Kim et al. (2014)
Camphor	DPP-4 Inhibitory activity. Male albino mice (CD-1 line). OGTT.	Potent DPP-4 inhibitory activity with IC_{50} values in the range of 1.27–15.78 μM. Reduced blood glucose levels.	Kuranov et al. (2018)
Carvacrol	HFD-Induced diabetic mice. (HOMA-IR) index.	Reduced blood glucose and insulin levels. Lowered (HOMA-IR) index. Decreased mRNA expression of gluconeogenic genes, PEPCK and G6Pase.	Woon et al. (2013)
	HFD-induced type 2 diabetic C57BL/6J mice. Biochemical estimations. Histology of pancreas.	Combination of carvacrol and rosiglitazone: Decreased plasma glucose, insulin, and HbA_{1c}. Decreased G6Pase and FBPase activities. Increased glucokinase and glucose-6-phosphate dehydrogenase activities in the liver. Protective effect on pancreatic islets.	Ezhumalai et al. (2014)
	Cerulein-induced acute pancreatitis. Amylase and lipase measurement.	Decreased amylase and lipase levels. Increased glycogen content of hepatocytes.	Bakır et al. (2016)
	Cerulein-induced acute pancreatitis. Amylase and lipase measurement for pancreatic function assessment. Histology of pancreas.	Reduced amylase and lipase levels. Protective effect on pancreatic islets. Increased endogenous antioxidant defense mechanisms in AP-induced pancreatic damage.	Kılıç et al. (2016)
	α-Amylase and α-glucosidase inhibition assays.	Inhibited α-amylase activity with $IC_{50} = 152.3 \pm 1.21$ μg/mL. Inhibited α-glucosidase activity with $IC_{50} = 94.02 \pm 0.78$ μg/mL.	Govindaraju and Arulselvi (2018)
	β-Galactosidase inhibition assay.	The combination of cinnamaldehyde, carvacrol and thymol exposure displayed synergistic effects on the inhibition of β-galactosidase.	Wang et al. (2017c)
	L-Arginine-induced pancreas damage in rats. Measurement of serum α-amylase and lipase activities. Histological analysis of pancreas tissues.	Increased serum α-amylase activit, followed by inflammatory cell infiltration. Prevented the increase in serum α-amylase and lipase activities. Prevented oxidative tissue damage by mitigating cell oxidative mechanisms.	Stojanović et al. (2018)
	STZ-Induced diabetic mice. Determination of blood glucose level. L-Arginine-induced pancreatitis. Histological analysis of pancreas tissues. Measurement of serum α-amylase and lipase activities.	Oral application did not alter the blood glycemia levels throughout the examination period. Increased pancreatic tissue weight. Ameliorated α-amylase and lipase activity. In high doses, carvacrol damagedpancreatic tissue, but the lower one moderately preventedL-arginine-induced pancreatic damage.	(Vujicic et al., n.d.; Vujicic et al., 2018) Stojanović et al. (2019)
Carvone	STZ-Induced diabetic rats. Estimation of blood glucose and plasma insulin.	Decreased plasma glucose levels. Increased plasma insulin level.	Muruganathan et al. (2013)
	STZ-induced diabetic rats. Biochemical analysis. Histopathological study of pancreas.	Decreased plasma glucose levels, HbA_{1c}. Improved insulin level. Restored the activities of carbohydrate metabolic enzymes. Reduced the STZ-induced damage to β-cells of the pancreas.	Muruganathan and Srinivasan (2016)
	HFD-Fed C57BL/6 mice. Glucose tolerance test and insulin tolerance test. Determination of HOMA-IR.	Restrained the hyperglycemia and insulin resistance.	Alsanea and Liu (2017)
Caryophyllene	STZ-Induced diabetic rats. Assessment of oral glucose tolerance.	Decreased glucose and HbA_{1c}. Increased plasma insulin levels.	

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Table 6 (*continued*)

Compounds	Methods	Keys results	References
	The activities of gluconeogenic enzymes. Determination of glycogen content and assay of glycogen synthase and glycogen phosphorylase activities. Immunohistochemical localization.	Ameliorated the altered activities of carbohydrate metabolic enzymes. Insulinotropic effect supported by immunohistochemical studies.	Basha and Sankaranarayanan (2014)
	Cell culture (MIN6 β-cells). Glucose-stimulated insulin secretion (GSIS) assay. Determination of insulin secretion.	Promoted GSIS in a dose-dependent manner. The effect on GSIS are dependent on activation of type 2 cannabinoid receptor (CB2R).	Suijun et al. (2014)
	STZ-induced diabetic rats. Measurement of plasma glucose and insulin. Assessment of proinflammatory cytokines in plasma and pancreatic tissue homogenate. Histopathological study of pancreas.	Decreased blood glucose levels. Increased plasma insulin levels. Decreased proinflammatory cytokines TNF-α and IL-6. Protective effect on pancreatic β-cells.	Basha and Sankaranarayanan (2016)
	Cell culture (human HepG2 hepatocytes).	Phosphorylation of AMPK. The activation of AMPK could be mediated by the CB2R-dependent Ca^{2+} signaling pathway.	Kamikubo et al. (2016)
	Cell culture (HEK293 cells). α-Glucosidase inhibition assay. Histology of pancreas.	Inhibited α-glucosidase activity. Combination of caryophyllene and L-arginine was the most potent combination since it was able to inhibit 53.28% enzyme activity at 20 µg mL^{-1}. No abnormalities in the histopathological results of pancreas.	Kaur et al. (2018)
	α-Glucosidase inhibition assay. Kinetic study.	Inhibited α-glucosidase activity. Compound **12** was the best inhibitor with $IC_{50} = 2.73 \pm 0.13$ µM. The inhibitors belong to a non-competitive type.	Ma et al. (2018)
	STZ-Induced diabetic mice. OGTT and insulin evaluation. Assessment of proinflammatory cytokines.	Reduced glycemia in experimental diabetic mice. Attenuated TNF-α and IL-6.	Aguilar-Ávila et al. (2019)
	Cell culture (C2C12 Myotubes). Glucose uptake measurements. GLUT4 translocation analysis.	Improved glucose uptake activity and GLUT4 migration.	Geddo et al. (2019)
Geraniol	Fructose fed rats. IPGTT. Assessment of FBG and Insulin, HOMA-IR, QUICKI, McAuley Index, and HbA_{1c}.	Geraniol, alone and in combination with pioglitazone: Reduced FBG and glycemic excursion in the IPGTT. Suppressed HbA_{1c}. Improved insulin sensitivity.	Ibrahim et al. (2015)
	STZ-induced diabetic rats. Assessment of oral glucose tolerance. Biochemical assays. Estimation of carbohydrate metabolic enzymes. Histopathological study of pancreas.	Improved insulin levels. Decreased plasma glucose and HbA_{1C}. Ameliorated the altered activities of carbohydrate metabolic enzymes. Improved hepatic glycogen content. Preserved normal histological appearance of pancreatic β-cells.	Babukumar et al. (2017)
	STZ-Induced diabetic rats. Measurement of blood glucose level.	Alleviated the increase in hyperglycemia.	El-Bassossy et al. (2017)
	STZ-Induced diabetic rats. Intestinal glucose absorption studies. Kidney glycogen studies. Effect of GLUT2 inhibition on liver. OGTT. Renal glucose output.	Intestinal glucose absorption demonstrated 60.28% inhibition of transport at 648.34 µm. Inhibited glucose release from liver. Increased kidney glycogen content. Increased renal glucose output. Improved HbA_{1c} levels. Inhibited the overexpression of GLUT2.	Kamble et al. (2020)
Limonene	STZ-induced diabetic rats. Biochemical estimations.	Decreased plasma glucose and HbA_{1c}levels. Decreased gluconeogenic enzymes activities such as, G6Pase and FBPase. Increased liver glycogen.	Murali and Saravanan (2012)
	HFD-fed rats treated with L-NAME. Biochemical assays. HOMA-IR. Histopathological study of pancreas.	Decreased FBG and plasma insulin. Ameliorated insulin resistance. Restored pathological alteration of pancreas.	Victor Antony Santiago et al. (2012)
	HFD-Fed C57BL/6 mice. Cell culture (3T3-L1 cells). IPGTT.	In the preventive treatment: Lowered FBG levels. In the therapeutic treatment: Reduced FBG levels and glucose tolerance. Activated PPAR-α signaling.	Jing et al. (2013)
	STZ-Induced diabetic rats. Estimation of plasma glucose and insulin.	Decreased glucose level by 56.77%. Increased insulin level by 52.49%.	Murali et al. (2013)
	STZ-Induced diabetic rats. OGTT. Glucose uptake. Measurement of fructosamine.	No reduction of blood glucose up to 2 h. The combinatorial therapy (limonene and linalool) could lower blood glucose to 126 mg⁄dLin 45 days.	More et al. (2014)
	STZ-Induced diabetic rats. Assessment of blood glucose levels. Determination of plasma insulin.	Lowered blood glucose levels. Increased insulin levels.	Bacanlı et al. (2017)
	Hypoglycemic activity through an *insilico* docking approach. Molecular target such as glutamine: Fructose-6-phosphate amidotransferase was performed.	The docking studies of the ligand limonene with target protein showed that this is a good inhibitor, which docks well related to diabetes mellitus with -1.57768 kJ mol^{-1} Van der Waal energy and -17.6701 kJ mol^{-1} as docking energy.	Paarakh (2018)
	Cell culture (C2C12 skeletal muscle cells). 2-Deoxy-D-glucose uptake	Enhanced 2-Deoxy-D-glucose uptake. Stimulated the activation of p38 mitogen activated protein kinase (p38MAPK), protein kinase B (Akt) by increasing phosphorylation.	Soundharrajan et al. (2018b)
	Cell culture (3T3-L1 preadipocytes). Glucose uptake assay.	Increased activation of Akt by increasing its phosphorylation. Enhanced glucose uptake in differentiated adipocytes.	Soundharrajan et al. (2018a)

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Table 6 (*continued*)

Compounds	Methods	Keys results	References
	Alloxan-induced diabetic mice. Determination of blood glucose levels.	No hypoglycemic effect in alloxan-induced diabetic mice.	Sever Yılmaz and Özbek (2018)
Linalool	STZ-Induced diabetic rats.	Hypoglycemic effect.	Afifi et al. (1998)
	STZ-Induced diabetic rats. OGTT. Biochemical assays. Glucose utilization assay.	Reduced the $AUC_{glucose}$ values. Decreased blood glucose, HbA_{1c}, fructosamine, TNF-α and IL-6. Increase insulin level.	Deepa and Anuradha (2011)
	STZ-Induced diabetic rats. OGTT. *In vitro* glucose uptake. Measurement of fructosamine.	Decreased blood glucose levels. Increased glucose uptake in a dose-dependent manner. Enhanced glucose uptake with insulin to 2.3 mg/g tissue in 30 min. Lowered blood glucose to 126 mg/dl in 45 days by the combinatorial treatment (limonene and linalool). Decreased HbA_{1c} levels.	More et al. (2014)
Menthol	STZ–Nicotinamide-induced diabetic rats. OGTT. Biochemical analysis. Histological observations in pancreas.	Reduced blood glucose and HbA_{1c}levels. Increased plasma insulin and liver glycogen levels. Ameliorated the pathological abnormalities in pancreatic islets. Suppressed the pancreatic β-cells apoptosis.	Muruganathan et al. (2017)
Myrtenol	Immunoblot analysis. Wistar albino male rats. Biochemical assays. RT-PCR.	Up-regulated the TNF-α protein expression by immunoblot. Ameliorated the altered enzymes of carbohydrate metabolism, lysosomal and mitochondrial enzymes, and the tumor suppressor protein p53.	Hari Babu et al. (2012) Lingaiah et al. (2013)
	STZ-Induced diabetic rats. Assessment of glucose, insulin, OGTT, and HbA_{1c} levels. Assessment of hexokinase activity in liver. Assessment of glucose-6-phosphate dehydrogenase activity in liver. Assessment of G6Pase activity in liver and kidney. Assessment of FBPase in liver and kidney. Assessment of glycogen content in liver and muscle. Histological evaluation of pancreas.	Reduced plasma glucose and HbA_{1c}levels. Increased insulin levels. Improved carbohydrate metabolism such as hexokinase, G6Pase, FBPase, and glucose-6-phosphate dehydrogenase. Improved hepatic and muscle glycogen content. Protective effect on pancreatic islet cells.	Rathinam et al. (2014)
	STZ-Induced diabetic rats. Plasma glucose and pancreatic insulin assay.	Decreased hyperglycemia. Improved pancreatic insulin levels.	Ayyasamy and Leelavinothan (2016)
	STZ-Induced diabetic rats. Plasma glucose and insulin assay.	Increased plasma glucose levels, plasma and tissues glycoproteins such as hexose, hexosamine, fucose and sialic acid. Increased plasma insulin levels.	Pari (2016)
	STZ-induced diabetic rats. Assessment of glucose and insulin. Western blot analysis. Histological evaluation of pancreas.	Decreased plasma glucose levels. Improved plasma insulin levels. Up regulated the IRS2, Akt and GLUT2 in liver and IRS2, Akt and GLUT4 protein expression in skeletal muscle. Enhanced glucose uptake in liver and skeletal muscle. Protected pancreatic islets.	Rathinam and Pari (2016)
	STZ-Induced diabetic rats. Assessment of proinflammatory cytokines.	Decreased the levels of proinflammatory cytokines, and NF-κB p65.	Rathinam et al. (2019)
p-cymene	Resolution–alternating least squares (MCR–ALS) analysis based on combined spectroscopic and electrochemical methods.	Protection effect of *p*-cymene and thymoquinone mixture on the glycation of bovine serum albumin.	Benvidi et al. (2018)
Phytol	Diabetic insulin-resistant rats. Intra-peritoneal glucose (GTT) and insulin glucose tolerance tests (IGTT). Molecular docking study.	Significantly improved glucose homeostasis and lowered TNF-α. Activation of nuclear receptors and heterodimerization of retinoid X receptor with PPARγ.	Elmazar et al. (2013)
	Mice fed high-fat and high fructose diet. Cell culture (3T3-L1 preadipocytes). OGTT and ITT. Measurement of glucose uptake.	Improved glucose tolerance. Increased the expression of PPARγ and glucose uptake (GLUT4). Activated PI3K/Akt signaling pathway.	(J. Wang et al., 2017)
	HFD-Fed mice.	Activated AMPKα signaling pathway.	Zhang, Ai et al., (2018)
Pinene	Cerulein-induced acute pancreatitis. Histological analysis of pancreas.	Reduced the production of TNF-α, IL-1β, and IL-6. Inhibited cell death and cytokine production in isolated pancreatic acinar cells (*in vitro*).	Bae et al. (2012)
	L-Arginine induced acute pancreatitis model. Assessment of proinflammatory cytokines. Histopathological evaluation pancreas.	Decreased the serum amylase, lipase and pancreatic edema. Attenuated the pancreatic injury.	Biradar and B, (2014)
	Alloxan-induced diabetic mice. Measurement of FBG levels.	Decreased FBG levels.	
Terpinolene	α-Glucosidase inhibitory activity. α-Amylase inhibitory activity. Cell culture (3T3-L1 pre-adipocytes). Total glucose uptake assay.	Exerted relatively weaker α-glucosidase inhibitory effect. No effect on glucose uptake in 3T3-L1 adipocytes.	Tan et al. (2016)
Thujone	STZ-Induced diabetic rats. Blood glucose, insulin, and liver glycogen.	Decreased plasma glucose level. Increased glycogen content. Increased the phosphorylation of Akt and GSK-3β.	Alkhateeb (2015)
	STZ-Induced diabetic rats. Measurement of blood glucose levels. Measurement of blood insulin levels. OGTT.	Improved plasma glucose level and glucose tolerance. No changes in the blood insulin levels. Restored the impaired GLUT4 translocation and fully ameliorated AMPK phosphorylation.	Alkhateeb et al. (2018)
Thymol		Decreased plasma glucose, insulin, insulin resistance, and HbA_{1c}.	

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Table 6 (*continued*)

Compounds	Methods	Keys results	References
	HFD-Induced diabetic C57BL/6J mice. OGTT. Measurement of plasma glucose, plasma insulin, and HbA_{1c}. HOMA-IR Index.		Saravanan and Pari (2015)
	HFD-Induced diabetic C57BL/6J mice. Estimation of blood glucose levels. Estimation of plasma insulin.	Lowered blood glucose and plasma insulin levels.	Saravanan and Pari (2016)
	STZ-Induced diabetic rats. Estimation of blood glucose levels. Estimation of plasma insulin.	Reduced blood glucose levels. Increased insulin levels.	Oskouei et al. (2019)
	STZ-Induced diabetic rats. RT-PCR.	Increased the expression of Mafa gene. Increased the expression of Pdx1 gene.	Saadat Brujeni (2019)
Thymoquinone	Normal albino rats. Measurement of blood glucose levels.	Reduced blood glucose levels.	Hawsawi et al. (2001)
	STZ-Induced diabetic hamsters. Measurement of blood glucose levels and HbA_{1C}. Estimation of liver glucose production.	Decreased blood glucose level. Decreased HbA_{1c} level. Decreased glucose production with gluconeogenic precursors (alanine, glycerol and lactate).	Farah et al. (2005)
	Cell culture (INS-1 cells). Insulin ELISA.	Increased glucose stimulated insulin secretion.	Chandra et al. (2009)
	STZ–Nicotinamide induced diabetic rats. Estimation of plasma glucose levels, plasma insulin, and HbA_{1C}. Assessment of hepatic hexokinase, Glucose 6-phosphate dehydrogenase, G6Pase, and FBPase. OGTT.	Decreased plasma glucose. Increased insulin levels. Decreased blood glucose levels. Increased activities of hexokinase, glucose 6- phosphate dehydrogenase. Decreased activities of gluconeogenic enzymes G6Pase and FBPase. Decreased HbA_{1C} levels.	Pari and Sankaranarayanan (2009)
	STZ-Induced diabetic rats. Biochemical investigation. Histological analysis of pancreas tissues.	Lowered serum glucose levels. Restored serum insulin levels. Preserved pancreatic β-cell integrity.	Abdelmeguid et al. (2010)
	STZ-Induced diabetic rats. Determination of plasma glucose concentrations. Determination of plasma immunoreactive insulin concentrations.	Decreased plasma glucose. Increased plasma insulin concentrations.	Farah et al. (2010)
	STZ-Induced cellular damage in pancreatic islets of rats.	Ameliorated the toxic effects of STZ on pancreatic β-cells.	Abdelmeguid et al. (2011)
	STZ-Induced diabetic rats. Estimation of blood glucose and plasma insulin. Estimation of pancreatic insulin levels.	Improved glycemic status. Increased plasma insulin levels. Increased pancreatic insulin levels. Protective action on pancreatic β-cell function.	Sankaranarayanan and Pari (2011)
	STZ-Induced diabetic rats. RT-PCR mRNA Expression of ICAM-1 and COX-2 in pancreatic tissue. The activity of the antioxidant enzyme superoxide dismutase (SOD) in pancreatic tissue.	Prohibited the increase in COX-2 mRNA expression. Restored SOD levels to normal.	Al Wafai (2013)
	Rats fed a fatty diet. Measurement of blood glucose levels. Measurement of plasma insulin.	Decreased plasma insulin. Increased plasma glucose level.	BacakGüllü & Avci, 2013
	STZ-Induced diabetic rats. Blood glucose assessment. ELISA Technique for insulin assay in serum.	Decreased blood glucose concentration. Lowered blood insulin concentration.	Al-Sa'aidi et al. (2014)
	STZ-Induced diabetic rats. Determination of HbA_{1c}. Measurement of FBG levels. Measurement of serum insulin concentrations (ELISA assay). Histological analysis of pancreas tissues.	Decreased FBG levels. Increased serum insulin level. Decreased HbA_{1c} level. Protective action on pancreatic islets of Langerhans.	Ashour (2015)
	STZ-Induced diabetic rats. Determination of plasma glucose and insulin levels. ELISA.	Decreased TNF-α and IL6. Reduced plasma glucose levels. Increased insulin level. Improved antioxidant status and reduced lipid peroxidation in pancreas.	Bashandy et al. (2015)
	STZ-Induced diabetic rats. Determination of blood glucose level. Histological analysis of pancreas tissues.	Decreased blood glucose levels. Preserved pancreatic β-cells.	Sangi et al. (2015)
	STZ-Induced diabetic rats. Measurement of glucose and insulin levels.	Decreased serum glucose level. Increased serum insulin level.	Manal Abduallah (2017)
	STZ-induced diabetic rats. Assessment of glucose and HbA_{1C}. Immunohistochemistry assay.	Thymoquinone alone and/or in combination with metformin: Reduced and normalized the elevation of glucose level. Reduced the HbA_{1C} level. Increased Glut-2 expression. Increased insulin receptor.	Aarag et al. (2017)
	STZ-Induced diabetic rats. Assessment of FPG and HbA_{1c} levels. Measurement of serum insulin levels. HOMA-IR and insulin sensitivity index (ISI).	Decreased FBG and HbA_{1c} levels. Increased serum insulin levels. Enhanced glucose uptake by different body cells. Increased peripheral insulin sensitivity.	El-Shemi et al. (2018)

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Table 6 (*continued*)

Compounds	Methods	Keys results	References
	Histopathology of pancreas. Immunostaining of pancreatic tissues for insulin.	Increased value of ISI. Reduced HOMA-IR. Protective/regenerative action on pancreatic islets. Regenerative effect on the mass of functionally active insulin synthetizing β-cells.	
	Diet-induced obesity mice. OGTT and ITT. Cell culture (HepG2 cells).	Reduced the diabetic phenotype by decreasing FBG and fasting insulin levels. Increased glucose tolerance and insulin sensitivity. Increased *p*-Akt in high-glucose treated cells. Activation of SIRT-1-dependent pathways.	Karandrea et al. (2017)
	Pancreas injuries induced by morphine in mice. Histological examination of pancreas. Morphometric measurement of pancreas. Hormone insulin and blood glucose measurement.	Boosted pancreas weight, diameter and number of the islets. Increased serum levels of insulin. Reduced glucose levels in all doses.	Salahshoor et al. (2017)
	STZ-Induced diabetic rats. Measurement of blood glucose value and insulin level. Histological examination of pancreas. Immunohistochemistry of pancreas. Measurement of pancreatic islet size.	Reduced FBG levels. Increased insulin level. Improved histopathological picture. Improved hepatic glycogen contents.	Abdelrazek et al. (2018)
	STZ-Induced diabetic rats. Measurement of blood glucose and HbA_{1c} levels.	Reduced blood glucose and HbA_{1c}levels in a dose-dependent manner.	Rani et al. (2018)
Tocopherol	GK rats (a model of non-obese type 2 diabetes). IPGTT. Measurement of HbA_{1c}.	Increased insulin secretion. Decreased blood glucose levels. Reduced HbA_{1c} levels.	Ihara et al. (2000)
	STZ-Induced diabetic rats. Determination of blood glucose and HbA_{1c} levels.	Reduced glycemia and HbA_{1c}values.	Roldi et al. (2009)
	Poloxamer-407 (PX-407)-induced diabetic rats. Determination of plasma glucose and HbA_{1c} levels. Measurement of serum insulin (SI). HOMA-IR index. GLP-1 Content in the cecum. Histopathology of pancreas. Molecular docking studies.	Reduced the insulin levels and insulin resistance. Increased pancreatic weight. Increased GLP-1 concentration. Inhibited the activity of DPP-4 and PPARγ with conserved binding interactions.	Bharti et al. (2013)

diabetic potential of thymol in HFD-induced diabetic C57BL/6J mice. In 2015, they a glucose solution administered (per os) to these animals (OGTT) already treated with increasing doses of thymol (10 mg, 20 mg and 40 mg/kg bw). The authors measured blood sugar, plasma insulin, HbA_{1c}, and the insulin resistance index (Saravanan and Pari, 2015). Thymol was able to treat hyperglycemia by normalizing all the tested parameters. The same observation was noted in 2016 after force-feeding the animals with 40 mg/kg b.w. of thymol and estimation of glycaemia levels and plasma insulin (Saravanan and Pari, 2016). The same parameters were also estimated by Oskouei et al. (2019) after testing two doses of thymol (20 and 40 mg/kg b.w.) on STZ-induced diabetic rats, and the results showed an attenuation of blood glucose and an increase in the insulin levels. Saadat Brujeni, (2019) also used the same experimental model with the use of the RT-PCR technique to investigate the expression levels of the genes involved in insulin transcription. They recorded an increase in the expression of the Mafa and Pdx1 genes. MafA regulated the secretion of insulin stimulated by glucose *in vivo*. While Pdx1 is a transcription factor necessary for the development of insulin-secreting beta cells.

8.1.11. Tocopherol

Ihara et al. (2000) investigated the antidiabetic effect of α-tocopherol, which is the most common form of vitamin E in the body. GK rats (a model of type-2 diabetes) received a diet rich in this compound (0, 20 or 500 mg/kg b.w.) and the authors measured insulin secretion, blood glucose concentrations (by IPGTT) and HbA_{1c} levels. α-Tocopherol supplementation significantly improved glycemic control by increasing insulin secretion and decreasing blood glucose and HbA_{1c} levels. This was in line with the results obtained by Roldi et al. (2009) using another experimental model. Bharti et al. (2013) treated diabetic rats, induced by poloxamer-407, with tocopherol from the seeds of *Cucurbita pepo*. Blood samples were collected to determine the glucose and insulin levels. After rats scarification, the cecum was removed to determine the glucagon like peptide-1 (GLP-1) contents and the pancreas was examined *in situ*. The tocopherol-treated diabetic rats exhibited a significant decrease in insulin resistance and insulin levels with a potent increase in GLP-1 concentration and pancreatic weight. Similarly, the tocopherol inhibited the activity of diabetic proteins (DPP-4 and PPAR-γ) with a marked interaction potential in molecular docking (*in silico*) (Bharti et al., 2013).

8.1.12. Carvone

Muruganathan and his collaborators were the first to assess the antihyperglycemic capacity of the carvone (Muruganathan et al., 2013; Muruganathan and Srinivasan, 2016). In 2013, they performed the first measurement of blood glucose and plasma insulin in STZ-induced diabetic rats. While in 2016, they studied the biochemical parameters and examined pancreatic tissue in the same experimental model. They found that this molecule exhibited significant anti-diabetic potential by improving the insulin levels, plasma glucose and HbA_{1c}, as well as by restoring the activities of carbohydrate metabolic enzymes. They confirmed that this molecule protected β-cells against streptozotocin damages. This antihyperglycemic property has also been proven by Alsanea and Liu, (2017) with a mastery of insulin resistance, using the HOMA-IR index, the glucose tolerance test, and the insulin tolerance test against experimental diabetes (HFD-fed mice).

8.1.13. 1,8-cineole

It is also known as eucalyptol, which is a colorless organic natural compound found in certain eucalyptus essential oil (Galan et al., 2020). This compound improved acute pancreatitis (AP) in mice induced by cerulein, by reducing histological damage, pancreatic edema and NF-κB expression, and also by improving the anti-inflammatory IL-10 cytokine level (Lima et al., 2013). These results indicated that eucalyptol can protect the pancreatic β-cells *via* an anti-inflammatory and antioxidant mechanism. The only work studied the antidiabetic power of this monoterpene was performed by Paul and Bhattacharjee, (2018) who showed potent inhibitory power against α-amylase ($IC_{50} = 0.78 \pm 0.05$

mg/mL).

8.1.14. Camphene

Park and collaborators measured blood glucose and insulin levels in HFD-fed mice (Park, 2012, 2013). They found that camphene can reduce the FBG level and blood insulin level, accompanied by an improvement in insulin resistance in the liver tissue and a reduction in the expression of cytokines (TNF-α or IL-6) activating inflammation. One year later, Kim et al. (2014) induced insulin resistance in mice through a HFD, and the glucose tolerance test showed that this compound lowered blood glucose levels and the area under the glucose concentration–time curve, with attenuation of the elevation in plasma glucose (−30%) and insulin levels (−37%).These effects were manifested by the increased AMPK activation, activation of insulin signaling molecules, and stimulation of the translocation of GLUT2 to the plasma membrane of the liver.

8.1.15. Thujone

Alkhateeb and coworkers studied the ability of thujone to improve glucose homeostasis when administered (60 mg/kg/day) to diabetic rats induced by STZ for 4 weeks (Alkhateeb, 2015). They measured their plasma glucose level, liver glycogen, and insulin levels with the determination of Akt and glycogen synthase kinase (GSK)-3β by Western blot analysis. The results showed that thujone exhibited a hypoglycemic activity *in vivo* associated with an increase in glycogen production *via* the activation of Akt/GSK-3β signaling pathway.Three years later, Alkhateeb et al. (2018) followed the same experimental protocol as their first study. They confirmed the hypoglycemic effect of thujone was related to an improvement in AMPK phosphorylation and a restoration of impaired GLUT4 translocation.

8.1.16. Others terpenoids

Other terpenoids demonstrated potent antidiabetic properties *via* different mechanisms. Bisabolene was evaluated by Abdjul et al. (2016) for its inhibitory effect on protein tyrosine phosphatase 1B (PTP1B) in Huh-7 human hepatoma cells. It inhibited the activity of this phosphatase (IC_{50} = 1.9 μM) and improved the phosphorylation levels of Akt stimulated by insulin. Borneol, natural bicyclic monoterpene, was administered (20 and 50 mg/kg b.w.) to STZ-induced diabetic rats (Madhuri and Naik, 2017). The authors estimated glycemia, HbA1c, liver glycogen and plasma insulin levels. They also determined β-cells function, their number and architecture. Borneol-treatment improved hyperglycemia and the function of β-cells by increasing their number leading to an increase in insulin secretion and HOMA-β cell functioning index. In addition, the histology of pancreas highlighted a preservation of pancreatic islets architecture and maintained the integrity of β-cells. Camphor, a Russian research team evaluated its antidiabetic potential *in vivo* with the OGTT in male albino mice (CD-1 line) and *in vitro* by the inhibition of dipeptidyl peptidase-4 (DPP-4) (Kuranov et al., 2018). They observed a reduction in blood glucose in mice and a potent DPP-4 inhibitory activity with IC_{50} values between 1.27 and 15.78 μM. Menthol was administered (25, 50 and 100 mg/kg/day) to STZ–nicotinamide-induced diabetic rats for 45 days (Muruganathan et al., 2017). To study menthol antidiabetic effect, the authors collected blood samples and pancreatic fragments for biochemical and histological analysis, respectively. Menthol decreased the induced hyperglycemia and increased plasma insulin and liver glycogen levels. These effects were attributed to the improvement of pancreatic abnormalities and the inhibition of pancreatic β-cells apoptosis. A recent study examined the protective capacity of a mixture of *p*-cymene and thymoquinone against glycation of bovine serum albumin (BSA) (Benvidi et al., 2018). The authors used multivariate curve resolution–alternating least squares (MCR–ALS) method and they subsequently found that this mixture showed a significant protective effect on the glycation of BSA. Tan and collaborators tested the inhibitory activity of terpinolene against α-amylase and α-glucosidase as well as the total glucose uptake in 3T3-L1 pre-adipocytes (Tan et al., 2016). This terpene exhibited a relatively weak inhibitory effect on α-glucosidase with no effect on glucose absorption in 3T3-L1 adipocytes.

8.2. Antidiabetic properties of flavonoids

8.2.1. Apigenin

The antidiabetic effect of apigenin was reported in several works using *in vitro* and *in vivo* models (Table 7). In the *in vivo* studies done by (Cazarolli et al., 2009a; Panda and Kar, 2007a) and (Osigwe et al., 2017) the potential of this compound was tested in regulating hyperglycemia using alloxan-induced diabetic mice. The results showed that apigenin improved blood glucose by several mechanisms such as increasing the levels of serum insulin, decreasing glucose concentration and hepatic G-6-Pase activity (Panda and Kar, 2007a), and also by increasing the liver and muscle glycogen content (Osigwe et al., 2017). On the other hand, this compound was found to have an acute effect on blood glucose level in diabetic rats by stimulating insulin secretion, potentiating glucose-induced insulin secretion in hyperglycemic rats, and increasing 14C-glucose uptake in soleus muscle (at 50 and 100 μM). It also stimulated glycogen synthesis in rat soleus muscle (Cazarolli et al., 2009a, 2009b). In 2012, Cazarolli et al. (2012) demonstrated in another study that apigenin was able to increase glucose uptake in soleus muscle acting through insulin signaling pathways such as insulin receptor tyrosine kinase activity, PI3K, atypical PKCs and MEK in hyperglycemic normal rats.In streptozotocin-induced Cazarolli et al., 2009a, 2009b diabetic rats, Hossain et al. (2014) studied the mechanistic role of apigenin in controlling hyperglycemia and damages of vital tissues by the analysis of GLUT4 and CD38 protein expression patterns using Western blot assay, and histopathological alterations in some vital organs. The results revealed that this compound improved glucose homeostasis by enhancing GLUT4 translocation in skeletal muscles, decreasing the expression of CD38 by approximately 11% and preserving β-cells. In another study, Ren et al. (2016) investigated the ameliorative effect of apigenin on type 2 diabetic (T2D) rats and its underlying mechanism of action. Diabetes was induced by high fat diet and a low dose of STZ. The results indicated that this flavonoid significantly ameliorated glucose homeostasis by decreasing the levels of blood glucose, serum lipid and insulin resistance index and improved impaired glucose tolerance. It ameliorated vascular endothelial dysfunction, increased insulin-mediated NO production and inhibited NF-κB-mediated inflammatory response in endothelial cells. Thus, in HFD-induced obese mice apigenin ameliorated metabolic disturbances by different mechanisms such as reducing levels of fasting blood glucose and plasma insulin and HOMA-IR, and decreased the activity of hepatic gluconeogenic enzymes (PEPCK and G6Pase) (Jung et al., 2016). According to the *in vitro* studies (Esmaeili and Sadeghi, 2009; Sahnoun et al., 2018; Wang et al., 2017b; Yamagata et al., 2010, 2011; Zeng et al., 2016), the antidiabetic effect of apigenin was demonstrated by several methods. Using inhibitory kinetics method, Zeng et al. (2016) demonstrated the potent inhibitory effect of apigenin on α-glycosidase with the IC_{50} value of $(10.5 \pm 0.05) \times 10^{-6}$ mol L^{-1}. Sahnoun et al. (2018) studied apigenin inhibitory effect on human pancreatic α-amylase by α-amylase inhibitory assay and supported their finding by *in silico* studies. This flavonoid exhibited a competitive inhibition towards human α-amylase with an IC_{50} of 75.12 μM, which was 1.74-fold of that of acarbose (acarbose, IC_{50} = 43 μM). Other studies showed that apigen ininhibited tumor necrosis factor-αand glucose-induced LOX-1 expression in human endothelial cells and prevented diabetic complications such as arteriosclerotic vascular disorder by regulating the activation of NF-κB (Yamagata et al., 2010, 2011). Using Western blot analysis, Wang et al. (2017b) revealed that the pretreatment with apigenin effectively reduced ROS levels and suppressed cell apoptosis of pancreatic β cells stressed by different concentrations of STZ. Esmaeili and Sadeghi (2009) showed that this compound increased insulin secretion and protected pancreatic β-cells from oxidative stress induced by streptozotocin.

8.2.2. Catechin

Catechin is a flavonoid that possesses the capacity to improve glucose homeostasis by different mechanisms reported in several works. In STZ-induced diabetic rats, the oral administration of catechin significantly reduced plasma glucose and increased tissue glycogen and 14C-glucose oxidation without any change in the plasma insulin leveland C-peptide. Also, it restored the altered glucokinase, G6Pase, glycogen synthase and glycogen phosphorylase levels and enhanced GLUT4 mRNA, protein expression and the antioxidant defense system. It produced better glucose tolerance, activated insulin receptor and peroxisome proliferator-activated receptor gamma (Daisy et al., 2010; Pitchai and Manikkam, 2012; Samarghandian et al., 2017). Another study showed that the oral administration of catechin to rats before soluble starch or sucrose administration lowered plasma glucose levels, increased insulin activity, inhibited intestinal α-amylase and sucrose (Matsumoto et al., 1993). In 2011, the authors used high-fat diet-fed to induce hyperglycemia and showed that tea catechins decreased the expression of insulin receptor (IR)-β and glucose transporter 4 (GLUT4), markers for insulin resistance (Imada et al., 2011). Using the same method, Huang and collaborators revealed that the oral administration of catechin significantly enhanced insulin secretion and reversed glucose intolerance (Huang et al., 2011). The study of Igarashi et al. (2007) found that dietary catechins lowered glucose tolerance and improved oxidative status in type 2 diabetic rats.Catechin also revealed potent enzyme inhibitory activity of α-glucosidase and α-amylase (Matsui et al., 2007; Xu et al., 2013; Yilmazer-Musa et al., 2012). Yilmazer-Musa et al. (2012) demonstrated the potent inhibitory effect of catechin onα-amylase ($IC_{50} = 160 \pm 6$ μg/mL) and α-glucosidase ($IC_{50} =$ 31 μg/mL) compared with acarbose. Xu et al. (2013) reported interesting anti-α-amylase activity $IC_{50} = 637.5 \pm 7.8$ L μmol/L by catechin. Using human intestinal epithelial Caco-2 cells, Shimizu et al. (2000) showed that catechin inhibited intestinal glucose uptake. Murase et al. (2009) examined the effect of catechin on the AMPK signaling pathway in cultured cells (Hepa 1-6, L6, and 3T3-L1) and demonstrated that catechin with a gallocatechin moiety or a galloyl residue activated LKB1/AMPK. In another study, Kamiyama et al. (2010) investigated the *in vitro* inhibition of mammalian α-glucosidase and glycogen phosphorylase (GP) by catechin derivatives, and the results showed that catechin 3-gallate (CG), gallocatechin 3-gallate (GCG), epicatechin 3-gallate (ECG), and EGCG, were good inhibitors of maltase, with IC_{50} values of 62, 67, 40, and 16 μM, respectively, and inhibited GP b, with IC_{50} values of 35, 6.3, 27, and 34 μM, respectively. EGCG also inhibited maltase expressed on Caco-2 cells ($IC_{50} = 27$ μM).

8.2.3. Cyanidin

The antidiabetic effect of cyanidin was reported by many investigators (Adisakwattana et al., 2004, 2009, 2011; Akkarachiyasit et al., 2010; Cásedas et al., 2019; Choi et al., 2017a, 2017b; Kyungha; Daveri et al., 2018; Gharib et al., 2013; Inaguma et al., 2011; Lee et al., 2015a, 2015b, p. P21; Matsukawa et al., 2015; Sasaki et al., 2007; Suantawee et al., 2017; Kyungha; Talagavadi et al., 2016; Tsuda et al., 2003). Cyanidin was tested for its antidiabetic effect *in vivo* using HFD-fed study with C57BL/6J mice (Daveri et al., 2018; Tsuda et al., 2003) and streptozotocin induced diabetic mice (Gharib et al., 2013). In HFD-fed mice, the results showed that this flavonoid ameliorated hyperglycemia, hyperinsulinemia and hyperleptinemia and decreased TNF-α mRNA level. It also decreased insulin resistance and improved insulin sensitivity (Tsuda et al., 2003). This result was confirmed by Gharib et al. (2013) who revealed thatthe daily administration of 100 mg/kg of cyanidin chloride to diabetic mice reduced albumin glycation and HbA1c glycation to 46.00 ± 2.50% and 4.95 ± 0.20%, respectively. The study of Sasaki et al. (2007)showed that rats fed diets supplemented with cyanidin resulted in lowering the gene expression level of G6Pase, reduced blood glucose concentration, enhanced insulin sensitivity, and upregulated GLUT4 and downregulated RBP4 in the white adipose tissue. The *in vitro* antidiabetic effect of cyanidin was tested by several research groups through examining its capacity to inhibit α-amylase, α-glycosidase and dipeptidyl peptidase-4 (Adisakwattana et al., 2004, 2009, 2011; Kyungha; Akkarachiyasit et al., 2010; Cásedas et al., 2019; Choi et al., 2017a). Adisakwattana et al. (2004) revealed that cyanidin-3-rutinoside inhibited α-glucosidase in a dose-dependent manner with IC_{50} value of 19.7 ± 0.24 μM. In another study, the same research group tested the inhibitory activity of cyanidin-3-galactosideagainst α-glucosidase and showed an IC_{50} value of 0.50 ± 0.05 mM against intestinal sucrose (Adisakwattana et al., 2009). Cyanidin-3-galactoside and cyanidin-3-glucoside were the most potent inhibitors of intestinal sucrase and pancreatic α-amylase with IC_{50} values of 0.50 ± 0.05 and 0.30 ± 0.01 mM, respectively. The combination of cyandin-3-glucoside, cyanidin-3-galactoside or cyanidin-3,5-diglucosides with a low concentration of acarbose showed a synergistic inhibition of intestinal maltase and sucrose (Akkarachiyasit et al., 2010). The authors showed in another study that cyanidin 3-rutinoside exhibited potent enzymatic inhibitory activity against intestinal maltase, and sucrase with IC_{50} values of 2.323 ± 14.8 and 250.2 ± 8.1 μM, respectively (Adisakwattana et al., 2011). Choi et al. (2017a) and collaborators studied the inhibitory effect of cyanidin-3-*O*-glucoside. They revealed potent inhibition of α-amylase and α-glucosidase with $IC_{50} = 7.5$ and 13.72 μM, respectively (Choi et al., 2017a). Cásedas et al. (2019) tested the ***in vitro*** antidiabetic effect of cyanidin-3-*O*-glucoside using α-glucosidase and dipeptidyl peptidase-4 (DPP-4) and revealed an important inhibition of both enzymes with IC_{50} values of 479.8 μM and 125.1 μM, respectively. The *in vitro* antidiabetic effect of cyanidin was also studied by cell culture. The authors tested the pancreatic β-cells MIN6N and INS-1 using cell viability assay and Western blot analysis (Lee et al., 2015a, 2015b; Suantawee et al., 2017). In MIN6N pancreatic β-cells, this compound improved glucose homeostasis by different mechanisms such as by decreasing the generation of intracellular reactive oxygen species, DNA fragmentation and apoptosis, preventing pancreatic β-cell apoptosis and increasing insulin secretion (Lee et al., 2015a). It also decreased H_2O_2-induced cell death, regulated apoptotic signaling pathways and prevented oxidative stress-induced β-cell apoptosis (Lee et al., 2015b). In pancreatic β-cells INS-1, it stimulated insulin secretion and increased intracellular Ca^{2+} signals in a concentration-dependent manner(Suantawee et al., 2017). Inaguma et al. (2011, p. P21); Matsukawa et al. (2015), and Choi et al. (2017b) tested this activity in 3T3-L1 adipocytes cells by glucose uptake assay and Western blotting of insulin signaling proteins. The study of (Inaguma et al., 2011, p. P21; Matsukawa et al., 2015) demonstrated that this flavonoidameliorated insulin sensitivity, promoted adipocyte differentiation and the uptake of glucose in a dose-dependent manner, decreased TNF-α concentration,activated insulin signaling and increased glucose uptake.It also enhanced phosphorylation of insulin receptor substrate 1 (IRS-1) and Akt, as well as it augmented the activation of phosphatidylinositol-3-kinase (PI3K) in the insulin signaling pathway (Choi et al., 2017a). Using murine hepatocytes and Hela cells, this flavonoid activated AMPK and suppressed its downstream kinase mTOR/S6K in both *in vitro* and *in vivo* systems, increased the expression of GLUT1 and GLUT4 in the liver, improved glucose tolerance in normal and obese mice and increased insulin sensitivity in mice (Talagavadi et al., 2016).

8.2.4. Delphinidin

The *in vivo* and *in vitro* anti-diabetic activity of delphinidin was investigated in several studies (Daveri et al., 2018; Gharib et al., 2013; Hidalgo et al., 2017; Jayaprakasam et al., 2005; Lai et al., 2019; Mojica et al., 2017; Rojo et al., 2012). The *in vivo* effect was studied using HFD-fed mice (Daveri et al., 2018; Gharib et al., 2013; Rojo et al., 2012). The results showed that the supplementation with delphinidin decreased insulin resistance and improved insulin sensitivity(Daveri et al., 2018). Gharib et al. (2013) revealed that the treatment with 100 mg/mL of delphinidin reduced albumin glycation to 30.50 ± 3.46% and HbA1c glycation to 3.60 ± 0.25%. The study of Rojo et al. (2012)

Table 7
Flavonoids.

Compounds	Methods	Keys results	References
Apigenin	Alloxan-induced diabetic mice. Insulin estimation.	Increased concentrations of serum insulin. Decreased glucose concentration and hepatic G6Pase activity.	Panda and Kar (2007a)
	Determination of serum glucose levels. Determination of insulin levels. Studies on ^{14}C-glucose uptake in rat soleus muscle	Lowered blood glucose. Stimulated insulin secretion. Increased ^{14}C-glucose uptake (at 50 and 100 μM). Apigenin (100 μM) and insulin (10 nM) did not show any synergistic effect on glucose uptake.	Cazarolli et al. (2009a)
	Hyperglycemic rats. Glycogen synthesis in normal rat soleus muscle.	Lowered blood glucose. Stimulated insulin secretion. Stimulatedof glycogen synthesis in muscle.	Cazarolli et al. (2009b)
	Rat isolated islets in STZ-induced oxidative stress. Measurement of insulin release.	Increased insulin secretion. Protective effect on pancreatic islets.	Esmaeili and Sadeghi (2009)
	Human endothelial cells.	Inhibited high glucose level *in vitro*.	Yamagata et al. (2010)
	Human endothelial cells. Western blot analysis.	Inhibited high glucose level *in vitro*.	Yamagata et al. (2011)
	Hyperglycemic normal rats. Determination of the serum glucose level. Studies on glycogen content. Studies on ^{14}C-glucose uptake in rat soleus muscle.	Potential hypoglycemic activity. Increased muscle and liver glycogen content. Increased glucose uptake in soleus muscle acting through insulin signaling pathways (insulin receptor tyrosine kinase activity, PI3K, atypical PKCs and MEK).	Cazarolli et al. (2012)
	STZ-induced diabetic rats. Determination of average fasting blood glucose level. Histopathological study of pancreas. Western blot analysis.	Control of blood glucose level. Enhanced GLUT4 translocation. Protective effect on pancreas.	Hossain et al. (2014)
	HFD-induced obese mice. Determination of fasting blood glucose, plasma insulin and HOMA-IR. Hepatic enzymes activity.	Decreased fasting blood glucose and plasma insulin levels. Decreased insulin resistance, hyperinsulinemia and hepatic gluconeogenic enzymes activities.	Jung et al. (2016)
	HFD − STZ induced diabetic rats. OGTT. Biochemical assessment. Western blot analysis.	Decreased levels of blood glucose. Decreased insulin resistance index. Improved impaired glucose tolerance.	Ren et al. (2016)
	α-Glucosidase inhibition assay. *In vitro* enzymatic inhibition Alloxan-induced diabetic rats.	Inhibited α-glucosidase activity with $IC_{50} = (10.5 \pm 0.05) \times 10^{-6}$ mol L^{-1} Inhibition ofα-Glucosidase was in a non-competitive manner. Reduced blood glucose. Increased liver and muscle glycogen content.	Zeng et al. (2016)
	STZ-induced pancreatic *β*-cell damages. Western blot analysis.	Reversed cell apoptosis of pancreatic β cells.	Wang et al. (2017a)
	α-Amylase inhibition assay. Docking studies.	Inhibitedhuman and *Aspergillus oryzae* S2 *α*-amylases in a competitive manner.	Sahnoun et al. (2018)
Arbutin	Healthy and fasting dogs.	Decreased blood sugar	Michel (1936)
	α-Amylase and *α*-glucosidase inhibition assays.	Inhibited*α*-amylase and *α*-glucosidase in a dose-dependent manner. At the highest concentration (100 mg/ml), arbutin inhibited 75% of *α*-glucosidase activity and 81% of *α*-amylase activity.	Yousefi et al. (2013)
	Alloxan-induced diabetic rats.	The use of arbutin in a swim workout course exhibited apositive effect on glucose and insulin levels.	Azarbayjani et al. (2014)
	Alloxan-induced diabetic rats. Plasma glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-1 receptor (GLP1R) assay. Exercise training protocol (aerobic training).	Combination of AT/arbutin decreased GLP-1 and GLP1R concentrations.	Farzanegi (2014)
Catechin	Starch or sucrose solution was administered orally to Wistar rats. Measurement of blood glucose and insulin. *α*-Amylase assay. Sucrase assay.	Suppressed the increase of plasma glucose levels. Suppressedinsulin activity. Inhibited *α*-amylase activity. Inhibited intestinal sucrase.	Matsumoto et al. (1993)
	Cell culture (human intestinal epithelial Caco-2 cells). Glucose uptake experiments.	Inhibited intestinal glucose uptake. Inhibited SGLT 1 in a competitive manner,	Shimizu et al. (2000)
	Type 2 diabetic Goto-Kakizaki rats. Blood glucose tolerance test.	Lowered blood glucose levels.	Igarashi et al. (2007)
	α-Glucosidase inhibition assay. Male Sprague-Dawley rats.	Inhibited α-glucosidase activity. Reduced blood glucose level.	Matsui et al. (2007)
	Cell culture (Hepa 1–6, L6, and 3T3-L1). Measurement of AMPK activity. Western blot analysis.	Catechins with a gallocatechin moiety or a galloyl residue activated AMPK. Induced phosphorylation of LKB1.	Murase et al. (2009)
	Cell culture (Rat L6 myoblasts). Normal rats and Kir6.2 k/o mice. IPGTT and OGTT in animals. ITT in animals. Deoxyglucose uptake assay. Western blot analysis.	Epigallocatechin-3-gallate (EGCG) acutely increasedblood glucose levels and insulin resistance. Decreased basal and insulin-stimulated glucose uptake by EGCG in a dose dependent manner.	(Park et al., 2009a)
	STZ-induced diabetic rats. Estimation of glucose and tissue glycogen. Determination of plasma insulin and C-peptide.	Reduced plasma glucose. Increased tissue glycogen, and ^{14}C-glucose oxidation without any change in plasma insulin and C-peptide.	Daisy et al. (2010)

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Table 7 (*continued*)

Compounds	Methods	Keys results	References
	Estimation of glucose metabolizing enzymes. Histopathological study of pancreas. GLUT4 protein expression analysis. Western blot analysis.	Restored the altered glucokinase, G6Pase, glycogen synthase and glycogen phosphorylase levels. Enhanced GLUT4 mRNA and protein expression.	
	Cell culture. Measurement of rat intestinal α-glucosidase activity. Measurement of glycogen phosphorylase b (GP b). Maltase activity in Caco-2 cells.	Catechin 3-gallate (CG), gallocatechin 3-gallate (GCG), epicatechin 3-gallate (ECG), and EGCG, were good inhibitors of maltase, with IC_{50} values of 62, 67, 40, and 16 μM, respectively. EGCG inhibited maltase expressed on Caco-2 cells (IC_{50} = 27 μM). Gallated catechins CG, GCG, ECG, and EGCG inhibited GP b, with IC_{50} values of 35, 6.3, 27, and 34 μM.	Kamiyama et al. (2010)
	Cell culture (hamster pancreatic β-cell-derived HIT-T15 cells). Insulin secretion. HFD-induced diabetic mice. Western blot analysis. OGTT and ITT.	Enhanced insulin secretion in a dose dependent manner. Reversed glucose intolerance in HFD-induced diabetic mice.	Huang et al. (2011)
	HFD-fed Mice. BT1 containing 3000 mg/L total catechins and 864 mg/L caffeine. BT2 containing 1437 mg/L total catechins and 594 mg/L caffeine. Western blot analysis	Both BT1 and BT2 increased plasma glucose and counteracted the HFD-caused decrease in the expression of insulin receptor (IR)-β and GLUT4, markers for insulin resistance.	Imada et al. (2011)
	STZ-induced diabetic rats. Docking analysis.	Producedbetter glucose tolerance. Activating IR and PPARγ.	Pitchai and Manikkam (2012)
	α-Amylase and α-glucosidase inhibition assays	Catechin 3-gallates are less effective inhibitors of α-amylase, they are potent inhibitors of α-glucosidase.	Yilmazer-Musa et al. (2012)
	Porcine pancreatic α-amylase assay. Rat intestinal α-glucosidase assay. Inhibitory kinetic assay. Glucose transport assay.	The seven catechins showed inhibitory effect on α-amylaseinhibition, with the IC_{50} ranging from 29.0 to 637.5 μmol/L. EGCG inhibited porcine pancreatic α-amylase in a non-competitive manner. The inhibition over rat intestinal α-glucosidase was mixed competitive. The Ki of the EGCG against α-amylase and α-glucosidasewas 5.9 ± 0.4 and 87.8 ± 10.2 μg/mL, respectively. CM and EGCG inhibited glucose transport in a dose-dependent manner.	Xu et al. (2013)
	STZ-induced diabetic rats. Measurement of blood glucose.	Decreased blood glucose levels in a dose dependent manner. Protective effects against oxidative damage.	Samarghandian et al. (2017)
Cyanidin	HFD-fed induced hyperglycemia in mice. Measurement of glucose, insulin and leptin levels.	Ameliorates hyperglycemia, hyperinsulinemia and hyperleptinemia. Decreased TNF-α mRNA level.	Tsuda et al. (2003)
	α-Glucosidase inhibition assay. Kinetics of enzyme inhibition.	Inhibited α-glucosidase in a dose-dependent manner (IC_{50} = 19.7 ± 0.24 μM). Inhibition in a competitive manner with a K_i value in the range of 1.31-1.56 × 10^{-5} M.	Adisakwattana et al. (2004)
	Measurement of glucose, insulin, and RBP4 levels. Insulin tolerance test. Immunoblot analysis of GLUT4 protein. Lowered gene expression level of G6Pase.	Reduced blood glucose concentration and enhanced insulin sensitivity. Upregulated GLUT4 and downregulated RBP4 in the white adipose tissue.	Sasaki et al. (2007)
	α-Glucosidase inhibition assay. Measurements of the kinetics constant.	IC_{50} = 0.50 ± 0.05 mM against intestinal sucrase with mixed inhibition. Synergistic inhibition ofcyanidin-3-galactoside on intestinal α-glucosidase (maltase and sucrase) when combined with acarbose.	Adisakwattana et al. (2009)
	Intestinal α-glucosidase inhibition assay. Pancreatic α-amylase inhibition assay.	Cyanidin-3-galactoside and cyanidin-3-glucoside were the most potent inhibitors against intestinal sucrase and pancreatic α-amylase with IC_{50} values of 0.50 ± 0.05 and 0.30 ± 0.01 mM, respectively.Combination of cyandin-3-glucoside, cyanidin-3- galactoside or cyanidin-3,5-diglucosides with a low concentration of acarbose showed synergistic inhibition on intestinal maltase and sucrase.	Akkarachiyasit et al. (2010)
	Intestinal α-glucosidase inhibition assay. Enzyme kinetics. Plasma glucose concentration by the oral maltose or sucrose tolerance test.	The IC_{50} values of cyanidin 3 rutinoside against intestinal maltase, and sucrase were 2323 ± 14.8 and 250.2 ± 8.1 μM, respectively. Inhibited intestinal sucrase in a mixed type manner. Synergistic inhibition in combination of cyanidin 3-rutinoside with acarbose against intestinal maltase and sucrase. Suppressed postprandial plasma glucose.	Adisakwattana et al. (2011)
	Cell culture (3T3-L1 cells).	Amelioratedinsulin sensitivity. Up-regulatedGLUT4 gene expression. Promotedadipocyte differentiation and uptake of glucose in a dose-dependent manner. Decreased TNF-α concentration.	Inaguma et al. (2011)
	Isolation of human omental adipocytes. Glucose uptake assay. Assessment of PPARγ activity Western blot analysis.	Exerted insulin-like activity in human omental adipocytes. Increased glucose uptake. Increased GLUT4 translocation and adiponectin secretion. Increased nuclear PPARγ activity.	Scazzocchio et al. (2011)
	Male BALB/c mice. Measurement of glycated albumin	Reduced albumin glycation to 46.00 ± 2.50%. Decreased HbA1c glycation to 4.95 ± 0.20%.	Gharib et al. (2013)
	Cell culture (MIN6N pancreatic β-cells). Cell viability assay. Western blot analysis. Measurement of insulin secretion.	Decreased generation of intracellular reactive oxygen species, DNA fragmentation and rate of apoptosis. Prevented pancreatic β-cell apoptosis. Increased insulin secretion.	Lee et al. (2015a)

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Table 7 (*continued*)

Compounds	Methods	Keys results	References
	Cell culture (MIN6N pancreatic β-cells). Cell viability assay. Western blot analysis. Measurement of insulin secretion.	Decreased H_2O_2-induced cell death in the MIN6N pancreatic β-cells. Regulatedapoptotic signaling pathways in pancreatic MIN6N β-cells. Preventedoxidative stress-induced β-cell apoptosis.	Lee et al. (2015b)
	Cell culture (mouse 3T3-L1 and C2C12 cells). Western blotting of insulin signaling proteins. Assay for glucose uptakein 3T3-L1 adipocytes.	Induced differentiation into smaller adipocytes which correlated with increased PPARγ gene expression. Decreased TNF-α secretion. Activating insulin signaling. Increased glucose uptake. Induced differentiation of 3T3-L1 preadipocytes into smaller, insulin-sensitive adipocytes, and activatedof skeletal muscle metabolism.	Matsukawa et al. (2015)
	Cell culture (murine hepatocytes and Hela cells). AMPK activity assay. Glucose and insulin tolerance tests. Western blot analysis.	Activated AMPK and suppressed its downstream kinase mTOR/S6K both *in vitro* and *in vivo* systems. Increased expression of GLUT1 and GLUT4 in the liver. Improved glucose tolerance in normal and obese mice. Increased insulin sensitivity in mice	Talagavadi et al. (2016)
	α-Amylase and α-glucosidase inhibition assay. STZ-induced diabetic mice. Measurement of blood glucose level.	Inhibited of α-amylase and α-glucosidase activity (IC_{50} = 7.5 and 13.72 μM, respectively). Reduced postprandial blood glucose levels.	(Choi et al., 2017a)
	Cell culture (3T3-L1 preadipocytes). Glucose uptake assay. Western blot analysis.	Increased glucose uptake, which was associated with enhanced plasma membrane GLUT4 expression in 3T3-L1 adipocytes. Enhanced phosphorylation of insulin receptor substrate 1 (IRS-1) and Akt, as well as augmented activation of phosphatidylinositol-3-kinase (PI3K) in the insulin signaling pathway.	(Choi et al., 2017b)
	Cell culture (Pancreatic β-cells INS-1). Insulin determination.	Stimulated insulin secretion and increased intracellular Ca^{2+} signals in a concentration-dependent manner. Up-regulatedinsulin secretion genes.	Suantawee et al. (2017)
	Inhibition of enzymes involved in type 2 diabetes [α-glucosidase and dipeptidyl peptidase-4 (DPP-4)]	Inhibitedα-glucosidase (IC_{50} = 479.8 μM). Inhibited DPP-4 (IC_{50} = 125.1 μM).	Cásedas et al. (2019)
	HFD-fed mice. Metabolic measurements. Western blot analysis.	Decreased insulin resistance. Improved insulin sensitivity.	Daveri et al. (2018)
Delphinidin	Rodent pancreatic β-cells (INS-1832/13). Insulin secretion studies.	Delphinidin-3-glucoside was the most effective insulin secretagogues.	Jayaprakasam et al. (2005)
	Mice received either a low fat diet (LFD) or HFD.	Delphinidin-3-glucoside did not have significant hypoglycemic activity.	Grace et al. (2009)
	Hyperglycemic obese C57BL/6J mice fed a HFD.	Decreased fasting blood glucose levels in obese C57BL/6J mice.	Rojo et al. (2012)
	Cell culture (H4IIE hepatoma cells and L6 myoblasts from rat skeletal muscles). Glucose production assay. Glucose uptake.	Decreased glucose production in rat liver cells. Increased glucose uptake in L6 myotubes.	
	Male BALB/c mice. Measurement of glycated albumin.	Reduced albumin glycation to 30.50 ± 3.46%. Decreased HbA1c glycation to 3.60 ± 0.25%.	Gharib et al. (2013)
	Glucose uptake experiments—Tissue. Glucose uptake experiments—cultured cells. Western blot analysis.	Inhibited glucose absorption in both mouse jejunum and a human enterocytic cell line. Affected the function of sodium-glucose cotransporter 1.	Hidalgo et al. (2017)
	α-Amylase, α-glucosidase, and DPP-4 inhibition assays. Caco-2 cell proliferation. Glucose uptake *in vitro*.	The inhibitory potential on α-glucosidase was 44.5%. The inhibitory potential on α-amylase was 24.2%. The inhibitory potential on DPP-4 enzyme was 78.8%. Decreased glucose uptake (37.1%).	Mojica et al. (2017b)
	HFD-fed mice. Metabolic measurements. Western blot analysis.	Decreased insulin resistance. Improved insulin sensitivity.	Daveri et al. (2018)
	Cell culture (rat pancreatic β-cell line RIN-m5F). Western blot analysis.	Decreased high-glucose-induced apoptosis of pancreatic β-cells. Induced autophagy in RIN-m5F cells. Decreased the level of cleaved caspase 3. Increased phosphorylation level of AMPKα Thr172. Attenuated the negative effects of high-glucose stress to cells.	Lai et al. (2019)
Epicatechin	Alloxan induced diabetic rats. Histopathological study of pancreas.	Decreased blood sugar levels. Protective effect on pancreas.	Chakravarthy et al. (1981)
	Alloxan induced diabetic rats. Histopathological study of pancreas. Immunoreactive insulin studies.	Decreased blood sugar levels. Increased serum insulin levels. Regeneration of β-cells.	Chakravarthy et al. (1982)
	Alloxan induced diabetic rats.	Lowered blood glucose levels.	Sheehan et al. (1983)
	Islets isolation. Insulin secretion. Islet cultures.	Increased insulin secretion from isolated islets of Langerhans in a dose-dependent manner.	Hii and Howell (1984)
	STZ-induced diabetic. Spontaneously diabetic BB/E rats.	Failed to reverse diabetes in both groups of rats. Failed to halt the progression of the disease in the prediabetic BB/E rats.	(bone et al., 1985)
	Islets isolation. Glycogen content of rat diaphragm. Glucagon release from islets of Langerhans.	Increased glycogen content of rat diaphragm in a dose dependent manner. Stimulated the incorporation of U^{14}–C glucose into glycogen of rat diaphragm in a dose related manner.	Ahmad et al. (1989)
	Islets isolation. Immature and mature rat islets *in vitro*.	Stimulated conversion of proinsulin to insulin. Stimulated insulin release from islets of Langerhans *in vitro*.	Ahmad (1991)
	Erythrocyte membrane AChE in normal and type 2 diabetic patients.	Pronounced insulin-like effect on erythrocyte membrane-bound AChE in type 2 diabetic patients.	Rizvi and Zaid (2001)
			Kim et al. (2003)

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Table 7 (*continued*)

Compounds	Methods	Keys results	References
	STZ-induced β-cell damage. Blood glucose measurements. Islets isolation. Measurement of insulin release.	The blood glucose concentrations of epicatechin + STZ–treated rats were maintained within the upper limit of the normal range. Epicatechin alone did not affect insulin release.	
	High fructose diet-fed rats. Metabolic measurements. Western blot analysis.	Decreased insulin resistance. Enhancedinsulin signaling in the liver and adipose tissue. Attenuatedendoplasmic reticulum stress in liver and adipose tissues	Bettaieb et al. (2014)
	Cell culture (rat Ins-1E cells). Determination of insulin secretion	Enhanced insulin secretion. Protectedpancreatic β-cell viability.	Martín et al. (2014)
	HFD-fed mice. Analysis of blood glucose, insulin, and leptin.	Decreased blood glucose and insulin levels. Increased blood leptin concentrations. Increased muscular membrane protein levels of GLUT4.	Shih et al. (2015)
	Cell culture (L6 myoblasts). Glucose uptake assay.	Promoted glucose uptake and translocation of GLUT4 in the cells. Activation of PI3K signaling in skeletal muscle cells.	Ueda-Wakagi et al. (2015)
	HFD-fed mice. Metabolic measurements. Western blot analysis.	Improved insulin sensitivity. Decreased blood glucose levels.	Cremonini et al. (2016)
	STZ-nicotinamideinduced diabetic rats. OGTT. Determination of insulin and C-peptide levels. HOMA-IR	Treatment of diabetic rats with epicatechin and/or gallic acid markedly improved. Oral glucose tolerance. Serum insulin level. mRNA expression of GLUT4. Insulin resistance. Treatment with epicatechin and gallic acid together was the most effective in improving the previous indices.	Ibrahim et al. (2018)
Hesperetin	Goto-Kakizaki (GK) rats with type 2 diabetes.	Normalized glucose metabolism by altering the activities of glucose-regulating enzymes and reducing the levels of lipids in the serum and liver of the GK rats.	Akiyama et al. (2009b)
	Cell culture (3T3-L1 cells).	Inhibited TNF-α-stimulated FFA secretion from mouse adipocytes. Blocked TNF-α-induced activation of the NF-κB and ERK pathways.	Yoshida et al. (2010)
	STZ-induced diabetic rats.	Improved glycemic status. Decreased plasma glucose levels. Increase plasma insulin level.	Revathy and Abdullah (2016)
	α-Glucosidase inhibition assay. Kinetic analysis.	Inhibition of α-glucosidase activity with $IC_{50} = 0.38 \pm 0.05$ mM In a slope-parabolic mixed-type manner ($K_{slope} = 0.23 \pm 0.01$ mM).	Gong et al. (2017)
	STZ-induced diabetic rats. Histopathological study of pancreas.	Inhibited enzymes involved in glucose metabolism. Prevented the development of insulin resistance. Normalized plasma glucose and insulin levels.	Revathy (2017)
	STZ-induced diabetic rats. Plasma insulin level determination. Plasma glucose level determination.	Declined plasma glucose. Improved plasma insulin and glycogen levels. Improved hepatic glucose metabolic enzymes.	Revathy et al. (2018)
Hesperidin	db/db Mice (a model for type 2 diabetes). Blood glucose determination. Plasma insulin and C-peptide levels. Hepatic glycogen assay. Hepatic enzyme activities. Histopathological study of pancreas.	Reduced blood glucose. Elevated hepatic glucokinase activity and glycogen concentration. Lowered activity of hepatic G6Pase and phosphoenolpyruvate carboxykinase (PEPCK). Elevated plasma insulin and C-peptide levels.	Jung et al. (2004)
	Goto-Kakizaki (GK) rats with type 2 diabetes.	Normalized glucose metabolism by altering the activities of glucose-regulating enzymes and reducing the levels of lipids in the serum and liver of the GK rats.	Akiyama et al. (2009b)
	STZ-induced diabetic mice.	Attenuated maternal glycaemia.	Toumi et al. (2009)
	STZ-induced marginal type 1 diabetic rats. Blood glucose levels. Hepatic glucose-regulating enzyme activities. Serum insulin.	Decreased blood glucose by altering the activity of glucose-regulating enzymes.	Akiyama et al. (2009a)
	Type 2 diabetic rats (HFD and STZ).	Decreased mRNA expression of TNF-α and resistin Increased serum insulin levels.	Abdel-Moneim et al. (2011)
	HFD-Fed low dose STZ-treated type 2 diabetic rats. Serum glucose, blood glycosylated hemoglobin and serum insulin levels.	Ameliorated the elevated levels of glucose, glycosylated hemoglobin and the lowered serum insulin level and hepatic and muscle glycogen content of insulin resistant diabetic rats. Alleviate resistin levels.	Ahmed et al. (2012)
	Cell culture (RAW 264.7 cells and 3T3-L1 preadipocytes).	Ameliorated TNF-α-mediated insulin resistance in differentiated 3T3-L1 cells.	Chae and Shin (2012)
	STZ-Induced diabetic rats. Histopathological study of pancreas.	Increased insulin concentrations. Decreased TNF-α levels. Decreasedthedegenerated islet cells.	Dokumacioglu et al. (2018)
	STZ-Induced diabetic rats. Fasting plasma glucose, insulin, glycosylated hemoglobin, and carbohydrate metabolic enzymes. OGTT.	Reduced plasma glucose levels in a dose-dependent manner. Increased insulin levels. Decreased glycosylated hemoglobin. Decreased G6Pase and fructose-1,6-bisphosphatase (FBPase). Improved glycogen content in the hepatic tissue.	Sundaram et al. (2019)
Kaempferol	Alloxan-induced diabetic rats. Serum glucose determination.	Lowered blood glucose (at higher dose 200 mg/kg). Hypoglycemic effect (at all doses tested).	de Sousa et al. (2004)
	Cell culture (3T3-L1 cells). Glucose uptake assay.	Improved insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes. Kaempferol could not induce differentiation of 3T3-L1 preadipocytes as traditional PPARγ agonist.	Fang et al. (2008)

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Compounds	Methods	Keys results	References
	Alloxan-induced diabetic rats. Serum glucose determination. ^{14}C-Glucose uptake in the rat soleus muscle studies. Glycogen content measurements.	Glucose uptake (35% and 21%). Kaempferol and insulin did not show a synergistic effect on glucose uptake. Increased glycogen content in the muscle.	Zanatta et al. (2008)
	Male Wistar rats. Glycogen synthesis in rat soleus muscle.	The PI3K–GSK-3 pathway and MAPK–PP1 pathway are involved in the stimulatory kaempferol 3-neohesperidoside effect on glycogen synthesis in rat soleus muscle.	Cazarolli et al. (2009c)
	Cell culture (insulin-secreting HIT-T15 cells). Measurement of intracellular ROS levels. Apoptosis determination by ELISA	Kaempferol protectedHIT-T15 pancreatic β-cells from dRib-induced associated oxidative damage.	Lee et al. (2010)
	Male Sprague–Dawley rats. Glucose intestinal absorption (GIA).	Increased the K_M without changes in the V_{MAX} of GIA. Additive inhibitory effect on GIA, when combined with phlorizin.	Rodríguez et al. (2010)
	α-Glucosidase inhibition assay.	Potent inhibitor of α-glucosidase *in vitro* with over 8-times more activity than acarbose.	Habtemariam (2011)
	Type 2 diabetic KK-A^y mice. Measurement of the fasting blood glucose levels and glucose tolerance test. Measurements of the insulin level.	Decreased fasting blood glucose levels. Decreased HbA_{1c} level.	Zang et al. (2011)
	Cell culture (INS-1E β-cells and human islets). Cell apoptosis assay. Insulin secretion and content assays.	Cytoprotective effects on cultured clonal β-cells and pancreatic human islets. Inhibited cellular apoptosis, and reduced caspase-3 activity in β-cells and human islets exposed to chronic high glucose, in a dose dependent manner. Improved expression of anti-apoptotic proteins Akt and Bcl-2. Improved insulin secretory function and synthesis in β-cells and human islets.	Zhang and Liu (2011)
	STZ-Induced diabetic rats. Measurement of the fasting blood glucose. Measurements of the plasma insulin level.	Decreased fasting blood glucose. Decreased insulin resistance. Improved disorders of glucose metabolism.	Liu et al. (2012)
	Cell culture (INS-1E cells and human islets). Cell apoptosis assay. Caspase-3 activity assay. Insulin secretion and content assays.	Inhibited apoptosis and reduced caspase-3 activity in INS-1E cells and human islets. Improved insulin secretion, synthesis, and pancreatic and duodenal homeobox-1 (PDX-1) expression.	Zhang et al. (2013)
	HFD-Induced obese mice. Measurements of pancreatic insulin content. Cell culture (C2C12 mouse cells). Glycogen synthesis.	Ameliorated hyperglycemia and hyperinsulinemia. Improved peripheral insulin sensitivity in obese mice fed a HFD. Prevented high fatty acid-impaired glucose uptake, glycogen synthesis, AMPK activity, and Glut4 expression in skeletal muscle cells (*in vitro*). Improved hyperglycemia, glucose tolerance, and blood insulin levels in obese diabetic mice, which are associated with the improved islet β-cell mass.	Alkhalidy et al. (2015)
	Cell culture (MIN6 pancreatic β-cells).	Improved β-cell proliferation through IRS2-related FoxO1 signaling.	Li Ji et al. (2015); Li Wang et al. (2015)
	HFD/STZ-induced diabetic rats. Insulin tolerance test. Serum biochemical assays.	Ameliorated insulin in a dose-dependent manner. Restored insulin resistance induced alteration of glucose disposal. ReducedTNF-α and interleukin-6 (IL-6) levels.	Luo et al. (2015)
	HFD-fed mice. Measurements of fasting blood glucose levels, HbA_{1c} and blood glucose tolerance test. Measurements of insulin and TNF-α levels.	Decreased fasting blood glucose, serum HbA_{1c} levels and improved insulin resistance. Decreased PPAR-γ expression.	Zang et al. (2015)
	α-Glucosidase inhibition assay. Determination of inhibitory type.	Notable inhibition activity on α-Glucosidase in a mixed-type manner [$IC_{50} = (1.16 \pm 0.04) \times 10^{-5}$ mol L^{-1}].	Peng et al. (2016)
	α-Amylase inhibition assay. α-Glucosidase inhibition assay.	Inhibited α-amylase and α-glucosidase with IC_{50} 51.24 and 29.37 μg/mL, respectively.	Ibitoye et al. (2018)
	α-Amylase inhibition assay. α-Glucosidase inhibition assay. Kinetics modes.	Competitive inhibitor for α-amylase. Non-competitive inhibitor for α-glucosidase.	Sheng et al. (2018)
	Cell culture (RIN-5F cell). Islets isolation.	Increased cell viability and anti-apoptotic activity in RIN-5F cells and murine pancreatic islets. Activation of autophagy *via* AMPK/mTOR pathway.	Varshney et al. (2017)
	Determinations of α-amylase and α-glucosidase inhibitory activities. Determinations of AGEs inhibitory activity.	Inhibitory activity against α-glucosidase, α-amylase, and formation of advanced glycation end-products	Yin et al. (2018)
	STZ-induced diabetic mice. Glycogen content measurement.	Improved hyperglycemia and reduced the incidence of diabetes. Reduced hepatic glucose production. Plasma insulin and glucagon levels were not altered. Restored hexokinase activity in the liver and skeletal muscle of diabetic mice. Suppressed hepatic pyruvate carboxylase activity and gluconeogenesis.	Alkhalidy et al. (2018b)
	HFD-fed obese mice. Pyruvate and glucose oxidation. Glycogen content. Glucose production. Enzyme activity assays.	Regulated hepatic gluconeogenesis and blood glucose homeostasis. Improved blood glucose level. Reduced hepatic glucose production. Improved whole-body insulin sensitivity. Increased Akt and hexokinase activity. Decreased pyruvate carboxylase (PC) and G6Pase activity in the liver without altering their protein expression. Kaempferol-induced autophagy restores the β-cells dysfunction.	Alkhalidy et al. (2018a)

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Compounds	Methods	Keys results	References
	Cell culture (RIN-5F cell line). Islets isolation. Insulin secretion and content analysis.		Varshney et al. (2017) Deux études et une seule référence
Luteolin	STZ-Induced diabetic rats. Histopathological study of pancreas. Peripheral glucose consumption.	Increased pancreatic insulin. Decreased glycemia levels (>50%). Increased insulin blood levels. Increased pancreas weight.	Zarzuelo et al. (1996)
	α-Amylase inhibition assay. α-Glucosidase inhibition assay.	Inhibited α-glucosidase by 36% at 0.5 mg/mL and was stronger than acarbose. Inhibited α-amylase although it was less potent than acarbose.	Kim et al. (2000)
	α-Glucosidase inhibition assay. Maltase activity. Sucrase activity. Blood glucose determination.	Potent maltase inhibitory activity with the IC_{50} of 2.3 mM. No significant change in blood glucose level with the doses of 100 and 200 mg/kg. Luteolin given at less than 200 mg/kg did not possess the ability to suppress the glucose production from carbohydrates through the inhibition of α-glucosidase action in the gut.	Matsui et al. (2002b)
	Cell culture (3T3-L1 cells). Glucose uptake assay. Western blot analysis.	Increased the response of glucose uptake to insulin stimulation in 3T3-L1 adipocytes. Enhanced Akt2 phosphorylation in an insulin-stimulated state. Decreased mRNA levels of TNF-α and interleukin 6. Enhanced PPARγ transcriptional activity in 3T3-L1 adipocytes.	Ding et al. (2010)
	Cell culture (endothelial cells).	Increased insulin-mediated endothelium-dependent relaxation in rat aorta. Reduced gene over-expressions for TNF-α and IL-6. Restored insulin signaling cascades with elevated insulin-dependent production of nitric oxide.	Deqiu et al. (2011)
	Assay for protein tyrosine phosphatase 1B (PTP1B) inhibition. Assay for aldose reductase (AR) inhibition.	Luteolin exerted the strongest inhibitory activity against PTP1B and rat lens AR.	(Choi Islam et al., 2014)
	Cell culture (Min6 cells). Islets isolation. Glucose-stimulated insulin secretion assay.	Inhibited uric acid-induced nitric oxide production. Inhibited uric acid-activated NF-κB in Min6 cells. Restored islet insulin secretion. No effect on pancreatic β-cells viability.	Ding et al. (2014)
	α-Glucosidase inhibition assay. Inhibitory kinetic analysis.	Inhibited α-glucosidase activity in a concentration dependent-manner [$IC_{50} = (1.72 \pm 0.05) \times 10^{-4}$]. Luteolin was a non-competitive inhibitor. Luteolin had a single inhibition site on α-glucosidase, and the K_i value was calculated to be $(1.40 \pm 0.02) \times 10^{-4}$ mol L^{-1}.	Yan et al. (2014)
	KK-A^y mice Measurement of fasting blood glucose levels and glucose tolerance test. Measurements of the insulin and HbA_{1c} levels. HOMA-IR.	Improved blood glucose, HbA_{1c}, insulin, and HOMR-IR levels.	Zang et al. (2016)
	HFD-fed mice. Cell culture (RAW264.7 macrophages and 3T3-L1 cells).	Improved insulin resistance. Suppressed inflammatory macrophage infiltration and polarization in mouse epididymal adipose tissues. Luteolin activated AMPKα1 in macrophages to inhibit their inflammatory polarization and enhanced insulin signals in adipocytes.	(L. Zhang et al., 2016)
Malvidin-3-*O*-glucoside	Diabetic C57bl/6J mice. Cell culture (caco-2 cell). Determination of ^{14}C-fructose uptake.	Exhibited significant hypoglycemic activity at a dose of 300 mg/kg. Inhibited ^{14}C-fructose uptake. The highest concentration was also able to cause a ≅ 15% reduction in uptake.	Grace et al. (2009) Andrade et al. (2017)
	α-Glucosidase, α-amylase, and DPP-4 inhibition assays. Caco-2 cell proliferation. Glucose uptake *in vitro*.	Inhibited of α-glucosidase activity (42.8%). Inhibited of α-Amylase activity (29.6%). Inhibited of DPP-4 activity (82.4%). After 30 min of treatment, malvidin showed the highest decrease in glucose uptake (55.2%)	Mojica et al. (2017b)
	α-Glucosidase, α-amylase, and DPP-4 inhibition assays. Caco-2 cell proliferation.	Inhibited α-glucosidase activity(42.8%). Inhibited α-amylase activity (29.6%). InhibitedDPP-4 activity (82.4%).	Mojica et al. (2017a)
	α-Glucosidase and α-amylase inhibition assays.	Potent inhibitory of α-Glucosidase (IC_{50} = 55 μg/mL)	Rodriguez and Karakayaa (2017)
Myricetin	Preparation of isolated adipocytes. Purification of insulin receptors. D-Glucose transport. Translocation of Glut4 glucose transporters.	Stimulated lipogenesis in rat adipocytes and enhanced the stimulatory effect of insulin. Stimulated both D-glucose and D-3-*O*-methyl-glucose uptake in rat adipocytes. Increased V_{max} of glucose transport. The stimulation of glucose transport was not a consequence of glucose transporter translocation.	Ong and Khoo (1996)
	STZ-induced diabetic rats. Determination of glycogen content. Determination of G6Pase. Glycogen synthase and phosphorylase assays.	Stimulated glucose transport in rat adipocytes and enhanced insulin-stimulated lipogenesis. Reduced hyperglycemia in diabetic rats (50%). Increased hepatic glycogen and G6Pase content. Increased hepatic glycogen synthase I activity without having any effect on total glycogen synthase.	Ong and Khoo (2000)
			Liu Liou et al. (2005)

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Compounds	Methods	Keys results	References
	STZ-induced diabetic rats. Plasma glucose determination. Intravenous glucose challenge test (IVGCT). Measurement of glucose uptake into soleus muscle. Measurement of glycogen synthesis in hepatocytes.	Decreased plasma glucose concentrations in a dose-dependent manner. Stimulatory effect on glucose uptake of the soleus muscles isolated from STZ-diabetic rats in a concentration-dependent manner. Myricetin enhanced glucose utilization to lower plasma glucose in diabetic rats lacking insulin.	
	Isolated adipocytes. Glucose uptake assays. GLUT4 3D molecular comparative modelling.	Inhibited the uptake of methylglucose by adipocytes. Inhibit the transport of glucose in isolated rat adipocytes stimulated with insulin	Strobel et al. (2005)
	STZ-induced diabetic rats. Plasma glucose determination.	Decreased plasma glucose concentration in a dose-dependent manner. Increased the expression of the GLUT 4 in soleus muscle and in reduced expression of PEPCK in liver.	Liu et al. (2006)
	Obese Zucker rats. Measurement of the glucose-insulin index	Improved insulin sensitivity through increased post-receptor insulin signaling mediated by enhancements in IRS-1-associated PI3-kinase and GLUT 4 activity in muscles of obese Zucker rats.	Liu et al. (2007a)
	Fructose chow-fed rats. OGTT. Plasma analysis. Measurement of glycogen synthesis in hepatocytes. *In vivo* insulin receptor activation.	Decreased high glucose level. Decreased insulin resistance. Increased the whole-body insulin sensitivity. Improved insulin sensitivity through the enhancement of insulin action on IRS-1- associated PI 3-kinase and GLUT 4 activity in soleus muscles of animals exhibiting insulin resistance.	Liu et al. (2007b)
	Fructose-fed rats. Plasma glucose measurement. *In vivo*insulin receptor activation. HOMA-IR	Decreasedplasma glucose leveland increased plasma β-endorphin. Amelioration of impaired signaling intermediates downstream of insulin receptors.	Tzeng et al. (2011)
	Cell culture (skeletal muscle cell line C2C12 myoblasts). Glucose uptake activity assay.	Increased glucose uptake with both protein kinase B (Akt) and AMPK activities. Decreased insulin resistance.	Ding et al. (2012)
	STZ-induced diabetic rats. OGTT. Plasma glucose measurement.	Decreased plasma glucose levels. Increased insulin levels.	Kandasamy and Ashokkumar (2012)
	High-fat, high-sucrose (HFHS) diet-fed mice. Serum glucose and insulin measurement. HOMA-IR.	Decreased serum glucose, insulin levels, and HOMA-IR values. Reduced TNF-α and IL-6.	(Choi Kang et al., 2014)
	STZ-induced diabetic rats. Estimation of plasma glucose, insulin, and glycosylated hemoglobin. Estimation of carbohydrate metabolic enzymes. Estimation of hepatic and muscle glycogen. Histopathological study of pancreas.	Normalized carbohydrate metabolic products like glucose, glycated hemoglobin, glycogen phospharylase and gluconeogenic enzymes. Increased insulin, glycogen, glycogen synthase and insulin signaling molecules expression like GLUT2, GLUT4, insulin receptor-1 (IRS1), IRS2 and protein kinase B (PKB). Cytoprotective effect on pancreas.	Kandasamy and Ashokkumar (2014)
	STZ-induced diabetic rats. α-Glucosidase inhibitory activity *in vivo*. Male C57BL/KsJ-*db/db* mice.	Reduced serum fasting glucose, blood glycated hemoglobin, and maltase activities of the small intestine in *db/db* mice. Inhibitedα-glucosidase activity.	Kang et al. (2015)
	α-Amylase and α-glucosidase inhibition assays. Cell culture (3T3-L1 pre-adipocytes). Glucose uptake in mature adipocytes.	Inhibited both α-amylase and α-glucosidase. Exhibited 'insulin-like' effect by enhancing the accumulation of lipids, glucose uptake and adiponectin secretion by activating insulin signaling pathway similar to insulin. Upregulated Akt1, PPARγ and glucose transporter genes in addition to protein kinase, AMP activated and adiponectin to stimulate glucose uptake.	Arumugam et al. (2016)
	α-Amylase and α-glucosidase inhibition assays.	Inhibition of α-amylase activity with $IC_{50} = 662$ μg/ml. Inhibition of α-glucosidase activity with $IC_{50} = 3$ μg/ml. The inhibition effect on α-amylase was reversible and competitive, and the effect on α-glucosidase was reversible but non-competitive.	Meng et al. (2016)
	Islets isolation. Insulin secretion assay in Wistar rats. Glucose tolerance test. HbA1c measurement.	Glucoregulatory activity.	Li, Zhang et al. (2017); Li, Zheng et al. (2017)
	db/db male mice. Glucose tolerance test. Blood glucose level determination. Insulin tolerance test. Blood glucose level determination.	Improved systemic insulin resistance by activating brown adipose tissue (BAT) and increased adiponectin expression in BAT.	Hu et al. (2018)
Naringenin	Glucose uptake assay. Cell culture (primary rat preadipocytes).	Stimulated glucose uptake (163%) in rat adipocytes.	Lim et al. (2008)
	Non-insulin-dependent diabetes mellitus (NIDDM) rat models. Oral glucose tolerance tests. α-Glucosidase inhibition assay. *In vitro*inhibition of 11β-HSD1.	Decreased plasma glucose. No inhibition of α-glucosidase activity *in vitro*. Inhibition of 11β-HSD1 activity by 39.49%.	Ortiz-Andrade et al. (2008)
	Cell culture (3T3-L1 cells).	Inhibited TNF-αstimulated FFA secretion from mouse adipocytes. Blocked the TNF-αinduced activation of the NF- κB and ERK pathways.	Yoshida et al. (2010)
	Cell culture (L6 rat myotubes). Glucose uptake assay.	Stimulated glucose uptake in L6 myotubes in a dose- and time-dependent manner. No increase in glucose uptake in myoblasts. Increased AMPK phosphorylation/activation.	Zygmunt et al. (2010)
			Annadurai et al. (2012)

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Compounds	Methods	Keys results	References
	STZ–nicotinamide-induced diabetic rats. Determination of blood glucose, glycosylated hemoglobin and serum insulin. Histopathological study of pancreas.	Lowered fasting blood glucose levels and glycosylated hemoglobin. Elevated serum insulin levels. Protective effect on pancreas.	
	STZ–nicotinamide-induced diabetic rats.	The values of hematological, mRNA transcript and protein indices of inflammation were all lower than those in diabetic rats.	Annadurai et al. (2013)
	Incubation of INS-1E cells. Insulin content determination.	Enhanced glucose-stimulated insulin secretion. Enhanced glucose sensitivity in INS-1E cells. Modulated gene expression profiles to improve β-cell survival and function during glucotoxicity.	Sumangala Bhattacharya et al. (2014a)
	Myotube cultures. Glucose uptake assay.	Naringenin enhanced phosphorylation of TBC1D1 suggesting that this compound enhanced the translocation of GLUT4 containing vesicles and thereby glucose uptake *via* a TBC1D1-dependent mechanism.	Sumangala Bhattacharya et al. (2014b)
	HFD fed STZ induced diabetic rats. α-Glucosidase inhibitory assay. Kinetics of α-glucosidase inhibition.	Competitive inhibition of intestinal α-glucosidaseactivity *in vivo*. Lowered postprandial blood glucose levels.	Priscilla et al. (2014)
	HFD fed STZ induced type 2 diabetic rats. Estimation of fasting blood glucose level and plasma insulin. Histopathological study of pancreas.	Reduced hyperglycemia and hyperinsulinemia. Modulated the expressions of GLUT4 and TNF-α. Restored histological abnormalities. Enhanced insulin sensitivity.	Priscilla et al. (2015)
	STZ-induced diabetic rats. Oral glucose tolerance test. Blood glucose levels determination. Insulin concentrations. Insulin resistance index.	Decreased blood glucose and insulin resistance index. Improved impaired glucose tolerance.	Ren et al. (2016)
	STZ-induced diabetic mice. Blood glucose and glycosylated hemoglobin determination.	Lowered blood glucose and glycosylated hemoglobin.	Sharma et al. (2016)
	Tsumura suzuki obese diabetes (TSOD) mice. Oral glucose tolerance test.	Naringenin attenuated hypoglycemic action of pioglitazone in TSOD mice. Naringenin did not affect fasting blood glucose levels.	Yoshida et al. (2017)
	Nicotineamide (NA)/STZ-induced diabetic rats. Biochemical analysis.	Alleviated the lowered serum insulin and C-peptide levels, the depleted liver glycogen content, the elevated liver G6Pase and glycogen phosphorylase activities. Enhanced mRNA expression of insulin receptor β-subunit and GLUT4.	Ahmed et al. (2017)
	STZ-induced diabetic rats. Measurement of blood glucose levels and liver glycogen levels. Molecular studies	Reduced blood glucose levels. Strong binding affinity towards PPARγ and GLUT4. Exhibited antidiabetic effects through the dual activation of PPARγ/GLUT4 signaling pathways.	Singh et al. (2018)
Naringin	C57BL/KsJ-db/db Mice. Blood biomarkers. Hepatic glycogen assay. Hepatic enzyme activities. Histopathological study of pancreas.	Reduced blood glucose. Elevated hepatic glucokinase activity and glycogen concentration. Increased plasma insulin, C-peptide, and leptin.	Jung et al. (2004)
	STZ-induced diabetic rats. Biochemical analysis.	Decreased blood glucose and glycated hemoglobin. Increased plasma insulin and liver glycogen. Increased activity of hexokinase and decreased activities of G6Pase and FBPase in liver and kidney.	Punithavathi et al. (2008)
	STZ-Nicotinamide induced diabetic rats. Determination of plasma glucose, insulin, hemoglobin and glycosylated hemoglobin. Determination of carbohydrate metabolic enzymes. Determination of glycogen.	Decreased blood glucose. Increased insulin. Reduced glycosylated hemoglobin. Increased hepatic glucokinase activity and glucose-6-phosphate dehydrogenase. Decreased the activity of G6Pase and FBPase.	Pari and Suman (2010)
	HFD-fed low dose STZ-induced diabetic rats. Biochemical analysis.	Decreased glucose levels, FFA, TNF-α, and resistin. Increased serum insulin levels.	Abdel-Moneim et al. (2011)
	HFD–STZ-induced diabetic rats. Glucose tolerance and insulin tolerance tests. Serum insulin, IL-6, and TNF-α. Insulin resistance and β-cell function	Decreased insulin resistance, hyperinsulinemia, hyperglycemia, TNF-α, IL-6, and increased β-cell function in a dose-dependent manner. Increased PPARγ expression in liver and kidney.	Kumar Sharma et al. (2011)
	HFD-Fed low dose STZ-induced diabetic rats. Biochemical analysis.	Ameliorated the elevated levels of glucose, glycosylated hemoglobin, and the lowered serum insulin level and hepatic and muscle glycogen content of insulin resistant diabetic rats.	Ahmed et al. (2012)
	STZ-Induced diabetic rats. Blood glucose testing. Plasma insulin.	Hypoglycemic effects of naringin require insulin, suggesting a beneficial effect in type 2 as opposed to type 1 diabetes.	Xulu and Oroma Owira (2012)
	STZ-Induced diabetic rats. Blood glucose measurement.	Decrease blood glucose level.	Al-Kurdy (2014)
	Cell culture (L6 myoblast cell line). Modulation of glucose uptake.	Increase theuptake of fluorescent labeled glucose in differentiated L6 myoblast.	Dhanya et al. (2015)
	Cell culture (RIN-5F cells). Insulin secretion.	Reduced glucose-dependent insulin secretion in a concentration-dependent manner. Prevented pancreatic β-cell dysfunction and apoptosis.	Nzuza et al. (2016)
	NA/STZ-Induced diabetic rats. Biochemical analysis.	Alleviated the lowered serum insulin and C-peptide levels, the depleted liver glycogen content, the elevated liver G6Pase and glycogen	Ahmed et al. (2017)

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Table 7 (*continued*)

Compounds	Methods	Keys results	References
		phosphorylase activities. Enhanced the mRNA expression of insulin receptor β-subunit and GLUT4.	
	HFD-Fed-low dose of STZ-induced diabetic rats. Biochemical analysis. OGTT. Assay of carbohydrate metabolic enzymes. Estimation/Assay of glycogen and glycogen metabolic enzymes.	Reduced plasma glucose and blood glycosylated hemoglobin levels. Increased plasma insulin level. Improved activities of the hepatic key enzymes of carbohydrate metabolism in a dose dependent manner.	Pari and Chandramohan (2017)
	STZ-induced diabetic mice. Glucose and insulin measurements. Histopathological study of pancreas. Apoptosis measurement.	Ameliorated hyperglycemia and islet dysfunction in insulin-deficient diabetic mice in a dose dependent manner. Protectedpancreatic β-cell apoptosis by inhibiting both the intrinsic (mitochondria- mediated) and extrinsic (death receptor-mediated) pathways.	Lim et al. (2018)
Peonidin	Sprague-Dawley Rats. Blood glucose level determination.	Inhibited maltase activity (IC_{50} = 200 μM). Decreased blood glucose level by 16.5%. Inhibited glycemic rise (ED_{20} = 69 mg/kg).	Matsui et al. (2002a)
Petunidin	Insulin secretion studies.	Marginal effect on the insulin secretion from rodent pancreatic β-cells (INS-1832/13) *in vitro*.	Jayaprakasam et al. (2005)
	Docking study. α-Amylase inhibition assay.	Inhibition of α-amylase activity. Sloweddown the glucose release in blood stream.	Vellingiri et al. (2016)
Quercetin	STZ-Induced diabetic rats. Plasma glucose level determination. Glucose tolerance test. Hepatic glucokinase assay. Histopathological study of pancreas.	Decreased plasma glucose level in a dose dependent manner. Improved glucose tolerance tests. Increased hepatic glucokinase activity. Regeneration of pancreatic islets.	Vessal et al. (2003)
	STZ-Induced diabetic rats. Measurement of fasting blood sugar.	Ameliorated diabetic status about 25%.	Shetty et al. (2004)
	STZ-Induced diabetic rats. Biochemical analysis. Histopathological study of pancreas. Immunohistochemical procedures.	Protective effect in diabetes by decreasing oxidative stress and preservation of pancreatic β-cell integrity.	Coskun et al. (2005)
	STZ-Induced diabetic rats. Histopathological study of the pancreas. Biochemical analysis. Pancreatic insulin contents.	Decreased blood glucose level. Increased pancreatic insulin contents. Protected and preserved pancreatic β-cell architecture and integrity.	Adewole et al. (2007)
	Cell culture (3T3-L1 cells). [^{3}H]-2-Deoxy-D-glucose uptake assay.	Improved insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes. Partial agonist of PPARγ.	Fang et al. (2008)
	Alloxan-induced diabetic rats. Biochemical analysis.	Prevented serum glucose elevation. Inhibited renal glucose reabsorption.	Lukačínová et al. (2008)
	High fructose diet-fed rats. Assay of glucose, insulin and insulin sensitivity indices. Activities of glucose and glycogen metabolizing enzymes. Activities of hexokinase and pyruvate kinase, G6Pase and FBPase in liver and skeletal muscle.	Decreased blood glucose levels. Improved insulin signaling and sensitivity and the effect was comparable with that of metformin. Reduced plasma glucose levels and insulin by 25%. Reduced $AUC_{glucose}$ and $AUC_{insulin}$ values. Decreased activities of G6Pase and FBPase. Increased activity of glycogen phosphorylase enzyme and content of glycogen.	Kannappan and Anuradha (2009)
	Hepatic gene expression of BALB/c mice with STZ-induced diabetes.	Decreased blood glucose levels. Improved plasma insulin levels. Reduced hepatic oxidative stress in STZ-induced diabetic mice. Improved pancreas functions by enabling the recovery of cell proliferation through the inhibition of *Cdkn1a* expression.	Kobori et al. (2009)
	α-Glucosidase inhibition assay. Kinetics measurements.	Inhibition of α-glucosidase activity with IC_{50} = 0.017 mmol × L^{-1}	Li et al. (2009)
	STZ-Induced diabetic rats. Plasma glucose determination. Glucose tolerance test.	Decreased blood glucose level. Decreased glucose tolerance curves.	Abdelmoaty et al. (2010)
	Cell culture (C2C12 murine skeletal myoblasts and H4IIE murine hepatocytes). Glucose uptake assay. Western immunoblot analysis.	Enhanced glucose uptake by 38–59% in the absence of insulin. Stimulated AMPK pathway at concentrations of 25–100 μM.	Eid et al. (2010)
	STZ-Nicotinamide induced diabetic rats. Blood glucose determination. Inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) assay.	Decreased blood glucose level. Inhibited 11β-HSD1.	Torres-Piedra et al. (2010)
	Cell culture (mouse embryonic fibroblasts). HFD-Fed rats. Measurement of plasma concentrations of insulin and glucose. PPARγ mRNA measurement.	Inhibited the expression of PPARγ*in vivo*. Preventedimpairment of insulin sensitivity.	Wein et al. (2010)
	Cell culture (INS-1 cells). Rat pancreatic islets preparation. Insulin secretion. Western blot analysis.	Potentiated glucose-induced insulin secretion. Protected β-cell function and viability. Potentiated ERK1/2 phosphorylation.	Youl et al. (2010)
	STZ-Induced diabetic rats. Biochemical assays.	Decreased blood glucose levels and insulin resistance. Increased insulin levels and β-cell function.	El-Baky (2011)

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Table 7 (*continued*)

Compounds	Methods	Keys results	References
	Measurement of control of postprandial hyperglycemia in STZ-induced diabetic rats. Measurement of control of fasting hyperglycemia in *db/db* mice.	Decreased plasma glucose levels STZ-treated rats. Reduced both plasma glucose and blood HbA_{1C} of *db/db* mice. Reduce small intestine maltase activities.	Kim et al. (2011)
	Evaluating the postprandial blood glucose level after maltose and glucose loading in normal and STZ-induced diabetic rats.	Ameliorated postprandial hyperglycemia in STZ-induced diabetic rats loaded with maltose.	Hussain et al. (2012)
	STZ-Nicotinamide induced diabetic rats. Glucose tolerance test. Glucose uptake assay. Glucose transport inhibitor activity.	Increased glucose uptake. Decreased glucose transport activity.	Jadhav and Puchchakayala (2012)
	db/db mice. Biochemical analyses.	Lowered plasma glucose levels. Reduced HOMA-IR without significant influence on insulin levels.	Jeong et al. (2012)
	STZ-Induced diabetic rats. Blood glucose test. Histopathological study of the pancreas. Immunohistochemical study of pancreas.	Decreased blood glucose levels. Reversed most of the pancreatic morphological changes. Increased β-cells number.	Rifaai et al. (2012)
	Cell culture (C2C12 skeletal muscle cells). Glucose uptake assay. Immunoblot analysis.	Attenuated the effects of TNF-α. Improved insulin sensitivity and glucose uptake in a dose-dependent manner *via* the activation of the protein kinase B (Akt) and AMPK pathways.	Dai et al. (2013a)
	Alloxan-induced diabetic mice. Fasting blood glucose estimation. Estimation of glucose metabolic enzymes. GLUT-4 estimation.	Decreased fasting blood glucose levels. Increased hexokinase activity. Decreased FBPase and G6Pase activities. Increased GLUT4 expression levels.	Alam et al. (2014)
	High-fat and high-sucrose diet-fed rats. Glucose tolerance test. HOMA-IR. Serum glucose, insulin, fructosamine and free fatty acids measurement.	Reduced fructosamine, basal glucose, insulin, and consequently HOMA-IR.	Arias et al. (2014)
	Cell culture (L6 myoblasts). 2-NBDG uptake.	Increased glucose uptake in L6 myotubes was attributed to GLUT 4 translocation, the most downstream factor in the insulin signaling cascade, which increased two to threefoldsby the prolonged pretreatment of quercetin (10 μM).	Dhanya et al. (2014)
	Cell culture (L6 skeletal muscle cells, murine H4IIE and human HepG2 hepatocytes). Determination of G6Pase activity in H4IIE hepatocyte. Measurement of glycogen synthase (GS) activity in HepG2 hepatocytes	Increased glucose uptake, GLUT4 translocation and GLUT4 protein content in L6 myotubes. Increased AMPK phosphorylation in L6 myotubes. Induced hepatic AMPK activation and inhibited G6pase in H4IIE hepatocytes. Increased GS activity.	Eid et al. (2015)
	α-Amylase and α-glucosidase inhibition assays. Enzyme kinetics tests.	Inhibitedof α-amylase activity with IC_{50}values of 770 μg/ml. Inhibition of α-glucosidase activity with IC_{50} values of 32 μg/ml. The effect on α-amylase was reversible and competitive. The effect on α-glucosidase was reversible but non-competitive.	Meng et al. (2016)
	Cell culture (L6 myoblasts). 2-NBDG uptake.	The effect on 2-NBDG uptake in L6 myotubes was not through insulin signaling pathway, but through AMPK pathway and its downstream target p38 MAPK. AMPK signaling pathway contributed to the correction of insulin resistance through bypassing the insulin-regulated system for GLUT4 translocation.	Dhanya et al. (2017)
	STZ-Induced diabetic rats. Investigated the antidiabetic action of quercetin alone and in combination with resveratrol. Measurement of blood glucose levels. OGTT. Biochemical analysis. Measurements of serum insulin, C-peptide, and $HbA1_c$. Measurements of hepatic glucose regulating enzymes. Histopathological study of pancreas.	Improved serum blood glucose levels and insulin levels. Maintained activities of hepatic glucose metabolic enzymes and structure of pancreatic β-cells	Yang and Kang (2018)
	Fructose-STZ induced diabetic rats. Determination of HbA1c. Determination of hepatic glycogen content. Determination of hexokinase and G6Pase activities. Histopathological study of pancreas.	Reduced blood glucose levels, glycosylated hemoglobin, and hepatic glycogen. Improved hexokinase and G6Pase activities. Reduced glycemia in the glucose tolerance test. Restored the damage caused by fructose-STZ in the pancreas to near normal.	Oyedemi et al. (2020)
Quercetin-3-*O*-glucoside	Alloxan-induced diabetic rats. Determination of G6Pase activities. Serum glucose estimation. Human Insulin-Specific Radioimmunoassay (RIA)	Decreased serum glucose concentrations with a parallel increase in insulin level. Inhibited hepatic G6Pase activity.	Panda and Kar (2007b)
Quercitrin	STZ-Induced diabetic rats. Biochemical assays. Histopathological study of the pancreas.	Decreased fasting plasma glucose. Increased insulin levels. Increased glycogen content in liver and muscle. Increased hexokinase activity. Decreased G6Pase and FBPase activities in the tissues. Protected the pancreas.	Babujanarthanam et al. (2009)

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Compounds	Methods	Keys results	References
	STZ-induced diabetic rats. Biochemical assays. Histopathological study of the pancreas.	Decreased fasting plasma glucose. Increased insulin levels. Protected the pancreas.	Babujanarthanam et al. (2011a)
	STZ-induced diabetic rats. Biochemical assays. Determination of plasma insulin and C-peptide.	Decreased fasting plasma glucose and HbA1c. Increased insulin and C-peptide.	Babujanarthanam et al. (2011b)
	Cell culture (RINm5F rat insulinoma cells). Glucose-stimulated insulin secretion (GSIS) assay.	Quercetin/quercitrin protected against cytokine-induced cell death. Improved GSIS. Inhibited translocation of nuclear factor-κB (NF-κB).	Dai et al. (2013b)
	STZ-Induced diabetic rats. Measurement of blood glucose levels.	Reduced blood glucose levels.	US (2019)
Isoquercitrin	Rats were administered 20% glucose solution by oral gavage. OGTT.	Antihyperglycemic activity in a time-dependent manner by delaying the post-oral glucose load glycemic peak at 30 min.	Paulo et al. (2008)
	STZ-Induced diabetic rats. Determination of fasting blood glucose (FBG). OGTT. Biochemical assays. Glucose consumption measurement. Histopathological study of the pancreas.	Improved FBG and glucose tolerance. Protected pancreatic β-cell.	Huang et al. (2017)
	STZ-Induced diabetic mice. NCI–H716 cells. DPP-4 inhibition assays. Measurement of FBG and OGTT. Measurement of GLP-1 and insulin.	Inhibited DPP-4 in a competitive manner, with IC_{50} and K_i values of 96.8 and 236 μM, respectively. Decreased FBG level. Inhibited postprandial blood glucose changes in a dose-dependent manner. Increased secretions of serum GLP-1 and insulin in a concentration-dependent manner.	Zhang, Zhang et al., (2018)
Resveratrol	STZ-Induced diabetic rats and STZ-nicotinamide diabetic rats. Intravenous glucose challenge test (IVGCT). Determination of plasma glucose and plasma insulin. Measurement of glucose uptake and glycogen synthesis in hepatocytes.	Reduced plasma glucose concentration by 25.3 ± 4.2 and 20.3 ± 4.2%, in STZ-DM and STZ-nicotinamide DM rats, respectively. Decreased insulin secretion and delayed the onset of insulin resistance (in STZ-nicotinamide DM rats). Increased stimulation of glucose uptake in a dose-dependent manner. Promotedglycogen synthesis by hepatocytes.	Su et al. (2006)
	STZ-Induced diabetic rats. OGTT. Determination of serum insulin concentration. Cell culture (C2C12 cells). Glucose uptake.	Induced hypoglycemic effect in insulin-deficient STZ-diabetic rats *via* PI3K-Akt-signaling pathway to enhance glucose uptake into skeletal muscle. Increased insulin secretion in rats with sufficient insulin secretion function. Lowered plasma glucose through insulin-dependent and -independent mechanisms. Increased GLUT4 expression in the soleus muscle.	Chi et al. (2007)
	STZ-Nicotinamide induced diabetic rats. Measurement of FBG, OGTT and HbA_{1c}. Insulin estimation.	Decreased blood glucose levels and HbA_{1c}. Improved plasma insulin levels.	Palsamy and Subramanian (2008)
	STZ-induced diabetic rats. Cell culture (H9c2 cells). Measurement of blood glucose Glucose uptake. Western blot analysis.	Increased glucose uptake with H9c2 cardiac myoblast cells. Decreased blood glucose levels. Increased AMPK phosphorylation. Increased Glut-4 expression.	Penumathsa et al. (2008)
	STZ-Nicotinamide-induced diabetic rats. Biochemical estimations.	Reduced blood glucose and HbA_{1c} levels. Increased plasma insulin level. Improvedhexokinase, pyruvate kinase, G6Pase, FBPase, glucose-6-phosphate dehydrogenase, glycogen synthase and glycogen phosphorylase in liver and kidney tissues. Improved hepatic glycogen content.	Palsamy and Subramanian (2009)
	Diet-induced obese and diabetic mice.	CNS resveratrol delivery normalized diet-induced hyperglycemia. CNS resveratrol delivery improved hepatic PEPCK expression and pyruvate-induced hyperglycemia. Improved hypothalamic nuclear factor-κB inflammatory signaling.	Ramadori et al. (2009)
	STZ-Nicotinamide induced diabetic rats. Determination of FBG, plasma insulin, and HbA_{1c}. Assay of TNF-α, IL-1b, and IL-6. Histopathological study of the pancreas.	Decreased blood glucose levels, HbA_{1c}, TNF-α, IL-1b and IL-6. Increased insulin secretion. Protectedpancreatic β-cells.	Palsamy and Subramanian (2010)
	HFD-Fed diabetic mice. Oral glucose tolerance test and insulin assays. GLP-1 measurement.	Reduced the development of glucose intolerance. Increased portal vein concentrations of both GLP-1 and insulin. Increased levels of colonic proglucagon mRNA transcripts. Improved levels of active GLP-1 and control of glycemia.	Dao et al. (2011)
	Wrn mutant mice. Measurement of blood glucose concentration Measurement of serum insulin. HOMA-IR.	Improved hyperglycemia and insulin resistance phenotype. Increased genes involved in the insulin signaling pathway.	Labbé et al. (2011)
	NOD mouse model of type 1 diabetes. Histopathological study of pancreas.	Prevented and treated type 1 diabetes. Protected pancreatic islets.	Lee, Yang et al. (2011)
	db/db mice. RIN-5F cells derived from rat pancreatic β-cells. Measurement of blood glucose.	Suppressed the rise in the blood glucose level. Increased serum insulin concentration. Increased glucose uptake in a dose-dependent manner in the absence of	Minakawa et al. (2011)

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Table 7 (*continued*)

Compounds	Methods	Keys results	References
	Determination of glucose uptake by cultured L6 myotubes.	insulin. Translocated the GLUT4 to plasma membrane. Protected pancreatic β-cells.	
	STZ-Induced diabetic rats.	Decreased serum glucose concentration.	Mohamad Shahi, Haidari, & Shiri, 2011
	ob/ob Mice (a model of type 2 diabetes). Measurement of plasma glucose and insulin. OGTT.	Antihyperglycemic activity with an improvement in the insulin levels. Improved glucose excursion in the OGTT.	Sharma et al. (2011)
	C57BL/KsJ-db/db mice. Determination of blood glucose, HbA_{1c} and IPGTT. Determination of plasma insulin and glucagon. Measurement of glucose regulating enzyme activities and glycogen content in the liver. Western blot analysis.	Lowered fasting blood glucose and HbA_{1c} levels. Increased insulin secretion. Improved glucose homeostasis in liver and skeletal muscle. Induced activation of AMPK and downstream targets regulates glucose metabolism in db/db mice.	Do et al. (2012)
	STZ-Induced diabetic rats. Measurement of FBG concentration and an IPGTT. Immunohistochemical study of pancreas.	Prevented hyperglycemia in STZ-treated rats. Inhibited apoptosis of pancreatic β-cell. Inhibited the cleavage of poly(ADP-ribose) polymerase.	Ku et al. (2011)
	db/db Mice. Glucose and insulin tolerance tests. Immunohistochemical study of pancreas.	Improved glucose tolerance. Preserved the pancreatic β-cell mass.	Lee et al. (2012)
	Alloxan-induced diabetic mice. Determination of blood glucose levels. Histopathological study of the pancreas.	Decreased blood glucose levels. Alleviated the pancreas damage. Inhibitedthe proinflammatory factor, NF-κB.	Ramar et al. (2012a)
	Methylglyoxal-induced diabetic mice. Oral glucose tolerance test and insulin tolerance test. HOMA-IR. Immunohistochemical study of pancreas.	Improved blood glucose level. Improved insulin resistance as demonstrated by the reduced 86.2% insulin levels. Reducedthe value of HOMA-IR index Protected pancreatic islets.	Cheng, Cheng et al., (2015)
	STZ-Induced diabetic rats. Measurement of FBG concentration.	Combination with vitamin C decreased FBG levels.	Lalitha et al. (2015)
	Pregnant db/+ gestational diabetes mellitus mouse model. Glucose tolerance test. Insulin tolerance test. Measurement of serum glucose and insulin. Liver G6Pase activity.	Improved glucose metabolism and insulin tolerance. Increased AMPK activation, which in turn reduced the production and activity of G6Pase in both pregnant db/+ females and their offspring.	Yao et al. (2015)
	STZ-induced diabetic rats. Estimation of blood glucose, HbA_{1c}, and insulin. Histopathological study of pancreas.	Reduced blood glucose and HbA_{1c}. Increased insulin secretion from β-cells. Decreased pancreatic β-cell damage.	Kaur et al. (2016)
	Alloxan-induced diabetic rats. Estimation of blood glucose levels. OGTT. HOMA-IR method.	Resveratrol alone and/or in combination with vitamin-E exhibited significant hypoglycemic effects, glucose tolerance effects and improved insulin sensitivity.	Rehman et al. (2018)
	STZ-induced diabetic rats. Cotreatment with quercetin and resveratrol. Measurement of blood glucose levels. OGTT. Measurements of serum insulin, C-peptide, and HbA_{1c}. Measurements of hepatic glucose regulating enzymes. Histological analysis of pancreas tissues.	Decreased serum blood glucose levels and insulin levels. Maintained the activities of hepatic glucose metabolic enzymes and structure of pancreatic β-cells.	Yang and Kang (2018)
Rutin	STZ-induced diabetic rats. Measurements of plasma insulin, C-peptide, and HbA_{1c}.	Decreased FBG and HbA_{1c}. Increased insulin and C-peptide.	Kamalakkannan and Prince (2006)
	STZ-induced diabetic rats. Measurements of FBG concentration and plasma insulin. Determination of hexokinase, G6Pase, and FBPase activities. Histological analysis of pancreas tissues.	Decreased fasting plasma glucose. Increased insulin levels. Increased glycogen content in the liver and muscle. Increased hexokinase activity. Decreased G6Pase, and FBPase activities in the tissues. Protective effect on pancreatic islets.	Prince and Kamalakkannan (2006)
	α-Glucosidase inhibition assay. Kinetics measurements.	Inhibited α-glucosidase activity with $IC_{50} = 0.196$ mmol × L^{-1}	Li et al. (2009)
	A type 2 diabetic rat model. STZ-nicotinamide induced diabetic rats. Glucose tolerance test. Glucose uptake assay. Glucose transport inhibitor activity.	Decreased non-fasting blood glucose levels in a dose dependent manner. Increased glucose uptake. Decreased glucose transport activity.	Hunyadi et al. (2012a) Jadhav and Puchchakayala (2012)
	Isolated soleus muscles from rats. Studies on ^{14}C-glucose uptake in rat soleus muscle.	Stimulated glucose uptake in the rat soleus muscle *via* the PI3K, atypical protein kinase C and mitogen-activated protein kinase (MAPK) pathways.	Kappel et al. (2013)
	Cell culture (L6 myoblasts). 2-NBDG uptake.	Increased glucose uptake in L6 myotubes was attributed to GLUT 4 translocation, the most downstream factor in the insulin signaling cascade, which increased two to threefold on chronic pretreatment of quercetin (10 μM).	Dhanya et al. (2014)
	Cell culture (C2C12 cells). S961-Treated C57BL/6 mice. Insulin receptor kinase (IRK) activity.	Potentiated insulin receptor kinase phosphorylation. Promoted GLUT4 translocation.	Hsu et al. (2014)

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Table 7 (*continued*)

Compounds	Methods	Keys results	References
	OGTT. Measurement of GLUT4 translocation. Glucose uptake assay.	Ameliorated blood glucose levels. Rutin plus insulin enhanced cellular glucose uptake.	
	HFD-fed and STZ-treated type 2 diabetes in rats. Estimation of plasma glucose and HbA_{1c}. Insulin resistance. Histological analysis of pancreas tissues.	Reduced plasma glucose, HbA_{1c} and pro-inflammatory cytokines (IL-6 and TNF-α), Improved histo-architecture of β-islets.	Niture et al. (2014)
	α-Amylase and α-glucosidase inhibition assays.	Inhibited α-amylase (IC_{50} = 0.043 μM) and α-glucosidase (IC_{50} = 0.037 μM) activities. Combination of quercetin and rutin had higher synergistic inhibitory abilities on the enzymes than the individual flavonoids.	Oboh et al. (2015a)
	Diabetes C57BL/6J mice. Intravenous glucose tolerance test. Cell culture (Mouse cell lines 3T3-L1 and C2C12).	Decreased serum glucose levels. Down-regulated the expression levels of protein-tyrosine phosphatase 1B in myocyte C2C12 in a dose-dependent manner.	Lee et al. (2016)
	Human-amylin (hA) transgenic mice.	Suppressed hA-aggregation *in vitro* and doubled the lifespan of diabetic mice. Delayed the *in vivo* progression of diabetes in hA-transgenic mice	Aitken et al. (2017)
Strictinin ellagitannin	α-Glucosidase inhibition assay. C57BL/6J mice.	Inhibition of α-glucosidase activity with IC_{50} = 2.4 μg/mL (mixed type). Improved oral sucrose tolerance at dose 100 mg/kg.	Guo Yuchen (2019)

suggested thatthe oral administration of pure D3S5G (delphinidin 3-sambubioside-5-glucoside) dose-dependently decreased fasting blood glucose levels in obese C57BL/6J mice and glucose production in rat liver cells, and increased glucose uptake in L6 myotubes.In another study,Mojica et al. (2017a) investigated the *in vitro* antidiabetic effect of this compound using α-amylase, α-glucosidase, and DPP-4 inhibition assays, Caco-2 cell proliferation and glucose uptake. The results showed that delphinidin inhibited α-glucosidase (37.8%), α-amylase (35.6%), dipeptidyl peptidase-IV (34.4%), reactive oxygen species (81.6%), and decreased glucose uptake. Using jejunum samples from RF/J mice, and the human intestinal cell lines HT-29, Caco-2, and NCM460, Hidalgo et al. (2017) and collaborators revealed that delphinidin inhibited glucose absorption in both mouse jejunum and a human enterocytic cell line, and affected the function of sodium-glucose cotransporter 1. Lai et al. (2019) tested the *in vitro* antidiabetic effect by Western blot analysis using rat pancreatic β-cell line RIN-m5F, and showed that this flavonoid decreased high-glucose-induced apoptosis of pancreatic β-cells and the level of cleaved caspase-3, induced autophagy in RIN-m5F cells, increased the phosphorylation level of AMPKα Thr172 and also attenuated the negative effects of high-glucose stress on the cells. Jayaprakasam et al. (2005) studied the ability of delphinidin to stimulate insulin secretion from rodent pancreatic β-cells (INS-1832/13) *in vitro*. The results indicated that delphinidin-3-glucoside is the most effective insulin secretagogues.

8.2.5. Epicatechin

The antidiabetic effect of epicatechin was reported by many researchers *in vitro* and *in vivo* (Ahmad, 1991; Ahmad et al., 1989; Bettaieb et al., 2014; Bone et al., 1985; Chakravarthy et al., 1981, 1982; Cremonini et al., 2016; Hii and Howell, 1984; Ibrahim et al., 2018; Kim et al., 2003; Martín et al., 2014; Sheehan et al., 1983; Shih et al., 2015; Ueda-Wakagi et al., 2015). Epicatechin was tested for its antidiabetic effect *in vivo* using alloxan-induced diabetes (Chakravarthy et al., 1981, 1982; Sheehan et al., 1983), STZ-induced diabetes (Bone et al., 1985; Ibrahim et al., 2018; Kim et al., 2003) and HFD-fed mice (Bettaieb et al., 2014; Cremonini et al., 2016; Shih et al., 2015). In alloxan-induced diabetic mice, epicatechin decreased blood sugar levels, increased serum insulin levels and stimulated the regeneration of β-cells (Chakravarthy et al., 1981, 1982; Sheehan et al., 1983). Other studies tested its effect in STZ-induced diabetic mice and revealed that this compound improved blood glucose by several mechanisms such as by decreasing blood glucose and insulin resistance, enhanced insulin signaling in the liver and adipose tissue, attenuated endoplasmic reticulum stress in liver and adipose tissue, increased blood leptin concentrations, and increased muscular membrane protein levels of GLUT4 (bone et al., 1985; Kim et al., 2003; Ibrahim et al., 2018). In high fructose diet-fed rats the administration of epicatechin improved glucose homeostasis by decreasing insulin resistance, enhancing insulin signaling in the liver and adipose tissue, attenuating endoplasmic reticulum stress in the liver and adipose tissue (Bettaieb et al., 2014). It was also decreased blood glucose and increased blood leptin concentrations and muscular membrane protein levels of GLUT4 (Shih et al., 2015) as well as improved insulin sensitivity and decreased blood glucose levels (Cremonini et al., 2016). The antidiabetic effects of epicatechin was tested *in vitro* by several authors by isolating the islets of Langerhans (Ahmad, 1991; Ahmad et al., 1989; Hii and Howell, 1984). The first study demonstrated that epicatechin increased the incorporation of U^{14}–C glucose into glycogen of the rat diaphragm (increasing its glycogen content). Also, it increased insulin and oxygen uptake in fat cells, muscles and liver (Ahmad et al., 1989). While in another study, epicatechin stimulated the conversion of proinsulin to insulin and also stimulated insulin release from the islets of Langerhans *in vitro* (Ahmad, 1991). On the other hand, the study of Hii and Howell, (1984) reported that this flavonoid (1 mM) increased insulin secretion from isolated rat islets of Langerhans. Using L6 myoblasts cell and glucose uptake assay, 3-*O*-acyl-epicatechin increased glucose uptake activity and GLUT4 translocation through the activation of PI3K signaling in skeletal muscle cells (Ueda-Wakagi et al., 2015). In another work, Martín et al. (2014) revealed that the treatment with EC (5–20 M) enhanced the antioxidant enzymes and insulin secretion in Ins-1E cells damaged by *tert*-butyl hydroperoxide(*t*-BOOH).

8.2.6. Hesperetin

Many studies evaluated the antidiabetic effect of hesperetin using *in vivo* and *in vitro* methods (Akiyama et al., 2009b; Gong et al., 2017; Revathy, 2017; Revathy and Abdullah, 2016; Revathy et al., 2018; Yoshida et al., 2010). In STZ-induced diabetic rats, it was noticed that hesperetin improved glucose homeostasis by different mechanisms such as its capacity to normalize plasma glucose and insulin levels, to inhibit enzymes involved in glucose metabolism, to prevent the development of insulin resistance, and to improve glycogen levels and hepatic glucose metabolic enzymes (Revathy, 2017; Revathy and Abdullah, 2016; Revathy et al., 2018). In Goto-Kakizaki (GK) rats with type 2 diabetes, this flavonoid normalized glucose metabolism by altering the activities of glucose-regulating enzymes and reduced the levels of lipids in the serum and liver (Akiyama et al., 2009b). Gong and collaborators tested the inhibition of α-glucosidase using kinetic analysis and showed important inhibitory effect with IC_{50} of 0.38 ± 0.05 mM (Gong et al., 2017). Using 3T3-L1 adipocytes cells Yoshida et al. (2010) revealed that hesperetin inhibited TNF-α-stimulated FFA secretion from mouse adipocytes and blocked TNF-α-induced activation of the NF-κB and ERK pathways.

8.2.7. Hesperidin

The antidiabetic effect of hesperidin was investigated experimentally in several works (Abdel-Moneim et al., 2011; Ahmed et al., 2012; Akiyama et al., 2009a, 2009b; Chae and Shin, 2012; Dokumacioglu et al., 2018; Jung et al., 2004; Sundaram et al., 2019; Toumi et al., 2009). This compound was tested for its antidiabetic effect *in vivo* using STZ-induced type 1 diabetic rats (Akiyama et al., 2009a; Dokumacioglu et al., 2018; Sundaram et al., 2019; Toumi et al., 2009), and type 2 diabetes (Abdel-Moneim et al., 2011; Ahmed et al., 2012; Akiyama et al., 2009b; Jung et al., 2004). The first study revealed that hesperid in improved blood glucose by several mechanisms such as its capacity to decrease blood glucose by altering the activity of glucose-regulating enzymes, reducing the levels of lipids in the serum and liver (Akiyama et al., 2009a), attenuating maternal glycaemia (Toumi et al., 2009), increasing insulin concentrations, decreasingTNF-α levels and the degeneration of the islet cells (Dokumacioglu et al., 2018), decreasing glycosylated hemoglobin and G6Paseand fructose-1,6-bisphosphatase, as well as improving glycogen content in the hepatic tissue (Sundaram et al., 2019). In type 2 diabetes model, the oral administration of hesperidin at a dose level of 50 mg/kg ameliorated the elevated levels of glucose, glycosylated hemoglobin and the lowered serum insulin level and hepatic and muscle glycogen content of insulin resistant diabetic rats. This compound was also found to alleviate lipid profile and serum adiponectin and resistin levels (Ahmed et al., 2012). In another study Abdel-Moneim et al. (2011)and collaborators revealed that this flavonoid increased serum insulin levels, decreased TNF-α and resisted mRNA expression. Jung et al. (2004) suggested that in rats fed with high fat diets, hesperidin reduced blood glucose and hepatic G6Paseand phosphoenolpyruvate carboxykinase (PEPCK) activities, and elevated hepatic glucokinase activity, glycogen concentration, plasma insulin and C-peptide levels. Hesperidin showed normalized glucose metabolism by altering the activities of glucose-regulating enzymes and reduced the levels of lipids in the serum and liver of the Goto-Kakizaki (GK) rats with type 2 diabetes (Akiyama et al., 2009b). In another study, Chae and Shin, (2012) investigated the antidiabetic effect of this compound *in vitro* using RAW 264.7 cells and 3T3-L1 preadipocytes. The results showed that hesperidin ameliorated inflammation-mediated insulin resistance in adipose tissue by the inhibition of LPS-induced production of IL-6, TNF-α, and NO by RAW264.7 cells in a dose-dependent manner, and the inhibition of TNF-α-induced production of IL-6 and PGE2 in differentiated 3T3-L1 cells, while upregulated TNF-α-suppressed the expression of adiponectin and PPAR-γ mRNA.

8.2.8. Kaempferol

The evaluation of the antidiabetic effect of kaempferol was evaluated by several methods (Alkhalidy et al., 2015; Alkhalidy et al., 2018a; Alkhalidy et al., 2018b; Cazarolli et al., 2009c; de Sousa et al., 2004; Fang et al., 2008; Habtemariam, 2011; Ibitoye et al., 2018; Lee et al., 2010; Li Ji et al., 2015; Li Wang et al., 2015; Liu et al., 2012; Luo et al., 2015; Peng et al., 2016; Rodríguez et al., 2010; Sheng et al., 2018; Varshney et al., 2017; Varshney et al., 2017; Yin et al., 2018; Zanatta et al., 2008; Zang et al., 2011; Zang et al., 2015; Zhang et al., 2013; Zhang and Liu, 2011). In alloxan induced diabetic, the oral administration of kaempferitrin at 50, 100, and 200 mg/kg produced a significant hypoglycemic effect in normal and in alloxan-induced diabetic rats (de Sousa et al., 2004). Zanatta et al. (2008) reported also that the administration of 100 mg/kg of kaempferol 3-neohesperidoside by oral gavage increased glycogen content in muscles and stimulated glucose uptake in the rat soleus muscle *via* the PI3K and PKC pathways. Other studies (Alkhalidy et al., 2018b; Liu et al., 2012; Luo et al., 2015) investigated the *in vivo* antidiabetic properties in STZ-induceddiabetic rat. The authors revealed that the oral administration of kaempferol (50, 100 and 200 mg/kg) decreased fasting blood glucose and insulin resistance, and improved the disorders of glucose metabolism (Liu et al., 2012). This compound restored insulin resistance, induced alteration of glucose disposal and reduced in TNF-α and interleukin-6 (IL-6) levels (Luo et al., 2015). It was reported that kaempferol improved hyperglycemia, reduced the incidence of diabetes, and reduced hepatic glucose production. It also restoredhexokinase activity in the liver and skeletal muscle of diabetic mice and suppressed hepatic pyruvate carboxylase activity and gluconeogenesis (Alkhalidy et al., 2018a). The oral administration of kaempferol (50 mg/kg/day) significantly improved blood glucose control in HFD-induced obese mice, which was associated with reduced hepatic glucose production and improved whole-body insulin sensitivity.In addition, kaempferol treatment increased Akt and hexokinase activity, and decreased pyruvate carboxylase (PC) and glucose-6 phosphatase activity in the liver (Alkhalidy et al., 2018a). Using the same methodology, Zang and collaborators reported that the treatment with 0.15% dietary KG decreased fasting blood glucose, serum HbA1c (hemoglobin A1c) levels and improved insulin resistance. It also showed that KG decreased peroxisome proliferator-activated receptor (PPAR-γ) and sterol regulatory element-binding protein (SREBP-1c) expression (Zang et al., 2015). Alkhalidy et al. (2015) revealed that the dietary intake of kaempferol (0.05% in the diet) significantly ameliorated hyperglycemia, hyperinsulinemia, and the circulating lipid profile, which were associated with the improved peripheral insulin sensitivity in obese mice fed a high-fat (HF) diet. It impaired glucose transport-4 (Glut4) and AMPdependent protein kinase (AMPK) expression in both muscle and adipose tissues from obese mice, and prevented high fatty acid-impaired glucose uptake, glycogen synthesis, AMPK activity, and Glut4 expression in skeletal muscle cells (*in vitro*) (Alkhalidy et al., 2015). In another study Cazarolli et al. (2009c) reported that kaempferol 3-neohesperidoside stimulated glycogen synthesis in rat soleus muscle. Zang et al. (2011) reported that this compound decreased fasting blood glucose levels and HbA1clevel in type 2 diabetic KK-Ay mice.

The antidiabetic effect of kaempferol was also tested *in vitro* by several methods such as theα-glucosidase and α-amylase inhibitory assays. The results revealed potent inhibition of both enzymes by this flavonoid (Yin et al., 2018) and (Sheng et al., 2018). In another study, kaempferol produced potent inhibitory effect of α-amylase (IC_{50} = 51.24 μg/mL) and α-glycosidase (IC_{50} = 29.37 μg/mL) (Ibitoye et al., 2018). Peng et al. (2016) and Habtemariam, (2011) reported also potent inhibition of α-glucosidase with $IC_{50} = 1.16 \pm 0.04 \times 10^{-5}$ mol.L^{-1} and 19.36 ± 2.43 μM, respectively. To study the mechanism of the antidiabetic activity of this compound, several groups used the cell culture assay. Fang et al. (2008) showed that kaempferol served as weak partial agonists in the peroxisome proliferator-agonist receptor γ (PPARγ) reporter gene assay and significantly improved insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes. Using INS-1E β-cells and human islets, and different tests such as cell apoptosis and caspase-3 activity assays as well as insulin secretion and content assays, Zhang and collaborators reported that kaempferol inhibited cellular apoptosis and reduced caspase-3 activity in β-cellsand human islets exposed to chronic high glucose in a dose dependent manner. It also improved the expression of anti-apoptotic proteins Akt and Bcl-2, and insulin secretory function and synthesis in β-cellsand human islets (Zhang and Liu, 2011). It is also inhibited apoptosis and reduced caspase-3 activity in INS-1E cells and human islets and improved insulin synthesis and pancreatic and duodenal homeobox-1 (PDX-1) expression (Zhang et al., 2013). In others study, kaempferol treatment increased cell viability and anti-apoptotic activity in PA-stressed RIN-5F cells and murine pancreatic islets, activated the autophagy *via* AMPK/mTOR pathway and induced autophagy restores the β-cells dysfunction (Varshney et al., 2017). Lee et al. (2010) investigated the protective effect of kaempferol on β-cells (HIT-T15 cells) from dRib induced oxidative damage and the results demonstrated that this flavonoid reduces dRib mediated β-cell damage interfering with ROS metabolism and showed protective effect against lipid peroxidation.

8.2.9. Arbutin

The antidiabetic effect of arbutin was investigated in several works

(Azarbayjani et al., 2014; Farzanegi, 2014; Michel, 1936; Yousefi et al., 2013). Arbutin was tested for its antidiabetic effect using alloxan-induced diabetic mice (Azarbayjani et al., 2014; Farzanegi, 2014). The results revealed that the oral administration of arbutin significantly increased GLP-1 and GLP1R levels (Farzanegi, 2014) and significantly decreased serum glucose concentration and insulin levels (Azarbayjani et al., 2014). According to α-amylase and α-glucosidase inhibitory assays, this flavonoid exhibited the highest inhibitory activity in a dose-dependent manner with an inhibition of 75% for α-glucosidase and 81% for α-amylase inhibitory assays (Yousefi et al., 13).

8.2.10. Luteolin

Luteolin is a flavonoid derivative found in many Moroccan antidiabetic medicinal plants. Scientific reports highlighted the *in vitro* and *in vivo* antidiabetic effects of this substance (Choi, Islam et al., 2014; Choi, Kang, Lee, and Kim et al., 2014; Deqiu et al., 2011; Ding et al., 2010, 2014; Kim et al., 2000; Matsui et al., 2002b; Yan et al., 2014; Zang et al., 2016; Zarzuelo et al., 1996; Zhang et al., 2016b). An *in vitro* study was carried out by Kim et al. (2000) on the inhibitory effect of luteolin onα-amylase and α-glucosidase. Luteolin inhibited of α-glucosidase by 36% at 0.5 mg/mL compared with acarbose, which was used as the standard drug. However, the inhibition of α-amylase was less potent than acarbose. In another study, Yan et al. (2014) reported that luteolin reduced the activity of α-glucosidase at dose dependent-manner [$IC_{50} = 1.72 \pm 0.05.10^{-4}$ mol/L. The authors showed that this compound was a non-competitive inhibitor with a single inhibition site on α-glucosidase ($K_i = 1.40 \pm 0.02 \times 10^{-4}$ mol/L) (Yan et al., 2014).

In an animal model, luteolin was tested for its effect against α-glucosidase, maltase, and sucrase activities as well as its effect on blood glucose (Matsui et al., 2002b). This compound inhibited maltase activity ($IC_{50} = 2.3$ mM). However, it did not show any effect on blood glucose level (at the doses of 100 and 200 mg/kg) and other enzymes activity (α-glucosidase and sucrase) in the gut at the dose less than 200 mg/kg (Matsui et al., 2002a). *In vivo* investigation of the antidiabetic effects of luteolin using STZ-induced diabetic rats highlighted several antidiabetic pathways such as the increase in pancreatic insulin, the decrease in glycemia levels, the increase in insulin blood levels, and the decrease in pancreas weight (Zarzuelo et al., 1996). Luteolin exhibited an antidiabetic phenotype in the *in vitro* cell culture model. In 3T3-L1 cell lines, luteolin increased the response of glucose uptake to insulin stimulation in 3T3-L1 adipocytes, enhanced Akt2 phosphorylation in an insulin-stimulated state, decreased mRNA levels of TNFα and interleukin-6, and enhanced PPARγ transcriptional activity in 3T3-L1 adipocytes (Ding et al., 2010). In another study, Deqiu et al. (2011) showed that luteolin increased insulin-mediated endothelium-dependent relaxation in rat aorta, and reduced gene over-expressions (TNF-α and IL-6), restored insulin signaling cascades, elevated insulin-dependent production of nitric oxide in endothelial cells cultivated *in vitro* (Deqiu et al., 2011).

The study of Zhang et al. (2016a,b) revealed the hypoglycemic effect of luteolin by different mechanisms including the improvement of insulin resistance, and the suppression of inflammatory macrophage infiltration. *In vitro* investigation using RAW264.7 macrophages and 3T3-L1 cell lines revealed that this compound activated AMPKα1 in macrophages to inhibit their inflammatory polarization and enhanced insulin signals in adipocytes Zhang et al. (2016a,b). Luteolin inhibited protein tyrosine phosphatase 1B (PTP1B) and aldose reductase (AR) activities (Choi Islam et al., 2014; Choi Kang et al., 2014). In Min6 cell lines, luteolin reduced uric acid-induced nitric oxide production and inhibited uric acid-activated NF-κB in Min6 cells and restored islet insulin secretion (Ding et al., 2014). In another cellular *in vivo* (HFD-fed mice) and *in vitro* (RAW264.7 macrophages and 3T3-L1 cells) system, luteolin improved insulin resistance, suppressed inflammatory macrophage infiltration and polarization in mouse epididymal adipose tissues. The inhibition of the anti-inflammatory polarization and enhancement of insulin signals in adipocytes was mediated by the activation of AMPKα1 in macrophages (Zhang et al., 2016b). On the other hand, using KK-A^y mice measurement of fasting blood glucose levels and glucose tolerance test, Zang et al. (2016) showed that luteolin improved blood glucose, HbA1c, and insulin levels.

8.2.11. Malvidin-3-O-glucoside

The first experimental study evaluating the antidiabetic effect of malvidin-3-O-glucoside was carried out in 2009. In fact, Grace et al. (2009) reported significant hypoglycemic activity at a dose of 300 mg/kg in diabetic mice C57bl/6J. In 2017, several *in vitro* studies were carried out to assess the antihyperglycemic potential of this compound. The study of the inhibition of α-glucosidase and α-amylase wascarried out by Rodriguez et al. (2017). It revealed that malvidin-3-O-glucoside is a strong inhibitor ($IC_{50} = 55$ μg/mL) of α-glucosidase and α-amylase. Mojica et al. (2017a) and Mojica et al. (2017b) studied three molecular markers of diabetes in an *in vitro* cell culture model (Caco-2). The inhibition of α-glucosidase activity by malvidin-3-O-glucoside (100 μM) was 42.8%. It also inhibited the activity of α-amylase (29.6%) with a value lower than the positive control acarbose (66.8%). The inhibition of DPP-IV activity was high (82.4%) but lower than the positive control sitagliptin (99.6%). The absorption of glucose *in vitro* in Caco-2 cells was also studied by the same author (Mojica et al., 2017a) and showed that malvidin-3-O-glucoside significantly reduced the absorption of glucose in Caco-2 cells (55.2%) after 30 min of treatment. This same model (caco-2 cell) was used for the determination of the absorption of ^{14}C fructose. Malvidin-3-O-glucoside inhibited the absorption of ^{14}C fructose, and the highest concentration led to a 15% reduction in absorption (Andrade et al., 2017).

8.2.12. Naringin

The antihyperglycemic efficacy of naringin was evaluated *in vivo* in several studies using diabetic animal models induced by streptozotocin. All these studies confirmed the hypoglycemic effect of naringin. Naringin lowered plasma glucose levels (Al-Kurdy et al., 2014; Lim et al., 2018; Punithavathi et al., 2008), improved islet dysfunction in diabetic insulin-deficient mice in a dose-dependent manner and protected pancreatic β cells from apoptosis by inhibiting the intrinsic (mediated by mitochondria) and extrinsic (mediated by death receptors) pathways (Lim et al., 2018). Xulu et al. (2012) suggested that the hypoglycemic effect of naringin depended on the presence of insulin which explains the beneficial effect in type 2 diabetes as compared with type 1 diabetes. Using the same experimental protocol, Punithavathi et al. (2008) showed that the oral administration of high doses of naringin and vitamin C significantly decreased blood sugar and glycated hemoglobin and increased plasma insulin and hepatic glycogen. The diabetic rats in this study also showed a significant increase in the activity of hexokinase and a significant decrease in the activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase in the liver and kidneys.

Two other studies induced type 2 diabetes in rats by injecting nicotinamide (NA)/streptozotocin (STZ). Pari et al. (2010) showed in these rats that the administration of naringin significantly lowered blood sugar and glycosylated hemoglobin and increased the level of insulin. On an enzymatic level, the treatment with naringin resulted in a significant increase in the hepatic activity of glucokinase and glucose-6-phosphate dehydrogenase, while the activity of glucose-6-phosphatase and fructose 1.6 bisphosphatase was decreased. According to Ahmed et al. (2017), naringin showed potent anti-diabetic effect. Naringin treatments in rats reduced the levels of serum insulin, C peptides, hepatic glycogen levels, elevated liver glucose-6-phosphatase and glycogen phosphorylase levels. The treatment also improved the expression of the mRNA of the insulin receptor b subunit, GLUT4 and adiponectin in the adipose tissue of type 2 diabetic rats. Naringin supplementation significantly reduced blood sugar in male type 2 diabetic mice (C57BL/KsJ-db/db). Plasma insulin, peptide C and leptin levels and glucokinase hepatic activity and glycogen concentration were significantly elevated in the naringin supplemented group. Naringin also

significantly reduced the activity of hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (Jung et al., 2004).

A type 2 diabetic rat animal model induced by a high-fat diet (HFD)/streptozotocin (STZ) was adopted by several researchers. The administration of naringin lowered the levels of glucose, FFA, TNF-α, and resistin and increased the level of serum insulin (Abdel-Moneim et al., 2011). Naringin supplementation potentially affected elevated glucose and glycosylated hemoglobin levels, lowered serum insulin and hepatic and muscular glycogen levels, and lowered serum adiponectin and resistin levels in resistant diabetic rats' insulin (Ahmed et al., 2012). The results of the study by Pari et al., 2017 also showed the anti-hyperglycemic effect of naringin. In addition to reducing plasma glucose, blood glycosylated hemoglobin and increasing plasma insulin levels, this flavonoid improved the levels of altered hepatic key enzymes (hexokinase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucose-6-phosphate dehydrogenase, glycogen synthase, glycogen phosphorylase) in a dose-dependent manner, to increase the glycogen content and the number of β cells immunoreactive at l insulin from the pancreas of diabetic rats.

The fundamental study by Kumar Sharma et al. (2011) provided convincing evidence that naringin significantly decreased insulin resistance, hyperinsulinemia, hyperglycemia and protected B cells in type 2 diabetic rats by partially regulating oxidative stress, inflammation (TNF-α, IL-6) and the production of deregulated adipocytokines by an increase in PPARγ, HSP-27 and HSP-72. The anti-hyperglycemic efficacy was demonstrated by *in vitro* studies on cell cultures using L6 myoblastic cells (Dhanya et al., 2015) and RIN-5F cells (Nzuza et al., 2016). The results of the study of the modulation of glucose absorption by naringin showed that it increased the absorption of fluorescently labeled glucose in the differentiated myoblast L6 (Dhanya et al., 2015). In addition, naringin prevented the dysfunction of pancreatic b cells, which considerably reduced the inhibition of insulin secretion induced by HIV-1 protease inhibitors in patients on antiretroviral therapy (Nzuza et al., 2016).

8.2.13. *Quercetin-3-O-glucoside*

Panda et al. (2007b) studied the potential activity of quercetin-3-O-glucoside in the regulation of hyperglycemia in diabetic rats induced by alloxan. The administration of 15 mg/kg/day quercetin-3-O-glucoside for 10 days decreased serum glucose concentrations in parallel with an increase in insulin level and inhibition of hepatic G6Pase activity in diabetic rats.

8.2.14. *Quercitrin*

Several studies demonstrated the anti-hyperglycemic efficacy of quercitrin *in vivo* in diabetic rats induced by streptozotocin (STZ). These results showed a decrease in fasting blood sugar (Babujanarthanam et al., 2009, 2011a, 2011b; Us et al., 2019), an increase in plasma insulin levels (Babujanarthanam et al., 2009, 2011a, 2011b), a decrease in glycosylated hemoglobin and an increase in the level of peptide C (Babujanarthanam et al., 2011b). The glycogen content in the liver and muscles and the activity of hexokinase increased, while the activities of glucose 6-phosphatase and fructose 1,6-bisphosphatase decreased in tissues (Babujanarthanam et al., 2009). The histopathological study of the pancreas revealed a protective role of quercitrin as shown by the expansion of the islets of Langerhans and the reduction of fatty infiltrates in these islets (Babujanarthanam et al., 2009, 2011a).

The protective effect of quercitrin on cytokine-induced B cell damage in RINm5F rat insulinoma cells was evaluated. Quercitrin protected cells against death induced by cytokines, improved the secretion of glucose-stimulated insulin (GSIS). These effects were associated with an inhibition in the translocation of the nuclear factor κB (NF-κB) (Dai et al., 2013b).

8.2.15. *Isoquercitrin*

The antihyperglycemic potential of isoquercitrin was first studied in 2008 by Paulo et al. (2008). In this study, 100 mg/kg of isoquercitrin was administered to rats to assess their glucose tolerance over time. Isoquercitrin showed antihyperglycemic activity as a function of time by delaying the glycemic peak of the post-oral glucose load to 30 min. Huang et al. (2017) studied the effects of isoquercitrin on liver damage in diabetic Wistar rats by intraperitoneal injection of 40 mg/kg of streptozotocin after a 30-day high calorie diet. The oral administration of isoquercitrin (10 mg/kg/day and 30 mg/kg/day) for 21 days improved the clinical symptoms, fasting glucose and glucose tolerance in a dose-dependent manner. Histologically, isoquercitrin showed a protective effect on pancreatic cells. On the other hand, Zhang Ai et al., (2018); Zhang, Zhang et al., (2018) studied *in vitro* the inhibitory effect of isoquercitrin on dipeptidyl peptidase IV (DPP-IV). The results of this study showed a powerful inhibitory effect on DPP-4 in a competitive manner with an IC_{50} of 96.8 and a Ki of 236 mM. In the same study, they also studied the effect of isoquercitrin on the release of GLP-1 in an experimental model *in vitro* and *in vivo*. *In vitro*, isoquercitrin stimulated the release of GLP-1 in NCI–H716 cells, while *in vivo*, the administration of isoquercitrin for 8 weeks in type 2 diabetic mice induced by streptozotocin decreased significantly the fasting blood sugar and increased serum GLP-1 and insulin levels in a concentration-dependent manner. The oral glucose tolerance test in these mice showed that isoquercitrin significantly inhibited variations in postprandial blood sugar in a dose-dependent manner.

8.2.16. *Rutin*

Since 2006, two studies looked at the anti-diabetic properties of rutin. Kamalakkannan et al. (2006) administered rutin orally to diabetic rats induced with streptozotocin resulting in a significant reduction ofthe fasting glycemia, glycosylated hemoglobin and increased insulin and peptide C. The same year, Prince et al. (2006) used the same *in vivo* study protocol. The results of their latest study confirmed the hypoglycemic effect of rutin shown by the previous study. In fact, rutin also caused a decrease in fasting blood sugar and an increase in insulin levels. In addition, rutin also increased the glycogen content in the liver and muscles and hexokinase activity, while the activities of the metabolic carbohydrate enzymes (G6Pase and FBPase) were suppressed in the tissues. The histopathological study of the pancreas in this study revealed a protective role of rutin by the expansion of the pancreatic islets and the reduction of the fat which infiltrates them.

In 2009, an *in vitro* study was carried out by Li et al. (2009) on the inhibition of α-glucosidaseshowing that rutin is an effective inhibitor with an inhibitory concentration 50 of 0.196 mmol × L-1. In 2012, Hunyadi et al.,(2012) reproduced the same *in vivo* protocol which was carried out in 2006. They administered 250 and 750 mg/kg for 11 days to a type 2 diabetic rats induced by streptozotocin and noted a decrease in non-fasting blood sugar levels in a dose-dependent manner.

In the same year, a second *in vivo* study demonstrated the hypoglycemic effect of rutin. After 14 days of administration of the 100 mg/kg dose of rutin to diabetic rats induced by nicotinamide and streptozotocin, the glycemia was significantly decreased in the glucose tolerance test. To explore the mechanism of action of rutin as an anti-diabetic agent, the inhibitory activity on glucose transport and absorption of glucose by an isolated rat hemi-diaphragm were estimated. The results showed a significant increase in the glucose uptake by the rat semi-diaphragm and a significant decrease in the glucose transport activity (Jadhav et al., 2012).

The following year, Kappel et al. (2013) studied the *in vitro* effect of rutin on the absorption of glucose ^{14}C in the isolated soleus muscle of rats and explained the mechanism of action involved in this phenomenon. The results of this study showed a similarity in the action of rutin on glucose absorption compared with the insulin signaling pathways, which constitutes solid evidence of the insulin-mimetic role of rutin in the homeostasis of glucose. Rutin stimulated the absorption of glucose in the soleus muscle of rats *via* the PI3K, atypical protein kinase C and mitogen activated protein kinase (MAPK) pathways.

In 2014, several studies looked at the anti-diabetic properties of rutin. Oboh et al. (2015a), studied the effect of rutin alone and rutin-quercitin combinations on the activities of α-amylase and α-glucosidase. The results showed that rutin alone had the strongest inhibition of the activities of α-amylase (IC_{50} = 0.043 μM) and α-glucosidase (IC_{50} = 0.037 μM). Rutin-quercitin combination (75:25) showed the highest synergistic inhibitory activity on the tested enzymes.

In the same year Niture et al. (2014) studied the anti-diabetic effect of rutin in type 2 diabetic rats induced by a diet high in fat (HFD)/streptozotocin (STZ). The administration of rutin (50 and 100 mg/kg) orally for three weeks significantly reduced blood sugar, glycosylated hemoglobin and pro-inflammatory cytokines (IL-6 and TNF-α). Histologically, rutin improved the histological architecture of the β islands and reversed the enlarged hepatocytes.

Moreover, in 2014, several studies looked at the molecular mechanisms of rutin. Hsu et al. (2014), studied in a cellular model (C2C12 cells) the ability of rutin to improve the activity of insulin-dependent kinase receptors (KRIs) and to reduce the S961-mediated inhibition of the insulin-dependent translocation of the transporter glucose 4 (GLUT4). In the same study, they also tested the effects of rutin treatment in an *in vivo* model of insulin resistance and type 2 diabetes (C57BL/6 mice treated with S961) using an orally glucose tolerance test (OGTT). The results of this study showed that rutin can serve as a potential agent for glycemic control by improving the activity of insulin dependent kinase receptors (IRK), thus inducing the insulin signaling pathway causing increased translocation of GLUT4 and increased glucose uptake. *In vivo*, rutin treatment resulted in a normoglycemic effect in the OGTT test, which was consistent with the *in vitro* results.

Dhanya et al. (2014) studied the anti-diabetic potential of rutin and its quercetin metabolite under oxidative stress induced by tertiary butyl hydrogen peroxide (TBHP) while measuring the absorption of the fluorescent glucose analog, 2-NBDG in differentiated rat L6 myoblasts. In the same study, they also elucidated the mechanism by which flavonoid pretreatment changed glucose absorption through measuring surface GLUT 4 levels by the immunofluorescence test. The results of this study showed that these flavonoids increased glucose absorption after pretreatment in the presence of oxidative stress. The increased absorption of glucose in L6 myotubes was attributed to the translocation of GLUT 4, the factor that affects the insulin signaling cascade. This increased in absorption was doubled and tripled during the long-term pretreatment of quercetin and rutin. In 2016, Lee et al. (2016) studied the anti-diabetic effect of rutin extracted from the buckwheat tartar sprouts using a type 2 diabetic mouse model (C57BL/6J) and mouse cell lines 3T3-L1 and C2C12. *In vivo* results showed that the administration of rutin significantly reduced serum glucose levels in the intravenous glucose tolerance test. *In vitro*, rutin downregulated the expression levels of the protein-tyrosine phosphatase 1B which constitutes a negative regulator of the insulin pathway, both at the transcriptional and translational level in the C2C12 myocytes in a dose-dependent manner. In 2017, Aitken et al. (2017) studied the effect of rutin *in vitro* on the inhibition of the folding of human amylin (hA) and *in vivo* evaluating its anti-diabetic efficacy in human-amylin transgenic mice (Ha). The results showed that rutin suppressed the aggregations of human amylin which cause apoptosis in β cells *in vitro*, delayed the *in vivo* progression of diabetes in hA transgenic mice and doubled their lifespan.

8.2.17. Resveratrol

Resveratrol is a stilbene-type phytoalexin that was isolated for the first time in 1939 from *Veratrum grandiflorum* O. Loes. It is found in a wide variety of plants and fruits, such as legumes, grapes, and berries, and has many reported health benefits, including anti-diabetic properties. Many studies were performed *in vivo* to clarify the antidiabetic of the resveratrol. Su et al. (2006) studied the effect of resveratrol in streptozotocin-induced diabetic rats. In this study, two methods were used to examine the effect of resveratrol on the level of glucose in the blood including intravenous glucose challenge test, STZ-induced diabetic rats and STZ-nicotinamide diabetic rats by intravenous injection. The results showed that resveratrol reduced plasma glucose concentration by 25.3 ± 4.2 and 20.3 ± 4.2%, in STZ-DM and STZ-nicotinamide DM rats, respectively. Resveratrol decreased insulin secretion and delayed the onset of insulin resistance (in STZ-nicotinamide DM rats), increased stimulation of glucose uptake in a dose-dependent manner and promoted glycogen synthesis by hepatocytes.

Chi et al. (2007) used a cellular model (C2C12 cells) to study the molecular mechanisms of resveratrol in promoting glucose uptake in skeletal muscle. Resveratrol induced hypoglycemic effect in insulin-deficient STZ-diabetic rats *via* PI3K-Akt-signaling pathway resulting in the enhancement of glucose uptake into skeletal muscle and increased GLUT4 expression in the soleus muscle. The same authors reported that the resveratrol increased insulin secretion in rats with sufficient insulin secretion function and lowered plasma glucose through insulin-dependent and -independent mechanisms. Palsamy and Subramanian (2008) reported that oral supplementation of resveratrol for 30 day decreased blood glucose levels and HbA_{1c} and improved plasma insulin levels. The oral treatment of resveratrol normalized the activities of biochemical parameters such as creatinine, AST, ALT and ALP to near normalcy when compared with the control group.

In the same year, Penumathsa et al. (2008) suggested that the effect of resveratrol is non-insulin dependent and triggers some of the similar intracellular insulin signaling components in myocardium by examining resveratrol (RSV)-mediated Glut-4 translocation in the streptozotocin (STZ)-induced diabetic myocardium. After 30 day of administering 2.5 mg/kg dose of resveratrol to diabetic rats, resveratrol significantly decreased the blood glucose level when compared with the diabetic group alone. In the same study, the mechanism action of resveratrol on H9c2 cells demonstrated increased Adenosine Mono Phosphate Kinase (AMPK) phosphorylation, increased glucose uptake with H9c2 cardiac myoblast cells and increased Glut-4 expression compared with the diabetic group.

An interesting study on the effect of resveratrol in reducing the activities of the key enzymes in carbohydrate metabolism was carried out by Palsamy and Subramanian (2009). After 30 day of treatment, resveratrol reduced blood glucose, HbA_{1c} and insulin levels. On the other hand, resveratrol improved the activity of enzymes that are essential for carbohydrates metabolism including hexokinase, pyruvate kinase, G6Pase, FBPase, glucose-6-phosphate dehydrogenase, glycogen synthase and glycogen phosphorylase in the liver and kidney tissues. It also improved the storage of glucose in the liver in the form glycogen.

In the same year, a study was conducted by Ramadori et al. (2009) evaluating the effect of resveratrol on diet-induced diabetes in mice (C57BL/6 male). The results showed that the long-term intracerebroventricular infusion of resveratrol normalized hyperglycemia and improved hyperinsulinemia in diet-induced obese and diabetic mice. Resveratrol also improved the hypothalamic nuclear factor-κB inflammatory signaling by reducing the acetylated-RelA/p65 and total RelA/p65 protein contents, and inhibiting IkB kinase β mRNA levels. In addition, the CNS resveratrol delivery improved hepatic PEPCK expression and pyruvate-induced hyperglycemia.

Palsamy and Subramanian (2010) demonstrated that resveratrol exhibited a significant antidiabetic potential by reducing hyperglycemia, improving insulin secretion, and antioxidant competence in pancreatic β cells in diabetic rats. The oral administration of resveratrol at a dose of 5 mg/kg to diabetic rats for 30 days showed a significant decrease in blood sugar, glycosylatedhemoglobin, TNF-α, IL-1β, IL-6, NF-kB p65 and nitric oxide with concomitant elevation of plasma insulin. Diabetic rats treated with resveratrol showed a significant attenuation of lipid peroxide, hydroperoxide, and protein carbonyl levels in plasma and pancreatic tissues. The treatment also resulted in suppressing the activity of antioxidant enzymes (SOD, catalase, Gpx, and GST), as well as reducing plasma ceruloplasmin levels. Vitamin C, vitamin E, and GSH in diabetic rats returned to normal levels after resveratrol

administration. Based on histological and ultrastructural observations, it was reported for the first time that the oral administration of resveratrol can effectively save β cells from oxidative damage without affecting their function and structural integrity Palsamy and Subramanian (2010). In another study, Dao et al. (2011) delved deeply into the mechanism of action of resveratrol. The administration of resveratrol for 5 weeks in the wild type diabetic mice fed with a high-fat diet (HFD) suppressed the development of glucose intolerance and increased the concentrations in the portal vein of the glucagon type peptide 1 (GLP-1) and insulin as well as the intestinal content of the active GLP-1 (Dao et al., 2011). In another study that was done on mice with Werner syndrome showing a pro-oxidant status and shorter average life. Resveratrol supplementation improved the hyperglycemia and the insulin resistance phenotype in these Werner mutant mice. Resveratrol reversed the fatty liver, lipid peroxidation, and defenestration phenotypes observed in these mice. Analyses of microarrays enrichment and biological pathways on liver tissues revealed that resveratrol decreased lipogenesis and increased genes involved in the insulin-signaling pathway and glutathione metabolism in Werner mutant mice Labbé et al. (2011). The administration of resveratrol resulted in preventative activity and improved type 1 diabetes in NOD mice. Gene array analysis demonstrated a dramatic decrease in the expression of CCR6, which encodes chemokine receptor CCR6 (a mediated factor migration of inflammatory cells), in resveratrol-treated mouse splenocytes (Lee, Lee et al., 2011; Lee, Yang et al., 2011). The effect of the resveratrol in mice with type 1 diabetes and on a cell culture system (cultured L6 myotubes) was evaluated. Resveratrol suppressed the rise in the blood glucose level, increased serum insulin concentration, increased glucose uptake in a dose-dependent manner in the absence of insulin. It also translocated GLUT4 to the plasma membrane, and protected pancreatic β-cells Minakawa et al. (2011). In 2011, Mohamad Shahi, Haidari, & Shiri, 2011 demonstrated that resveratrol ameliorated dyslipidemia and hyperglycemia in diabetic rats. Diabetic rats treated with resveratrol showed a significant reduction in serum glucose concentration, and the plasma concentrations of total cholesterol and LDL-c. The bodyweight loss trend observed in diabetic rats was alleviated by resveratrol. The antidiabetic effect of resveratrol was evaluated in a genetic model for type-2 diabetes at doses of 5, 15, 50 mg/kg. The result of this study showed that the daily intake of the resveratrol for four weeks exhibited significant antihyperglycemic activity with an improvement in the insulin levels compared with the control mice. There was also a significant improvement in the glucose excursion in the oral glucose tolerance test performed for 120 min Sharma et al. (2011). Resveratrol ameliorated diabetes-related metabolic changes *via* the activation of AMP-activated protein kinase and its downstream targets in db/db mice as shown by Do et al. (2012). The addition of resveratrol in the mice diet at the doses of 0.005% or 0.02% w/w significantly decreased blood glucose, plasma free fatty acids, triglycerides, apo B/apo AI levels and increased plasma adiponectin levels. Resveratrol activated AMPK and the downstream targets leading to the suppression of blood HbA1c levels, hepatic gluconeogenic enzyme activity, and hepatic glycogen, while plasma insulin levels, pancreatic insulin protein, and skeletal muscle GLUT4 protein were higher after resveratrol supplementation. The high resveratrol dose also significantly increased hepatic glycolytic gene expression and enzyme activity, along with skeletal muscle glycogen synthase protein expression similar to rosiglitazone. Furthermore, resveratrol dose dependently decreased hepatic triglycerides content and the phosphorylated I kappa B kinase (p-IKK) protein expression, while hepatic uncoupling protein (UCP) and skeletal muscle UCP expression were increased (Do et al., 2012). Ku et al. (2011) demonstrated that resveratrol prevented streptozotocin-induced diabetes by inhibiting the apoptosis of pancreatic β-cell and the cleavage of poly (ADP-ribose) polymerase. Resveratrol treatment for 12 weeks improved glucose tolerance, attenuated β-cell loss, and reduced oxidative stress in type 2 diabetes. Resveratrol treatment significantly improved glucose tolerance after 2 h in db/db mice. This was associated with a significant increase in both pancreas weight and β-cell mass. Islet fibrosis was much less in resveratrol-treated mice. It also decreased urinary 8-OHdG levels and the percentage of islet nuclei that were positive for 8-OHdG immunostaining (Lee et al., 2012). Ramar et al. (2012) evaluated the protective effect of resveratrol against alloxan-induced diabetes in mice. The orally administration of the resveratrol at a dose of 75 mg/kg exerted antioxidant as well as anti-diabetic effects, consequently alleviated liver, kidney and pancreas damage caused by alloxan induced diabetes, probably through the inhibition of the proinflammatory factor, NFκB.

An *in vivo* study carried out by Cheng, Cheng, Lee, Chung, & Chang (2015); Cheng, Yu et al., (2015) on the activity of resveratrol against methylglyoxal-induced hyperglycemia and pancreatic damage. The authors suggested that it is possible for resveratrol to be used in the treatment of type-2 diabetes because it prevented pancreatic cell dysfunction. Their results showed that resveratrol significantly reduced serum glucose levels, improved insulin resistance, reduced the value of HOMA-IR index, reduced TNF-α contents, enhanced IRS-Tyr and increased the expressions of insulin and p-Nrf2 proteins.

Lalitha et al. (2015) demonstrated that the administration of resveratrol combined with vitamin C increased body weight, total protein, and decreased fasting blood sugar level, MDA and LH, when compared with the diabetic control group. Resveratrol-vitamin C significantly restored the levels of both enzymatic (SOD, CAT, GSSH) and non-enzymatic antioxidant enzymes (GSH). In the same year, Yao et al. (2015) investigated the effect of resveratrol on the pregnant db/+ GDM mouse model, and studied the underlying molecular mechanism. The oral administration of resveratrol at a dose of 10 mg/kg improved glucose metabolism and insulin tolerance. The molecular mechanism showed that RV relieved GDM symptoms through enhancing AMPK activation, which in turn reduced the production and activity of glucose-6-phosphatase in both pregnant db/+ females and their offspring. In 2016, Kaur et al. (2016) demonstrated that the resveratrol reduced blood glucose and HbA_{1c} in STZ-induced diabetic rats. Diabetic rats treated with resveratrol showed an increase in insulin secretion from β-cells and suppression of pancreatic β-cell damage.

In 2018, two studies were conducted to evaluate the antidiabetic effect of resveratrol. Rehman et al. (2018) evaluated the protective effect of resveratrol alone and in combination with vitamin E against alloxan-induced diabetes animal model. Resveratrol alone and/or in combination with vitamin-E exhibited significant hypoglycemic effects, and improved glucose tolerance and insulin sensitivity. The other study carried out by Yang and Kang (2018) investigated the combined antidiabetic action of quercetin and resveratrol in streptozotocin (STZ)-induced diabetic rats. The results revealed that the administration of resveratrol alone or in combination with quercetin significantly decreased serum blood glucose levels and insulin levels. In addition, it maintained the activity of hepatic glucose metabolic enzymes and the structure of pancreaticβ-cells.

8.2.18. Quercetin

In 2004, Shetty et al. (2004) studied the effect of feeding quercetin (1 g/kg) to rats subjected to streptozotocin-induced diabetes. After conducting several experiments, it was found that quercetin improved the diabetes state of rats by 25%. The next year, the protective effect of quercetin against β-cell damage in experimental rats subjected to streptozotocin (STZ)-induced diabetes was evaluated by coskun et al. (2005). This effect was determined by measuring glutathione peroxidase (GSHPx), superoxide dismutase (SOD) and catalase (CAT) activities. Serum nitric oxide (NO) and malondialdehyde (MDA) levels were also measured in pancreatic tissues. Immunohistochemical assays were done to examine quercet ineffect on pancreatic β-cells. The results of the study showed that giving quercetin with a concentration of 15 mg/kg by injection to diabetic rats decreased the elevated MDA and NO, and also increased glutathione peroxidase (GSHPx), superoxide dismutase (SOD) and catalase (CAT) activities. Quercetin treatment also preserved islet

cells.

Lukačínová et al. (2008) evaluated the protective effect of quercetin against alloxan-induced diabetes mellitus in rats. The oral administration of this compound (50 and 100 mg/kg) for 7 days prevented serum glucose elevation. In the same year, Fang et al. (2008) investigated the possible mechanism of the antidiabetic activity of quercetin on 3T3-L1 cells. The study showed that quercetin improved insulin-stimulated glucose uptake in mature 3T3-L1 adipocytes. Quercetin also showed significant inhibitory effect on NO production in macrophage cells. It acted on multiple targets to ameliorate hyperglycemia including acting as a partial agonist of PPARγ.

Using an acquired model of insulin resistance (IR) by high fructose diet, Kannappan et al. (2009) conducted their studies. The determination of tyrosine phosphorylation of proteins in response to insulin was evaluated by assaying protein tyrosine kinase (PTK) and protein tyrosine phosphatase (PTP) in liver. The administration of quercetin at dose of 50 mg/kg for 60 days improved insulin sensitivity and tyrosine phosphorylation in fructose-fed. Another study focused on the evaluation of the protective effect of dietary quercetin on BALB/c mice subjected to streptozotocin (STZ)-induced diabetes. It was found that feeding diabetic rats with a diet containing 0.5% quercetin for two weeks decreased blood glucose levels and improved plasma insulin levels. Quercetin improved liver and pancreas functions by enabling the recovery of cell proliferation through the inhibition of Cdkn1a expression (Kobori et al., 2009). In the same year, Li et al. (2009) studied the antidiabetic effect of quercetin using α-glucosidase inhibitors assay with fluorescence spectroscopy and enzymatic kinetics methods. The results showed that this compound was more effective inhibitors against R-glucosidase and the results were comparable to acarbose.

Streptozotocin (STZ)-induced diabetes in rats' model was used to evaluate the possible effect of quercetin on blood glucose and antioxidant enzymes (Abdelmoaty et al., 2010). The injection of quercetin in rats at dose of 15 mg/kg for 25 days prevented diabetes induced by streptozotocin and increased the antioxidant enzymes activities. In the same year, an *in vitro* study on C2C12 muscle cells was performed to elucidate the antidiabetic mechanism of quercetin Eid et al. (2010). The results of this study indicated that quercetin and quercetin 3-O-glycosides enhanced glucose uptake by 38–59% and 37% respectively in the absence of insulin. These two compounds stimulated AMP-activated protein kinase (AMPK) pathway. Torres-Piedra et al. (2010) carried out a study to investigate the hypoglycemic and antidiabetic effects of quercetin in acute and sub-acute experiments in diabetic rats. The oral administration of this compound at dose of 50 mg/kg for five days, resulted in a significant decrease of the total cholesterol, TG and LDL and an augmentation of HDL compared with the control group. The same authors evaluated *in vitro* the inhibitory activity of quercetin against 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1). The results showed that the quercetin was docked into the crystal structure of 11b-HSD1.

In an animal model, the protective effect of quercetin on β-cells functions, pancreatic sorbitol level and oxidative stress was evaluated in diabetic rats (Abd El-Baky & Amin, 2011). The administration of this compound at dose of 20 mg/kg for 8 weeks showed a significant decrease in elevated blood glucose, insulin resistance, MDA, sorbitol, and NO. Quercetin treatment significantly increased the antioxidant enzyme's activities, as well as insulin levels and β-cell function. Kim et al. (2011) conducted a study using an animal model of diabetes mellitus to investigate the hypoglycemic effects of quercetin. The oral administration of this compound at dose of 100 mg/kg to STZ-treated rats significantly reduced plasma glucose, blood glycated hemoglobin and maltase activities and the results were comparable to the control without significant effect on plasma insulin.

Hussain et al. (2012) studied the potential activity of quercetin to control postprandial blood glucose level after maltose and glucose loading in normal and STZ-induced diabetic rats. The oral administration of quercetin at doses of 300 and 600 mg/kg ameliorated postprandial hyperglycemia by 32.0% and 64.0% respectively, compared with acarbose. Jadhav et al. (2012) demonstrated that quercetin exhibited a significant antidiabetic activity as well as It reduced total cholesterol and triglycerides compared with the control group. Studying the antidiabetic mechanism of action of quercetin demonstrated a significant increase the uptake of glucose by rat hemidiaphragm, also a decrease in glucose transport activity. In the same year, Jeong et al. (2012) demonstrated the hypoglycemic, hypolipidemic, and antioxidant effects of dietary quercetin in an animal model of type 2 diabetes mellitus. C57BL/KsJ-db/db mice were fed diet containing quercetin at 0.04% and 0.08% of the diet for 6 weeks. The results showed that this compound significantly lowered plasma glucose levels, triglycerides, and insulin resistance (HOMA-IR) without significant influence on insulin levels. It also increased plasma adiponectin and HDL-cholesterol compared with the control group, while decreased plasma total cholesterol. Moreover, quercetin reduced thiobarbituric acid reactive substances (TBARS) levels and elevated the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) in the liver. Another study in 2012, Rifaai et al. (2012) illustrated the effect of quercetin on the histological changes which occur in the islet of Langerhans of the streptozotocin (STZ)-induced diabetic rats and the possible mechanisms through which quercetin produces its protective effect. The administration of this compound at a dose of 25 mg/kg for 30 days showed a significant increase in blood glucose levels. Concerning the histological study, the results showed that the quercetin reversed most of the pancreatic morphological changes caused by STZ, and interestingly some islets noticed with connections to some pancreatic ducts. In addition, quercetin increased β cells number compared with the control group and decreased iNOS and caspase 3 immunoreactivity in the islet's cells.

In 2013, Dai et al. (2013a) demonstrated that quercetin ameliorated tumor necrosis factor-alpha-induced insulin resistance and enhanced the basal and insulin stimulated uptake of glucose in a dose-dependent manner *via* the activation of the protein kinase B (Akt) and AMP-activated protein kinase (AMPK) pathways in C2C12 skeletal muscle cells. Quercetin suppressed nuclear factor-κB (NF-κB) signaling and the nitric oxide (NO)/inducible nitric oxide synthase (iNOS) system, the down stream signaling of AMPK transduction.

A study was conducted by Alam et al. (2014) to evaluate the protective effect of quercetin on hyperglycemia, oxidative stress, and DNA damage in alloxan induced type 2 diabetic mice. The result of this study indicated that quercetin was able to decrease in FBG level and liver and kidney marker enzymes. It decreased the thiobarbituric acid-reactive substance level while increased the GLUT4 expression levels. DNA damage was also suppressed by quercetin as demonstrated by single cell alkaline gel electrophoresis. In another study carried out by Arias et al. (2014) to show the quercetin mechanism involved in muscle fatty acids oxidation in rats. The administration of quercetin for 6 weeks at dose of 30 mg/kg in Wister rat fed with a high-fat high-sucrose diet reduced blood glucose, insulin, and HOMA-IR. No changes were observed in the activity of lipogenic enzymes and lipoprotein lipase. The expression of ACO, CD36, CPT-1b, PPAR-a, PGC-1a, UCP3, TFAM, and COX-2 remained unchanged. In the same year, Dhanya et al. (2014) evaluated the antidiabetic potential of quercetin under oxidative stress induced by tertiary butyl hydrogen peroxide (TBHP) in the L6 cells. The results of this study showed that quercetin decreased reactive oxygen species generated by TBHP in a dose-dependent manner in the L6 cells and remarkably retrieved the glutathione level which was drastically decreased by the oxidative challenge. Quercetin increased glucose uptake in L6 myotubes through GLUT 4 translocation pathway.

In 2015, Eid et al. (2015) studied the effect of quercetin on glucose homeostasis in L6 skeletal muscle cells, murine H4IIE and human HepG2 hepatocytes. The treatment of L6 skeletal muscle cells with quercetin (50 μM) stimulated AMPK and increased GLUT4 translocation and protein content. In H4IIE hepatocytes, quercetin induced hepatic AMPK activation and inhibited G6pase. In HepG2 hepatocytes, quercetin

exhibited a mild tendency to increase the activity of glycogen synthase (GS) and the rate-limiting enzyme of glycogen synthesis. An *in vitro* study was carried out by Meng et al. (2016) on the inhibitory effect of α-amylase and α-glucosidase inhibition assay of quercetin. This compound showed important inhibition of α-glucosidase with IC_{50} value of 32 μg/mL. Moreover, quercetin was effective inhibitor of α-amylase with IC_{50} value of 770 μg/mL. The inhibitory effect of quercetin on α-amylase was reversible and competitive, but the effect on α-glucosidase was reversible but non-competitive. In 2017, Dhanya et al. (2017) studied quercetin molecular mechanisms of action in skeletal muscle cells (L6 myotubes) with induced type 2 diabetes. The results showed that the effect of quercetin on 2-NBDG uptake in L6 myotubes was through adenosine monophosphate kinase (AMPK) pathway and its downstream target p38 MAPK.

The study was carried out by Oyedemi et al. (2020) to investigate the effect of quercetin in a type 2 diabetic animal model. Glucose tolerance, pancreatic antioxidant status, glucose-6-phosphatase, hexokinase activities and histopathological examinations of the liver and pancreas were determined. The oral administration of quercetin at the dosage of 25 and 50 mg/kg for 28 days reduced the level of blood glucose, glycosylated hemoglobin (Hb), and hepatic glycogen but enhanced plasma Hb concentration. The authors tested the effect of honey and found that it improved the activities of glucose-6-phosphatase and hexokinase. Quercetin also increased the antioxidant activity of pancreatic superoxide dismutase, catalase (CAT), and reduced glutathione while decreased the value for thiobarbituric acid reactive species. A significant reduction of glycemia was observed in the glucose tolerance test, 120 min after the glucose pulse. Histologically, this compound restored the damage caused by fructose-STZ in the liver and pancreas of diabetic animals reaching the normal status.

8.2.19. Myricetin

An *in vitro* study wascarried out by Ong and Khoo (1996) to evaluate the effect of myricetin on lipogenesis and glucose transport. In this study, several assays were conducted to demonstrate this effect such as lipogenesis assay, measurement of D-glucose transport, and 3-O-methyl-glucose transport. The results of this study showed that this compound was able to stimulate lipogenesis in rat adipocytes and enhance the stimulatory effect of insulin. Myricetin stimulated both D-glucose and D-3-O-methyl-glucose uptake in rat adipocytes. It also increased V_{max} of glucose transport. However, the stimulation of glucose transport was not a consequence of glucose transporter translocation.

Ong and Khoo (2000) evaluated the *in vivo* effect of myricetin on glycemia and glycogen metabolism in diabetic rats. In this study, streptozotocin was used to induce diabetes in mice by intraperitoneal injection, after that it was treated by intraperitoneal injection with myricetin for 4 days. The results showed this compound stimulated glucose transport in rat adipocytes, enhanced insulin-stimulated lipogenesis and reduced hyperglycemia in diabetic rats (50%). on the other hand, the results related to the effect of myricetin on glycogen metabolism showed that myricetin increased hepatic glycogen and G6Pase content. It also increased the activity of hepatic glycogen synthase I without having any effect on the total glycogen synthase.

In 2005, Liu, Kim et al. (2005); Liu, Liou, Lan, Hsu & Cheng (2005) studied the effect of myricetin to lower plasma glucose in diabetic Wistar rats. The rats were marked diabetic by given intravenous injection of 60 mg/kg of streptozotocin, after that the rats were treated by intravenous injection of myricetin for 2 weeks. The results showed that myricetin decreased plasma glucose concentrations in a dose-dependent manner and enhanced glucose utilization to lower plasma glucose in diabetic rats lacking insulin. In addition, soleus muscles were isolated from STZ-diabetic rats to study the effect of myricetin on glucose uptake by these muscles. This molecule stimulated glucose uptake by soleus muscles in a concentration-dependent manner. In the same year, Strobel et al. (2005) isolated adipocytes from rats to study the effect of myricetin on glucose uptake as well, in order to explain the mechanism contributing to this process. Myricetin inhibited the uptake of methyl-glucose by adipocytes and inhibited the transport of glucose in isolated rat adipocytes stimulated with insulin. Using the same method in 2005 Liu Kim et al. (2005); Liu Liou et al. (2005); Liu et al. (2006) found that myricetin decreased plasma glucose concentration in a dose-dependent manner. It also increased the expression of the GLUT 4 in soleus muscle and reduced expression of PEPCK in liver.

In 2007, Obese Zucker rats were used by Liu et al. (2007a) to study the effect of myricetin on improving of insulin sensitivity. The intravenous injection of myricetin three times daily for one-week improved insulin sensitivity through increased post-receptor insulin signaling mediated by the enhancements of IRS-1-associated PI3-kinase and the activates the GLUT 4 in muscles. The same authors carried out a study on the effect of myricetin in suppressing insulin resistance induced by a high-fructose diet in rats. Insulin-resistant rats were used and were fed with fructose chow for six weeks. The oral glucose tolerance test (OGTT) was performed to explain the effect of myricetin on the concentration of glucose in the blood. The results of this study showed that this compound decreased high glucose level, decreased insulin resistance, and increased the whole-body insulin sensitivity. In addition, the *in vivo* study of insulin receptor activation showed the ability of myricetin to improve insulin sensitivity through the enhancement of insulin action on IRS-1- associated PI 3-kinase and the activity of GLUT 4 in soleus muscles Liu et al. (2007b).

An intravenous injection of myricetin thrice daily to insulin resistance rats at dose of 1 mg/kg per injection for two weeks showed the importance of myricetin in decreasing plasma glucose level and increasing plasma β-endorphin (Tzeng et al., 2011). A study of insulin receptor activation was similar to Liu et al. (2007b), as it demonstrated that myricetin treatment ameliorated the impaired downstream signaling intermediates of insulin receptors. A study of the effect of myricetin on glucose uptake was performed by Ding et al. (2012). Skeletal muscle cell line C2C12 myoblasts were used in this assay. Myricetin increased glucose uptake with both protein kinase B (Akt) and AMPK activities as well as improved insulin sensitivity by decreasing insulin resistance.

Using animal models, several studies demonstrated the anti-hyperglycemic efficacy of myricetin in diabetic rats induced by streptozotocin (STZ). Kandasamy and Ashokkumar (2012) showed that the administration of myricetin at dose of 1 mg/kg decreased plasma glucose levels and increased insulin levels. In 2014 the same authors, showed that the administration of myricetin at dose of 1 mg/kg for 12 weeks increased insulin, glycogen, glycogen synthase and the expression of insulin signaling molecules such asGLUT2, GLUT4, insulin receptor-1 (IRS1), IRS2 and protein kinase B (PKB). The study also showed that this compound was capable to normalize thew levels of carbohydrate metabolic products, glycated hemoglobin, glycogen phosphorylase and gluconeogenic enzymes. Histopathological investigation showed that myricetin protected the pancreas cells against streptozotocin (STZ) damage Kandasamy and Ashokkumar (2014). In 2017, Kang et al. (2015) showed that myricetin inhibited the activity of α-glucosidase, reduced serum fasting glucose, blood glycated hemoglobin, and maltase activities of the small intestine in *db/db* mice.

Also in 2014, Choi Kang et al. (2014) studied the effect of myricetin on insulin resistance in mice. After 12 weeks of feeding the mice with a diet rich in sucrose, fat and myricetin at dose of 0.12%, a decrease in serum glucose, insulin levels and HOMA-IR values was observed. Also, the consumption of 0.12% myricetin significantly reduced the levels of TNF-α and IL-6 compared with the positive control group.

From 2016 to 2018, several studies were conducted to explain the anti-hyperglycemic effect of myricetin. Meng et al. (2016) used α-amylase and α-glucosidase inhibition methods to validate the anti-hyperglycemic effect of myricetin. The results showed that this compound inhibited α-amylase and α-glucosidase activity with IC_{50} = 662 μg/mL and 3 μg/mL, respectively. The inhibition of α-amylase was reversible and competitive, while the effect on α-glucosidase was

reversible but non-competitive. Arumugam et al. (2016) used the same method and showed that myricetin inhibited both α-amylase and α-glucosidase. An *in vitro* was also used by same authors to study the effect of myricetin on the glucose uptake into 3T3-L1 cells. Myricetin exhibited 'insulin-like' effect by enhancing the accumulation of lipids, glucose uptake and adiponectin secretion by activating insulin signaling pathway similar to insulin. The mechanism action of this effect was revealed by the upregulation of Akt1, PPARγ and glucose transporter genes in addition to protein kinase as well as the activation of AMP and adiponectin to stimulate glucose uptake. The glucoregulatory activity of myricetin was illustrated by Li, Zhang et al. (2017); Li, Zheng et al. (2017) while the improved systemic insulin resistance by activating brown adipose tissue (BAT) and increased adiponectin expression in BAT was shown by Hu et al. (2018).

8.2.20. Naringenin

Animal models were widely used to examine the anti-diabetic effect of naringenin. Ortiz-Andrade et al. (2008) used an animal model along with*in vitro* assays including α-glucosidase and 11β-HSD1 inhibitory assays to study the antihyperglycemic effect of naringenin. The results of this study showed when rats were given naringenin at a concentration of 50 mg/kg, the glucose plasma concentration was decreased. The *in vitro* assays indicated that 11β-HSD1 was inhibited by 39.49%, but no inhibition ofα-glucosidase activity was observed. Annadurai et al. (2012) studied the antihyperglycemic effect of naringenin in diabetic rats induced by streptozotocin (STZ)–nicotinamide. The oral administration of naringenin at 50 mg/kg for 21, lowered fasting blood glucose levels and glycosylated hemoglobin, but elevated serum insulin levels. Histologically, this compound protected the pancreatic cells. The next year, the same others showed that naringenin reduced hematological, mRNA transcript and protein indices of inflammation compared with the diabetic group (Annadurai et al., 2013).

Two studies were carried out by Priscilla et al. (2014) and Priscilla et al. (2015) to evaluate the antihyperglycemic effect of naringenin in diabetic rats induced by streptozotocin and fed with high fat diet. Naringenin showed the most potent competitive inhibition of intestinal α-glucosidase and lowered postprandial blood glucose levels. In the second study, naringenin reduced hyperglycemia and hyperinsulinemia in rats, enhanced insulin sensitivity and modulated the expressions of GLUT4 and TNF-α. Histologically, naringenin capable restored abnormalities in pancreatic tissues.

Several studies between 2016 and 2018 demonstrated the anti-hyperglycemic effect of naringenin *in vivo* in diabetic rats induced by streptozotocin (STZ). These results showed a decrease in blood glucose levels (Ren et al., 2016; Sharma et al., 2016; Singh et al., 2018), a decrease in insulin resistance index, an improve in impaired glucose tolerance Ren et al. (2016) and a suppression of glycosylated hemoglobin Sharma et al. (2016). Ahmed et al. (2017) showed that naringenin alleviated the lowered serum insulin and C-peptide levels, the depleted liver glycogen content, the elevated liver G6Pase and glycogen phosphorylase activity. Also, molecular studies that were carried out by Singh et al. (2018) revealed that this compound exhibited antidiabetic effect through the dual activation of PPARγ/GLUT4 signaling pathways by increasing the binding affinity towards PPARγ and GLUT4. In 2017, Male Tsumura Suzuki Obese Diabetes (TSOD) mice were used to investigate whether dietary naringenin affects the actions of pioglitazone. Naringenin attenuated the hypoglycemic action of pioglitazone in TSOD mice when it was administered orally with pioglitazone. However, naringenin did not affect fasting blood glucose levels.

The following year, Kappel et al. (2013) studied the *in vitro* effect of rutin on the absorption of glucose ^{14}C in isolated soleus muscles of rats and explained the mechanism of action involved in this phenomenon. Rutin showed similar action of on glucose absorption to the insulin signaling pathways suggesting insulin-mimetic role of rutin in the homeostasis of glucose. It stimulated the absorption of glucose in the soleus muscles of rats *via* the PI3K, atypical protein kinase C and mitogen activated protein kinase (MAPK) pathways (Kappel et al., 2013).

Several studies on culture cells were conducted to demonstrate the antidiabetic effect of naringenin. Among these studies one study was-conducted by Lim et al. (2008), who used lipogenesis, lipolysis and glucose uptake assays to show the antidiabetic effect of naringenin. The results show this compound stimulated glucose uptake (163%) in rat adipocytes. In another study Yoshida et al. (2010) clarified the mechanism action of antidiabetic effect of naringenin, using 3T3-L1 cells. Naringen ininhibited TNF-α stimulated FFA secretion from mouse adipocytes and blocked the TNF-α induced activation of the NF-κB and ERK pathways. Also in 2010, Zygmunt et al. (2010) carried out a study to evaluate the effect of this compound on glucose uptake into muscle cells (L6). Glucose uptake was increased in the muscle cells *via* the increase of AMPK phosphorylation/activation. In INS-1E cells, Bhattacharya et al. (2014a) conducted a study showing that naringenin enhanced insulin secretion and glucose sensitivity in INS-1E cells. Also, it modified the gene expression profiles to improve β-cellsurvival and function during glucotoxicity. Another study was published in the same year by Bhattacharya et al. (2014b) explaining that naringenin enhanced the phosphorylation of TBC1D1 in porcine myotube cultures, suggesting that this compound enhanced the translocation of GLUT4 containing vesicles and thus glucose uptake *via* a TBC1D1-dependent mechanism.

8.3. Antidiabetic properties of phenolic acids

8.3.1. Caffeic acid

The antidiabetic activity of caffeic acid was reported by several studies (Table 8). Its antihyperglycemic efficacy as well as its molecular mechanisms were also demonstrated. Hsu et al. (2000) tested the caffeic acid on insulin-resistant rat models. It was noticed that caffeic acid decreased plasma glucose levels in a dose-dependent manner. In the same study, caffeic acid increased glucose uptake by adipocytes in a concentration-dependent manner. This led to the conclusion that caffeic acid lowered the plasma glucose level by increasing its utilization (Hsu et al., 2000). In another study, caffeic acid was tested on streptozotocin-induced diabetic rats. The results showed that caffeic acid decreased plasma glucose concentration in a dose-dependent manner (Cheng et al., 2003; Ho et al., 2013). The mechanism by which caffeic acid lowered plasma glucose was by stimulating β-endorphin secretion from the adrenal medulla through the activation of α-adrenoceptors. The releasedβ-endorphin activated opioid μ-receptors to lower the higher plasma glucose concentration in the model of type I-like diabetes (Cheng et al., 2003). Moreover, it was reported that caffeic acid lowered plasma glucose and glycosylated hemoglobin levels in C57BL/KsJ-db/db mice. It also increased the plasma insulin, C-peptide, and leptin levels. In the other hand, it decreased plasma glucagon level. The antidiabetic mechanisms of caffeic acid in this mice model was determined. The increased plasma insulin level by caffeic acid was attributed to its antidegenerative effect on the islets of Langerhans. Also, caffeic acid increased glucokinase activity and its mRNA expression, while it decreased glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities and their respective mRNA expressions. Moreover, it reduced the glucose transporter 2 expression in the liver, and increased adipocyte glucose transporter 4 expression. Caffeic acid lowered the activity of some enzymes that play important roles in diabetes such as superoxide dismutase, catalase, and glutathione peroxidase and their respective mRNA levels, while it lowered the hydrogen peroxide and thiobarbituric acid reactive substances levels in the erythrocyte and liver of db/db mice (Jung et al., 2006).

Caffeic acid was also studied by (Celik et al., 2009) for is hypoglycemic and liver-protective activities in streptozotocin (STZ)-induced diabetic rats. It was shown that caffeic acid increased the expressions of glucokinase, and pyruvate kinase mRNAs in diabetic rats, while it decreased phoshoenolpyruvate carboxykinase mRNA expression. In addition, caffeic acid increased the level of plasma insulin that was induced by STZ treatment. The authors demonstrated that caffeic acid

decreased the fasting blood levels of glucose, alanine aminotransferase, cholesterol, and triglyceride, and reduced the plasma glucagon level induced by diabetes. Moreover, it was noticed by histopathological evaluation of the liver that caffeic acid reduced necrosis and anisonucleosis in hepatocytes, and connective tissue elevated in the portal region by diabetes. Caffeic acid increased glucose uptake in insulin resistant FL83B cells (Huang et al., 2009). This action was done by increasing insulin sensitivity, which restored the glucose uptake and promoted glucose utilization consequently.

The signalization pathways are another target of caffeic acid. Caffeic acid promoted insulin signaling in insulin-resistant FL83B cells, by activating the tyrosyl phosphorylation of IR as well as by increasing the expression of PI3K. PI3K plays a critical role in insulin signaling.It induces the phosphorylation of phosphoinositides to produce phosphatidylinositol-3,4,5-phosphates, which are associated with glucose transporter translocation and glycogen synthesis (Huang et al., 2009).

Moreover, caffeic acid increased the expression of glycogen synthase (major enzyme catalyzes glycogen synthesis) which promoted glycogen synthesis (Huang et al., 2009; Huang and Shen, 2012), decreased the expression of glycogen synthase kinase (Huang and Shen, 2012), and increased GLUT-2 protein expression in TNF-R-induced insulin-resistant FL83B cells that improved glucose intake by the cells (Huang et al., 2009). On the other hand, this phenolic acid regulated the plasma glucose level by inhibiting the expression of hepatic nuclear factor-4, and the expression of glycogen synthase kinase as well as the activity of phosphoenolpyruvate carboxykinase (Huang and Shen, 2012).

A recent study reported that caffeic acid improved hyperglycemia by stimulating AMPK activity of skeletal muscle, as well as by increasing insulin-independent glucose transport with a reduction of the intracellular energy status (Tsuda et al., 2012). In addition, caffeic acid exerted antidiabetic effect by stimulating glucose-stimulated insulin secretion and glucose sensitivity in INS-1E cells. It also modulated gene expression profiles to improve β-cell survival and function during glucotoxicity (Bhattacharya et al., 2014a).

Caffeic acid reduced postprandial hyperglycemia by inhibiting the key enzymes linked to type 2 diabetes, α-amylase and α-glucosidase (Oboh et al., 2015b). The inhibition of these two enzymes may lead to reduction in sugar absorption in the gastrointestinal tract. The inhibition of α-amylase and α-glucosidase by phenolic acids is in relation with their OH groups, which forms hydrogen bonds with specific amino acids at the enzyme's active sites (Oboh et al., 2015b). The efficacy of caffeic acid as antidiabetic compared to other phenolic acids can be explained by the fact that caffeic acid as a derivative of cinnamic acid contains two hydroxy groups in the structural formula is more potent than those containing single group (Huang et al., 2009).

8.3.2. Chlorogenic acid

Chlorogenic acid is known as an important natural antidiabetic compound. Its activity was examined by several researchers (Nicasio et al., 2005). reported a strong correlation between the chlorogenic acid content and antidiabetic activity in healthy male Balb-C mice. In addition, it was reported that the oral administration of chlorogenic acid produced a significant hypoglycemic effect, and decreased plasma glucose surge during the glucose tolerance test in streptozotocin-induced diabetic rats (Park et al., 2009b). It decreased glycosylated hemoglobin, increased the levels of plasma insulin, and glycogen, and reversed the altered activities of glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucokinase and hexokinase in streptozotocin-nicotinamide-induced diabetic rats (Karthikesan et al., 2010).

Chlorogenic acid exhibited a dose-dependent decrease of non-fasting blood glucose levels in streptozotocin-induced diabetic rats (Hunyadi et al., 2012). It decreased fasting blood glucose in *db/db* mice homozygous for diabetes, stimulated glucose transport in soleus muscle isolated from *db/db* mice, exhibited a dose- and time-dependent stimulation of glucose transport in L6 skeletal muscle cells, and increased GLUT 4 translocation through AMPK activation (AMPK is necessary for the glucose transport stimulation) (Ong et al., 2012). This acid increased glucose tolerance, and insulin sensitivity. On the other hand, it inhibited the gluconeogenesis through the downregulation of gluconeogenic enzyme G6Pase, stimulated glucose uptake in skeletal muscles by increasing GLUT-4 expression and translocation to plasma membrane, and increased AMPK phosphorylation in time- and dose-dependent manner (Ong et al., 2013).

(Jin et al., 2015) evaluated the antidiabetic effect of chlorogenic acid on female diabetic C57BL/BKS *db/db* mice. They demonstrated that chlorogenic acid decreased fasting plasma glucose, decreased glycosylated hemoglobin, and decreased aldose reductase activity. In addition, the phosphorylation of AMP-activated protein kinase (AMPK) in the liver and muscles, and the mRNA and protein levels of peroxisome proliferator-activated receptor alpha (PPAR-α) in the liver were all significantly promoted. Moreover, chlorogenic acid inhibited α-amylase and α-glucosidase (key enzymes linked to type 2 diabetes) activities in a dose-dependent manner (Oboh et al., 2015b).

8.3.3. Ferulic acid

The antidiabetic activity of ferulic acid (FA) was reported by several works. The data from the literature showed that ferulic acid exhibits interesting antihyperglycemic effect. This phenolic acid was known to lower plasma glucose in streptozotocin-induced diabetic mice (model of insulin-dependent diabetes mellitus), and KK-A^y mice and in type 2 diabetic mice *db/db* (model of non-insulin dependent diabetes mellitus) as well as in other diabetes models (Jung et al., 2007; Ohnishi et al., 2004; Song et al., 2014). The antidiabetic mechanisms were also demonstrated. Ferulic acid increased plasma insulin levels, stimulated hepatic glycogen synthesis, increased glucokinase activity, down-regulated glucose-6-phosphatase (G6pase) and phosphoenolpyruvate carboxykinase (PEPCK) (Jung et al., 2007; Son et al., 2011). It also decreased glucose levels by mitigating the pancreatic damage, increased insulin release, and decreased hepatic glycogenolysis (Azay-Milhau et al., 2013). FA positively affected the pancreas by increasing the number of islets (Prabhakar et al., 2013), and improved its histological appearance in streptozotocin-induced diabetic rats (Roy et al., 2013).

Recently, it was reported that FA improved hepatic ^{14}C-2-deoxy-glucose uptake and ^{14}C-glucose oxidation in type-2 diabetic rat, and reduced hepatic GLUT-2 gene expression (Narasimhan et al., 2015a). In addition, FA reduced the activity of gluconeogenic enzymes and improved the activity of glucokinase, improved glycogen synthesis, reduced hepatic glucose production, and reduced the negative regulators of insulin signaling (Narasimhan et al., 2015b). The combination of FA with metformin improved both the *in vitro* glucose uptake activity and the *in vivo* hypoglycemic effect (Nankar et al., 2017). On the negative side, it was reported that ferulic acid inhibited muscle glucose uptake in Wistar rats (Azay-Milhau et al., 2013).

8.3.4. Gallic acid

The antidiabetic activity of gallic acid (GA) was evaluated by several researchers. The positive effect of gallic acid was proven using several diabetic models such as alloxan-induced diabetes in female rabbits (Al-Salih, 2010), streptozotocin-induced diabetic rats (Abdel-Moneim et al., 2017, 2018; Ahad et al., 2015; Gandhi et al., 2014; Latha and Daisy, 2011), streptozotocin-induced diabetic Wistar rats (Punithavathi et al., 2011), male C57BL/6 mice (Bak et al., 2013), diet-induced obese mice (Ahad et al., 2015; Doan et al., 2015; Gandhi et al., 2014), and enzymes linked to type 2 diabetes (α-amylase and α-glucosidase) (Oboh et al., 2016). All these works proved that GA positively affected glucose metabolism in diabetes models.

The mechanisms by which GA improved hyperglycemia was also determined. Gallic acid mobilized GLUT-4 from specialized compartment to the plasma membrane that increased the glucose uptake. The translocation of GLUT-4 by GA was suggested to be mediated *via* PI3K

Table 8
Phenolic acids

Compounds	Methods	Keys results	References
3-Hydroxycinnamic acid	Anti-hyperglycemic activity: Using HepG2 and HIT-T15 cells.	Increased glucose uptake. Stimulation of glucokinase (Gck) activity. Stimulation of insulin secretion.	Jung et al. (2010)
	Alloxan-induced diabetic rats.	Decreased blood glucose levels. Reduced triglycerides, LDL, and VLDL.	Singh et al. (2012)
	Streptozotocin-induced diabetic Wistar rats.	Lowered blood glucose. Decreased glycosylated hemoglobin. Increased plasma insulin.	Ambika et al. (2013)
Caffeic acid	Diabetic rats of both: streptozotocin-induced and insulin-resistant models.	Decreased plasma glucose in a dose-dependent manner. An insulin dependent action. Reduced plasma glucose levels in insulin resistant rats. Increased glucose uptake in a concentration-dependent manner.	Hsu et al. (2000)
	Streptozotocin-induced diabetic rats.	Lowered plasma glucose concentration in a dose-dependent manner. Stimulation β-endorphin secretion from the adrenal medulla through the activation of alpha-adrenoceptors.	Cheng et al. (2003)
	Male C57BL/KsJ-*db/db* mice.	Reduced blood glucose and glycosylated hemoglobin levels. Increased plasma insulin. Decreased plasma glucagon level. Increased Gck activity and its mRNA expression and glycogen content and simultaneously lowered glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities and their respective mRNA expressions. Reduced hepatic glucose transporter-2 (GLUT2) expression. Adipocyte glucose transporter 4 (GLUT4) expression was greater than the control group.	Jung et al. (2006)
	Streptozotocin-induced diabetic rats.	Improved expression of Gck (3.4–14.9-folds), and pyruvate kinase (3.2–12.8-folds) mRNAs. Decreased phosphoenolpyruvate carboxykinase mRNA expression to varying degrees (1.2–5.5-fold). Decreased fasting blood glucose levels. Increased plasma insulin. Increased liver glycogen levels.	Celik et al. (2009)
	Insulin-resistant mouse hepatocytes (FL83B cells).	Promote insulin receptor tyrosyl phosphorylation. Up-regulated the expression of insulin signal associated proteins, including insulin receptor, phosphatidylinositol-3 kinase, glycogen synthase, and (GLUT2). Increased glucose uptake. Alleviated insulin resistance in cells.	Huang et al. (2009)
	Tumor necrosis factor-α-treated insulin-resistant mouse FL83B hepatocytes. Western blot analysis	Increased the expression of glycogen synthase. Decreased the expression of glycogen synthase kinase and phosphorylation of glycogen synthase at Ser641 in insulin-resistant mouse hepatocytes. Suppressed the expression of hepatic nuclear factor-4. Inhibitedthe activity of phosphoenolpyruvate carboxykinase.	Huang and Shen (2012)
	Rat skeletal muscle. Western blot analysis Isoform-specific AMPK activity assay.	StimulatedAMPK activity of skeletal muscle. Stimulatedinsulin-independent glucose transport with a reduction of the intracellular energy status.	Tsuda et al. (2012)
	Effect on glucose-stimulated insulin secretion (GSIS) in INS-1E cells.	Improved insulin secretion and insulin gene expression. Improved glucose sensitivity and survival probabilities of INS-1E cells subjected to glucotoxicity. Differential change of the expression profile of genes (Glut2, Gck, insulin 1 …). A positive influence on the expression of key β-cell survival and regulatory genes.	(S. Bhattacharya et al., 2014)
	Streptozotocin-induced type 1 diabetic rats. Key enzymes linked to type 2 diabetes (α-amylase and α-glucosidase).	Decreased plasma glucose. Inhibitory effect on α-amylase [IC_{50} (concentration of sample causing 50% enzyme inhibition) = 3.68 µg/mL] and α-glucosidase (IC_{50} = 4.98 µg/mL) activities.	Ho et al. (2013) Oboh et al. (2015b)
Chlorogenic acid	Hypoglycemic effect on healthy male Balb-C mice. Streptozotocin-induced diabetic rats.	Decreased plasma glucose levels (52.8%). Oral administration of chlorogenic acid (10 mg/kg) for 6 weeks produced a significant hypoglycemic effect. Decreased plasma glucose surge during the glucose tolerance test.	Nicasio et al. (2005) (Park et al., 2009b)
	Streptozotocin-nicotinamide-induced diabetic rats.	Chlorogenic acid at a dose of 5 mg/kg b.w has antidiabetic potential. After the experimental period of 45 days, supplementation with combined dose of tetrahydro curcumin/chlorogenic acid: Significantly decreased glycosylated hemoglobin. Increased the levels of plasma insulin, and glycogen. Significantly reversed the altered activities of glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucokinase and hexokinase.	Karthikesan et al. (2010)
	Streptozotocin-induced diabetic rats.	A dose-dependent decrease of non-fasting blood glucose levels.	Hunyadi et al. (2012b)
	Male *db/db* mice homozygous for diabetes spontaneous mutation. Oral glucose tolerance test.	Decreased fasting blood glucose in *db/db* mice. Stimulated glucose transport in soleus muscle isolated from *db/db* mice. Dose- and time-dependent stimulation of glucose transport by	Ong et al. (2012)

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Table 8 (*continued*)

Compounds	Methods	Keys results	References
	2DG Transport in soleus muscle. Cell culture and differentiation of L6 skeletal muscle. Western blot analysis.	chlorogenic acid in L6 skeletal muscle cells. AMPK is necessary for the glucose transport stimulation by chlorogenic acid. Chlorogenic acid increased GLUT 4 translocation through AMPK activation.	
	$Lepr^{db/db}$ mice. Oral glucose tolerance test. Glucose production assay. AMPK activity assay. Glucose profile. Hepatic (G6Pase) activity. Western blot analysis.	Lowered blood glucose in an OGTT. 2-Week treatment improvedglucose profile, glucose tolerance, and insulin sensitivity. Inhibited gluconeogenesis through the downregulation of gluconeogenic enzyme G6Pase. Stimulated glucose uptake in skeletal muscles by increasing GLUT 4 expression and translocation to plasma membrane. Increased AMPK phosphorylation in time- and dose-dependent manners. Inhibition and knockdown of AMPK abolished chlorogenic acid-inhibited gluconeogenesis.	Ong et al. (2013)
	Female diabetic C57BL/BKS *db/db* mice. Oral glucose tolerance test. Detection of blood biochemistry. RT-PCR Western blot analysis.	Decreased fasting plasma glucose. Decreased glycosylated hemoglobin. Decreased aldose reductase activity. The phosphorylation of AMP-activated protein kinase (AMPK) in the liver and muscle, and the mRNA and protein levels of peroxisome proliferator-activated receptor alpha (PPAR-α) in the liver were all significantly greater.	Jin et al. (2015)
	Key enzymes linked to type 2 diabetes (*in vitro*): α-Amylase and α-glucosidase inhibition assays	Inhibited α-amylase and α-glucosidase activities in a dose-dependent manner. α-Amylase (IC_{50} = 9.10 μg/mL). α-Glucosidase (IC_{50} = 9.24 μg/mL).	Oboh et al. (2015b)
Ferulic acid	Streptozotocin-induced diabetic mice and KK-A^{y} mice. Determination of blood glucose level.	Significantly suppressed blood glucose levels in STZ-induced diabetic mice (at 0.01% and 0.1%) and KK-A^{y} mice (at 0.05%).	Ohnishi et al. (2004)
	Type 2 diabetic mice (*db/db* mice). Blood analysis. Determination of hepatic glycogen content. Determination of hepatic glucokinase activity. α-Glucosidase inhibitory activity.	The inhibitory activity of ferulic acid was concentration dependent. Decreased blood glucose levels. Increased plasma insulin levels. Increased hepatic glycogen synthesis. Increased glucokinase activity.	Jung et al. (2007)
	Mice fed with a High-Fat Diet (HFD). Measurement of blood glucose level. Determination of glycogen and insulin levels. Measurement of hepatic glucose-regulating Enzyme activities	Decreased levels of blood glucose, glucose-6-phosphatase (G6pase) and phosphoenolpyruvate carboxykinase (PEPCK). Increased glycogen and insulin concentrations. Increased glucokinase (GK) activity.	Son et al. (2011)
	Alloxan-induced diabetic mice.	Decreased glucose levels. Mitigation of pancreatic damage.	Ramar et al. (2012b)
	Insulinotropic investigations. Insulin sensitizing investigation. Hepatocyte culture and glycogenolysis test. Evaluation of glucose 6-phosphatase activity in microsomal fractions of hepatic cells. Intraperitoneal glucose tolerance test.	Increased insulin release. Decreased hepatic glycogenolysis. Inhibition of muscle glucose uptake.	Azay-Milhau et al. (2013)
	Streptozotocin-induced diabetic rats. Histopathological analysis of the pancreas.	Reduced blood glucose levels by ferulic acid used alone and in combination with oral hypoglycemic drugs. Increased the number of islets.	Prabhakar et al. (2013)
	Streptozotocin-induced diabetic rats. Apoptosis by TUNEL assay (pancreatic β cell).	Improved blood glucose levels. Improved histological appearance of the pancreas.	Roy et al. (2013)
	Late-stage diabetes in obese rats.	Decreased serum glucose.	Song et al. (2014)
	High fat diet and fructose-induced type-2 diabetic adult male rat. Western blot analysis. mRNA levels of GLUT2. ^{14}C-2-Deoxyglucose uptakeand ^{14}C-glucose oxidation.	Improved hepatic ^{14}C-2-deoxyglucose uptake and ^{14}C-glucose oxidation in type-2 diabetic rat. Reduced hepatic GLUT2 gene expression.	Narasimhan et al. (2015a)
	High fat diet and fructose-induced type-2 diabetic adult male rat. Fasting blood glucose. Oral glucose tolerance test. Insulin tolerance test. Fasting serum insulin. Glycogen concentration. Homeostasis model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). Activity of glycogen synthase. Activity of glycogen phosphorylase. Activity of glucose-6-phosphatase (G6Pase). Activity of phosphoenolpyruvate carboxykinase. Activity of glucokinase. Western blot analysis.	Improved glucose and insulin tolerance. Improved glycogen concentration and activity of glycogen metabolizing enzymes. Reduced activity of gluconeogenic enzymes and improved activity of glucokinase. Improved glycogen synthesis. Reduced hepatic glucose production. Reduced negative regulators of insulin signaling.	Narasimhan et al. (2015b)
	Streptozotocin-induced diabetic rats.	Combining ferulic acid with metformin improved both, *in vitro* glucose uptake activity and *in vivo* hypoglycemic activity.	Nankar et al. (2017)
Gallic acid			

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Table 8 (*continued*)

Compounds	Methods	Keys results	References
	Cell culture and transfection of 3T3-L1 preadipocytes. GLUT4 translocation assay. Glucose uptake assay. Western blot analysis.	Increased glucose uptake activity. Involvement of insulin signaling proteins in the cellular phosphorylation. GLUT4 translocation in transfected 3T3-L1 preadipocytes.	Vishnu Prasad et al. (2010)
	Alloxan-induced diabetes (in female rabbits). Determination of blood glucose.	The synergistic effect of gallic acid and tannic acid has decreased blood sugar.	Al-Salih (2010a)
	Streptozotocin-induced diabetic rats. Determination of plasma glucose, insulin and C-peptide. Oral glucose tolerance test. Histopathological examination of the pancreatic sections.	Reduced plasma glucose level in a dose-dependent manner. Regeneration of β-cells of islets Increased plasma insulin, C-peptide and glucose tolerance level.	Latha and Daisy (2011)
	Streptozotocin-induced diabetic Wistar rats Histopathological examination of the pancreatic sections.	Protective effect on all the biochemical parameters studied and negatively affected by streptozotocin: Blood glucose, glycosylated hemoglobin, plasma insulin, hepatic hexokinase, glucose-6-phosphatase and fructose-1,6-bisphosphatase. Protective effects on pancreas.	Punithavathi et al. (2011)
	Male C57BL/6 mice. Glucose tolerance test. Reverse transcription-polymerase chain reaction (RT-PCR). Western blot analysis.	Improved glucose tolerance. Improved blood glucose concentrations. Induction of PPARγ expression. Activation of the Akt signaling pathway.	Bak et al. (2013)
	High-fat diet fed-streptozotocin-induced type 2 diabetic rats. RNA Extraction and reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. Western blot analysis. Oral glucose tolerance test. Insulin tolerance test.	Decreased fasting blood glucose and plasma insulin. Cytoprotective action on pancreatic β-cell. Enhanced level of peroxisome proliferator-activated receptor γ (PPARγ) expression. Improved insulin-dependent glucose transport in adipose tissue through translocation and activation of GLUT4.	Gandhi et al. (2014)
	High fat diet/streptozotocin-induced type 2 diabetic rats. Assessment-insulin resistance.	Decreased blood glucose levels. Decreased insulin resistance.	Ahad et al. (2015)
	Diet-Induced obese mice. Glucose tolerance test. Insulin tolerance test. Western blot analysis.	AMPK activation. Activation of the AMPK/Sirt1/PGC1α pathway Improved glucose and insulin homeostasis.	Doan et al. (2015)
	Rats fed a high-fructose diet induced diabetes. Oral glucose tolerance test. Homeostasis model assessment-insulin resistance. Western blot analysis.	Increased glucose uptake activity by 19.2% at a concentration of 6.25 μg/mL in insulin-resistant FL83B mouse hepatocytes. Alleviated hyperglycemia. reduced the scores of the homeostasis model assessment insulin resistance (HOMA-IR) index. Decreased levels of serum C-peptide. Upregulated the expression of hepatic insulin signal transduction related proteins, including insulin receptor, insulin receptor substrate-1, phosphatidylinositol-3 kinase, Akt/protein kinase B, and GLUT2. Downregulated the expression of hepatic gluconeogenesis-related proteins, such as fructose-1,6-bisphosphatase, and upregulated the expression of hepatic glycogen synthase and glycolysis-related proteins, including hexokinase, phosphofructokinase, and aldolase.	Huang et al. (2016)
	Key enzymes linked to type 2 diabetes (α-amylase and α-glucosidase).	Combination of 50% acarbose +50% gallic acid showed the highest α-glucosidase inhibitory effect. Combination of 75% acarbose +25% gallic acid showed the highest α-amylase inhibitory effect.	Oboh et al. (2016)
	Streptozotocin-induced diabetic rats. Western blot analysis. Biochemical examinations.	Decreased levels of serum glucose and blood glycosylated hemoglobin. Increased serum insulin level. Decreased of HOMA-IR.	Abdel-Moneim et al. (2017)
	Streptozotocin-induced diabetic rats. Biochemical examinations. PPARγ gene expression analysis using quantitative real time PCR (qRT-PCR).	Decreased OGTT AUC (the area under curve). Decreased blood glycosylated hemoglobin. Decreased serum insulin level. Significant amelioration in insulin sensitivity as evident by their effect on HOMA-IR and QUICKI.	Abdel-Moneim et al. (2018)
4-Hydroxybenzoic acid	Streptozotocin-induced diabetic rats.	Decreased plasma glucose levels in a dose-dependent-manner. No alteration in serum insulin level and liver glycogen content. Increased glucose consumption.	Peungvicha et al. (1998b)
	Normal Wistar rats. Biochemical examinations.	Hypoglycemic effect. Increased serum insulin levels. Increased liver glycogen content.	Peungvicha et al. (1998a)
p-Coumaric acid	L6 rat skeletal muscle cells. Western blot analysis. 2-NBDG Glucose uptake assay	Increased AMPK phosphorylation in a dose-dependent manner in differentiated L6 skeletal muscle cells. Enhanced 2-NBDG glucose uptake.	Yoon et al. (2013)
	Streptozotocin-induced diabetic rats. Biochemical estimations.	Improved glycemic and antioxidant status.	(Shairibha and Rajadurai, 2014)
	Streptozotocin-induced diabetic rats. Biochemical estimation.	Decreased the level of plasma glucose with a maximum plasma glucose lowering effect (22.01 mmol/L) at 100 mg/kg. Increased levels of insulin and C-peptide. Increased liver and muscle glycogen.	(Shairibha, Rajadurai et al, 2014)

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Table 8 (*continued*)

Compounds	Methods	Keys results	References
		Decreased levels of glycosylated hemoglobin. Increased hexokinase activity. Decreased G6Pase and fructose-1,6-bisphophatase activity.	
	Streptozotocin-induced diabetic rats. Biochemical estimation. Histopathological examination of pancreas.	Lowered blood glucose. Improved level of insulin. Protected the pancreas.	Amalan et al. (2015)
	Streptozotocin-induced diabetic rats. Biochemical estimation.	Lowered blood glucose level. Lowered gluconeogenic enzymes such as G6Pase and fructose-1,6-bisphosphatase. Increased activities of hexokinase and G6Pase dehydrogenase. Increased expression of GLUT2 mRNA in the pancreas.	Amalan et al. (2016)
	Streptozotocin-induced diabetic rats. Western blot analysis. Biochemical examinations.	Decreased levels of serum glucose and blood glycosylated hemoglobin. Increased serum insulin level. Decreased of HOMA-IR.	Abdel-Moneim et al. (2017)
	Streptozotocin-induced diabetic rats. Biochemical examination. PPARγ gene expression analysis using quantitative real time PCR (qRT-PCR).	Decreased OGTT AUC (the area under curve). Decreased blood glycosylated hemoglobin. Decreased serum insulin level. Significant amelioration in insulin sensitivity as evident by their effect on HOMA-IR and QUICKI.	Abdel-Moneim et al. (2018)
Rosmarinic acid	Porcine pancreatic α-amylase (*in vitro*).	Rosmarinic acid (RA) and purified RA inhibited α-amylase activity.	McCue and Shetty (2004)
	Fructose-fed mice. Biochemical examinations. Uptake of glucose by rat diaphragm.	Lowered fasting glucose concentration. Reduced $AUC_{glucose}$ and $AUC_{insulin}$ values. Increased glucose utilization. In the presence of both RA and insulin, the utilization of glucose was greater than when they were present alone. Reduced levels of glucose, insulin, fructosamine and glycated hemoglobin. Ameliorated insulin sensitivity index (ISI), HOMA, and QUICKI	Vanithadevi and Anuradha (2008)
	Streptozotocin-induced diabetic rats. Western blot analysis. Glucose measurement. Insulin measurement. Liver glycogen content.	Improved diabetic fasting blood glucose levels. No effects on the plasma insulin and liver glycogen content. Decreased plasma glucose levels.	Azevedo et al. (2011)
	HFD–STZ Induced diabetic rats. Oral glucose tolerance test. Determination of glucose, insulin, and glycosylated hemoglobin. Determination of homeostasis model of insulin assessment. Analysis of carbohydrate metabolizing enzymes.	Decreased the levels of blood glucose and glycosylated hemoglobin. Increased plasma insulin level. Restored activities of key carbohydrate metabolizing enzymes such as hexokinase, pyruvate kinase, G6Pase, fructose 1,6-bisphosphatase, G6Pase dehydrogenase, glycogen synthase and glycogen phosphorylase in the liver tissue.	Jayanthy and Subramanian (2014)
	α-Glucosidase activity.	RA extract inhibited the greatest α-glucosidase activity ($IC_{50} = 0.23 \pm 0.01$ mg/mL) among the supramolecular products.	Zhu et al. (2014)
	STZ-Induced diabetic rats and HFD-fed diabetic rats. Oral glucose tolerance test. Postprandial glucose test. Insulin tolerance test. HOMA-IR. Western blot analysis.	Hypoglycemic effect. Enhanced glucose utilization and insulin sensitivity in a dose-dependent manner. Increased GLUT4 expression in skeletal muscle. RA reduced hepatic PEPCK expression in both groups (STZ/HPD groups), suggesting that RA increased gluconeogenesis in the livers of diabetic rats.	Runtuwene et al. (2016)
	HFD–STZ Induced diabetic rats. Culture of L6 skeletal muscle cells. Evaluation of the glucose metabolism in skeletal muscle. Assay of glucose uptake in the L6 myotubes.	Activation of AMPK in the skeletal muscle of insulin resistant rats and in L6 myotubes. Increased glucose uptake. Increased translocation of GLUT4.	Jayanthy et al. (2017)
Salicylic acid	STZ induced diabetic rats. Determination of fasting serum glucose, and insulin levels. HbA1c Measurement.	Decrease glucose level and HbA1c formation. Decreased insulin level. Decreased advanced glycated end product (AGE) Decreases mortality of diabetic rats in comparison with the group without treatment.	Jafarnejad et al. (2008)
Sinapic acid	STZ-Induced diabetic rats. Biochemical measurements.	Reduced level of plasma glucose. Increased plasma insulin and C-peptide. Decrease HbA1c levels. Minimized alterations in the activities of carbohydrate metabolic enzymes (hexokinase, G6Pase, and fructose-1,6-phosphatase).	Kanchana et al. (2011)
	STZ-Induced diabetic rats. Assay of postprandial glucose. Hyperinsulinemic euglycemic clamping. Determination of glucose uptake into soleus muscle. Cell culture (L6 cell line). Assay of 2-NBDG uptake into L6 cells. Western blot analysis.	Anti-hyperglycemic effect. Decreased postprandial plasma glucose. Increased GLUT4 gene expression in soleus muscle. Increased glucose uptake in soleus muscle. Improved insulin resistance in fructose-rich chow-fed Rats.	Cherng et al. (2013)
	HFD–STZ Induced type 2 diabetic rats. Oral glucose tolerance test. Biochemical measurements.	Improved altered activities of carbohydrate metabolizing enzymes. Decreased fasting blood glucose, and glycosylated hemoglobin. Increased plasma insulin.	Nithya et al. (2017)

(*continued on next page*)

Table 8 (*continued*)

Compounds	Methods	Keys results	References
	Assay ofinsulin resistance. Carbohydrate metabolizing enzymes.		
Syringic acid	Alloxan-induceddiabetic rats. Determination of plasma glucose, insulin, C-peptide, plasma and tissue glycoproteins.	Decreased plasma glucose. Increased plasma insulin and C-peptide level. Decreased glycoproteins. Restored levels of plasma and tissue glycoprotein components.	Muthukumaran et al. (2013)
	Alloxan-induceddiabetic rats. Oral glucose tolerance test. Biochemical estimation. Histopathological study of pancreas.	Improved glycemic status in a dose-dependent manner. Increased insulin and glycogen levels with decreased glucose and HbA1c levels. Restored altered activities of carbohydrate metabolic enzymes. Regeneration of β-cell damage.	Srinivasan et al. (2014)
Vanillic acid	HFD-Fed rats. Hepatocyte cell line (FL83B). Tumor necrosis factor-alpha (TNF-α) induction of insulin resistance. Biochemical measurement. OGTT. HOMA-IR. Western blot analysis.	Decreased the levels of serum insulin and glucose. Reduced the values of area under the curve for glucose ($AUC_{glucose}$) in OGTT and HOMA-IR index. Up-regulated the expression of hepatic insulin-signaling and lipid metabolism-related protein (insulin receptor, phosphatidylinositol-3 kinase, and GLUT 2).	Chang et al. (2015)

signaling pathway, and it was independent of Akt or AMPK, in 3T3-L1 cells (Vishnu Prasad et al., 2010). GA regenerated β-cells of islets, and increased plasma insulin, C-peptide and glucose tolerance level in streptozotocin-induced diabetic rats (Latha and Daisy, 2011). GA protected the pancreas from streptozotocin induced toxicity, and increased insulin secretion, which is known to positively affect carbohydrate metabolism in the streptozotocin induced diabetic rats by reducing gluconeogenesis and increased glycolysis (Gandhi et al., 2014; Punithavathi et al., 2011). GA augmented the expression of PPARγ (important transcription factors for adipocyte differentiation) (Gandhi et al., 2014) and activated the Akt signaling pathway in male C57BL/6 mice (Bak et al., 2013).

Recent study by Doan et al. (2015) suggested that GA exerted its beneficial effects by activating the AMPK/Sirt1/PGC1α pathway in mice. Interestingly, GA increased the glucose uptake in rats fed a high-fructose diet induced diabetes. This effect was correlated with a decreased levels of serum C-peptide. In this context, it was suggested that GA upregulated the expression of hepatic insulin signal transduction related proteins, including insulin receptor, insulin receptor substrate-1, phosphatidylinositol-3 kinase, Akt/protein kinase B, and GLUT2. On the other hand, it downregulated the expression of hepatic gluconeogenesis-related proteins, such as fructose-1,6-bisphosphatase, and upregulated the of expression of hepatic glycogen synthase and glycolysis-related proteins, including hexokinase, phosphofructokinase, and aldolase (Huang et al., 2016). Moreover, GA inhibited some key enzymes linked to type 2 diabetes (α-amylase and α-glucosidase) which decreased intestinal glucose absorption (Oboh et al., 2016).

8.3.5. *p-Coumaric acid*

p-Coumaric acid has been known as an interesting antidiabetic compound. Its hypoglycemic efficacy was proved in diabetic models such as streptozotocin-induced diabetic rats, and L6 rat skeletal muscle cells. The data from these studies showed that *p*-coumaric acid decreased plasma glucose level, (Abdel-Moneim et al., 2017; Amalan et al., 2015, 2016; Shairibha and Rajadurai, 2014), increased insulin and C-peptide levels (Abdel-Moneim et al., 2017; Amalan et al., 2015; Shairibha, Rajadurai and Kumar, 2014), increased liver and muscle glycogen, decreased the levels of glycosylatedhemoglobin (Abdel-Moneim et al., 2017; Shairibha, Rajadurai et al, 2014), and decreased insulin resistance (Abdel-Moneim et al., 2018) in streptozotocin-induced diabetic rats. It demonstrated potent protection of the pancreas from streptozotocin-induced toxicity (Amalan et al., 2015). Moreover, *p*-coumaric acid increased hexokinase activity (a key enzyme of glycolysis), and decreased glucose-6-phosphatase (a key enzyme in the homeostatic regulation of blood glucose) and fructose-1, 6-bisphophatase (a key regulatory enzyme of the hepatic gluconeogenesis) activity (Amalan et al., 2016; Shairibha, Rajadurai et al, 2014). In addition, *p*-coumaric acid stimulated the expression of GLUT2 mRNA in the pancreas (Amalan et al., 2016).

8.3.6. *Rosmarinic acid*

The antidiabetic activity of rosmarinic acid was reported in several studies. The data proved that rosmarinic acid exhibited potent antihyperglycemic effect in diabetic models. Its activity was noticed by its ability to decrease plasma fasting glucose (Vanithadevi and Anuradha, 2008), increased plasma insulin level (Jayanthy and Subramanian, 2014), and enhanced glucose utilization (Runtuwene et al., 2016). The mechanisms by which rosmarinic acid exhibited its hypoglycemic effect were also determined. Rosmarinic acid deceased the intestinal glucose absorption trough the inhibition of α-amylase and α-glucosidase activities (McCue and Shetty, 2004), stimulated the activities of key carbohydrate metabolizing enzymes such as hexokinase, pyruvate kinase, G6Pase, fructose 1,6-bisphosphatase, G6Pase dehydrogenase, glycogen synthase and glycogen phosphorylase in the liver tissue (Jayanthy and Subramanian, 2014), increased mRNA expression and translocation of GLUT-4 (Jayanthy et al., 2017; Runtuwene et al., 2016), and activated AMPK.

8.3.7. *Salicylic acid*

The antidiabetic activity of salicylic acid was evaluated by Jafarnejad et al. (2008) in streptozotocin-induced diabetic rats. The study showed that salicylic acid exhibited potent antihyperglycemic activity noticed by a decrease in plasma glucose and HbA1c formation, decreased insulin level and glycated end product (AGE). It also showed an overall decrease in the mortality of diabetic rats in comparison with the group without treatment.

8.3.8. *Sinapic acid*

Sinapic acid also showed a potent antidiabetic effect. Its activity of lowering plasma glucose was previously proven in STZ induced diabetic rats (Cherng et al., 2013; Kanchana et al., 2011; Nithya et al., 2017). Sinapic acid increased glucose uptake and improved insulin resistance (Cherng et al., 2013). Moreover, it increased plasma insulin and C-peptide, restored the altered activity of carbohydrate metabolizing enzymes, and decreased HbA1c levels (Kanchana et al., 2011; Nithya et al., 2017). Interestingly, Cherng et al. (2013), reported that sinapic acid increased GLUT-4 gene expression in soleus muscle.

8.3.9. *Syringic acid*

The antidiabetic efficacy of syringic acid was demonstrated using alloxan-induced diabetic rats. This phenolic acid was decreased plasma glucose and increased plasma insulin and C-peptide level, and

glycoproteins (Muthukumaran et al., 2013). It increased glycogen levels and decreased HbA1c levels. Syringic acid restored altered activities of carbohydrate metabolic enzymes and regenerated *β*-cell damage (Srinivasan et al., 2014).

8.3.10. Vanillic acid

Vanillic acid exhibited antihyperglycemic activity *in vivo* in rats fed a high-fat diet. It decreased the levels of serum insulin and glucose. Chang et al. (2015) reported that vanillic acid reduced the values of area under the curve for glucose ($AUC_{glucose}$) in OGTT and HOMA-IR index. It up-regulated the expression of hepatic insulin-signaling and lipid metabolism-related protein (insulin receptor, phosphatidylinositol-3 kinase, GLUT 2) (Chang et al., 2015).

8.3.11. 4-Hydroxybenzoic acid

The antihyperglycemic efficacy of 4-hydroxybenzoic acid was evaluated *in vivo* using streptozotocin-induced diabetic rats as well as on normal Wistar rats. The data showed that 4-hydroxybenzoic acid decreased plasma glucose levels in a dose-dependent-manner by increasing its consumption. However, this phenolic acid did not affect the serum insulin level and liver glycogen content in streptozotocin-induced diabetic rats (Peungvicha et al., 1998b). On the other hand, 4-hydroxybenzoic acid decreased plasma glucose and increased serum insulin levels and liver glycogen content in normal Wistar rats (Peungvicha et al., 1998a).

8.3.12. 3-Hydroxycinnamic acid

Cinnamic acid was studied for its anti-hyperglycemic activity, using HepG2 and HIT-T15 cells. The reported results showed that this acid showed potentantidiabetic acid. Cinnamic acid increased glucose uptake and stimulated glucokinase (Gck) activity and insulin secretion (Jung et al., 2010). In addition, Singh et al. (2012) demonstrated that cinnamic acid decreased blood glucose levels and reduced triglycerides (LDL and VLDL). More recently, (Ambika et al., 2013), reported that cinnamic acid lowered blood glucose, decreased glycosylated hemoglobin, and increased plasma insulin (see Table 8).

8.4. Fatty acids

Moroccan medicinal plants with antidiabetic effects contain several fatty acids such as linoleic acid, phosphatidylcholine, palmitic acid, linolenic acid, oleic acid, and palmitoleic acid. Various pharmacological investigations demonstrated that these fatty acids exhibited antidiabetic and hypoglycemic effects with numerous mechanism insights. Table 9 summarizes all carried studies on fatty acids identified in Moroccan antidiabetic medicinal plants.

8.4.1. Linoleic acid

Several studies *in vitro* and *in vivo* methods showed that the improvement in blood sugar by linoleic acid was due to several mechanisms such as its capacity to diminish the enhanced intestinal uptake of glucose and galactose (Thomson et al., 1987), to increase insulin resistance in *trans*-10, *cis*-12 (t10,c12)-CLA and CLA mix-fed groups (Halade et al., 2010), and to improve insulin sensitivity (Noto et al., 2007a). Mohankumar et al. (2013) showed that LA exhibited isomer-specific effects on GLUT4 trafficking and the increase in glucose uptake induced by CLA treatment of L6 myotubes occured *via* pathways that are distinctive from those utilized by insulin. It was also able to preserve pancreatic islet size, to improve oral glucose tolerance and insulinemia, and to attenuate serum haptoglobin levels (Noto et al., 2007b). In other studies, Chung et al. (2005) demonstrated that the physiological level of *trans*-10, *cis*-12 CLA activated NFB- and ERK1/2-dependent cytokine production, which together suppressed PPAR and Glut4 levels and led to impaired glucose uptake. In addition, LA significantly ameliorated glucose homeostasis by alleviating fasting glucose, reduced glucose tolerance, alleviated insulin tolerance and decreased of the AUC of ITT (Zhang et al., 2016a), as well as induced *β*-cell apoptosis to a greater degree in the presence of high glucose levels than in the presence of low glucose levels in islets and MIN6 cells (Shirakawa et al., 2011).

8.4.2. Phosphatidylcholine

Phosphatidylcholine is a fatty acid that has also the capacity to improve glucose homeostasis by different mechanisms showed by several methods *in vivo* and *in vitro* (XU et al., 2012). showed that this compound ameliorates oral glucose tolerance, decreases glycosylated hemoglobin content, promotes secretion of fasting insulin and recovers damaged pancreas stici islets and β cells.It is also able to decrease blood glucose level, to increase insulin secretion and glycogen synthesis. In addition, it was reported that phosphatidylcholine causes a loss of 40–50% inactivity of the G6Pase enzyme system (Gumbhir et al., 1989; Hu et al., 2014). Phosphatidylcholine induces hypoglycemic effects also *via* up-regulating PI3K/PKB signal transduction pathway mediated by insulin, decreases fasting serum glucose levels and insulin, prevents the decrease in the number of islets and the β/αcell ratio in the pancreas, and increases the transepithelial absorption of insulin by facilitating a paracellular passage through a reversible opening of tight junctions (Buko et al., 1996; Carstens et al., 1993; Hu et al., 2013; Lee, Lee et al., 2011; Lee, Yang et al., 2011).

8.4.3. Palmitic acid

Palmitic acid improved blood glucose by several mechanisms that were demonstrated by different methods. Its effect was due to its capacity to induce a delay in the curve of tolerance to glucose and led to insulin resistance due to the increased phosphorylation in serine of the insulin receptor (Reynoso et al., 2003), to elevate glucose-stimulated insulin secretion and to ameliorate the first-phase insulin response (Blomqvist et al., 2005). It also decreased baseline GLUT2 mRNA expression in the liver and impaired central regulation of hepatic glucose (Cheng, Yu et al., 2015), and reduced GLUT4 pathway protein levels following a short period of treatment (Chen et al., 2016). However, palmitic acid resulted in a deterioration of glucose tolerance by suppressing insulin secretion from pancreatic *β*-cells and induced endoplasmic reticulum stress in pancreatic islets (Hirata et al., 2015).

8.4.4. Linolenic acid

Scientific data showed that linolenic acid improved glucose homeostasis by several mechanisms such as increasing the levels of enzyme activity (G6Pase) (Hun et al., 1999), improved insulin sensitivity, and reduced the expression of hepatic gluconeogenic enzymes and body mass (Oliveira et al., 2015; Zhang et al., 2016a). Linolenic acid altered circulating RBC (Red blood cell) and muscle LC-PUFA levels and improved glucose tolerance (Kavanagh et al., 2013).

8.4.5. Oleic acid

Several authors showed by different methods that oleic acid decreased the concentration of blood glucose. This effect was due to several mechanisms such as the protective effects against apoptosis in pancreatic AR42J cells by increasing in TAG accumulation and the up-regulation of Dgat2 and Cpt1 gene expressions may be possibly associated in part with the ability of OLA to protect cells from deleterious actions of PAM (Ahn et al., 2013), enhanced insulin secretion in a dose-dependent manner, acted as a conceivable agonist of G-protein-coupled receptor 40 (Badolato et al., 2017), reduced the expression of hepatic gluconeogenic enzymes, and improved insulin sensitivity (Oliveira et al., 2015). Oleic acid improved glucose homeostasis also by protecting INS-1E cells from apoptosis and maintaining the insulin secretion function and protected primary islets from endoplasmic reticulum stress (Liu et al., 2019).

8.4.6. Palmitoleic acid

It was shown that palmitoleic acid improved blood glucose by several mechanisms such as decreasing plasma glucose levels and

increasing insulin sensitivity, in part owing to suppressing proinflammatory gene expressions and improving hepatic lipid metabolism (Yang et al., 2011), altering circulating glucose and insulin levels (Long et al., 2014), decreasing HOMA-IR and plasma insulin levels, and altering expression of genes regulating glucose uptake (Duckett et al., 2014). Palmitoleic acid showed protective effect on caspase activation and cell viability in pancreatic β-cells (Welters et al., 2006).

8.4.7. Other fatty acids

The improvement of blood glucose by other fatty acids was investigated by several researchers. These studies demonstrated by different mechanisms that these compounds such as lipotoxic effect of stearic acid on mouse pancreatic β-cells *via* a miR-34a-5p-mediated PERK/p53-dependent pathway (Lu et al., 2016), enhanced glucose clearance rate and adipose tissue insulin sensitivity of erucic acid, without altering the insulin levels, thus indicating improved insulin sensitivity (Vemuri et al., 2018). Sookwong et al. (2011) showed that phosphatidyl ethanol amine tends to accumulate in blood and in organs that are involved in the pathogenesis of diabetes, such as the kidney, therefore may be a useful predictive marker for hyperglycemia, particularly in the early stages of diabetes. Tetradecanoic acid improved glucose homeostasis by its inhibitory activity of α-amylase and α-glucosidase. It showed maximum of 83% and 78% inhibition towards α-amylase and α-glucosidase at 1.12 μM, respectively (Lakshmanasenthil et al., 2018), while behenic acid decreased basal blood glucose level and increased insulin tolerance test (Moreira et al., 2017).

8.5. Antidiabetic properties of steroids

The antidiabetic effect of steroids was reported by some investigators (Table 10) (Ghosh et al., 2015; Hao et al., 2007; Jayasooriya et al., 2000; Jeong et al., 2004; Myint et al., 2012; Okahara et al., 2016). The campesterol was tested for its antidiabetic effect using alloxan-induced diabetic mice (Myint et al., 2012) and oral carbohydrate and fat load study with C57BL/6J mice (Okahara et al., 2016). In the first study, it showed that campesterol increased blood glucose level (19%). This result was confirmed by Okahara et al. (2016) which demonstrated a decrease of postprandial hyperglycemia in C57BL/6J mice after treatment with campesterol. However, other steroids containing in some Moroccan medicinal plants were found as promotors of diabetogenesis, glucose intolerance and hyperglycemia. Indeed, spinasterol and cholesterol showed their capacity to induce diabetes (Ghosh et al., 2015; Hao et al., 2007; Jayasooriya et al., 2000; Jeong et al., 2004). In STZ-induced diabetic mice, the administration of spinasterol at the higher concentrations did not lower serum glucose levels. Moreover, author showed that glucose level has been affected (hyperglycemia) after this treatment. On the other hand, the study of Jayasooriya et al. (2000) suggested that rats fed diets supplemented with and without cholesterol decreased serum glucose levels in rats fed cholesterol-free diets, but not in those fed cholesterol-enriched diets. These findings are contradictory with other results which found clearly that cholesterol induced hyperglycemia and glucose intolerance (Ghosh et al., 2015). These effects were investigated by Hao et al. (2007) and the link between cholesterol and hyperglycemia and glucose intolerance was related to the inhibition of insulin secretion by downregulation of metabolism through increasing neuronal nitric oxide synthase dimerization. However, molecular mechanisms involved in hyperglycemia induced by cholesterol remain unclear and further investigations should be carried out to find mechanistic targets for this question.

8.6. Antidiabetic properties of tannins

The antidiabetic effect of tannic acid was investigated experimentally in several works (Table 11) using *in vitro* and *in vivo* methods (Al-Salih, 2010; Babby et al., 2014; Esmaiel et al., 2019; Huang et al., 2019; Liu Kim et al. 2005; Liu Liou et al. 2005; Xiao et al., 2015; Zhao et al., 2013). The first study demonstrated that TA lowered blood glucose levels alone and in mixture with gallic acid in alloxan-induced diabetic rabbits (Al-Salih, 2010). In STZ-induced diabetic rats, the oral administration of TA significantly decreased the level of blood glucose and glycosylated hemoglobin as well as increased the plasma insulin and glycogen levels (Babby et al., 2014; Esmaiel et al., 2019). On the other hand, other studies (Huang et al., 2019; Xiao et al., 2015; Zhao et al., 2013)tested the inhibition of α-glucosidase and α-amylase using inhibitory kinetics method and molecular docking technique. The results showed the highest inhibitory effect of α-amylase (Zhao et al., 2013), and potent inhibitory of α-glycosidase (IC_{50} = 0.44 μg/mL) compared with inhibitory activity of acarbose (IC_{50} = 0.60 μg/mL) (Xiao et al., 2015). This result was confirmed by Huang et al., (2019) who demonstrated the important inhibition of α-glycosidase with IC_{50} values of 0.35 ± 0.02 μM. In another study, Liu Kim et al. (2005); Liu Liou et al. (2005) investigated the antidiabetic effect of tannic acid using glucose uptake assays and Western/Northern blot analyses as major tools and 3T3-L1 preadipocytes cells as a model. The results showed that TA induced phosphorylation of the insulin receptor (IR) and Akt, as well as translocation of glucose transporter 4 (GLUT 4) and the protein factors involved in the signaling pathway of insulin-mediated glucose transport.

9. Clinical trials of drugs containing in Moroccan medicinal plants

9.1. Flavonoids

9.1.1. Resveratrol

A study to illustrate whether the polyphenol resveratrol improves insulin sensitivity in type 2 diabetic patients was carried out by Brasnyó et al. (2011). The study was a random and double-blinded trial that was conducted on 19 patients. The group that received oral resveratrol at dose of 2 × 5 mg for 4 weeks showed improvement in insulin sensitivity, a decrease in insulin resistance and urinary ortho-tyrosine excretion. Resveratrol improved phosphorylated protein kinase B (pAkt): protein kinase B (Akt) ratio. However, it had no effect on parameters related to β-cell function (Table 12).

In 2012, Bhatt et al. (2012) carried out a clinical study to evaluate the effect of resveratrol on improving sugar level and the associated risk factors in Sixty-two patients with type 2 diabetes mellitus (T2DM). The oral supplementation of this compound at dose of 250 mg/day for a period of 3 months improved the sugar level, hemoglobin A1c, systolic blood pressure, total cholesterol, and total protein in patients with type 2 diabetes mellitus (T2DM). However, it had no effect on body weight, high-density lipoprotein and low-density lipoprotein cholesterols. In the same year, Yoshino et al. (2012) conducted a randomized, double-blind, placebo-controlled trial to evaluate the metabolic effect of resveratrol in nonobese, postmenopausal women with normal glucose tolerance. The administration of resveratrol supplementation (75 mg/day) for 12 weeks increased plasma resveratrol concentration. However, it did not increase liver, skeletal muscle, or adipose tissue insulin sensitivity. It also did not change the body composition, resting metabolic rate, plasma lipids, or inflammatory markers. Resveratrol did not affect its putative molecular targets, including AMPK, SIRT1, NAMPT, and PPARGC1A, in either skeletal muscle or adipose tissue. The results demonstrated that resveratrol did not have beneficial metabolic effect in nonobese, postmenopausal women with normal glucose tolerance.

The next year, Movahed et al. (2013) reported that the oral supplementation of resveratrol at dose of 1 g/day for 45 days decreased the systolic blood pressure, fasting blood glucose, hemoglobin A1c, insulin, and insulin resistance, while it increased HDL when compared with their baseline levels. Moreover, no change was detected in liver and kidney function markers. These findings showed that resveratrol supplementation exerted potent antidiabetic effect in patients with type 2 diabetes (Table 12).

Also, in 2014 two clinical studies were conducted to illustrate the

Table 9
Fatty acids.

Compounds	Methods	Keys results	References
Behenic acid	Basal blood glucose. Insulin tolerance test (ITT).	Structured lipids diet with behenic acid decreased basal blood glucose level and increased ITT.	Moreira et al. (2017)
Erucic acid	Oral glucose tolerance test. Plasma clinical parameters.	Enhanced glucose clearance rate and adipose tissue insulin sensitivity, without altering the insulin levels, thus improved insulin sensitivity.	Vemuri et al. (2018)
Linoleic acid	STZ-Induced diabetic rats.	Linoleic acid (LA) diet diminished the enhanced intestinal uptake of glucose and galactose in diabetic rats.	Thomson et al. (1987)
	Cell culture (Murine macrophage RAW264.7 cells).	The effect of conjugated linoleic acid (CLA) is similar to that seen with ligands for peroxisome proliferator-activated receptor (PPARγ), most notably of the PPARγ subtype.	Yu et al. (2002)
	High metabolic rate (MH) and low metabolic rate (ML) mice. Insulin tolerance tests. Basal insulin analysis.	CLA-Fed MH mice were resistant to insulin. CLA-Fed ML mice were slightly resistant to exogenous insulin.	Hargrave et al. (2003)
	Cell culture of primary human SV cells. Glut4 Levels.	CLA activatedNF-κBand ERK1/2-dependent cytokine production, which together suppressed PPARγ and Glut4 levels and led to impaired glucose uptake.	Chung et al. (2005)
	Fasting serum biochemistry and insulin resistance calculation. Western blot analysis.	CLA improved insulin sensitivity in *fa/fa* Zucker rats.	Noto et al. (2007b)
	fa/fa and lean Zucker rats Oral glucose tolerance test. Insulin and C-peptide assay. Pancreas islet size. Western blot analysis.	Small islet cell size (*fa/fa* Zucker rats). Improved oral glucose tolerance and insulinemia. CLA did not alter insulin sensitivity or islet size in lean Zucker rats.	Noto et al. (2007a)
	Insulin-resistant female C57Bl/6J mice. IVGTT. Serum metabolites. HOMA-IR and R-QUICKI.	Increased insulin resistance in *trans*-10, *cis*-12 (t10,c12)-CLA and CLA mix-fed groups (confirmed by HOMA-IR, R-QUICKI, and IVGTT).	Halade et al. (2010)
	Diabetic Gck $^{\pm}$ mice and euglycemic wild-type mice. Plasma glucose levels and blood insulin levels determination. Glucose-stimulated insulin secretion by islets. Histological analysis of the pancreas.	LA induced β-cell apoptosis to a greater degree in the presence of high glucose levels than in the presence of low glucose levels *in vitro* in islets and MIN6 cells.	Shirakawa et al. (2011)
	HFD-Fed mice. Blood glucose determination.	CLA (2%) showed good glycemic control.	Marques et al. (2012)
	Rat skeletal muscle cells. Cell culture (L6 myoblasts). Western blot analysis.	CLA exhibitedisomer-specific effects on GLUT4 trafficking and the increase in glucose uptake induced by CLA treatment of L6 myotubes occurs *via* pathways that are distinctive from those utilized by insulin.	Mohankumar et al. (2013)
	High-fructose and HFD-fed rats.	LA significantly ameliorated glucose homeostasis.	(Zhang et al., 2016a)
Linolenic acid	KK-A^{y}/TaJcl mice.	Rats given linolenic acid (LNA) showed high levels of enzyme activity (G6Pase).	Hun et al. (1999)
	Insulin resistant monkeys.	γ-Linolenic acid improved glucose tolerance.	Kavanagh et al. (2013)
	HFD-Fed mice. Intraperitoneal insulin-tolerance test. Intraperitoneal glucose tolerance test.	Improved insulin sensitivity. Decreased hepatic gluconeogenic enzymes.	Oliveira et al. (2015)
	High-fructose and HFD-fed rats.	α-Linolenic acid (ALA) significantly improved insulin sensitivity.	(Zhang et al., 2016a)
Oleic acid	Cell culture (AR42J cells). Western blot analysis.	Protective effects against apoptosis in pancreatic AR42J cells.	Ahn et al. (2013)
	HFD-Fed mice. Intraperitoneal insulin-tolerance test. Intraperitoneal glucose tolerance test.	Improved insulin sensitivity. Decreased hepatic gluconeogenic enzymes.	Oliveira et al. (2015)
	The synthesis of two oleic acid derivatives (AV1 and AV4). Cell culture (Pancreatic β-cell line INS-1832/13). Insulin secretion detection.	AV1Enhanced insulin secretion in a dose-dependent manner, behaving as a conceivable agonist of G-protein-coupled receptor 40.	Badolato et al. (2017)

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Table 9 (*continued*)

Compounds	Methods	Keys results	References
	Islet isolation (from adult male C57/BL6 mice).		
	HFD-Fed rats. Islet isolation. Cell culture (rat insulinoma cell line INS-1E cells). Insulin secretion analysis. Western blot analysis.	Protected INS-1E cells from apoptosis. Maintained insulin secretion function. Protected primary islets from endoplasmic reticulum stress. Improved insulin sensitivity in HFD rats.	Liu et al. (2019)
Palmitic acid	Normal Wistar rats. Glucose tolerance. Insulin signaling.	Delayed in the curve of tolerance to glucose. Insulin resistance due to the increased phosphorylation in serine of the insulin receptor.	Reynoso et al. (2003)
	Zucker fatty (*fa/fa*) rats. Plasma insulin. Plasma glucose.	Elevated glucose-stimulated insulin secretion. Ameliorated first-phase insulin response. Fasting hyperinsulinemia and blood glucose levels were unchanged.	Blomqvist et al. (2005)
	Male C57BL/6J mice. Intraperitoneal glucose tolerance test. Western blot analysis.	Decreased baseline GLUT2 mRNA expression in the liver. Impaired central regulation of hepatic glucose.	Cheng, Yu et al., (2015)
	Male (C57BL/6) mice. Plasma glucose level measurements. Glucose tolerance test. Insulin tolerance test. Isolation of pancreatic islets. Histological analysis of the pancreas.	Decreased glucose tolerance. Suppression of insulin secretion. Insulin staining was clearly weakened in islets. Induced endoplasmic reticulum stress in pancreatic islets.	Hirata et al. (2015)
	Cell culture. Western blot analysis.	Reduced GLUT4 pathway protein levels following a short period of treatment.	Chen et al. (2016)
Palmitoleic acid	Cell culture (rat pancreatic β-cell line BRIN-BD11).	Protective effects on caspase activation and cell viability in pancreatic β-cells exposed to palmitate.	Welters et al. (2006)
	KK-A^y Mice with genetic type 2 diabetes. Insulin tolerance test. Plasma glucose level determination.	Decreased plasma glucose levels. Improved insulin sensitivity.	Yang et al. (2011)
	Obese lambs. Glucose and insulin concentration.	Increased blood glucose levels. Altered insulin levels.	Long et al. (2014)
	Obese sheep. Glucose and insulin concentration. Western blot analysis.	Decreased plasma insulin levels. HOMA-IR levels decreased over time. Altered expression of genes regulating glucose uptake.	Duckett et al., (2014)
Phosphatidylcholine	High cholesterol diet feeding to mature male guinea pigs. Guinea pig liver microsomes. Assay of G6Pase activity	Phosphatidylcholine supplementation led to a loss of 40%–50% in activity of the G6Pase enzyme system.	Gumbhir et al. (1989)
	Rabbit nasal mucosa (*in vitro*).	Didecanoyl-L-α-phosphatidylcholine increased the transepithelial absorption of insulin by facilitating a paracellular passage through a reversible opening of tight junctions.	Carstens et al. (1993)
	Alloxan-induced diabetic rats. Blood glucose content. Histological analysis of pancreas.	Polyenoyl-phosphatidylcholine prevented the decrease in the number of islets and the β/α cell ratio in the pancreas of the diabetic rats. Decreased blood glucose content.	Buko et al. (1996)
	*db/db*Mice. HFD-Fed mice. Glucose tolerance test. Insulin tolerance test.	Dilauroyl phosphatidylcholine decreased serum glucose. Improved glucose homeostasis in two mouse models of insulin resistance.	Lee, Lee et al., (2011)
	STZ-Induced diabetic rats. Fasting blood-glucose determination. Oral glucose tolerance test. Glycated hemoglobin determination. Fasting insulin determination. Histological analysis of pancreas.	Ameliorated oral glucose tolerance. Decreased glycosylated hemoglobin content. Promotedsecretion of fasting insulin. Recovered the damaged pancreatic islets and β cells.	Xu et al. (2012)
	STZ-Induced diabetic rats. Fasting serum glucose		Hu et al. (2013)

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Table 9 (*continued*)

Compounds	Methods	Keys results	References
	determination. Insulin levels determination. Western blot analysis.	Decreased fasting serum glucose levels and insulin. Hypoglycemic effects *via* up-regulating PI3K/PKB signal transduction pathway mediated by insulin.	
	STZ-induced diabetic rats. Blood glucose parameters. Serum insulin level. Glycogen content. Western blot analysis.	Decreased blood glucose level. Increased insulin secretion. Increased glycogen synthesis. Anti-hyperglycemic activity through the up-regulating PI3K/PKB signal pathway mediated by insulin.	Hu et al. (2014)
Phosphatidylethanolamine	STZ-induced diabetic rats. Blood glucose and insulin levels.	Amadori-glycatedphosphatidyl ethanolamine may be a useful predictive marker for hyperglycemia, particularly in the early stages of diabetes.	Sookwong et al. (2011)
Stearic acid	Un-acclimated cultures. inhibition of glucose degradation	No synergistic inhibition of glucose degradation with the other acids tested.	Lalman and Bagley (2002)
	C57BL/6 mice. Cultured rat insulinoma INS-1 cells. Determination of microRNA (miR) profiles of islets. TUNEL assay and insulin labelling.	Lipotoxic effect on mouse pancreatic β-cells *via* a miR-34a-5p-mediated PERK/p53-dependent pathway.	Lu et al. (2016)
Tetradecanoic acid	α-Amylase and α-glucosidase inhibitory activity. Enzyme inhibition kinetics study. *In silico* studies by docking.	α-Amylase and α-glucosidase inhibitory activity in a dose dependent manner and in non-competitive mechanism. Maximum of 83% and 78% inhibition towards α-amylase and α-glucosidase at 1.12 μM, respectively.	Lakshmanasenthil et al. (2018)

antidiabetic effect of resveratrol. In one of these studies, Méndez-del Villar et al. (2014) explained that the administration of resveratrol (500 mg) three times per day before meals for 90 days significantly decreased weight, body mass index BMI, fat mass, waist circumference (WC), AUC of insulin, and total insulin secretion. While, Williams et al. (2014) demonstrated that the administration of a single dose (300 mg) of resveratrol decreased post absorptive insulin levels and was accompanied by elevated skeletal muscle phosphorylation of p38 MAPK. No changes were detected in either skeletal muscle or adipose tissue insulin signaling.

In 2015, double-blind, randomized, placebo-controlled clinical study was carried out by Chen et al. (2015) to evaluate the effect of resveratrol on insulin resistance, glucose and lipid metabolism in 60 subjects with non-alcoholic fatty liver disease. The administration of resveratrol (2 capsules, 150 mg) twice daily for three months decreased aspartate aminotransferase, glucose and low-density lipoprotein cholesterol, alanine aminotransferase, total cholesterol and homeostasis model assessment insulin resistance index compared with the placebo group. In addition, resveratrol reduced the levels of tumor necrosis factor-alpha, cytokeratin 18 fragments, and fibroblast growth factor 21, while it elevated the adiponectin level.

Thazhath et al. (2016) evaluated the effect of resveratrol treatment on GLP-1 secretion, gastric emptying, and glycemic control in type 2 diabetes in fourteen patients. The results showed that the administration of resveratrol (500 mg twice daily) for 5 weeks did not affect fasting and postprandial blood glucose, HbA_{1c}, and plasma total GLP-1. In the same year, a double-blind, randomized, placebo-controlled study was carried out by Banaszewska et al. (2016) on 34 subjects with polycystic ovary syndrome to evaluate the endocrine and metabolic effects of resveratrol on polycystic ovary syndrome. This study demonstrated that the administration of resveratrol (1500 mg p.o. daily) for 3 months decreased the total by 23.1%, fasting insulin level by 31.8% and dehydroepiandrosterone sulfate by 22.2%, while it increased the insulin sensitivity index by 66.3%. No effect on inflammation markers and endothelial function were observed. Another study was conducted by Most et al. (2016) on 38 overweight and obese subjects to investigate the longer-term effect of resveratrol combined with epigallocatechin-3-gallate supplementation on the metabolic profile, mitochondrial capacity, fat oxidation, lipolysis, and tissue-specific insulin sensitivity. The results showed that the administration of EGCG + RES supplementation (80 and 282 mg/d, respectively) for 12 weeks increased the oxidative capacity in permeabilized muscle fibers. It reduced fasting and postprandial respiratory quotient compared with placebo. However, the combinedresveratrol-epigallocatechin-3-gallate had no effect on insulin-stimulated glucose disposal, suppression of endogenous glucose production, or lipolysis. Timmers et al. (2016) reported that the administration of resveratrol supplementation at dose of 150 mg/day for 30 days did not improve hepatic or peripheral insulin sensitivity (Table 12).

A randomized, placebo-controlled, double-blind, parallel group clinical trial was conducted by Kjær et al. (2017) to evaluate the effect of resveratrol on inflammation. This study demonstrated that the oral supplementation with 1000 mg/day and 150 mg/day for 16 weeks did not improve inflammatory status, glucose homeostasis, blood pressure, or hepatic lipid content in middle-aged men with MetS. Another study was carried out by Made et al. (2017) in 45 overweight and slightly obese volunteers to investigate the effects of the long-term intake of *trans*-resveratrol on vascular function. The results showed that the administration of *trans*-resveratrol at dose of 150 mg/day for 4 weeks did not change plasma biomarkers of endothelial function or inflammation in the fasting state or postprandial phase.

In 2018, De Ligt et al. (2018) studied the effect of resveratrol on enhancing metabolic health in men at risk of developing T2D as well as its effect on stimulating brown adipose tissues (BAT). The administration of resveratrol at dose of 150 mg/day for 30 days for 13 male first-degree relatives (FDR) of patients with T2D improved the *ex vivo* muscles mitochondrial function on a fatty acid-derived substrate. However, resveratrol did not improve insulin sensitivity.

9.1.2. Catechin

Nagao et al. (2009) carried out a double-blind controlled study to investigate the effect of a catechin-rich beverage in patients with type 2 diabetes not receiving insulin (Ins) therapy. The results showed that the ingested green tea containing either 582.8 mg of catechins or 96.3 mg of catechins per day for 12 weeks increased adiponectin and increased insulin secretion. However, no difference was noted in glucose and hemoglobin A(1c). The results of this study indicated that the ingestion of catechin-rich beverage prevented obesity, recovered Ins-secretory ability, and maintained low hemoglobin A(1c) levels in type 2 diabetic patients who did not yet require insulin therapy. In 2014, Takahashi et al.

Table 10
Antidiabetic effect of steroids identified in Moroccan medicinal plants.

Compounds	Methods	Keys results	References
Campesterol	Alloxan-induced diabetic mice.	Increased blood glucose level (19%).	Myint et al. (2012)
Cholesterol	Oral carbohydrate and fat load study with C57BL/6J mice.	Decreased postprandial hyperglycemia in C57BL/6J mice.	Okahara et al. (2016)
	Rats fed diets supplemented with and without cholesterol.	Decreased serum glucose levels in rats fed cholesterol-free diets, but not in those fed cholesterol-enriched diets.	Jayasooriya et al. (2000)
	Mice, cells, and islets. Cholesterol assay in islets. Glucose-stimulated insulin secretion measurements. Glucokinase activity assay.	A direct link between elevated serum cholesterol and reduced insulin secretion, with normal secretion restored by cholesterol depletion. Excess cholesterol inhibited theinsulinby downregulating metabolism through increased neuronal nitric oxide synthase dimerization.	Hao et al. (2007)
	High fat high cholesterol diet (Western diet). Intraperitoneal glucose tolerance tests (IPGTT).	Induced hyperglycemia. Induced glucose intolerance.	Ghosh et al. (2015)
Spinasterol	STZ-Induced diabetic mice.	α-Spinasterol (0.5 and 2.5 mg/kg/day) did not lower serum glucose levels.	Jeong et al. (2004)

Table 11
Tannic acid.

Compounds	Methods	Keys results	References
Tannic acid	Glucose uptake assay. Cell culture (3T3-L1 preadipocytes). Northern blot analyses.	Induced phosphorylation of the insulin receptor (IR) Induced translocation of GLUT 4	Liu Kim et al. (2005)
	Alloxan induced diabetic rabbits. Determination of glucose.	Tannic acid (TA) lowered blood glucose levels alone and in mixture with gallic acid.	Al-Salih (2010b)
	α-Amylase inhibition assay.	Inhibition of α-amylase activity.	Zhao et al. (2013)
	STZ-induced diabetic rats. Estimation of blood glucose. Estimation of plasma insulin. Estimation of glycosylated hemoglobin. Estimation of liver glycogen.	Decreased blood glucose level. Increased plasma insulin levels. Decreased level of glycosylated hemoglobin. Increased liver glycogen.	Babby et al. (2014)
	α-Glucosidase inhibition assay. Inhibitory kinetics.	Anti-α-glucosidase activity of TA (IC_{50} = 0.44 μg/mL) was superior to that of acarbose (IC_{50} = 0.60 μg/mL).	Xiao et al. (2015)
	STZ-Induced diabetes in rats.	Decreased blood glucose level.	Esmaiel et al. (2019)
	α-Glucosidase inhibition assay. Molecular docking technique.	Inhibition of α-glucosidase (IC_{50} = 0.35 ± 0.02 μM) in a reversible and mixed competitive manner.	Huang et al. (2019)

(2014) evaluated the effect of ingestion of catechin-rich green tea on postprandial hyperglycemia and oxidative stress in healthy post-menopausal women. The results showed that the administration of a catechin-rich green tea at dose of catechins (615 mg/350 mL) beverage per day for 4 weeks improved postprandial glucose status and redox homeostasis.

9.1.3. Epicatechin

A randomized study, double-blind, placebo-controlled on thirty-seven healthy men and women (Dower et al., 2015), was carried out study to investigate the effect of pure epicatechin on vascular function and cardiometabolic health. The results showed that the administration of epicatechin supplementation at dose of 100 mg/day for 4 weeks improved fasting plasma insulin and insulin resistance and had no effect on fasting plasma glucose. However, epicatechin supplementation did not change flow-mediated dilation, BP, arterial stiffness, nitric oxide, endothelin 1, or blood lipid profile.

9.1.4. Quercetin

In the same study of epicatechin, Dower et al. (2015) demonstrated that the administration quercetin-3-glucoside supplementation at dose of 160 mg/day for 4 weeks had no had no effect on flow-mediated dilation, insulin resistance, or other CVD risk factors.

9.2. Phenolic acids

9.2.1. Catechol

Green tea extract with catechol-*O*-methyltransferase led to higher insulin concentrations at 0, 0.5 and 1.0 h post-meal. This finding was reported by Dostal et al. (2017) after conducting a randomized, double-blind feeding study in sixty Caucasian post-menopausal women to evaluate the acute effect of green tea extract supplementation on the post-prandial response to a high-carbohydrate meal by assessing appetite-associated hormones and glucose homeostasis marker concentrations.

9.2.2. Chlorogenic acid

In 2003, a study was carried out by Johnston et al. (2003) to investigate the effect of chlorogenic acids present in coffee on modulating glucose uptake, gastrointestinal hormone and insulin secretion in humans. The administration of a single dose of chlorogenic acids (400 mL = equivalent to 2.5 mmol chlorogenic acid/L) randomly and cross-over for 9 healthy fasted volunteers decreased glucose-dependent insulinotropic polypeptide secretion and increased glucagon-like peptide 1 secretion. Another study was conducted by vanDijk et al. (2009) to evaluate the acute effect of chlorogenic acid on glucose tolerance. Oral glucose tolerance test (OGTT) was used in 15 overweight men to evaluate the results of this study. The administration of chlorogenic acid (1 g) during the test reduced glucose and insulin concentrations 15 min following an OGTT compared with placebo. In 2018, Zuñiga et al. (2018) reported that the oral administration of chlorogenic acid at dose of 400 mg three times per day for 12 weeks in 15 patients with impaired glucose tolerance (IGT), decreased fasting plasma glucose (FPG), insulino genic index, waist circumference, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and very low-density lipoprotein levels, while increased insulin sensitivity. A randomized, double-blind, placebo-controlled clinical trial was performed in 30 patients with impaired glucose tolerance (IGT) to evaluate the effect of chlorogenic acid on glycemic control, insulin secretion, and insulin sensitivity in these patients.

9.2.3. Gallic acid

A placebo-controlled pilot study on 19 patients (12 males and 9 females) with T2D was performed by Ferk et al. (2017) to evaluate the effect of gallic acid (GA) on preventing oxidative stress in these patients.

Table 12
Clinical trials.

Chemical family	Molecules	Model	Dose	Effects	References
Flavonoids	Catechin	Patients with type 2 diabetes who were not receiving insulin therapy in a double-blind controlled study.	A catechin-rich beverage: 582.8 mg of catechins (catechin group; n = 23) or 96.3 mg of catechins (control group; n = 20) per day for 12 weeks.	The prevention of obesity; The recovery of Ins-secretory ability; Maintaining low hemoglobin A1c levels in diabetic patients who didnot yet require insulintreatment.	Nagao et al. (2009)
	Catechin	Healthy postmenopausal women. Phase III.	A catechin-rich green tea (615 mg/350 mL) beverage per d for 4 weeks.	Improved postprandial glucose status and redox homeostasis.	Takahashi et al. (2014)
	Epicatechin	37 healthy men and women aged 40–80 years with a systolic blood pressure between 125- and 160-mm Hg at screening. A randomized, double-blind, placebo-controlled crossover trial.	Epicatechin (100 mg/d) for 4 weeks.	Epicatechin supplementation improved fasting plasma insulin and insulin resistance and had no effect on fasting plasma glucose.	Dower et al. (2015)
	Quercetin	37 healthy men and women aged 40–80 years with a systolic blood pressure between 125 and 160 mm Hg at screening. A randomized, double-blind, placebo-controlled crossover trial.	Quercetin-3-glucoside (160 mg/d) for 4 weeks.	Quercetin-3-glucoside supplementation had no effect on insulin resistance.	Dower et al. (2015)
	Resveratrol	19 patients included in the double-blind study were randomized into two groups. Phase III.	Oral 2 × 5 mg resveratrol for 4 weeks.	Decreased insulin resistance. Increased the phosphorylated protein kinase B (pAkt): protein kinase B (Akt) ratio. No effect on parameters related to β-cell function. Improved insulin sensitivity.	Brasnyó et al. (2011)
		62 patients with T2DM were enrolled in a prospective, open-label, randomized, controlled trial.	250 mg/d for a period of 3 months.	Improved glycemic control. Improved the mean hemoglobin A1c.	Bhatt et al. (2012)
		Non-obese, postmenopausal women with normal glucose tolerance. A randomized, double-blind, placebo-controlled trial	12 weeks of resveratrol supplementation (75 mg/d).	It did not increase liver, skeletal muscle, or adipose tissue insulin sensitivity. It did not change inflammatory markers.	Yoshino et al. (2012)
		66 subjects with T2DM. A randomized placebo-controlled double-blinded parallel clinical trial.	(1 g/d) for 45 days.	Decreased fasting blood glucose, hemoglobin A1c, insulin, and insulin resistance.	Movahed et al. (2013)
		12 patients with diagnosis of metabolic syndrome. A randomized, double-blind, placebo-controlled clinical trial.	Administration of *trans*-resveratrol (500 mg) three times per day before meals for 90 days.	Decreased the area under the curve (AUC) of insulin, and total insulin secretion.	(Méndez-del Villar et al., 2014)
		8 sedentary and overweight men.	Single dose (300 mg)	Decreased post absorptive insulin levels. Elevated skeletal muscle phosphorylation of p38 MAPK. No change in either skeletal muscle or adipose tissue insulin signaling.	Williams et al. (2014)
		Double-blind, randomized, placebo-controlled trial. 60 subjects with non-alcoholic fatty liver disease	2150 mg resveratrol capsules twice daily for three months.	Decreased glucose level. Decreased (HOMA-IR) index. Reductions of the levels of TNF-α and fibroblast growth factor 21.	Chen et al. (2015)
		14 patients with diet-controlled type-2 diabetes. A double-blind, randomized, crossover design.	(500 mg twice daily) over two to 5weeks intervention periods with a 5-week washout period in between.	No effect on fasting and postprandial blood glucose, HbA_{1c}, and plasma total GLP-1.	Thazhath et al. (2016)
		34 subjects with polycystic ovary syndrome. A randomized double-blind, placebo-controlled trial.	Resveratrol (1500 mg p.o.) administered daily over a period of 3 months.	Decreased fasting insulin level by 31.8%. Increased insulin sensitivity index by 66.3%. No effect on markers of inflammation.	Banaszewska et al. (2016)
		38 overweight and obese subjects. Randomized double-blind study.	Resveratrol and epigallocatechin-3-gallate (80 and 282 mg/d, respectively) supplementation for 12 weeks.	No effect on insulin-stimulated glucose disposal or suppression of endogenous glucose production.	Most et al. (2016)
		17 well-controlled subjects with T2D. A randomized double-blind crossover study.	(150 mg/d) for 30 days.	No effect on hepatic or peripheral insulin sensitivity.	Timmers et al. (2016)
		Middle-aged community-dwelling men (N = 74) with metabolic syndrome. A randomized, placebo-controlled, double-blind, parallel group clinical trial.	Daily oral supplementation with 1000 and 150 mg for 16 weeks.	No beneficial effect on glucose homeostasis.	Kjær et al. (2017)
			(150 mg/d) for 4 weeks.		Made et al. (2017)

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Table 12 (*continued*)

Chemical family	Molecules	Model	Dose	Effects	References
		45 overweight and slightly obese volunteers (25 men and 20 women). A Randomized Placebo-Controlled Trial.		No effect on fasting concentrations of plasma glucose and plasma insulin.	
		13 male first-degree relatives (FDR) of patients with T2D. A randomized, placebo controlled, cross-over trial.	(150 mg/day) for 30 days.	Resveratrol did not improve insulin sensitivity, expressed as the rate of glucose disposal during a two-step hyperinsulinemic-euglycemic clamp.	de Ligt et al. (2018)
Phenolic acids	Catechol	Caucasian post-menopausal women. A randomized, double-blind feeding study.	Daily for 12 months.	Green tea extract with the high-activity form of catechol-*O*-methyltransferase had higher insulin concentrations at time 0, 0.5 and 1.0 h post-meal.	Dostal et al. (2017)
	Chlorogenic acid	9 healthy fasted volunteers (4 men and 5 women). A 3-way, single-blind, randomized, crossover study.	2.5 mmol chlorogenic acid/L	Decreased glucose-dependent insulinotropic polypeptide secretion. Increased glucagon-like peptide 1 secretion.	Johnston et al. (2003)
		15 overweight men. A randomized crossover trial.	1 g chlorogenic acid during a 2-h oral glucose tolerance test (OGTT).	Reduced glucose and insulin concentrations 15 min following an OGTT.	van Dijk et al. (2009)
		15 patients with impaired glucose tolerance. A randomized, double-blind, placebo-controlled clinical trial.	400 mg three times per day for 12 weeks.	Decreased FPG and insulin secretion. Increased insulin sensitivity.	Zuñiga et al. (2018)
	Gallic acid	Patients (12 males and 9 females) with T2D A placebo-controlled pilot study	(15 mg88/p/d) for 7 days	No effect on blood glucose. Prevented oxidative DNA damage. Reduced markers which reflect inflammation.	Ferk et al. (2017)
	Salicylic acid	5 diabetic and non-diabetic patients	(0.9–1.8 g/day) over several months.	Increased plasma insulin levels (especially in response to a glucose load).	Hyams et al. (1971)
		14 healthy volunteers (12 males, 2 females). 7 patients with T2D.	3 g per day for 3 days.	Acetyl-salicylic acid impairs insulin action in healthy and in T2D man. Reduced clearance rate of insulin. Reduced hepatic glucose production due to greater insulin availability.	Bratusch-Marrain et al. (1985)
		6 overweight and obese non-diabetic men. Phase III.	(4.5 g/day) for 1 week.	Impairedinsulin clearance but does not ameliorate lipid-induced insulin resistance and *β*-cell dysfunction.	Xiao et al. (2009)
Fatty acids	Linoleic acid (LA)	14 patients with noninsulin-dependent diabetes mellitus in a crossover study.	–	No effect on glycemic control and carbohydrate tolerance.	Heine et al. (1989)
		32 subjects with stable, diet-controlled T2D. A randomized, double-blind, placebo-controlled trial.	3.0 g/d for 8 weeks.	Increased fasting glucose concentrations and reduced insulin sensitivity.	Moloney et al. (2004)
		Healthy overweight and obese male and female adults (118). A randomized, double-blind, placebo-controlled trial.	Conjugated linoleic acids (CLA) 3.4 g/day for 6 months.	No effect on glucose metabolism or insulin sensitivity.	Syvertsen et al. (2007)
		Young and older, lean and obese men. A double-blind placebo-controlled, randomized crossover study.	3 g/day for 12 weeks.	CLA plus *n*-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) showed no significant effects on HOMA-IR in any group but did increase fasting glucose in older obese men.	Sneddon et al. (2008)
		Young and older, lean and obese men. A double-blind, placebo-controlled randomized crossover design.	3 g daily for 12 weeks.	No significant difference in fasting levels of glucose, insulin or C-peptide after CLA/n-3 LC-PUFA treatment. No effect on insulin secretion or estimated sensitivity. Reduced insulin sensitivity in older obese men.	Ahrén et al. (2009)
		12 male participants completed a cross-over trial.	3.8 g/day for 8 week.	Increased muscle glycogen content after a single bout of exercise. Elevated muscle glucose transporter type 4 expression after exercise. No effect on P-Akt/Akt ratio. Impaired glucose tolerance.	Tsao et al. (2015)
		Children and adolescents with obesity. A randomized, double-blinded placebo-controlled clinical trial	(3 g/day) 3 times a day for 16 weeks.	Improved insulin sensitivity.	Garibay-Nieto et al. (2017)
		38 obese patients with T2D. A non-randomized study.	–	LA was positively correlated with total insulin secretion.	Nemati et al. (2017)
					Naughton et al. (2018)

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Table 12 (*continued*)

Chemical family	Molecules	Model	Dose	Effects	References
		Overweight/obese individuals. Single-blinded 3-way cross-over pilot study.	Nutritional composition of experimental meals per 100 g (LA = 14.9 g).	Increased resistin levels, an adipokine which decreases insulin sensitivity. Significant peak in blood glucose levels.	
	Linolenic acid	48 healthy volunteers (13 males, 35 females). A randomized strictly controlled dietary study.	6 g/day for 3 weeks.	No effect on fasting serum concentrations of insulin, fructosamine, insulin sensitivity and of HbA_{1c}. Fasting serum glucose levels did not change significantly.	Egert et al. (2008)
		38 subjects with normal or moderately high fasting serum triglyceride (TG) levels. A randomized, double-blind, controlled, crossover study.	1.25 and 2.50 g with a six days washout period.	The suppressive effect of α-linolenic acid-enriched diacylglycerol on the serum TG level correlated significantly with fasting insulin level. Higher fasting serum insulin levels.	Ando et al. (2016)
	Myristic acid	26 men with newly diagnosed T2D and 27 non-diabetic men.	–	The best metabolite for predicting the risk of diabetes.	Ha et al. (2012)
	Oleic acid	32 overweight subjects. A single-blind, randomized crossover study.	High oleic blended cooking oil was incorporated into diet supplying 30% energy as fat.	No effect on markers of insulin resistance (glucose, C-peptide, insulin, fructosamine, HbA1c, HOMA-IR, HOMA-β, and QUICKI) and glucose tolerance.	Lee et al. (2016)
	Palmitic acid	15 non-insulin-dependent diabetic patients. A randomized crossover study with three 3-week diet interventions separated by 2-week washout periods.	Diet rich in palmitic acid (45 E% fat [16 E% palmitic acid], 40 E% carbohydrate, 15 E% protein).	No differences in effects between the diet periods were seen for fructosamine, HbA_{lc} or fasting blood glucose.	Storm et al. (1997)
		25 healthy men and women. A randomized, double-blind, crossover study.	The saturated fat diet (S) had 9% of energy as palmitic acid.	Unaffected insulin secretion.	Lovejoy et al. (2002)
		5 non-diabetic subjects with normal glucose tolerance.	50 and 500 µM	Production of insulin receptors.	Stentz and Kitabchi, 2006
		A cross-over designed feeding trial in 53 healthy Asian men and women (20–50 years).	A test meal (3.54 MJ, 14 g protein, 85 g carbohydrate and 50 g fat as PO).	Palmitic acid in the *sn*-2 position didnot adversely affect insulin secretion and glucose homeostasis.	Filippou et al., 2014
		12 healthy males. A randomized, controlled, crossover double-blind design study.	Meals containing 50 g fat [palm stearin and palm kernel (80:20); IE vs. non-IE].	Increased insulin, glucose, paracetamol, and insulinotropic polypeptide concentrations.	Hall et al. (2016)
		A longitudinal study of 38 obese diabetic patients with Roux-en-Y gastric bypass.	Serum stearic acid/palmitic acid (S/P) ratio	(S/P) ratio as a potential predictor of diabetes remission.	Zhao et al. (2017)
	Phosphatidylcholine (PC)	27 healthy subjects (men and women).	–	The half-maximal insulin concentration was directly correlated with fatty acid elongation in PC.	Clore et al. (1998)
		The nurses' health study (NHS), NHS II, and the health professionals' follow-up study.	130 food items administered every 2 or 4 years combined with the PC contents.	Increased the risk of T2D by 17% with an increase of 100 mg choline from PC.	Li Ji et al. (2015); Li Wang et al. (2015)
		Sedentary obese adults (n = 14), individuals with T2D (n = 15), and endurance-trained athletes (n = 15).	Skeletal muscle PC.	Total muscle PC is positively related to insulin sensitivity. A single session of exercise significantly alteredskeletal muscle PC levels.	Newsom et al. (2016)
		54 knee OA patients. A two-stage case–control study design.	–	Abnormal unsaturated PC metabolism is associated with both type 2 diabetes and OA.	Zhang et al. (2016a,b)
		13 Normoglycemic normal weight men and 13 dysglycemic overweight men.	Skeletal muscle PC.	Exercise intervention for 12 w enhanced insulin sensitivity by 33%, skeletal muscle levels of PC by 21%. PC:PE ration is inversely related to insulin sensitivity.	Lee et al. (2018)
	Stearic acid	15 non-insulin-dependent diabetic patients. A randomized crossover study with three 3-week diet interventions separated by 2-week washout periods.	Stearic acid (44 E% [percent of total energy] fat [13 E% stearic acid], 40 E% carbohydrate, 15 E% protein),	No differences were seen in the effects between the diet periods for fructosamine, HbA_{lc} or fasting blood glucose.	Storm et al. (1997)
		15 young healthy female subjects. A randomized crossover design.	5 E% stearic was substituted for 5 E% of saturated fatty acids in the baseline diet.	A diet rich in stearic acid did not deteriorate glucose tolerance or insulin action.	Louheranta et al. (1998)
		14 obese sedentary individuals, 15 patients with T2D and 15 endurance trained athletes.	Sphingolipids containing stearate (18:0).	Sphingolipids containing stearate (18:0) are uniquely related to insulin resistance in skeletal muscle.	Bergman et al. (2016)
		50impaired fasting glucose (IFG) and 50 healthy subjects	Stearic acid (C18:0) concentration in healthy (82.91 ± 29.24 µg/mL) and IFG subjects (115.30 ± 59.33 µg/mL).	Increased postprandial C18:0 in IFG subjects; and the rise in postprandial C18:0 was inhibited by low glycemic index load.	Liu et al. (2016)
					Zhao et al. (2017)

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Table 12 (*continued*)

Chemical family	Molecules	Model	Dose	Effects	References
		A longitudinal study of 38 obese diabetic patients with Roux-en-Y gastric bypass.	Serum stearic acid/palmitic acid (S/P) ratio	(S/P) ratio as a potential predictor of diabetes remission.	
		In a population-based risk factor study (n = 8045), in a cohort of participants undergoing elective coronary angiography for suspected stable angina pectoris (n = 3344).	Ceramide lipids	Stearic acid (18:0) ceramide showedthe strongest association with incident diabetes. The stearic ceramide/palmitic acid ratio predicts incident diabetes.	Hilvo et al. (2018)
		85 healthy, overweight adult volunteers. Double-blind clinical trial.	Chemically-interesterified fats rich in stearic acids for 8 weeks.	No significant difference in surrogate biomarkers of insulin resistance.	Ng et al. (2018)
Fatty acids	Lipoic acid	26 patients with T2D. A randomized, double-blind, placebo-controlled trial.	Daily supplementation with 600 mg for 4 months.	Lipoic acid supplementation did not affect insulin sensitivity.	De Oliveira, Rondó, Luzia, D'Abronzo, & Illison, (2011)
Tannins	Tannic acid	10 non-insulin-dependent diabetes mellitus (NIDDM) patients were tested twice in random order.	150 mg	No differences were observed for insulin levels between the tannic acid and placebo tests. The difference of glucose excursion was statistically significant.	Gin et al. (1999)

The results showed that the consumption of GA at dose of 15 mg/p/day for 7 days prevented oxidative DNA damage and reduced markers related to inflammation. However, GA did not affect blood glucose.

9.2.4. *Salicylic acid*

In 1971, Hyams et al. (1971) evaluated the effect of 3-methyl salicylic acid on plasma insulin and glucose tolerance in five diabetic and non-diabetic subjects. After several months, the trial showed that the oral administration of 3-methyl salicylic acid to diabetic and non-diabetic patients with concentrations ranged between 0.9 and 1.8 g per day increased plasma insulin levels (especially in response to a glucose load). A few years later, Bratusch-Marrain et al. (1985) carried out study on 14 healthy volunteers (12 males, 2 females) and 7 patients with type 2 diabetic to evaluate the effect of acetyl-salicylic acid on glucose utilization and insulin secretion. A reduce in clearance rate of insulin and in hepatic glucose production due to greater insulin availability was observed when consuming acetyl-salicylic acid at dose of 3 g per day for 3 days. In addition, acetyl-salicylic acid impaired insulin action in healthy and in T2D patients. In 2009, Xiao et al. (2009) studied the effect of sodium salicylate on chronically elevated plasma non-esterified lipid-induced insulin resistance and β-cell dysfunction in six overweight and obese nondiabetic men. The results showed that the oral administration of sodium salicylate (4.5 g/day) for 1-week impaired insulin clearance but did not ameliorate lipid-induced insulin resistance and β-cell dysfunction.

9.3. *Fatty acids*

9.3.1. *Linoleic acid (LA)*

In 1989, a study was conducted by Heine et al. (1989) demonstrated the effect of linoleic-acid-enriched diet on serum lipoprotein and apolipoprotein concentrations and insulin sensitivity in 14 patients with noninsulin-dependent diabetes mellitus (NIDDM). Linoleic acid reduced atherogenic lipoprotein level but did not affect glycemic control and carbohydrate tolerance. A study was conducted on patients with type 2 diabetes mellitus to investigate the effect conjugated linoleic acid supplementation on markers of glucose and insulin metabolism, lipoprotein metabolism, and inflammatory markers (Moloney et al., 2004). The administration of linoleic acid supplementation at dose of 3.0 g/d for 8 weeks increased fasting glucose concentrations and reduced insulin sensitivity as measured by homeostasis model assessment. Total HDL-cholesterol concentration was increased but the ratios of LDL to HDL cholesterol and fibrinogen concentrations were reduced. However, the linoleic acid supplementation did not show any effect on the inflammatory markers of CVD (C-reactive protein and interleukin 6). Using the same method, Syvertsen et al. (2007) studied the effect of conjugated linoleic acid supplementation on insulin resistance in overweight and obese male and female adults. The results of this study showed that the administration of linoleic acid supplementation at dose of 3.4 g/day for 6 months did not affect glucose metabolism or insulin sensitivity in a population of overweight or obese volunteers.

Also, in 2008 a double-blind placebo-controlled, randomized crossover study wascarried out by Sneddon et al. (2008) to evaluate the effect of linoleic Acid and ω-3 fatty acid mixture on body composition, adiposity, and hormone levels in young and older, lean, and obese men. The results showed that the administration of this mixture at a dose of 3g–3g (CLA, n-3 LC-PUFA)/day for 12 weeks prevented any increase in the abdominal fat mass and raised fat-free mass and adiponectin levels in younger obese individuals without deleteriously affecting insulin sensitivity. However, these parameters in the young and older lean and older obese individuals were unaffected, apart from increased fasting glucose in older obese men. Using the same method, Ahrén et al. (2009) reported that the administration daily of the mixture at the same concentration did not affect the fasting levels of glucose, insulin or C-peptide, and insulin secretion or estimated sensitivity. However, the mixture of conjugated linoleic acid (CLA) plus n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) reduced insulin sensitivity in older obese men.

To illustrate the effect of conjugated linoleic acid (CLA) supplementation on glycogen resynthesis in exercised human skeletal muscle, Tsao et al. (2015) conducted a cross-over study in twelve male participants. After 8 weeks of linoleic acid (CLA) administration at a concentration of 3.8 g/day, it increased muscle glycogen content after a single bout of exercise, elevated the muscle glucose transporter type 4 expression after exercise and impaired glucose tolerance. Two years later, Garibay-Nieto et al. (2017) carried out a study on children and adolescents suffering from obesity to evaluate the effects of conjugated linoleic acid (CLA) on insulin sensitivity. The duration of the study was 16 weeks, during which the participants received daily conjugated linoleic acid at a concentration of 3 g resulting in improving insulin sensitivity. In the same year, a non-randomized study wasconducted by Nemati et al. (2017) to evaluate the effect of linoleic acid on changes of non-esterified fatty acids (NEFA) in relation to β-cell function (BCF) and insulin resistance in obese patients with type 2 diabetes (T2D). The results of this study showed that the linoleic acid was positively correlated with the total insulin secretion. In 2018, a single-blinded 3-way cross-over pilot study was conducted in eight overweight or obese subjects to demonstrate the effect of linoleic acid on appetite and metabolic markers (Naughton et al., 2018). At the end of the experiment, it was noted that people who consumed meals containing linoleic

acid at a concentration of 14.9 g increased resist in levels, an adipokine which decreases insulin sensitivity. Furthermore, all meals used in this study shows increase fullness and reduce desire to eat.

9.3.2. Linolenic acid

In 2008, a randomized strictly controlled dietary study wasconducted by Egert et al. (2008) in 48 healthy volunteers (13 males, 35 females) to investigate the effect of linolenic acid on parameters of glucose metabolism. The administration of linolenic acid dietary at dose of 6.0 g/day for 3 weeks did not affect fasting serum concentrations of insulin, fructosamine, insulin sensitivity and of HbA1c. It also did not significantly change fasting serum glucose levels. A few years later, Ando et al. (2016) reported that the oral administration a single dose of linolenic acid significantly lowered TG level compared with control. Linolenic acid suppressed the post prandial serum TG level in subjects with normal or moderately high fasting serum triglyceride (TG) levels.

9.3.3. Myristic acid

In 26 men with type 2 diabetes and 27 non-diabetic men, Ha et al. (2012) conducted this study to determine whether circulating metabolic intermediates are associated with inflammation, oxidative stress, and arterial stiffness. They also investigated the levels of circulating metabolic intermediates that may predict the risk of developing diabetes. The results of this study showed that myristic acid has been the best metabolite for predicting the risk of diabetes.

9.3.4. Oleic acid

To study the effect of oleic acid on markers of insulin resistance and glucose tolerance in 38 overweight subjects, Lee et al. (2016) carried out a single-blind, randomized crossover study to compare this effect of high oleic blended cooking oil (HOBO) vs. oleic acid-rich extra virgin olive oil (OO) diets. The results showed that the high oleic blended cooking oil diet did not affect markers of insulin resistance (glucose, C-peptide, insulin, fructosamine, HbA1c, HOMA-IR, HOMA-β, and QUICKI) and glucose tolerance in overweight individuals.

9.3.5. Palmitic acid

Palmitic acid did not show effect on the level of fructosamine, HbAlc or fasting blood glucose during a study conducted by Storm et al. (1997) on 15 patients using a randomized crossover protocol with three-week diet interventions separated by 2-week washout periods. Using the same protocol, Lovejoy et al. (2002) carried out a study to investigate the effect of palmitic acid on insulin action in 25 healthy men and women. The saturated fat diet (S) had 9% of energy as palmitic acid. At the end of the experiment, it was found that subjects who consumed a diet containing 9% of energy as palmitic acid did not affect their insulin sensitivity or secretion.

An *in vitro* study was performed to investigate the effect of various concentrations of palmitic acid in the activation of T-lymphocytes and human aortic endothelial cells (HAEC) (Stentz and Kitabchi, 2006). To perform this study, blood samples were collected from five non-diabetic subjects with normal glucose tolerance after 8–10 h of overnight fast. The results showed that the palmitic acid activated of T-lymphocytes and human aortic endothelial cells (HAEC) by developing insulin receptors. In 2014, Filippou et al. (2014) reported that palmitic acid in the *sn*-2 position did not adversely affect insulin secretion and glucose homeostasis. This was across-over trial conducted on 53 healthy Asian men and women (20–50 years) by feeding them a meal that contained 3.54 MJ, 14 g protein, 85 g carbohydrate and 50 g fat PO for 6 weeks.

In 2016, study was carried out by Hall et al. (2016) to investigate the effect of palmitic acid on postprandial lipidemia in 12 healthy males. After the participants finished their meals that contained 50 g fat [palm stearin and palm kernel (80:20); IE vs. non-IE], it was found that palmitic acid increased insulin, glucose, paracetamol, and insulinotropic polypeptide concentrations in participants. In the same year, Zhao et al. (2017) evaluated in 38 obese diabetic patients with Roux-en-Y gastric bypass the potential of estimating elongase and desaturase activities as predictive markers for diabetes remission. It was found that serum stearic acid/palmitic acid (S/P) ratio could be used as a potential predictor of diabetes remission.

9.3.6. Phosphatidylcholine (PC)

The study of phosphatidylcholine (PC) effect on skeletal muscle phosphatidylcholine fatty acids and insulin sensitivity in 27 normal patients was conducted by Clore et al. (1998). The results showed that the half-maximal insulin concentration was directly correlated with fatty acid elongation in PC. In 2015, study was carried out by Li Ji et al. (2015); Li Wang et al., (2015) to evaluate the effect of dietary phosphatidylcholine intake in men and women with type 2 diabetes (three ongoing cohorts: The Nurses' Health Study (NHS), NHS II, and the Health Professionals Follow-Up Study (HPFS)). PC increased the risk of T2D by 17% with an increase of 100 mg choline from PC.

Another study was conducted by Newsom et al. (2016) to determine the relationships between skeletal muscle PC, PE, and insulin sensitivity, and whether PC and PE are dynamically regulated in response to acute exercise in sedentary obese adults (OB; n = 14), individuals with type 2 diabetes (T2D; n = 15), and endurance-trained athletes (ATH; n = 15). The results showed that the total muscle PC was positively related to insulin sensitivity. Also, a single session of exercise significantly altered skeletal muscle PC levels. In the same year, Newsom et al. (2016) studied how OA patients with metabolic syndrome (MetS) demonstrated different metabolism than OA patients without a MetS component as well as healthy individuals. The study demonstrated that abnormal unsaturated PC metabolism was associated with both type 2 diabetes and OA. In 2018, a study was conducted by Lee et al. (2018) who evaluated the relationships between skeletal muscle PC:PE, physical exercise, and insulin sensitivity by measuring CP and PE in biopsies of m. vastus lateralis obtained from 13 normoglycemic and 13 overweight men with dysglycemia. The results of this study indicated that the exercise intervention for 12 w enhanced insulin sensitivity by 33%, skeletal muscle levels of PC by 21%. PC:PE ratio was inversely related to insulin sensitivity.

9.3.7. Stearic acid

In 1997, Storm et al. (1997) compared the effect on lipid levels, glycemic control, and diurnal blood pressure of two diets rich in stearic acid with a carbohydrate-rich diet in 15 non-insulin-dependent diabetic patients. The results of this study reported that no differences in the effects between the diet periods on fructosamine, HbA_{1c} or fasting blood glucose. Also, in 1998, Louheranta et al. (1998) examined the effects of a high-stearic acid diet on glucose metabolism, serum lipids and lipoproteins, and blood coagulation factors in 15 healthy female subjects. They found that a diet rich in stearic acid did not deteriorate glucose tolerance or insulin action.

A study was conducted by Bergman et al. (2016) to study the relationships and the effect of acute exercise (1.5 h at 50% VO2max) and recovery on muscle sphingolipid content in 14 obese sedentary individuals, 15 patients with T2D and 15 endurance trained athletes. It was revealed that sphingolipids containing stearate were uniquely related to insulin resistance in skeletal muscle. In the same year, Liu et al. (2016) examined the postprandial change in free fatty acid (FFA) profiles in subjects with impaired fasting glucose (IFG). They also evaluated the effect of low glycemic index (GI) load on postprandial FFA profiles and inflammation. An increase in postprandial FFA profiles in IFG subjects and a rise in postprandial was inhibited by low glycemic index load Zhao et al. (2017) evaluated the potential application of estimation elongase and desaturase activities as predictive markers for T2DM remission after Roux-en-Y gastric bypass (RYGB) in 38 obese diabetic patients. They found that the serum stearic acid/palmitic acid ratio as a potential predictor of diabetes remission.

A study was conducted in a population-based risk factor study (FINRISK 2002, n = 8045), in a cohort of participants undergoing

elective coronary angiography for suspected stable angina pectoris (Western Norway Coronary Angiography Cohort [WECAC], n = 3344) and in an intervention trial investigating improved methods of lifestyle modification for individuals at high risk of the metabolic syndrome (Prevent Metabolic Syndrome [PrevMetSyn], n = 371). Hilvo et al. (2018) investigated four ceramides and their ratios and found stearic acid (18:0) ceramide showed the strongest association with incident diabetes. Stearic ceramide/palmitic acid ratio predicted the incident of diabetes. In the same year, Ng et al. (2018) investigated the effects of CIE fats rich in palmitic and stearic acids on insulin resistance, serum lipids, apolipoprotein concentrations, and adiposity, using C16:0-rich natural palm olein (NatPO) as the control. No significant difference in surrogate biomarkers of insulin resistance was detected.

10. Nutritional value of anti-diabetic medicinal plants

10.1. *Arbutus unedo L.*

The data from the literature showed that *Arbutus unedo* is a plant of high medicinal interest. This was confirmed by the high amount of bioactive molecules containing in its chemical composition, as well by its safety even at high doses (Mrabti et al., 2018). A study carried out in Spain provided important data on the nutritional value and biomass production, and macro and micronutrient composition of wild strawberry fruits. They have shown that the fruit of *A. undo* can be considered a very important source of health-promoting compounds such as vitamin C and dietary fiber (202.6 mg/100 g and 42.6%, respectively). It was also reported to be rich in total available carbohydrates, sugars, potassium and secondary metabolites such as phenolic compounds (Ruiz-Rodríguez et al., 2011). In addition, another investigation showed that the fruit of *A. unedo* contains a high concentration of carbohydrates, which varied from 42% to 52% (Ayaz et al., 2000). Similar concentrations were found in *A. unedo* fruits harvested in northwestern Turkey (Şeker & Toplu, 2010). According to a study conducted by (Doukani & Tabak, 2015), the fruits of *A. unedo* contained 68.18% water, 17.66% soluble solids (sugars, salts, proteins and carboxylic acids …), 19% dietary fiber and 0.082% pectin. Mineral composition analysis revealed that *A. unedo* (roots and leaves) is a good source of Ca, Mg, P, Na and K, which are very important in human nutrition (Mrabti et al., 2017). Moreover, other results showed that the strawberry tree fruits could be considered an interesting source of bioactive compounds for dietary supplements or functional foods.

10.2. *Lepidium sativum L.*

The nutritional value of *Lepidium sativum* L. seeds have been reported by numerous studies. Various parameters have been determined including minerals, proteins, fatty acids and amino acid contents. The reported results showed that for 100g of the plant in the raw state exist the following nutrients amounts: Carbohydrate (5.5–8.7 g), fiber (1.1 g), protein (2.6–5.8 g), fat (0.7–1 g), water (80%), vitamins (346 mg of vitamin A, C 69 mg of vitamin, 80 mg of folate or vitamin B9, vitamin B1, B2, vitamin K), and minerals (81 mg of calcium, 1.3 mg of iron, phosphorus, potassium, magnesium, and others) (Mali et al., 2008). Another study reported that the seeds of *L. sativum* (dry weight) contained high levels of proteins (20.84%), fat (23.83%) and crude fiber (7.15%) (Alshammari et al., 2017). Fatty acid analysis has shown that *L. sativum* oil contains high levels of unsaturated fatty acids such as the essential fatty acids; linoleic acid (30.6%), and linolenic acid (29.3%) (Moser et al., 2009). These data highlighted the potential of *Lepidium sativum* seeds as a source of useful chemical constituents for human nutrition.

10.3. *Carum carvi*

The nutritional analysis of *Carum carvi* seeds (100g) showed the presence of the following content: water (9.87g), protein (19.77g), total lipids (14.59 g), carbohydrates (49.90g), fiber total dietary (38.0g), sugars (0.64g), calcium (689 mg), iron (16.23 mg), magnesium (258 mg), phosphorus (568 mg), potassium (1351 mg), sodium (17 mg), zinc (5.50 mg), ascorbic acid (21.0 mg), thiamine (0.3606 mg), riboflavin (0.379 mg), niacin (3.606 mg), vitamin B6 (0.360 mg), folate (10 μg), vitamin A (18 μg), and vitamin E (2.50 mg) (Al-Snafi, 2015). In addition, these seeds contained 6.2–10.1% vegetable oil consisting mainly of petroselinic acid (29.46–40.6%) and linoleic acid (35–37%). Other fatty acids such as linoleic, palmitic, myristic and capric acids were also identified in this vegetable oil, but at lower concentrations (Laribi et al., 2013; Reiter et al., 1998). The chromatographic analysis of total sterol in *Carum carvi* seeds showed a variation from 0.2 to 0.7%, where the β-sitosterol and stigmasterol were the major components (35–40%), while brassicasterol and campesterol were identified as minor compounds. On the other hand, α-tocopherol (vitamin C) was the major tocopherol of caraway seed oils, which was about 2.5 mg/100g (Elgersma et al., 2013). Vegetable seeds produce about 0.48–1.41% of yellowish-colored essential oil with a fragrant odor. More than forty volatile compounds have been characterized in this oil, among them, carvone (76.78–80.53%) and limonene (13.05–20.29%), which were the most important ones (Laribi et al., 2010). From these data, it can be concluded that the constituents of *Carum carvi* are a promising source for human nutrients as well as for drugs discovery.

10.4. *Crocus sativus*

Crocus sativus or saffron has a long history of use as a spice for many centuries. A number of investigations about the safety and the toxicity of saffron and its components have been conducted (Khan et al., 2020). According to the chemical analysis, *C. sativus* has been known to contain several chemical substances, such as carbohydrates, minerals, mucilage, vitamins (especially riboflavin and thiamine) (Selamoglu and Ozgen, 2016). In another study carried out on the stigmata of *C. sativus*, the analyses of the chemical composition revealed, approximately, 12% protein, 5% crude fiber, 5% fat, 5% minerals (Mn, Mg, P, Cu, Ca, Zn, Fe, …), 10% moisture, and 63% sugars, including starch, reducing sugars, pentosans, gums, pectin, and dextrins (% w/w). Trace amounts of riboflavin and thiamine vitamins have also been identified in saffron (Melnyk et al., 2010). These data show that saffron is an extraordinary rich source of nutraceutical and pharmaceutical components with several benefits for human health.

10.5. *Foeniculum vulgare*

The chemical composition and the nutritional value of different parts of *Foeniculum vulgare* (fennel) (shoots, leaves, stems and inflorescences) have been reported by Barros et al. (2010). The main nutrients containing in fennel seeds varied highly. In fact, the protein content was about 1.08% in stems and 1.37% in inflorescences, and the total sugar content varied from 1.29 in leaves to 6.57% in shoots. The inflorescences and stems had the highest carbohydrate content (22.81 and 21.91%, respectively), and this content was lower in leaves (18.44%) (Barros et al., 2010). Fennel seeds consist of 10–14.41% vegetable oil, with petroselinic acid as major fatty acid (70–80%). Other fatty acids such as linoleic acid, palmitic acid, and oleic acid were also noticed. On the other hand, the sterol and tocopherol reveal that fennel seeds contain 66 mg/100g of phytosterols: stigmasterol, β-sitosterol and campesterol are the main components; while the total vitamin E content is about 20.1 mg/100 g, the predominant tocopherol is γ-tocotrienol with 18.2 mg/100 g. With regard to the aerial parts, leaves and shoots have the highest tocopherol content with 55.68 and 34.54 μg/g of MS, α-tocopherol shows the highest concentration in all aerial parts of the fennel (Cosge et al., 2008). More than 87 volatile compounds have been identified in fennel oil, in which *trans*-anethole was the most important one. In addition, fenchone, estragole, and D-limonene were also found in

fennel essential oils at high concentrations (Barros et al., 2010).

10.6. *Nigella sativa*

The seeds of *Nigella sativa* are widely consumed as a spice and as a drug in folk medicine. Some studies showed that the seeds of *N. sativa* seeds are composed of lipids, carbohydrates, and proteins in variable proportions. In total, these proportions have been shown to be between 22.0 and 53.4% lipids, 23.5 and 40% carbohydrates, and 20.0 and 31.2% proteins. In addition, these seeds contained ash with values ranged from 3.7 to 4.8%. *Nigella sativa* seeds, also contains vitamins and various minerals (Al-Jasass & Al-Jasser, 2012; Atta, 2003). Among the mineral elements found in *Nigella* oil, we can cite those described by Sheikh Rouhou's team: potassium (783 and 708 mg/kg), magnesium (235 and 260 mg/kg), phosphate (48.9 and 51.9 mg/kg), sodium (20.8 and 18.5 mg/kg), iron (8.65 and 9.42 mg/kg), zinc (8.04 and 7.03 mg/kg), manganese (4.43 and 3.37 mg/kg) and copper (1.65 and 1.48 mg/kg) (Cheikh-Rouhou et al., 2007). More recently, Al-Jasass showed that *N. sativa* seeds contained a high level of potassium (823 mg/100g), followed by calcium (160 mg/100g), magnesium (80 mg/100g), and iron (65 mg/100g). These seeds also contained low levels of zinc (2.5 mg/100g), manganese (1.5 mg/100g), and copper (0.9 mg/100g) (Al-Jasass & Al-Jasser, 2012). Moreover, numerous vitamin have been detected in this plant such as retinol (vitamin A), ascorbic acid (vitamin C), thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pyridoxine (vitamin B6), folic acid (vitamin B9), and various derivatives of tocopherol (vitamin E) (Al-Jassir, 1992; Al-Saleh et al., 2006; Hassanein et al., 2011; Ramadan & Mörsel, 2003).

10.7. *Origanum vulgare* L.

The consumption of herbs is not sufficient to represent a significant source of vitamins and minerals in our daily intake. However, *Origanum vulgare* L. contains vitamins in high amounts such as vitamin E, riboflavin (vitamin B2), pyridoxine (vitamin B6), niacin (vitamin B3), folate (vitamin B9), panthotenate (vitamin B5), and biotin (vitamin B8) (Kurşat et al., 2011). Oregano also contains minerals such as iron, copper, sulfur, chlorine, iodine, and selenium. In addition, the non-polar fraction of *O. vulgare* extracts contains α-, β-, γ- and δ-tocopherols, involved in the antioxidant property of oregano. Among these homologues, γ-tocopherol was reported to be main one, which was noticed in greater quantities (Ashfaqullah and Tamta, 2019). Moreover, it was estimated that 100 g of fresh oregano leaves contained 310 mg of calcium, 53 mg of magnesium, 39 mg of phosphorus, 0.9 mg of zinc, and 0.3 mg of manganese. Similarly, the value of one teaspoon of dried oregano contained 0.2 g of protein, 0.18 g of fat, 1.16 g of carbohydrates, 0.8 g of fiber, and an energetic value of 6 calories. Compared to basil, oregano was 65% more energetic and had more than twice of fat content (Ashfaqullah and Tamta, 2019). Oregano has also been shown to be rich in essential oils. The major compound of its essential oil was carvacrol followed by thymol, *p*-cymene and γ-terpinene with 85.49%, 3.78%, 2.62% and 2.06%, respectively (Bampidis et al., 2005).

10.8. *Trigonella foenum graecum* L.

Trigonella foenum graecum is one of the oldest medicinal and culinary plants. Chemistry data have shown that its seeds contain 45–60% carbohydrates, 20–30% lysine and tryptophan proteins, 5–10% oil (lipid), mucous fibers, trigonelline (0.20–0.38%), choline (0.5%), free amino acids such as 4-hydroxy-isoleucine (0.09%), arginine, histidine and lysine, calcium and iron, vitamins A1, B1, C and 0.015% volatile oils (Moradi & Zadeh, 2013). This plants was also reported to contain 3–4% ash, 3–5% moisture, 25–30% protein, 7–9% lipids, and 20–25% insoluble fiber (Goesaert et al., 2009). Moreover, the mineral content analysis showed that fenugreek contains a total ash content of 3.9 g/100 g, calcium (70 mg), magnesium (160 mg), iron (12.5 mg), copper (1.8 mg), zinc (7.0 mg), manganese (1.0 mg), and phosphorus (370 mg/100g) (Billaud & Adrian, 2001). Fenugreek oil, which is highly unsaturated, contains only 15–19% saturated fatty acids, in which palmitic acid is the main one. Fenugreek contains 18–27% monounsaturated acids, represented by oleic and erucic acids. In conclusion, the richness of fenugreek seeds in proteins, carbohydrates and lipids gives it interesting nutritional properties.

10.9. *Zizyphus lotus* L.

The fruit of *Zizyphus lotus* L. has been consumed by human for a long time, with no anti-nutritional or toxic effects reported. A sample from Algeria was studied after its collection in order to determine its nutritional value. The results showed that the main biomass compounds were sugars (65.90%), crude fiber (8.41%), crude protein (3.80%), pectin (3.78%), ash (3.28%), crude fat (1.32%). In addition, elemental analysis of the fruit in mg/100g dry matter (DM) indicated the presence of appreciable levels of zinc (0.44), potassium (134.99), sodium (11.45), phosphorus (10.62), manganese (2.17), magnesium (397.91), and iron (1.33). The fatty acids analysis by GC-MS revealed the presence of 15 fatty acids; the unsaturated ones were about 71%, in which oleic acid represented 49% of the total mixture, followed by of linoleic acid with 22% (Abdeddaim et al., 2014). Moreover, another investigation showed that *Z. lotus* is highly rich in nutrients, which was composed of 12.8–13.6% carbohydrates including: 5.6% sucrose, 1.5% glucose, 2.1% fructose, and 1% starch (Meena et al., 2014). Likewise, (Bal, 1981), found that the pulp contains the following amino acids: asparagine, arginine, glutamic acid, aspartic acid, glycine, serine, and threonine. This plant was also reported as an important source of vitamin C and vitamin A (Bal & Mann, 1978). These data confirm the high nutritional value of this plant.

11. The use of Moroccan anti-diabetic medicinal plants in food preservation

11.1. *Thymus capitatus*

The use of Moroccan anti-diabetic plants in the food industry has been proven by some studies. Indeed, essential oils and plant extracts have shown an enormous capacity to preserve food products (milk, cheese, fish, etc.). Obviously, *Thymus capitatus*, a medicinal plant endemic to the Mediterranean region, has shown promising capacities in food preservation. Indeed, Arras and colleagues showed that the *T. capitatus* essential oil (TCEO) had fungitoxic activity *in vitro* by inhibiting the growth of two phytopathogenic fungi (*Penicillium italicum* and *Botrytis cinerea*) responsible for the rotting of several crops, in particular citrus fruits (Arras et al., 1995). The following year, and in order to control post-harvest diseases of citrus, the same authors tested the capacity of TCEO to protect 'Minneola' tangelo fruit against a decay induced by *P. digitatum* which was prepared and sprayed on the surface of the fruit (Arras et al., 1996). The results showed a high control of pathogens *via* the reduction of their viability.

Moreover, Karoui et al. (2011) used thyme flowers to improve thermal stability of corn oil under heating and deep-frying conditions. For this, the authors determined several parameters such as the peroxide value, oxidative stability index, specific absorptivity values (K_{232} and K_{270}), free fatty acid content, colour and chlorophyll, carotenoid and total phenol contents. Therefore, thyme supplementation prevented thermal oxidation based on the increase in induction time observed for the flavoured oil characterized by low content of free fatty acids, K_{232} and K_{270}, and peroxide value. This may be due to the richness of thyme flowers in phenolic and antioxidant compounds, pigments, and organic acids, which migrated to corn oil during the aromatization process.

Strawberry is a fruit often attacked by phytopathogenic pests, and in order to preserve it for a very long time, some coating techniques of polysaccharides in combination with natural resources have been

adopted. In this sense, Martínez and collaborators evaluated the effect of the application of edible coatings, based on chitosan incorporated with TCEO, on strawberries stored under refrigeration conditions (Martínez et al., 2018). The results of this application showed an increase of fruit shelf life (up to 15 days) and inhibition of microbial development (molds, aerobic mesophylls, and yeasts), and subsequently a delay the loss of the antioxidant and physicochemical strawberries properties.

Furthermore, the use of *T. capitatus* as a food preservative has also been improved by Jemaa et al. (2018) who developed an encapsulation system of TCEO based on the nano-emulsion by subsequently evaluating the antibacterial and antioxidant activities of this oil. In fact, nano-encapsulated TCEO showed promising antibacterial (inhibitory zone of 15.8 mm against *Staphylococcus aureus*) and antioxidant (IC_{50} = 390 μg/mL) effects, able to inhibit bacterial spoilage of food.

11.2. *Origanum compactum*

Origanum compactum was exploited in several biotechnological applications in the food industry (Hammou, 2011; Sedaghat Doost et al., 201; Zantar et al., 2014).In 2011, Hammou and co-workers investigated the antibacterial activity of *O. compactum* EO (OCEO) at different concentrations against two strains of *Escherichia coli* (*E. coli* O157:H7 and *E. coli* ATCC 25922), in order to increase the shelf life of tryptic soy broth and in sheep natural sausage casings without using salt (Hammou, 2011). It was noted that the essential oil (0.03 or 0.06%) inhibited the growth of the two strains tested during storage (at 25 and 7 °C) in casings.

The use of nanotechnologies showed major benefits in the food industry. In fact, the formulation of *O. compactum* essential oil nanoemulsions as natural food preservatives was the subject of the study by Sedaghat Doost et al. (2018) where they found that Quillajasap on in biosurfactant could stabilize these nanoemulsions. Additionally, incorporation of sunflower oil (6.9%) at microfluidization pressure (73.5 MPa) was able to make a long-term stable nanoemulsion without change in antibacterial effect. The essential oil of this plant (from north-eastern Morocco) was evaluated for its preservative power of fresh goat cheese *via* the determination of its antimicrobial activities, monitoring of yeast and mold growth, and the study the physico-chemical and microbiological characteristics of cheese stored at 8 °C (Zantar et al., 2014). Consequently, OCEO (0.05 and 0.1%) inhibited coliforms from the first day of storage with extended shelf life of fresh goat cheese.

11.3. *Eucalyptus globulus*

In 2011, Djenane and colleagues investigated the *in vitro* antibacterial effect of *Eucalyptus globulus* leaf EO, against *Staphylococcus aureus* and *Escherichia coli* O157: H7, inoculated experimentally in minced beef and stored at 5 ± 2 °C (Djenane et al., 2011). The oil tested had a remarkable antibacterial effect by effectively inhibiting the growth and reducing the number of bacteria. Interestingly, a decrease of 2.50 CFU/g was recorded after 1 week of storage against *S. aureus*. Recently, a research team was interested in the development of a natural beverage preservative (Boukhatem et al., 2020). For this, the authors determined *in vitro* the antioxidant and antimicrobial properties of *E. globulus* EO (EGEO) in a real juice matrix (Orangina fruit juice). The results showed that EGEO had better metal ion chelation activity (8.43 ± 0.03 mg/mL) compared to the reference (140.99 ± 3.13 mg/mL) and a strong inhibition against food spoilage microorganisms compared to synthetically preserved juice.

11.4. *Nigella sativa*

Contamination of seeds, particularly with aflatoxins, is a serious problem in the food industry. These mycotoxins, often produced by *Aspergillus flavus*, can be present in many food products (dry foods, spices, etc.) stored in hot and humid atmosphere. In order to overcome this problem, a Jordanian research team proposed *Nigella sativa* (the crude extract and oil) as a natural alternative for inhibiting the production of aflatoxins (B1, B2, G1, and G2) (Maraqa et al., 2007). The plant ingredients showed significant fungal antitoxic activity against different types of aflatoxins naturally generated by *A. flavus*, indicating that *N. sativa* may be a good food preservative for controlling mycotoxin effects. Likewise, a Jordanian researcher evaluated the ability of *N. Sativa* seed oil (NSSO) to preserve date paste and to control food spoilage microorganisms existing in these stored pastes (Bahtiti, 2015). Consequently, NSSO (400 ppm) improved the sensory quality of date paste (taste, texture, flavour, and color) during 4 months of storage at room temperature, and it also decreased (2.6–3.7 log cycles) the population of microorganisms, which remarkably extended the shelf life of the date paste.

11.5. *Opuntia ficus indica*

Numerous studies have tested the effect of *Opuntia ficus indica* in maintaining the quality of food products during storage (Allegra et al., 2016; Chougui et al., 2015; Del-Valle, 2005; Palmeri et al., 2018). In addition, edible coating of foods has provided an alternative to disposable packaging to ensure their protection during storage and against mechanical damage. In order to obtain an adequate coating, Del-Valle, (2005) used the mucilage of *Opuntia ficus indica* (OFI) as an edible coating to increase the protection and shelf life of strawberries (*Fragaria ananassa*). The findings revealed that the coating of the samples improved the shelf life of the fruits, while maintaining their sensory and physical characteristics. This method has also been applied in the preservation of kiwifruit slices (Allegra et al., 2016). The surfaces of kiwifruit cuts were treated with mucilage extracted from OFI and stored (5 °C) for various periods (3, 5, 7, and 12 days), measuring the microbiological, physical, and sensory properties, as well as the O_2 and CO_2 content of the packaging. Up to 12 days of storage, the treated kiwifruit slices exhibited high firmness, low weight loss, good visual quality, with maintenance of ascorbic acid and pectin content. This indicates that the OFI edible coating was shown to be effective in maintaining the quality of fresh cut kiwifruit slices. On the other hand, vitamin E is a very potent natural antioxidant which protects oils and margarines from oxidation and rancidity, and thus allows them to optimally retain all their properties. There, Chougui et al. (2015) used the hydro-ethanolic extract of OFI peels as a substitute for vitamin E. They found that this extract was rich in phenolic compounds known by their antioxidant properties, which was shown by an important antiradical activity and a reducing power close to those of standards widely used in food preservation. Interestingly, the incorporation of OFI peel extract (50 ppm) in margarine extended its shelf life without changing its physicochemical and microbiological characteristics.

In order to maintain the overall quality of sliced beef, an Italian research team tested the effect of the application of OFI fruit extract, under domestic storage conditions, on packaged beef samples *via* the evaluation of physicochemical parameters, color, texture, and *in vitro* microbial growth (Palmeri et al., 2018). The addition of the extract showed broad-spectrum antimicrobial activity during the storage period, with preservation of beef color and texture.

11.6. *Perilla frutescens*

The preservative capacity of *Perilla frutescens* on different food products was examined in several studies (Lee et al., 2015; Li, Zhang et al. 2017; Li, Zheng et al. 2017; Zhao et al., 2019). Indeed, Lee et al. (2015) investigated the capacity of *P. frutescens* water extract (PFWE) to preserve the physicochemical qualities of cooked beef patties with evaluation of its antioxidant (DPPH and ABTS radicals) and antimicrobial (*E. coli* O157:H7) properties. The authors recorded a high content of phenolic compounds, important effective concentrations for the scavenging of DPPH (EC_{50} = 0.437 mg/mL) and $ABTS^+$ (EC_{50} = 4.509

mg/mL) radicals, and significant inhibition ($p < 0.05$) of bacterial growth. This corroborates the results obtained during the treatment of cooked beef patties, stored at 4 °C for 21 days, with PFWE, which inhibited the oxidation of lipids and the growth of aerobic bacteria in the meat, subsequently improving its sensory qualities and redness scores. However, the rapid photo-degradation and oxidation of the essential oil of this plant has limited its use in the food industry. To overcome these disadvantages, a Chinese research laboratory adopted the technique of microencapsulation based on the formation of a polymer coating encompassing essential oils (Li, Zhang et al. 2017; Li, Zheng et al. 2017). In fact, the preparation of Perilla EO-loaded microcapsules by ionic gelation inhibited several bacterial strains and delayed EO volatilization. In addition, the prepared microcapsules delayed strawberry decay and retained their flavor, and decreased nutrient loss, so they can be used as an antibacterial and preservative in the food industry.

It is well known that seafood cannot preserve its freshness outside of the refrigerator, hence the need to find natural preservatives. Zhao et al. (2019) proposed *P. frutescens* leaf extract (PLE) as a natural food additive for this role. In fact, PLE showed important free radical scavenging activity against DPPH (IC_{50} = 12,15 μg/mL) and ABTS (IC_{50} = 7.26 μg/mL) radicals. Besides, the incorporation of PLE (0.03%) in surimi fish balls allowed to delay the process of lipid and protein oxidation during storage, to inhibit the growth of *E. coli*, and to increase the overall acceptability of the samples compared to the control group.

11.7. *Rosmarinus officinalis*

Rosemary (*Rosmarinus officinalis*) was exploited by many researchers for use as an ingredient to improve the shelf life of food products (Peiretti et al., 2012; Sirocchi et al., 2017; Vilela et al., 2016; Çoban and Özpolat, 2013). Indeed, Çoban & Özpolat, (2013) studied the effect of *R. officinalis* extract, at different concentrations, on the shelf life of hot-smoked and vacuum-packed fish (*Luciobarbus esocinus*) fillets in terms of sensory, chemical, and microbiological quality. The addition of this extract increased the preservation time compared to the control, and controlled bacterial growth and chemical indices. In the same year, rosemary oil (0.2%, 1%, and 3%) also showed beneficial effects on minced trout (*Oncorhynchus mykiss*) muscle stored at 4 °C for different periods (Peiretti et al., 2012); by improving several characteristics such as oxidative stability, pH, and biogenic amine and fatty acid contents, which subsequently improved the quality of this ready-to-cook fish and its shelf life. Furthermore, Sirocchi et al. (2017) combined the essential oil of this plant with different packaging conditions (high-O_2, aerobic, vacuum) to extend the shelf life of beef meat. In fact, slices of this meat were wrapped with a coating of rosemary essential oil (REO) and stored at 4 °C for 20 days. The use of REO showed promising results under all storage conditions such as decreased counts of microorganisms, improved sensory quality, and extended shelf life (15 days) under conditions with high O_2 content. The same study was performed in the same year by a Portuguese research team where they found that ROS was able to maintain the red meat color, control pH, and reduce the development of spoilage microbiota in vacuum packaging (2 °C) (Vilela et al., 2016).

11.8. Others

Other medicinal plants were used in preserving different food products such as chickpeas (Bazargani-Gilani et al., 2015; Ehsani et al., 2014; Jannatiha et al., 2020; Kedia et al., 2016; Kumar et al., 2009; Raeisi et al., 2015; Viji et al., 2015; Zakipour et al., 2013), Tajik et al., 2015; Pabast et al., 2018; Langroodi et al., 2018; Lashkari et al., 2020; Gonçalves et al., 2017; da Rosa et al., 2020), and table grape (Geransayeh et al., 2012; Pina-Barrera et al., 2019).

Indeed, the genus of the mint family (*Mentha arvensis* and *Mentha spicata*) showed high fungitoxicactivityagainst*A. flavus*, at different concentrations and exposure durations, in the chickpea food system (Kedia et al., 2016; Kumar et al., 2009).

Regarding the preservation of fish, *M. arvensis* leaf extracts also increased the shelf life of Indian mackerel, which, proved by the decrease in biochemical quality indices, inhibition of lipid oxidation and improvement of sensory quality (Viji et al., 2015). Moreover, the combined application of *Zataria multiflora* EO (ZMEO) with sodium acetate (2%) extended the shelf life (to 21 days) of vacuum-packaged fish (trout) burgers, synergistically (Ehsani et al., 2014). Additionally, this essential oil exhibited the same effect (12 day extension) on fresh fillets of rainbow trout (*Oncorhynchus mykiss*) when it was combined with nisin (Zakipour et al., 2013). Raeisi et al. (2015) found that the coating of carboxymethyl cellulose (CMC) incorporated with ZMEO and grape seed extract improved the chemical, sensorial, and microbial properties of rainbow trout fillets during a twenty-day refrigerated storage.

On the other hand, this type of coating (CMC film) has also been applied recently by Jannatiha et al. (2020) using the essential oils (2.4%) of *Z. multiflora* and *Saturejakhuzistanica* which revealed a significant extension (from 6 to about 12 days) in the shelf life of chilled chicken legs with little undesirable effects on sensory qualities. This was in agreement with the findings of a study evaluating the effect of coating with chitosan enriched with ZMEO on the shelf life of chicken breast meat under refrigerated storage (Bazargani-Gilani et al., 2015).

Concerning the preservation of red meat, an Iranian research team evaluated the combinatorial effect of grape seed extract with ZMEO on the shelf life of raw buffalo patty (Tajik et al., 2015). Therefore, this combination controlled the growth of spoilage microorganisms and *Listeria monocytogenes*, inhibited oxidative deterioration of meat, and improved sensory qualities. Additionally, *Satureja khuzistanica* EO (SKEO) was suggested to be an ecological substitute for chemical preservatives (Pabast et al., 2018). Effectively, the authors have developed a new biodegradable coating integrated with nano-encapsulated SKEO capable of improving the quality characteristics of lamb meat. The same results were noted by other studies using the edible coating incorporated with ZMEO which improved the quality and shelf life of chilled meat products for more than two weeks (Langroodi et al., 2018; Lashkari et al., 2020).

Besides, the problem of deterioration of baked goods over time has been solved by the use of essential oils with antimicrobial and antioxidant properties. Interestingly, da Rosa et al. (2020) revealed that the application, *in situ*, of *Thymus vulgaris* and *Origanum vulgare* EOs encapsulated in zeinna no capsules showed potential antioxidant and antimicrobial activities, good physicochemical stability in storage for 3 months, high thermal resistance during baking, subsequently protecting the bread against the yeast and mold proliferation. In addition, Gonçalves and collaborators designed microparticles from thyme (*T. vulgaris*) EO to preserve cakes (Gonçalves et al., 2017). Accordingly, the free and encapsulated oils exhibited high activity, *in vitro*, against the molds and bacteria tested. In contrast, the microparticles have avoided the volatilization of the encapsulated oil; giving cakes a one-month shelf life without the application of synthetic preservatives.

Moreover, in developing countries, postharvest damage influences the quality and quantity of food and causes economic losses, especially for primary producers. This problem was addressed by Geransayeh and co-workers, who applied *T. vulgaris* EO (TVEO) at different concentrations to table grapes (*Vitis vinifera* L) (Geransayeh et al., 2012). As a result, the treated fruits showed a long shelf life with reduced decay. Recently, these grapes were treated with a multisystem coating based on polymeric nanocapsules rich in TVEO (Pina-Barrera et al., 2019). This coating-maintained quality characteristics for a long time, reduced fruit metabolism, and controlled the evaporation of volatile compounds from TVEO.

12. Conclusions and perspectives

Here, we reported the antidiabetic effects of Moroccan medicinal plants from their traditional use to the clinical applications of their bioactive compounds. It was noticed that several plants used in

Moroccan traditional medicinal have not been yet tested for their antidiabetic effects in laboratory. Therefore, further investigations are required regarding the *in vitro* and *in vivo* antidiabetic effects of other Moroccan antidiabetic medicinal plants. Toxicological investigations revealed that almost all these species possess good safety profile. However, more in-depth studies are needed to explore more of their toxicological parameters. Phytochemical characterization showed that these medicinal plants contain numerous bioactive compounds belonging to different chemical families. Pharmacological investigations of these remedies and their components showed that they exhibited remarkable antidiabetic effect. Clinical studies of some bioactive molecules showed pharmacokinetic aspects especially their availability. Further clinical investigations should be carried out testing these other bioactive compounds that showed remarkable *in vivo* antidiabetic effects to develop now antidiabetic drugs.

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