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Review

Caralluma europaea (Guss) N.E.Br.: A review on ethnomedicinal uses, phytochemistry, pharmacological activities, and toxicology

Hayat Ouassou [a], Mohamed Bouhrim [a], Loubna Kharchoufa [a], Hamada Imtara [b], Nour elhouda Daoudi [a], Amina Benoutman [c], Noureddine Bencheikh [a], Saber Ouahhoud [d], Amine Elbouzidi [e], Mohamed Bnouham [a,*]

[a] Laboratory of Bioresources, Biotechnology, Ethnopharmacology and Health, Mohammed First University, Faculty of Sciences, Oujda, Morocco
[b] Faculty of Arts and Sciences, Arab American University Palestine, P. O. Box 240, Jenin, Palestine
[c] Laboratory of Biology, Environment, and Sustainable Development, Higher Normal School, Abdelmalek Essaadi University, Tetouan, Morocco
[d] Laboratory of Biochemistry and Biotechnology, Department of Biology, Mohammed First University, Faculty of Sciences, Oujda, Morocco
[e] Faculty of Sciences, Mohamed First University, Boulevard Mohamed VI BP 717, Oujda, 60000, Morocco

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ABSTRACT

Ethnopharmacological relevance: *Caralluma europaea* (Guss) N.E.Br. (Apocynaceae), is a medicinal plant distributed in Morocco, Algeria, Tunisia, Libya, Egypt, Jordan, Spain, and Italy. The different parts of the plant are used traditionally to treat various diseases such as diabetes mellitus, flu, caught, kidney stones, cysts, respiratory infection, cancer, digestives disorders, urogenital infections, metabolic disorders, and cardiovascular problems.
Aim of the review: In this review, previous reports on *C. europaea* concerning its morphological description, geographical distribution, ethnomedicinal uses, phytochemistry, pharmacological properties, and toxicological studies were critically summarized.
Materials and methods: A systematic review of the literature on *C. europaea* was performed by searching the scientific databases Science Direct, PubMed, Scopus, and Google Scholar.
Results: In traditional medicine, *C. europaea* used to treat several illnesses including diabetes, cancer, and kidney stones. Our analysis of the previous reports confirmed the scientific evidence of *C. europaea* ethnomedicinal uses, especially the antidiabetic activity. However, there was no clear correlation between previous pharmacological reports on *C. europaea* and its other ethnomedicinal uses in the treatment of kidney stones, flu, caught, metabolic, digestive, cardiovascular and respiratory disorders. The essential oils and extracts of *C. europaea* exhibited several *in vitro* and *in vivo* pharmacological properties such as antidiabetic, antioxidant, anti-inflammatory, analgesic, anti-proliferative, antibacterial, antimicrobial, toxicological, and immunomodulatory effects. Phytochemical characterization of *C. europaea* revealed the presence of several classes of secondary metabolites such as terpenoids, polyphenols, and flavonoids compounds. Finally, the food preservative ability of the extracts and essential oil obtained from *C. europaea* has been fully discussed.
Conclusion: Ethnomedicinal surveys indicated the use of *C. europaea* for the treatment of numerous diseases. Pharmacological reports showed that *C. europaea* exhibited significant antidiabetic, antioxidant, anti-inflammatory, analgesic, anti-proliferative, antibacterial, antimicrobial, and immunomodulatory effects. Further studies on the phytochemistry of bioactive compounds should be performed by using bioactivity-guided

Abbreviations: CE, *Caralluma europaea*; DPPH, 1,1-diphenyl-2-picrylhydrazyl; FRAP, reducing power assay; BHT, butylated hydroxytoluene; MIC, minimum inhibitory concentration; MBC, minimum Bactericidal Concentration; RRBC, the rat red blood cells; DTH, delayed-type hypersensitivity; CEME, *C. europaea* methanolic extract; LD_{50}, the median lethal dose; AECe, aqueous extract of *C. europaea*; EACe, ethyl acetate fraction of *C. europaea*; NOAEL, no observed adverse effect level; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Eos, essential oils; IC_{50}, 50% inhibitory concentration; MCF-7, human breast cancer cells; MDA-MB-231, human breast cancer cells; 2n, somatic chromosome number; SGLT1, sodium-dependent Glucose Transporter; GLUT2, glucose transporter 2; STZ, Streptozotocin.

* Corresponding author. Laboratory of Bioresources, Biotechnology, Ethnopharmacology and Health, Mohammed First University, Faculty of Sciences, Boulevard Mohammed VI, Oujda, 60000, Morocco.

E-mail addresses: hayatouassou@gmail.com (H. Ouassou), mohamed.bouhrim@gmail.com (M. Bouhrim), Khloubna43@gmail.com (L. Kharchoufa), hamada.tarayrah@gmail.com (H. Imtara), Nourelhoudada95@gmail.com (N. Daoudi), aminabenoutman4@gmail.com (A. Benoutman), nordin0112013@gmail.com (N. Bencheikh), Sabir.ouahhoud@gmail.com (S. Ouahhoud), amine.elbouzidi.pro@gmail.com (A. Elbouzidi), mbnouham@yahoo.fr (M. Bnouham).

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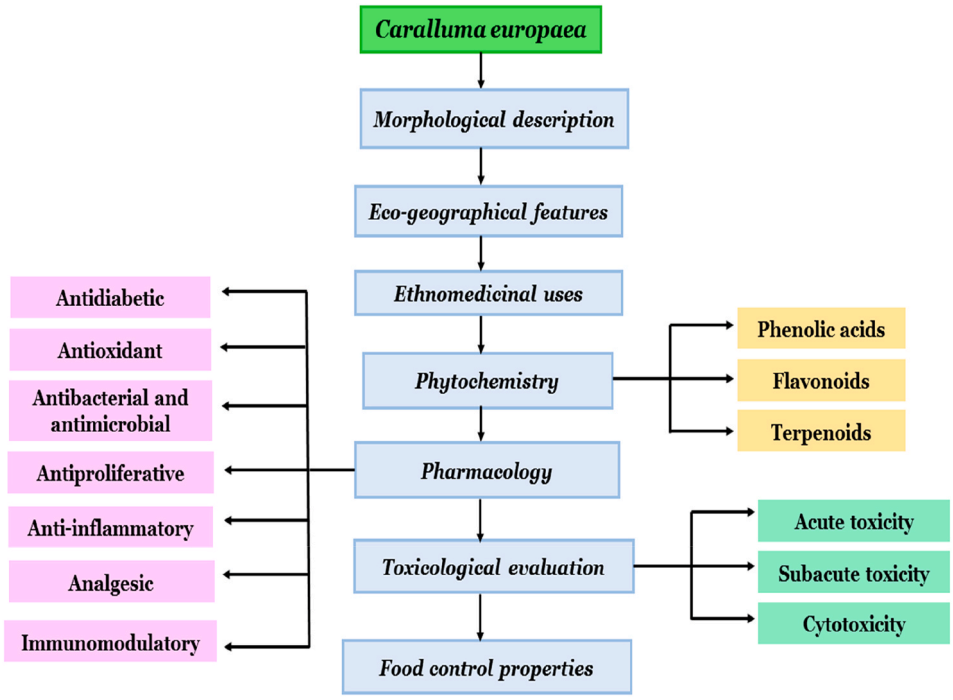
isolation strategy and improve their biological potency as well as scientific exploitation of traditional uses. An in-depth investigation is needed to valid the food preservative properties.



1. Introduction

Since prehistoric times, humans have been using plants in traditional medicine in order to cure and prevent various human disorders (Yuan et al., 2016; Taib et al., 2020). Various parts of plants such as seeds, roots, leaves, fruits, flowers, or even the whole plants have been heavily used for medicinal purposes (Pan et al., 2014). The most common reasons for using medicinal plants are their safety, effectiveness, economic feasibility, and ease of availability (Ekor, 2014; Taib et al., 2020). Also, more than 90% of traditional medicine recipes/remedies contain medicinal plants (Sofowora et al., 2013).

The importance of using medicinal plants gradually increases in pharmaceutical treatments, either directly, or as a raw material to isolate complex chemical structures with specific biological activities (Yuan et al., 2016). Many important medicines are natural products or derived from natural products. In addition, more than 39.1% of all Food and Drug Administration (FDA) approved drugs are of natural origin. Natural products and their derivatives represent an immensely rich source of chemical diversity with various bioactive properties (Boy et al., 2018). This is coupled to an increasing perception that natural products are generally safer in comparison to the synthetic ones (Adebayo et al., 2020). Among a number of medicinal plants, species belonging to the genus Caralluma are widely used in traditional medicine. This genus belongs to the family Apocynaceae (subfamily: Asclepiadoideae). It comprises 120 species. *Caralluma* species have been used in the Arabic and Indian traditional medicine to treat diabetes, cancer, tuberculosis, snake and scorpion bites, skin rashes, scabies, fever, and inflammation (Adnan et al., 2014). In India and Pakistan, *Caralluma* species have been used as emergency food for the last centuries (Sireesha and Sreenivasulu, 2018).

Caralluma europaea (Guss.) N.E.Br is a species of the genus *Caralluma*, family Apocynaceae. It is a low perennial, mat-forming succulent plant (5–25 cm in height) known locally in Morocco as daghmous, Zakkum, and Tikiwt (Bellakhdar et al., 1991; Issiki et al., 2017; Dra et al., 2019a). *C. europaea* is distributed in many countries such as Egypt, Spain, Italy, Libya, Tunisia, and Algeria with little difference in morphology (Adnan et al., 2014; Issiki et al., 2017).

In Morocco, this plant is used in traditional medicine against several diseases especially diabetes (Benkhnigue et al., 2014; Hachi et al., 2015; Barkaoui et al., 2017; Katiri et al., 2017). It is also used to treat other illnesses such as cancer, kidney stones, cysts, cough, asthma, insomnia, respiratory infection, digestives disorders, urogenital infections, and cardiovascular problems (Lahsissene et al., 2009; Chebat et al., 2015; Dallahi et al., 2016; Daoudi et al., 2016; Nassiri et al., 2016; Ennacerie et al., 2017; Khouchlaa et al., 2017; Chaachouay et al., 2020; Mechchate et al., 2020).

In vitro and *in vivo* pharmacological investigations indicated the potential activity of *C. europaea* extracts and essential oils as antidiabetic, antimicrobial, antibacterial, antioxidant, antiproliferative, immunomodulatory, anti-inflammatory, and analgesic agents (Hajji et al., 2016; Issiki et al., 2017; Dra et al., 2018, 2019a, 2019b; Ouassou et al., 2018; Aaziz et al., 2019; Bourhia et al., 2020). The toxicological studies of *C. europaea* were evaluated. Revealing the toxicity of any medicinal plant is essential to promote the therapeutic use of the plant. The phytochemical analysis of the extracts of *C. europaea* revealed the presence of various bioactive compounds belonging to several phytochemical classes such as flavonoids, terpenoids, and phenolic acids (Formisano et al., 2009; Zito et al., 2010; Hajji et al., 2016; Dra et al., 2018, 2019a; Aaziz et al., 2019).

In the current review, we summarized *C. europaea* morphological description, geographical distribution, ethnomedicinal uses, phytochemical components, toxicological, pharmacological properties, and

food preservative properties. We provide our viewpoints on future perspective of *C. europaea*. To the best of our knowledge, there has not been a recent review that covers all aspects of this plant, and we hope this article will be helpful to provide a better understanding of this plant.

2. Methodology

The literature on *C. europaea* botanical description, ethnomedicinal uses, secondary metabolites, biological properties were collected, analyzed and summarized in this review from 2005 to 2020. Online search engines such as Scopus, PubMed, Science-Direct, and Google Scholars were used to explore the published papers on *C. europaea*. We selected about 200 potentially interesting articles and other literature related to the geographical distribution, morphology, ethnobotany, phytochemistry, pharmacology and toxicity of *C. europaea*. We reviewed the reference lists of about 94 of the selected literature having more detailed, comprehensive and accurate information. Several terms were used as keywords such as *Caralluma europaea*, *Caralluma europaea* essential oils, traditional uses of *Caralluma europaea*, antioxidant effects of *Caralluma europaea*, antidiabetic effects of *Caralluma europaea*, antimicrobial effects of *Caralluma europaea*, the chemical composition of *Caralluma europaea*, the toxicity of *Caralluma europaea* and other related words. All published work on *C. europaea* in different languages (French or English) was cited in this review. The first phase of identification and examination was based on titles of the studies. Any title that had the potential to be included was then screened for the abstract; subsequently, the full text was evaluated if the title and abstract of the study were inconclusive of inclusion or exclusion from the current systematic review. Chemical structures were drawn using ADC/ChemSketch. PubChem database was used to check the structures of the secondary metabolites reported from the plant.

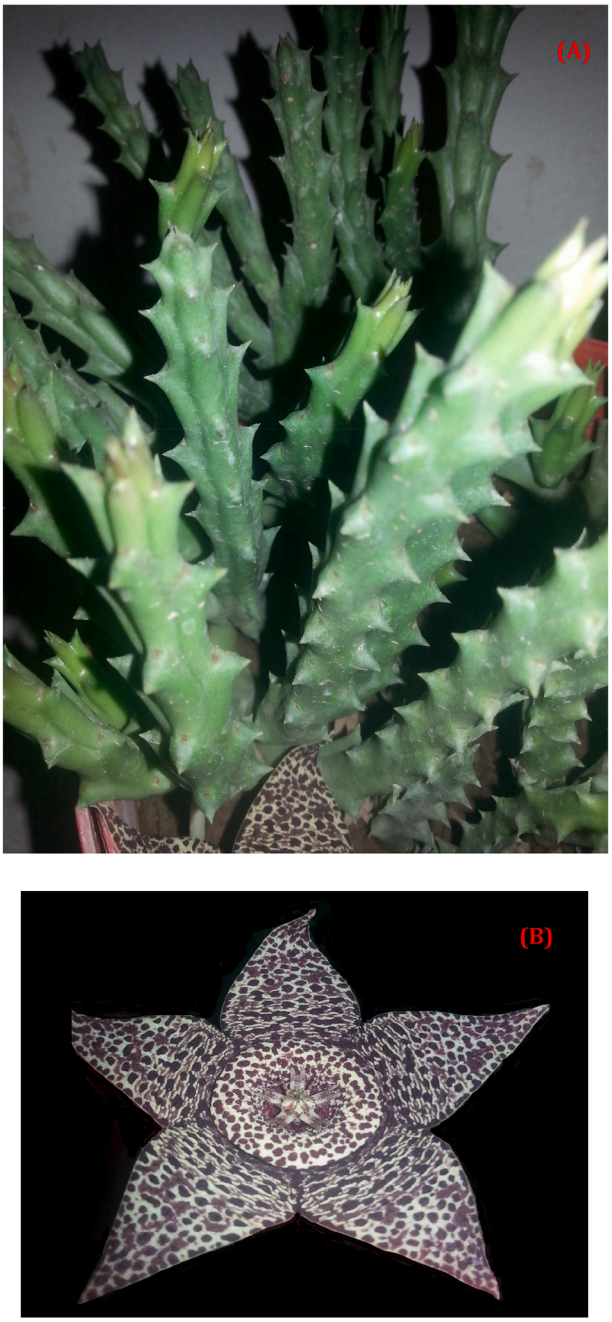


Fig. 1. A) habitus of *Caralluma europaea* (Guss.) N. E. Br; **B)** *C. europaea* flower.

3. Morphological description of *Caralluma europaea*

Caralluma europaea is a low, perennial, mat-forming succulent. The stems are ascending or sprawling up to 5–25 cm in height (Fig. 1), green, four angled (tetragonal), flat to concave. The colour varies from uniform bright green to dark green or dark blue-green. In Europe, the stems are dark green, in west Morocco, they are green or blue-green, and often speckled with dark green or purple. Along the Mediterranean Sea coast up to Egypt only greenish stems are found (Meve and Heneidak, 2005). The leaves are 1.5–2.6 × 2 mm in length, sessile, orbicular, caduceus, shortly acuminate. The flowers are in umbel shape. The diameter of flowers is about 2 cm, yellowish with reddish-brown or purplish bands to entirely purplish (Zito and Sajeva, 2011). The flowering time generally occurred (peak season) at the end of March to late June. The star-shaped fleshy flowers of this plant produce the worst smell of all succulent plants (Adnan et al., 2014). The calyx is 1.5–3 × 1–1.5 mm in length. The corolla is 10–20 mm in diameter, with five petals. Basal coloration of the corolla surface is predominantly white in the west, but cream in the east. Dense brick-red to purple-red transversal stripes or streaks are found in Europe and Africa, whereas in the Sinai and the Orient brownish coloration on a creamy background with rather few and thin brownish stripes and uniformly brownish tips of corolla lobes dominates. In addition, an unusual form exists in the Moroccan Anti-Atlas with coarse brownish bands on greenish background (Jonkers and Walker, 1993; Meve and Heneidak, 2005). Furthermore, the details of corona and their structural coloration are rather similar over the whole area of distribution. The corona generally purplish, however, east of the Suez it is occasionally yellow to yellowish-brownish (Meve and Heneidak, 2005). Interstaminal corona lobes 1–2 × 1–1.2 mm, bifid, tips of the deltoid to subulate segments rounded, often knobby, shiny-yellow. Staminal corona lobes 1.0 × 0.5 mm, linear-ovate to spathulate, rounded, incumbent on the anthers. The male flowers have short stamens, arising from the base of the corolla; anthers are lacking appendages. The fruit is formed of two dehiscent follicles containing small seeds (Nadia et al., 2016). Additionally, seeds are 7–9 × 4.5–6 mm in length, ovoid, winged, with a yellowish tuft of hairs (18–30 mm) (Castroviejo, 1998). *C. europaea* possesses somatic 2n = 22 chromosomes (Castroviejo, 1998). The Karyotype analysis indicated a homogeneous genome of predominantly metacentric to sub-metacentric chromosomes for *C. europaea* (Meve and Heneidak, 2005). According to Meve and Heneidak (2005) the chromosome lengths in Africa and Europe is 1.22 μm (1.07–1.38 μm), while east of the African continent, the average chromosome length is 1.11 μm (1.06–1.19 μm). Many studies have demonstrated the taxonomic value of chromosomal information in the Asclepiadoideae family, where, the basic chromosome number x = 11 is found to be predominant, occurring in 96% of the taxa investigated, and over 90% are euploid diploids (Albers and Meve, 2001; Meve and Heneidak, 2005).

4. Eco-geographical features of *C. europaea*

Caralluma europaea is widely distributed in the Mediterranean basin Egypt, Jordan, Spain, Libya, Tunisia, Algeria, and Morocco (Meve and Heneidak, 2005; Zito et al., 2013). It is the only representative to grow freely on the European continent (Jonkers and Walker, 1993). *C. europaea* was discovered on the island of Lampedusa (Italy) by Gussone in 1832. In Morocco, it can be found in the Anti-Atlas, Middle Atlas, and the Rif (Audissou, 2005). According to Meve and Heneidak (2005), *C. europaea* prefers shaded stands and varies in habit depending on the edaphic conditions. In Lampedusa, *C. europaea* grows along the coast up to 300 m from the sea. it was also reported that this species does not grow very close to the sea but in the more elevated part of the Island (Bruyns, 1987). It is growing in different microhabitats in Lampedusa and shows high variability. In sandy soil, *C. europaea* has a strong tendency to form rhizomes, while, on rocks it usually has erect stems that follow the fissure of the rock (up to 30 mm in diameter). On the granites of the Anti-Atlas in Morocco, *C. europaea* usually has 25 cm tall thick stems (Jonkers and Walker, 1993). In Egypt, the erect stems grow on rocky slopes among rocks or in fissures of smooth rocks. The stems are found measuring just around 20 cm in length (Boulos, 2005; Meve and Heneidak, 2005). *C. europaea* is adapted to sunny conditions and grows in dry regions. Given the variation in topography and climate in Morocco, it is not surprising to find local differences in the habit of this plant.

5. Ethnomedicinal uses

Ethnomedicinal uses of different parts of the genus *Caralluma* have been traditionally used in the treatment of different diseases. The preparation methods, uses and applications of several *Caralluma* species are well-documented in ethnobotanical studies around the world as a traditional remedy for treating some health problems (Mahmood et al., 2010, 2011; Manzoor et al., 2013; Adnan et al., 2014). In Pakistan, *Caralluma* used as a traditional anti-diabetic therapeutic agent equally well in both urban and rural population (Mahmood et al., 2010). The juicy stems of some species of *Caralluma* are consumed as food (Raees, 2018). Also, some species of *Caralluma* have been utilized as antipyretic (Rauf et al., 2013), antirheumatic (Vajha and Chillara, 2014), anti-gastric (Zakaria et al., 2002). The genus *Caralluma* possesses other traditional actions, such as anti-inflammatory, anti-hyperglycemic, antidiabetic, anti-trypanosomal, antiulcer, neuroprotective, anti-obesogenic, anti-atherosclerotic, and antiparasitic therapeutic agent (Zakaria et al., 2001; Adnan et al., 2014). Among the medicinal plants of this genus, *C. europaea* is widely distributed in different countries (Meve and Heneidak, 2005). Several ethnomedicinal surveys reported the importance of *C. europaea* in Moroccan folk medicine (Benkhnigue et al., 2014; Chebat et al., 2015; Hachi et al., 2015; Dallahi et al., 2016; Daoudi et al., 2016; Nassiri et al., 2016; Barkaoui et al., 2017; Ennacerie et al., 2017; Katiri et al., 2017; Khouchlaa et al., 2017; Laadim et al., 2017; Ben Akka et al., 2019; Slighoua et al., 2019; Chaachouay et al., 2020; Mechchate et al., 2020). The applications of *C. europaea* in folk medicine against several diseases are listed in Table 1. The traditional use of *C. europaea* depends on the part used by the plant. The main medicinal uses of this plant in Moroccan traditional medicinal systems include the treatment of diabetes (Benkhnigue et al., 2014; Hachi et al., 2015; Barkaoui et al., 2017; Katiri et al., 2017; Laadim et al., 2017), as well as the treatment of kidney stones (Khouchlaa et al., 2017; Chaachouay et al., 2020). In Morocco, different parts of *C. europaea* are being used to treat many disorders including cancer, digestives disorders, urogenital and respiratory infections (Chebat et al., 2015; Daoudi et al., 2016; Nassiri et al., 2016; Ennacerie et al., 2017). The seeds and leaves of *C. europaea* are utilized to treat cysts, cough, asthma, and insomnia (Dallahi et al., 2016). The aerial parts mixed with water or milk have been reported to treat flu, tiredness, cardiovascular, and menstrual cycle problems (Mechchate et al., 2020). Moreover, Slighoua et al. (2019) reported that the stems are used for the treatment of female infertility. In addition, Ben Akka et al. (2019) reported that the aerial parts of *C. europaea* are used to treat metabolic and genitourinary problems. In Libya, the plant is mainly used to treat diabetes and hair-fall (El-Mokasabi et al., 2018).

5.1. Posology

For diabetes, the stems juice of *C. europaea* are orally taken with water or milk (one glass per day after breakfast). Also, the stems roasted are administered with garlic and tomato once a day as an anti-diabetic salad.

A half teaspoon of powder of *C. europaea* mixed in hot milk is prescribed as an antidiabetic (once a day after breakfast) (Benkhnigue et al., 2014).

6. Phytochemistry of *C. europaea*

The chemical composition of *C. europaea* extracts and essential oils was investigated by several research groups (Meve and Heneidak, 2005; Formisano et al., 2009; Zito et al., 2010; Hajji et al., 2016; Dra et al., 2018, 2019a; Bourhia et al., 2020). The analysis of the chemical

Table 1
Ethnomedicinal use of *C. europaea*.

Plant part	Preparation	Administration	Traditional uses	References
Leaves and roots	Powder	Not defined	Brain cancer	Chebat et al. (2015)
Leaves	Decoction	Not defined	Respiratory infection	Ennacerie et al. (2017)
Leaves	Infusion	Not defined	Kidney stones	Chaachouay et al. (2020)
Leaves	Decoction	Not defined	Digestives disorders, Urogenital infections	(Daoudi et al., 2016; Nassiri et al., 2016)
Aerial parts	Decoction	Oral	Diabetes	Katiri et al. (2017)
Aerial parts	Juice is mixed with water or milk	Not defined	Diabetes, Flu, Tiredness, Cardiovascular problems, Cancer, Regulate menstrual cycle	Mechchate et al. (2020)
Aerial parts	Not defined	Not defined	Genitourinary, Metabolic	Ben Akka et al. (2019)
Stem	Decoction, infusion, and raw	Oral	Diabetes	Barkaoui et al. (2017)
Seeds and leaves	Decoction Powder mixed with honey	Not defined	Cysts, Cough, Asthma, Insomnia	(Lahsissene et al., 2009; Dallahi et al., 2016)
Aerial parts	Juice is mixed with milk	Oral	Kidney stones	Khouchlaa et al. (2017)
stem	Mixed with orange juice	Oral	Female infertility	Slighoua et al. (2019)
Leaves	Not defined	Not defined	Cysts, Diabetes	Hachi et al. (2015)
Not defined	Not defined	Not defined	Diabetes, Hair-fall	El-Mokasabi et al. (2018)
Stem	Juice, powder	Oral	Diabetes	(Benkhnigue et al., 2014; Idm'hand et al., 2020)

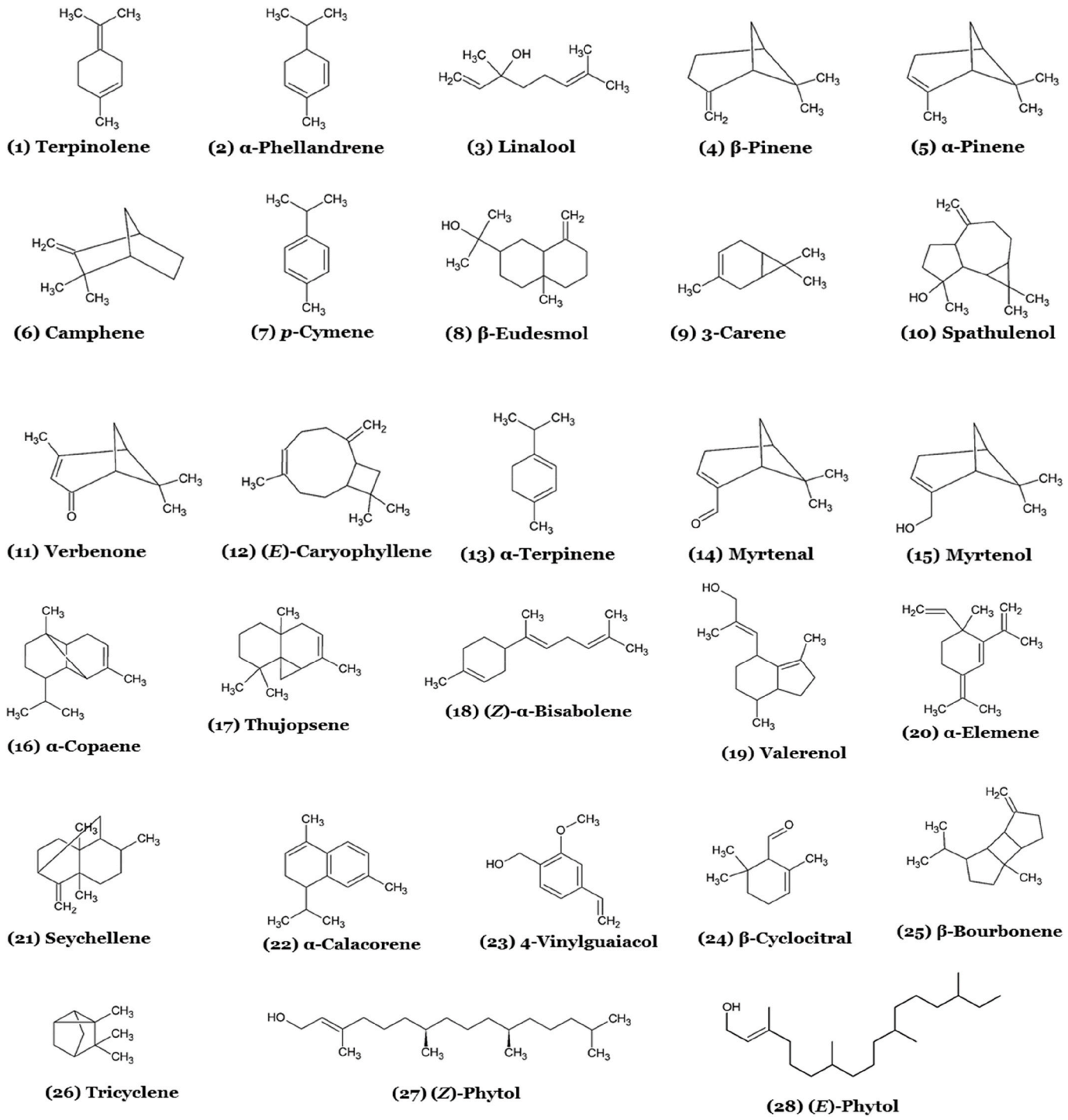


Fig. 2. Structures of some potent compounds identified in *C. europaea* essential oils.

composition of the extracts and essential oils of *C. europaea* from different countries (Morocco and Italy) allowed scientists to identify more than 70 compounds, representing three major classes of secondary metabolites including terpenoids, flavonoids and phenolic compounds (Figs. 2–4; Tables 2 and 3) (Formisano et al., 2009; Zito et al., 2010; Dra et al., 2018; Bourhia et al., 2020). The chemical composition of *C. europaea* essential oils from Morocco and Italy is almost similar. It is mainly composed of terpinolene **(1)**, α-terpinene **(13)**, linalool **(3)**, α-Phellandrene **(2)**, Tricyclene **(26)**, α-Pinene **(5)**, β-Pinene **(4)**, Camphene **(6)**, and Verbenone **(11)** (Formisano et al., 2009; Zito et al., 2010; Dra et al., 2018). *C. europaea* essential oil from Morocco is composed mainly of Tricyclene (1.1%) **(26)**, α-Pinene (1.8%) **(5)**, Camphene (3.3%) **(6)**, β-Pinene (5.1%) **(4)**, α-Phellandrene (3.1%) **(2)**, α-Terpinene (16.2%) **(13)**, Terpinolene (19.5%) **(1)**, Linalool (15.3%) **(3)**, Verbenone (0.8%) **(11)**, Thujopsene (4.1%) **(17)**, (Z)-α-Bisabolene (1.5%) **(18)**, β-Eudesmol (3.7%) **(8)**, Monoterpene hydrocarbons (53.4%), Oxygenated monoterpenes (16.1%), Sesquiterpenes hydrocarbons (5.6%), and Oxygenated sesquiterpenes (3.7%) (Dra et al., 2018). The work of Formisano et al. (2009) showed that *C. europaea* oil from Italy comprises Tricyclene (1.2%) **(26)**, α-Pinene (1.9%) **(4)**, Camphene (2.5%) **(6)**, β-Pinene (3.8%) **(4)**, α-Phellandrene (1.4%) **(2)**, Carene 3 (0.5%) **(9)**, α-Terpinene (19.1%) **(13)**, *p*-Cymene (0.8%) **(7)**,

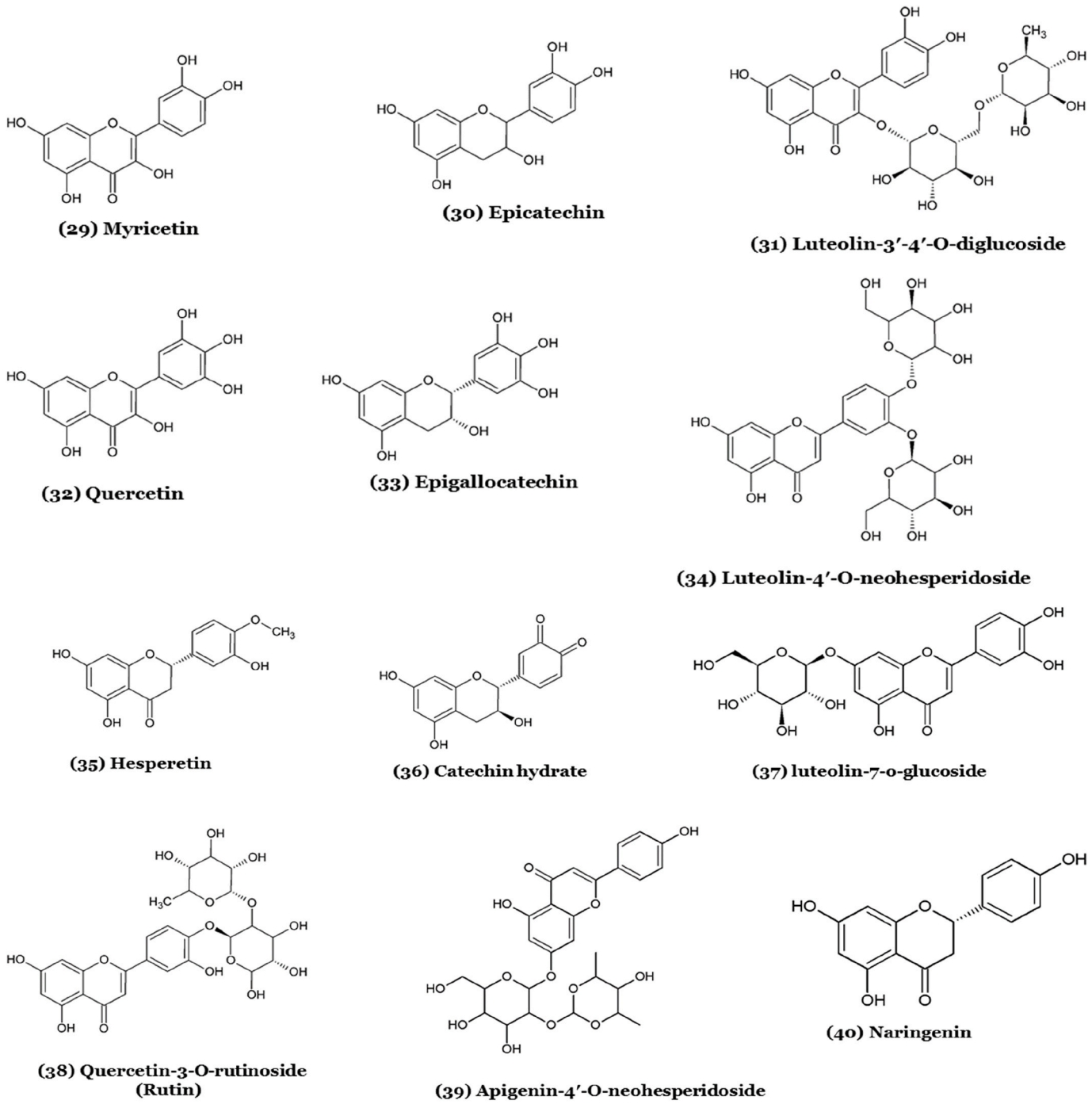


Fig. 3. Chemical structures of flavonoid compounds identified in *C. europaea*.

Terpinolene (23.3%) **(1)**, Linalool (18.4%) **(3)**, Myrtenal (0.6%) **(14)**, Myrtenol (0.6%) **(15)**, Verbenone (0.7%) **(11)**, α-Copaene (0.3%) **(16)**, β-Bourbonene (0.2%) **(25)**, α-Elemene (0.3%) **(20)**, (E)-Caryophyllene (0.6%) **(12)**, Seychellene (0.8%) **(21)**, and α-Calacorene (0.1%) **(22)**. A comparative study of the volatiles contained in the essential oils of the different parts of *C. europaea* from Italy showed different profiles of the essential oils with the presence β-Eudesmol (5.4–1.9%) **(8)**, (*E*)-Phytol (3.9–2.6%) **(28)**, Spathulenol (1.5%) **(10)**, β-Cyclocitral (0.1%) **(24)**, 4-Vinylguaiacol (0.4%) **(23)**, (Z)-α-Bisabolene (1.2%) **(18)**, Valerenol (1.2%) **(19)**, and (*Z*)-Phytol (1.7%) **(27)** (Table 2, Fig. 2) (Zito et al., 2010). The variability of the chemical composition of essential oils of *C. europaea* is perhaps due to different factors such as the origin of collection, the climate conditions, harvest period, and extraction method (Fidan et al., 2019). Chromatographic analysis of the chemical composition of *C. europaea* extracts revealed the presence of phenolic acids and flavonoids. In 2005, Meve and Heneidak (2005) identified some flavonoids in *C. europaea*. The main compounds identified are Luteolin-3′-4′-O-diglucoside **(31)**, Luteolin-4′-O-neohesperidoside **(34)**, Apigenin-4′-O-neohesperidoside **(39)**, and Quercetin-3-O-rutinoside **(38)** (Fig. 3). In addition, the chemical composition of *C. europaea* crude methanol and dichloromethane extracts revealed the presence of phenolic acids: gallic acid **(41)**, caffeic acid **(43)**, ferulic acid **(42)**, salicylic acid **(46)**, coumaric acid **(44)**, and rosmarinic acid **(49)**, and flavonoids compounds such as catechin hydrate **(36)**, epicatechin **(30)**, quercetin **(32)**, rutin **(38)**, and luteolin-7-o-glucoside **(37)**. Other polyphenols were isolated from the methanolic extract of *C. europaea* aerial

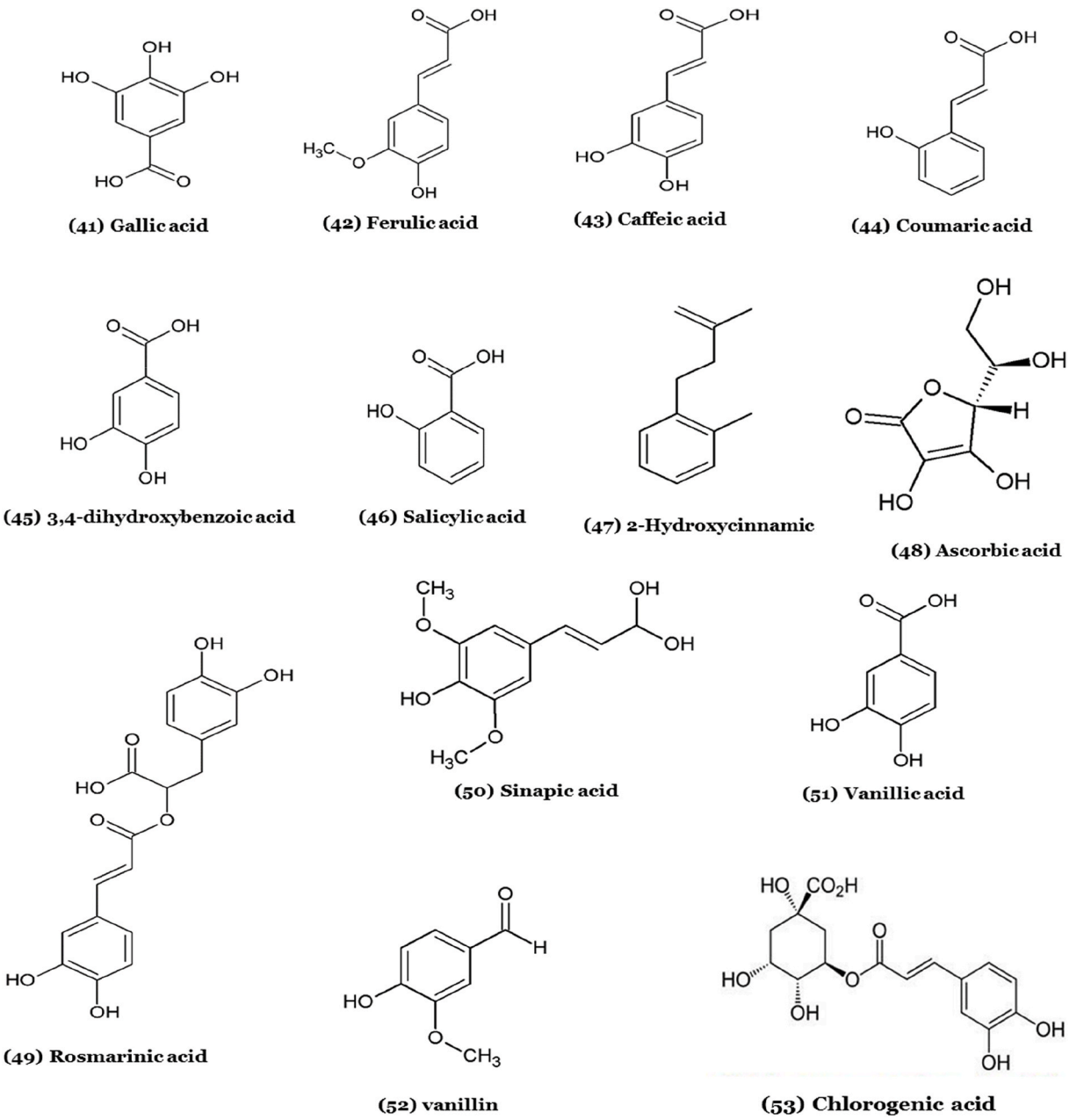


Fig. 4. Chemical structures of phenolic acids identified in *C. europaea*.

parts. The identified polyphenols were chlorogenic acid **(53)**, quercetin **(32)**, rutin **(38)**, ferulic acid **(42)**, epigallocatechin **(33)**, and 3,4 dihydroxybenzoic acid **(45)** (Figs. 3 and 4) (Dra et al., 2019a, 2019b). A study was carried out by Bourhia et al. (2020) indicated that the hydroethanolic extract was rich in polyphenols namely ferulic acid **(42)**, myricetin **(29)**, gallic acid **(41)**, quercetin **(32)**, and Hesperetin **(35)**. The work of Aaziz et al. (2019) showed that the ethyl acetate extract comprises rutin **(38)**, ferulic acid **(42)**, caffeic acid **(43)**, naringenin **(40),** 2- hydroxycinnamic **(47)**, sinapic acid **(50)**, coumaric acid **(44)** and quercetin **(32)**, while the ethanolic extract was rich in ascorbic acid **(48)**, vanillic acid **(51)**, ferulic acid **(42)**, caffeic acid **(43)**, naringenin **(40),** vanillin **(52)**, 2-hydroxycinnamic **(47),** sinapic acid **(50)**, coumaric acid **(44)**, and quercetin **(32)** (Table 3).

7. Pharmacological activities of *C. europaea*

7.1. Antidiabetic activity

Several studies have reported the *in vitro* and *in vivo* antidiabetic effect of *C. europaea*. The antihyperglycemic activity of the stems parts of the aqueous extract of *C. europaea* was evaluated on normal rats. A hypoglycemic effect was observed in normal rats after glucose tolerance test. Using, alloxan induced diabetic mice model, Ouassou et al. (2018) showed that the aqueous extract from *C. europaea* stems (200 mg/kg) reduced significantly blood glucose level in diabetic mice. Using the same experimental model, Dra et al. (2019b) revealed that *C. europaea* stem methanolic extract administrated at 250 mg/kg and 500 mg/kg reduced blood sugar significantly as observed at 6, 8 and 10 hours (from 386 ± 6.35 mg/dL to 157 ± 10.39 mg/dL at 8 h and to 87 ± 0.28 mg/dL at 10 h). Using the intestinal perfusion method (*in situ*), the authors

Table 2
Chemical composition of the essential oil of *Caralluma europaea* aerial part.

Country	Used part	Chemical compounds	References
Morocco	Aerial parts	Hexanol (0.9%), Heptanal (2.1%), Santolinatriene (3.3%), Tricyclene (1.1%), α-Pinene (1.8%), Camphene (3.3%), β-Pinene (5.1%), Hexanoic acid (1.4%), α-Phellandrene (3.1%), α-Terpinene (16.2%), Terpinolene (19.5%), Nonanal (0.7%), Linalool (15.3%), Octanoic acid (3.2%), Verbenone (0.8%), Nonanoic acid (1.2%), Thujopsene (4.1%), (Z)-α-Bisabolene (1.5%), β-Eudesmol (3.7%), Hexahydrofarnesylacetone (2.7%), Hexadecanoic acid (6.8%), Monoterpene hydrocarbons (53.4%), Oxygenated monoterpenes (16.1%), Sesquiterpenes hydrocarbons (5.6%), Oxygenated sesquiterpenes (3.7%), Carboxylic acids (12.6%), Carbonylic compounds (2.7%), Alcohols (0.9%), Aldehydes (2.8%), Other compounds (2.2%).	Dra et al. (2018)
Italy	Flowers	2-Methylbutanal (1.3%), Hexanol (1.1%), Heptanal (2.0%), Santolinatriene (2.2%), Tricyclene (1.2%), α-Pinene (1.9%), Camphene (2.5%), Benzaldehyde (0.4%), β-Pinene (3.8%), Phenol (0.8%), Hexanoic acid (1.7%), Octanal (0.8%), α-Phellandrene (1.4%), Carene 3 (0.5%), α-Terpinene (19.1%), *p*-Cymene (0.8%), Benzyl alcohol (0.5%), Phenylacetaldehyde (0.4%), Octanol (0.8%), Terpinolene (23.3%), Linalool (18.4%), Nonanal (1.0%), *(Z)*-Verbenol (0.4%), Octanoic acid (2.4%), Myrtenal (0.6%), Myrtenol (0.6%), 4-Ethylbenzaldehyde (0.2%), Verbenone (0.7%), 3-Ethyl-4-methyl-1H-pyrrole 2,5-dione (0.5%), Nonanoic acid (1.2%), Indole (0.8%), Decanoic acid (0.8%), α-Copaene (0.3%), β-Bourbonene (0.2%), α-Elemene (0.3%), *(E)*-Caryophyllene (0.6%), Seychellene (0.8%), 2; 6-Di-*tert*-butylbenzoquinone (0.2%), α-Calacorene (0.1%), 1S-cis-Calamenene (<0.1%), Dimethyl sulphide (<0.1%),	Formisano et al. (2009)
Italy	Fruit	Heptanal (<0.05%), α-Pinene (0.4%), Benzaldehyde (0.3%), 1-Octen-3-ol (0.6%), Octanal (0.1%), 2-Pentylfuran (0.1%), Phenylacetaldehyde (0.6%), Methyl benzoate (0.1%), Acetophenone (<0.05%), Nonanal (<0.05%), Safranal (0.2%), Decanal (0.4%), α-Ionene (<0.05%), β-Cyclocitral (0.1%), *(E)*-2-Decenal (0.3%), Undecanal (0.1%), 4-Vinylguaiacol (0.4%), 1,2-Dihydro-1,1,6-trimethylnaphthalene (0.5%), Dehydro-ar-ionene (0.2%), *(E)*- β-Damascenone (0.3%), β-Cubebene (<0.05%), 2-Ethyl-1,4-dimethylbenzene (0.2%), Dodecanal (0.7%), 2,5-Cyclohexadiene-1,4-dione, 2,6-bis(1,1-dimethylethyl) (0.3%), Spathulenol (1.5%), β-Eudesmol (5.4%), Pentadecanol (0.3%), Hexadecanal (0.7%), Hexahydrofarnesylacetone (2.8%), Hexadecanoic acid ethyl ester (0,7%), Hexadecanoic acid (9.6%), Octadecanol (0.2%), Heneicosane (3.2%), *(Z,Z)*-9,12-Octadecadienoic acid (2.4%), *(E)*-Phytol (3.9%), Docosane (1.4%), Tricosane (7.3%), Tetracosane (1.9%), Pentacosane (6.5%), 1-Hexacosene (2.1%), Hexacosane (2.9%), Tetracosanal (0.9%), 1-Tetracosanol (0.4%), Heptacosane (9.9%), Hexacosanal (1.9%), 1-Octacosene (1.8%), Octacosane (0.8%), Squalene (1.2%), Nonacosane (6.5%), Hentriacontane (7.7%), Dotriacontane (0.3%), Tritriacontane (1.4%).	Zito et al. (2010)
	Stems	Octane (0.3%), Naphtalene (<0.05%), α-Ionene (0.7%), Indole (0.6%), Methyl indole (<0.05%), Widdrene (4.9%), *(Z)*-α-Bisabolene (1.2%), β-Eudesmol (1.9%), Valerenol (1.2%), Tetradecanol (0.4%), Tetradecanoic acid (5.6%), 1-Octadecene (0.6%), Hexahydrofarnesylacetone (3.8%), 1-Nonadecene (0.4%), Nonadecane (0.8%), *(Z)*-Phytol (1.7%), Hexadecanoic acid (7.8%), 1-Eicosene (0.6%), Eicosane (0.9%), Octadecanal (1.1%), Heneicosane (2.5%), 2-Nonadecanone (0.4%), *(Z,Z)*-9,12-Octadecadienoic acid (5.2%), *(E)*-Phytol (2.6%), 1-Docosene (0.2%), Docosane (0.4%), Tricosane (4.4%), Tetracosane (1.7%), Docosanol (0.4%), 1-Pentacosene (2.1%), Pentacosane (5.4%), Heptacosane (6.1%), Octacosane (2.4%), Squalene (1.2%), Nonacosane (8.3%), Hentriacontane (9.5%), Dotriacontane (0.9%), Tritriacontane (1.4%).	

showed that the aqueous extract from *C. europaea* decreased significantly the percent of glucose absorbed across the intestine during the whole period of perfusion with glucose solution. As a result, this reduction can be explained by the inhibition of SGLT1 and or/GLUT2 transporters (Ouassou et al., 2018). Besides, the ethyl acetate extract was tested against α-glucosidase in an *in vitro* study (Ouassou et al., 2018). The results revealed that the ethyl acetate extract at 165 μg/mL and 328 μg/mL exhibit the potent inhibitory effect on α-glucosidase with the correspondent percentage of inhibition 40.78% and 66%. *Lineweaver-Burk* plot showed that the ethyl acetate extract of *C. europaea* inhibit competitively the enzyme. The *in vivo* α-glucosidase activity, showed that the ethyl acetate extract at 50 mg/kg possessed an inhibitory activity against rat's intestinal α-glucosidase in normal and STZ-diabetic rats after sucrose loading (2 mg/kg), especially at 30, 60, and 120 minutes (Ouassou et al., 2018).

In 2019, Loubna Dra et al. (2019a) tested the effect of the crude methanol extract (1, 5, and 10 mg/mL) from the aerial part of the plant against baker's yeast α glucosidase. As result, the crude methanol extract expressed an inhibitory effect against baker's yeast α-glucosidase with a percent inhibition of 43.5%, 53.5%, and 53.5%, respectively. Also, the dichloromethane crude extract exhibited moderate inhibitory activity by 70.3% at 5 mg/mL. Furthermore, the dichloromethane crude extract showed remarkable α-glucosidase inhibition on the rat's intestinal α-glucosidase with a percent inhibition values ranging from 54.6% and 97.9%, at 10 mg/mL. The α-amylase inhibition test showed that the methanol and dichloromethane crude extracts showed a significant capacity to inhibit this enzyme by a percentage of 52.1% and 53.2% of inhibition at 10 mg/mL (Dra et al., 2019a). The improvement in blood sugar observed by *C. europaea* in this work on various animal models could be largely attributed to the presence of phenolic acid and flavonoid compounds. Amongst the therapeutic targets referred by flavonoids to control diabetes mellitus, the restriction of the absorption of glucose through the inhibition of the digestive enzymes like α-glucosidase and α-amylase, (Tadera et al., 2006). Besides, the blockade of glucose cotransporters (Hajiaghaalipour et al., 2015), are considered as the most relevant mechanisms. Quercetin is known as inhibitors of the intestinal sodium-dependent glucose transporter 1 (SGLT1) and the glucose transporter 4 (GLUT4) (Strobel et al., 2005). In this respect, a positive correlation can be elaborated, between the antidiabetic potency of extracts of *C. europaea* and their content in phenolic compounds such as ferulic acid, quercetin, 3,4 dihydroxybenzoic acid, rutin, epigallocatechin, and catechin (Dra et al., 2019b).

7.2. Antioxidant activity

The *in vitro* antioxidant activity of *C. europaea* extracts was reported by many researchers (Dra et al., 2018, 2019a, 2019b; Aaziz et al., 2019; Bourhia et al., 2020). The studies found that the antioxidant effect of ethanolic extract of stems possesses an IC_{50} equivalent to 34.60 ± 0.30 μg/mL (Aaziz et al., 2019), while the hydroethanolic extract expressed an antioxidant activity, corresponding to the IC_{50} 1.628 mg/mL (Bourhia et al., 2020). However, the IC_{50} of the ethyl acetate fraction was 20.60 ± 0.120 μg/mL, if compared to that of ascorbic acid and BHT, which expressed the respective values 1.81 μg/mL and 2.39 μg/mL (Aaziz et al., 2019). Another report found that the methanolic extract from the aerial part of *C. europaea* expressed an antioxidant activity, corresponding to the IC_{50} 300 ± 0.005 μg/mL, this radical scavenging activity is lesser than the standards BHT and quercetin (IC_{50} values from 0.84 ± 0.04 μg/mL to 2.59 ± 0.07 μg/mL and from 0.95 ± 0.02 μg/mL to 2.62 ± 0.02 μg/mL, respectively) (Dra et al., 2019b). The crude methanol extract showed an important scavenging activity against DPPH radical at dose of 10 mg/mL with an inhibitory percentage of 83.5% (Dra et al., 2019a). In regard to the essential oil of stems, the IC_{50} was estimated by an $IC_{50} = 1.45 \pm 0.019$ mg/mL (Dra et al., 2018). In an *in vitro* studies (Aaziz et al., 2019; Dra et al., 2019b; Bourhia et al., 2020) tested the

Table 3
Chemical composition of *Caralluma europaea* extracts.

Country	Part	Extracts	Compounds groups	Compounds	References
Morocco	Aerial parts	Ethyl acetate extract, methanol extract, and aqueous extract	Phenolic compounds Flavonoids Alkaloids Tannins	–	Hajji et al. (2016)
		Methanol extract and fractions	Phenolic acids Flavonoids	4-Hydroxybenzaldehyde, Chlorogenic acid, 4-o-Caffeoylquinic acid, Caffeic acid, Syringic acid, Epicatechin, Coumaric acid, Ferulic acid, Salicylic acid, Naringenin-7-glucoside, Luteolin-7-o-glucoside, Rutin, Rosmarinic acid, ellagic acid, Quercetin.	
Morocco	Aerial organs	Dichloromethane extracts and fractions		Catechin hydrate, 4-Hydroxybenzaldehyde, Chlorogenic acid, 4-o-Caffeoylquinic acid, Caffeic acid, Epigallocatechin gallate, Syringic acid, Epicatechin, Coumaric acid, Ferulic acid, Salicylic acid, Naringenin-7-glucoside, Luteolin-7-o-glucoside, Rutin, Rosmarinic acid, Ellagic acid	Dra et al. (2019a)
Morocco	Aerial parts	Hydroethanolic extract	phenolic acids Flavonoids	Ferulic acid (2.772 μg/mL), Quercetin (0.77 μg/mL), Myricetin (0.350 μg/mL), Gallic acid (0.135 μg/mL), Hesperetin (0.034 μg/mL)	Bourhia et al. (2020)
Morocco	Aerial parts	Ethyl acetate extract	phenolic acids Flavonoids	Rutin (12,970 mg/100 g), Ferulic acid (13,908 mg/100 g), Caffeic acid (15,544 mg/100 g), Naringenin (12,926 mg/100 g), 2-Hydroxycinnamic (25,174 mg/100 g), Sinapic acid (18,296 mg/100 g), Coumaric acid (30,671 mg/100 g), Quercetin (36,186 mg/100 g).	Aaziz et al. (2019)
		Ethanolic extract		Ascorbic acid (12,488 mg/100 g), Catechic acid (13,109 mg/100 g), Vanillic acid (12,657 mg/100 g), Ferulic acid (12,698 mg/100 g), Caffeic acid (13,053 mg/100 g), Naringenin (12,743 mg/100 g), Vanillin (12,387 mg/100 g), 2-hydroxycinnamic (15,305 mg/100 g), Sinapic acid (14,489 mg/100 g), Catechin (24,797 mg/100 g), Coumaric acid (16,477 mg/100 g), Quercetin (18,719 mg/100 g).	
Morocco	Aerial parts	Methanolic extract	Phenolic compounds	Ferulic acid (52.08 mg/100 g), Quercetin (36.96 mg/100 g), 3,4-dihydroxybenzoic acid (12.18 mg/100 g), Rutin (10.08 mg/g), Epigallocatechin (4.746 mg/g), Catechin (1.344 mg/g).	Dra et al. (2019b)

antioxidant effect of the ethanolic extract, ethyl acetate, hydroethanolic, and methanolic extracts of *C. europaea* using FRAP assay. The extracts from *C. europaea* showed interesting antioxidant effect ($IC_{50} = 79.15 \pm 2.110$ μg/mL, 54.95 ± 1.040 μg/mL, 5.196 mg/mL, and 376 ± 0.003 μg/mL, respectively). Also, the essential oil obtained from the aerial part of *C. europaea* exhibited an antioxidant activity estimated by an $IC_{50} = 0.32 \pm 0.03$ mg/mL; yet, this effect is lower by comparison to the standards BHT and quercetin (Dra et al., 2018). Otherwise, the methanolic extract and the essential oil have been tested for their capacity for preventing the lipid peroxidation by inhibition of β-carotene bleaching. Consequently, methanolic extract and the essential oil showed an antioxidant activity on the β-carotene/linoleic acid system with IC_{50} values 48.61 ± 0.17 μg/mL and 1.17 ± 0.019 mg/mL, respectively (Dra et al., 2018, 2019b). Consequently, the antioxidant effect might be due to the antioxidant phytochemicals of the extracts. Phenolic compounds such as flavonoids and phenolic acids, are usually considered to be major contributors of antioxidant capacities of plants (Li et al., 2008; Zhang et al., 2015b). The chemical functional group and structure is OH for antioxidant capacity of phenolic compounds. Taking as an example the two flavonoids: quercetin and myricetin, the presence of the hydroxyl (OH) group at C-3 and the *ortho*-dihydroxyl at positions C-3′ and C-4′ of B ring are responsible for the better antioxidant activity to scavenge free radicals induced by quercetin, while the enhanced antioxidant effect of myricetin was justified by the extra hydroxyl at C-5′, and thereafter the three hydroxyl groups located at C-3′, C-4′, and C-5’ (Chen et al., 1996; Rice-Evans et al., 1996; Burda and Oleszek, 2001). However, the phenolic compounds without an ortho-dihydroxyl group exerted the lowest anti-radical effects (Zheng et al., 2010). In addition, the *ortho*-dihydroxyl systems of some tested flavonoids showed their ability to reduce the iron ion Fe^{3+} to Fe^{2+} (Sordon et al., 2019). Besides, the phenolic acids with more methoxylation, in conjugation with the catechol structure present an important antioxidant activity capacity, which enhances the ability to stabilize free radicals (Natella et al., 1999; Gulcin, 2020). In this context, a positive correlation could be elaborate, between the antioxidant capacity of extracts of *C. europaea* and their content in flavonoids and phenolic acids.

7.3. Anti-proliferative activity

The antiproliferative potential of natural compounds from the aerial parts of *C. europaea* has been assessed on two human breast cancer cell lines, MDA-MB-231 and MCF-7, using WST-1 assay. An important dose–response cytotoxic effect has been detected with the doses ranging from 15.6 to 500 μg/mL of the flavonoids fraction on MDA-MB-231, with an IC_{50} value of 43.62 ± 0.06 μg/mL, followed by the saponins fraction with IC_{50} value of 15.62 μg/mL. However, it was found that hydroethanolic extract and mucilage fraction were ineffective against MDA-MB-231 cell lines. Another study has showed that the concentration range from 1.562 to 50 μg/mL of *C. europaea* saponins fraction exhibited a significant antiproliferative activity on MCF7 cancerous cell with IC_{50} value of 5.097 μg/mL (Bourhia et al., 2020).

7.4. Antimicrobial and antibacterial activity

Several works have been carried out with the aim of highlighting the capacity of the essential oils and extracts of *C. europaea* to prevent the growth of microorganisms. The essential oil exhibited a remarkable antimicrobial effect on many bacterial and yeasts strains (*Staphylococcus aureus*, *Micrococcus luteus*, *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Candida albicans*, *Candida glabrata*, *Candida Krusei*, and *Candida Parapsilosis*) and with various zone of inhibition (Table 4). However, it showed no significant inhibition against *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The MIC and MMC values of *C. europaea* on bacterial strains are shown in Table 4. Based on these results, the essential oil inhibited Gram-positive bacteria at concentrations ranging from 3.75 to 7.5 mg/mL, in contrast Gram negative bacteria were inhibited with highest MIC values (30 mg/mL), indicating that essential oil has low activity against Gram-negative bacteria. Meanwhile, the essential oil has showed the marked anticandidal activity against Candida strains with inhibition zone diameters and MIC values varying

Table 4
Diameter of inhibition zone (mm), Minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) values (mg/ml) of *C. europaea*.

Country	Part	Methods	Results	Responsible compounds	Possible mechanisms	Ref
Morocco	aerial part (essential oil)	Diameter of inhibition zone (mm)	*Staphylococcus aureus* (18), *Micrococcus luteus* (15.50), *Bacillus cereus* (15.50), *Bacillus subtilis* (14.50), *Escherichia coli* (10), *Pseudomonas aeruginosa* (NA), *Klebsiella pneumonia* (NA), *Candida albicans* (14.50), *Candida kreusei* (14.50), *Candida glabrata* (16) *and Candida parapsilosis* (20).	monoterpene hydrocarbons (α-terpinene, α-pinene, β-pinene), oxygenated monoterpenes, carboxylic acids	Inhibition of respiration and alteration in permeability which leads to eventual death of the bacteria cells	Dra et al. (2018)
		Minimal inhibitory concentration (MIC= mg/mL)	*Staphylococcus aureus* (7.5), *Micrococcus luteus* (7.5), *Bacillus cereus* (3.75), *Bacillus subtilis* (3.75), *Escherichia coli* (30), *Pseudomonas aeruginosa* (30), *Klebsiella pneumonia* (30), *Candida albicans* (3.75), *Candida kreusei* (7.5), *Candida glabrata* (7.5) *and Candida parapsilosis* (1.88).			
		Minimal microbiocidal concentrations (MMC)	*Staphylococcus aureus* (15), *Micrococcus luteus* (15), *Bacillus cereus* (3.75), *Bacillus subtilis* (3.75), *Escherichia coli* (30), *Pseudomonas aeruginosa* (30), *Klebsiella pneumonia (30), Candida albicans (7.5), Candida kreusei (7.5), Candida glabrata* (15) *and Candida parapsilosis* (3.75).			
Morocco	aerial part (Ethyl acetate extract)	Diameter of inhibition zone (mm))	*Rhodococcus equi* (20)	–	cause damage to the bacterium's wall	Hajji et al. (2016)

from 12.50 to 17.50 mm and from 1.88 to 3.75 mg/mL, respectively (Dra et al., 2018). The presence of monoterpene hydrocarbons (α-terpinene, α-pinene, β-pinene), oxygenated monoterpenes and carboxylic acids in the essential oil of *C. europaea* are responsible for this activities against the types of strains studied. Moreover, several studies have shown that the antibacterial activity of essential oil is not directly related to a particular compound, but can be attributed to the additive or synergistic effects of the chemicals component with each other and minor constituents. These compounds give the essential oil the hydrophobic property that allows it to penetrate lipid components of bacterial cell membrane and mitochondria easily, to disrupt the cell structure and to render them more permeable to critical molecules, which leads to eventual death of the bacteria cells. In the context of increasing the activity of antibiotics against the continuous resistance caused by bacteria to these antibiotics, the same author studied the synergistic activity of *C. europaea* with many antibiotics (cefexime, ciprofloxacin, gentamycin and fluconazol). The result of the combined effect between essential oil of *C. europaea* and these antibiotics revealed that from 25 studied combinations, 16 (64%) showed total synergism, 5 (20%) had a partial synergism, and 4 (16%) had no effect. This synergistic effects appeared to be the result of various mechanisms, including the inhibition of protective enzymes produced by the bacteria, as well as the serial inhibition of common biochemical pathways (Imtara et al., 2018). Another study reported that the ethyl acetate extract of stems of *C. europaea* exhibited promising inhibitory effect against *Rhodococcus equi* with an inhibition zone of 20 mm compared to the effect of certain antibiotics such as Chloramphenicol (28,33 mm), Amoxicillin (10,33 mm), Cephalothin (9,66 mm) and Ampicillin (8,33 mm) (Hajji et al., 2016), while aqueous and methanolic extracts had no effect against *Rhodococcus equi.* This activity can be attributed to damage caused in the bacterium's wall by the ethyl acetate extract.

7.5. Anti-inflammatory activity

The pre-treatment with the ethanol and ethyl acetate extracts of stems of *C. europaea* at 100 and 200 mg/kg, expressed an important anti-inflammatory effect on xylene-induced mice ear edema test compared to the standard Diclofenac. The administration of the ethyl acetate extract of *C. europaea* (at 100 and 200 mg/kg) to the mice reduced the inflammatory effect in a dose-response manner after the xylene-induced edema. Moreover, the histological assessment of the ear tissues has been considered as direct evidence that the ethanol and ethyl acetate extracts expressed the strongest anti-inflammatory activity on the reduction of the acute inflammatory response (reduced in epidermis thickness, edema and infiltration of Polymorphonuclear (PMN) leukocytes), comparable to those of Diclofenac. The anti-inflammatory activity could be attributed to presence of *C. europaea*-derived compounds, such as phenolic compounds and flavonoids, which are known for their anti-inflammatory activity as NSAIDs by inhibiting the activity of cyclooxygenase. (Aaziz et al., 2019).

7.6. Immunomodulatory activity

Issiki et al. (2017) investigated the immunomodulatory reaction of the aqueous extract of *C. europaea* in mice. This study focused on the evaluation of hemagglutination antibody titer and delayed-type hypersensitivity response. The pre- and post-plant treatment (1 g/kg body weight) for 7 days showed a significant enhancement of antibody responsiveness to the rat red blood cells (RRBCs) in mice as compared to control, which indicates the enhanced responsiveness of B-lymphocytes involved in antibody synthesis. Furthermore, the aqueous extract (1 g/kg) expressed a significant increase in the delayed-type hypersensitivity (DTH) response (46%) in comparison to control group (21%). The mechanism behind this elevated DTH response indicates a stimulatory effect of the plant extract, which has occurred on the lymphocytes and accessory cell types required for the expression of this reaction. Hence, the increase in both, antibodies titer, and DTH response indicated that *C. europaea* extract has a significant immunostimulating effect on both humoral and cellular immune response. This plant is a rich source of terpenoids and flavonoids that can be responsible of this effect.

7.7. Analgesic effect

Analgesic effect of ethanolic and ethyl acetate fractions of *C. europaea* was assessed by using three methods: acetic acid-induced writhing in Swiss mice model, formalin-induced paw licking test, and Hot-Plate Test. In each test, two doses of each fraction were used: 100 and 200 mg/kg. Result studies have shown that both extracts induced a significant dose-dependent analgesic effect after the abdominal pain caused by the injection of acetic acid to the mice. This antinociceptive

effect can occur because of blocking of prostaglandin pathways or inhibition of endogenous mediators. The administration of the ethanol and ethyl acetate extracts at 100 and 200 mg/kg to the mice that underwent an inflammatory process provoked by the injection of formalin, revealed an antinociceptive and analgesic effects, with the reduction of both early and late nociceptive responses. The ethyl acetate extract was highly efficient at 200 mg/kg than that of the ethanol extract. Although, regarding the time latency in the hot-plate, only ethyl acetate extract has shown an important effect. The analgesic effect of the ethyl acetate extract (200 mg/kg) was much greater than that of the morphine. The mechanism was proposed to be related to its antioxidant activity (Aaziz et al., 2019).

8. Toxicology

The concern about the safety of medicinal plants has become a global approach pertained to the notable increased consumption of medicinal plants (Zhang et al., 2015a). Studies on system toxicity and safety evaluation of *C. europaea* and its extracts in the daily diet are still insufficient. There are a few studies investigated its toxicity (Table 5).

8.1. Acute toxicity

The acute toxicity test of *C. europaea* methanolic extract (CEME) of aerial parts, collected in Morocco have been evaluated on mice. The oral administration of a single dose (200, 500, 1000, 2000 mg/kg body weight) of CEME to mice did not cause death within the seven days of the study. No mortality, abnormal clinical signs, and significant body weight changes were observed after treatment with CEME in either sex. Thus, the oral lethal dose value (LD_{50}) of the CEME is greater than 2000 mg/kg body weight in mice (Dra et al., 2019b). Another study performed in albino mice evaluated the acute toxicity of the aqueous extract (AECe) and ethyl acetate fraction (EACe) of *C. europaea* stems (Ouassou et al., 2018). The aqueous extract (AECe) was administered orally, at single doses of 1000, 2000, 3000, 4000, 6000, and 8000 mg/kg body weight, respectively, while the control group received 10 mL/kg of distilled water. The ethyl acetate fraction (EACe) of *C. europaea* was administered orally, at single doses of 100, 300, 500, and 700 mg/kg of body weight. Indeed, no mortalities or signs of morbidity were recorded for *C. europaea* aqueous extract and ethyl acetate fraction in mice following oral administration during daily monitoring up to 14 days after the administration of the two extracts. Also, no significant changes were observed in daily food intake in the treated mice as compared to the controls. In 2019, Aaziz et al. (2019) studied the acute toxicity of the ethanolic and ethyl acetate crude extracts of *C. europaea* in mice by administering the doses orally (0.5, 1, 2.5 and 5 g/kg body weight) for 14 days. They found that the treatment by gavage did not cause any deaths or side effects. Hence, the median lethal dose (LD_{50}) was found to be higher or greater than 5 g/kg body weight in mice. On the other hand, the assessment of the acute toxicity study of aqueous extract from the aerial part of *C. europaea* in a single oral dose at 5 g/kg body weight was investigated by Issiki et al. (2017). Asthenia, hypoactivity, and urination were noticed immediately after gavages (15 min) and were more pronounced and persisted until the end of experimentation. The main behavioral signs of toxicity observed from the 3rd day of daily oral administration of aqueous extract of *C. europaea* at 5 g/kg were atypical locomotion, anorexia, asthenia, ataxia, diarrhea, and urination. No mortality was observed after 14 days of treatment (Issiki et al., 2017).

8.2. Subacute toxicity

Subacute toxicity of aqueous extract of *C. europaea* at 1 g/kg, 2.5 g/kg, and 5 g/kg of body weight have induced hyperactivity during the 1st week of the experimentation. At the end of the 2nd week, asthenia, hypoactivity, and urination with the loss of hair and weight (20%) were observed with doses of 2.5 and 5 g/kg. For the dose of 1 g/kg, no visible toxic effects were observed. No death was observed for all doses and the NOAEL was considered to be 1 g/kg/day. After 30 days of treatment

Table 5
Summary of toxicology screening for *Caralluma europaea*.

Model used	Part used	Extract type	Route	LD_{50}/dose range	Control	Results	Reference
Swiss albino mice	Aerial parts	Methanolic extract (CEME)	Oral	$LD_{50} > 2000$ mg/kg	10 mL/kg of distilled water	No mortality, no signs of toxicity and no significant body weight change	Dra et al. (2019b)
Swiss albino mice Swiss albino mice	Stem Aerial parts	Aqueous extract (AECe)	Oral Oral	1000 mg/kg-8000 mg/kg	10 mL/kg of distilled water.	No signs of toxicity and no changes in general behavior or other physiological activities of mice. No significant changes in daily food intake in the treated mice as compared to the controls. no mortality or signs of toxicity and no change body weight wasn't observed	Ouassou et al. (2018) (Aaziz et al., 2019)
		Ethyl acetate fraction (EACe) Ethanolic crude extract Ethyl acetate crude extract		100 mg/kg −700 mg/kg 0.5, 1, 2.5 and 5 g/kg $LD_{50} > 5$ g/kg	Distilled water 10 mL/kg of distilled water		
Male mice Swiss	Aerial parts	Aqueous extract	Oral	5 g/kg 1, 2.5, or 5 g/kg	Distilled water	Asthenia, hypoactivity, and urination were noticed immediately after gavages (15 min) Atypical locomotion, anorexia, asthenia, ataxia, diarrhea, and urination (from 3rd day of daily oral administration). No mortality was observed after 14 days of treatment Hyperactivity during the 1st week of the experimentation (1 g/kg, 2.5 g/kg, and 5 g/kg). At the end of the 2nd week, asthenia, hypoactivity, and urination with the loss of hair and weight (20%) were observed with doses of 2.5 and 5 g/kg. CE induced serious kidney and liver injury for the higher doses of 2.5 and 5 g/kg	Issiki et al. (2017)
Spleen cells from mice	Aerial parts	Aqueous extract		0.5 and 2 g/mL		The mortality rate of 80% and 90% of cells after 24 h of incubation, respectively, for 0.5 and 2 g/mL doses compared at 60% for the control. The mortality rate was dose and time-dependent. This confirms the toxicity effect *in vivo*	Issiki et al. (2017)

with the aqueous extract of the plant at the doses of 2.5 g/kg, and 5 g/kg showed significant increases in ALT, AST, creatinine, and urea. Therefore, *C. europaea* induced serious kidney and liver injuries for the higher doses of 2.5 and 5 g/kg. However, no change in blood parameters was recorded after the oral administration of the dose 1 g/kg. The histopathological analysis of the spleen, kidneys, and liver at the end of the study showed that for all the doses used, there were histopathological changes (Issiki et al., 2017).

8.3. Cytotoxicity

The cytotoxicity activity of the aqueous extract of *C. europaea in vitro* was tested on spleen cell suspension for 24 h with two doses: 0.5 and 2 g/mL and cell viability determined by the Trypan blue exclusion test (Issiki et al., 2017). The results have shown a mortality rate of 80% and 90% of cells after 24 h of incubation, respectively, for 0.5 and 2 g/mL doses compared at 60% for the control. The mortality rate was dose and time-dependent. This confirms the toxicity effect *in vivo*.

9. Food control properties

Medicinal aromatic plants (MAPs) and their extracts have been examined for their effectiveness for the quality and the safety of foodstuff (Fisher and Phillips, 2008; Gyawali and Ibrahim, 2014). Therefore, the majority of laboratories across the globe are involved in systematic screening of plant species for detecting and revealing new bioactive compounds. However, there is a need for scientific affirmation of bioactive compounds (Gokoglu, 2019). The antimicrobial and antioxidant properties of plant extracts can be beneficial for inhibition of both microbial and oxidation-induced food spoilage. Most of their properties are due to their essential oils (EOs) and other secondary plant metabolite components such as terpenoids, flavonoids, and polyphenols (Brenes and Roura, 2010; Hintz et al., 2015). Essential oils (EOs) can be identified from various components of the plant's leaves, barks, stems, roots, flowers, and fruit (Erasto et al., 2004). Typically, essential oils (EOs) constitute good effectiveness for food safety and preservation applications, by extending the storage life and preventing the spoilage of many products, by exerting an antimicrobial action against a large number of Gram-negative and Gram-positive bacteria (Hong et al., 2004; Rota et al., 2004). The main mode of action of essential oils is mediated via the interference of their phenolic compounds with the bacterial membrane, which promotes their ability to disrupt cell wall and cytoplasmic membrane, leading to lysis and leakage of intracellular compounds (Burt, 2004; Calo et al., 2015). Thereby, essential oils rich in linalool, α-Pinene, β-Pinene, α-terpinene, and Carboxylic acids were found to exhibit notable antibacterial (Deba et al., 2008; Okoh et al., 2010; Prakash et al., 2019), antimicrobial and, antifungal properties (Preethi et al., 2010). Likewise, flavonoids and polyphenols have also been recognized for their antimicrobial activity and many researchers have isolated and identified the structures of flavonoids having properties of antifungal, antiviral, and antibacterial activity. Because of this property, many flavonoids and polyphenols are now being used extensively in the fields of nutrition, food safety, and health (Panche et al., 2016). In fact, flavonols were showed remarkable activity against several Gram-positive (+) bacteria, such as *Staphylococcus aureus*, *Lactobacillus acidophilus*, and *Actinomyces naeslundii* and Gram-negative (−) bacteria, such as *Prevotella oralis*, *Prevotella melaninogenica*, *Porphyromonas gingivalis*, and *Fusobacterium nucleatum* (Daglia, 2012). Additionally, terpenoids compounds were found to exhibit an antimicrobial activity because of their functional groups (Hyldgaard et al., 2012). Fungal infection in food products results in a reduction of the color, flavor, texture, and the nutritional quality of food (Dhingra et al., 2001). Hence, during storage and transit, prevention of fungal growth by essential oils might be a benefit to reduce food loss and prevent the fungal infection. In recent years, plant essential oil used for their therapeutic antifungal potential (Baruah et al., 1996; Arras and Usai, 2001; Bosquez-Molina et al., 2010). The antifungal activity of essential oil might be caused by the properties of the mono- and sesquiterpene compounds present in the essential oils. On the other hand, botanical extracts and essential oils play a very important role in the eradication of insect pests that cause the infestation of stored food products or even stored grain and so the degradation of food products and grains quality (Isman, 2000). These botanicals act as repellents, toxicants, antifeedants against insect growth besides the impairment of ovicidal activity and extinction of insect eggs (Trivedi et al., 2018). Thus, to validate the insecticidal activity of EOs and their potential as active ingredients for commercial pesticides, several trials should be carried out testing essential oils produced in different years and geographical areas. Thus, the antimicrobial and antibacterial properties of essential oils of *C. europaea* could be indirectly implemented as natural food preservatives to combat food spoilage microorganisms.

10. Concluding remarks and future perspectives

In the present review, we summarize the knowledge on ethnobotanical, phytochemical and pharmacological activities of *C. europaea*. This medicinal plant has been used in traditional practices to treat diabetes, cancer, cyst, cough, asthma, insomnia, digestive, kidney disorders and others.

Based on the currently available information, numerous bioactive compounds have been identified and isolated from *C. europaea* extracts, and essential oils. These chemical compounds belong to flavonoids, phenolic acids, and terpenoids.

The pharmacological examination of *C. europaea* showed interesting pharmacological properties in various scientific investigations. In the pharmacological field, it demonstrated antidiabetic, antioxidant, antimicrobial, antibacterial, anti-proliferative, anti-inflammatory, immunomodulatory, analgesic, and toxicity properties of the plant extracts. The extracts of *C. europaea* also showed important activity *in vivo* models confirming the traditional uses and the *in vitro* assays results. Besides, some researchers performed the antidiabetic activity of *C. europaea*, and their results were summarized in this review. These results showed the most important role of traditional medicine in the choice of plants to be studied on a scientific basis. As we mentioned in this review, *C. europaea* has been used as an antidiabetic remedy and recent pharmacological investigation confirmed this traditional use. The extracts from this plant controlled diabetes by affecting various checkpoints that control blood sugar. However, other activities such as antiproliferative, anti-inflammatory and immunomodulatory effects should have priority for detailed investigations. In addition, detailed investigation on toxicological mechanisms of *C. europaea* are needed. Moreover, the essential oils of this plant demonstrated their effectiveness as a food preservative and its capacity to prevent food spoilage and to extend the storage life and quality of the stored products. Studies should, therefore, be carried out by investigating the industrial application. However, gaps exist in the scientific studies on *C. europaea*, and we have provided some recommendations that should have priority for detailed investigations.

Firstly, insufficient pharmacological studies have been conducted on *C. europaea*. Others studies should be carried out such as antihyperlipidemic, antihypertensive, vasorelaxant, nephroprotective, antifungal, hepatoprotective, and gastro-esophagusprotective activities. The available pharmacological activities are insufficient to affirm the ethnobotanical uses. Secondly, the pharmacological studies were mostly focused on the organic fractions of *C. europaea* with little attention on the aqueous extracts; we need to give attention to its traditional usage.

Thirdly, the reports on the pharmacological activities mentioned in this article did not demonstrate the molecular mechanisms by which extracts and essential oils from *C. europaea* act. In some biological properties, some authors suggested a positive correlation exists between the pharmacological activities and some of the isolated compounds of *C. europaea*, by reference to the literature data. However, research in this field should be put forward to understand the mechanism of action of the

bioactive substances of *C. europaea*.

Fourthly, clinical studies were not performed and there is an urgent need to perform clinical trials to promote the use of this plant. The future research will benefit future pharmaceutical applications of *C. europaea*. Taking these into consideration will have beneficial effects on the therapeutic potentials of *C. europaea*.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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