Review Article

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Mitigating digestive disorders: Action mechanisms of Mediterranean herbal active compounds

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Abstract: This study explores the effects of the Mediterranean diet, herbal remedies, and their phytochemicals on various gastrointestinal conditions and reviews the global use of medicinal plants for common digestive problems. The review highlights key plants and their mechanisms of action and summarizes the latest findings on how plant-based products influence the digestive system and how they work. We searched various sources of literature and databases, including Google Scholar, PubMed, Science Direct, and MedlinePlus. Our focus was on gathering relevant papers published between 2013 and August 2023. Certain plants exhibit potential in preventing or treating digestive diseases and cancers. Notable examples include *Curcuma longa, Zingiber officinale, Aloe vera, Calendula officinalis, Lavandula angustifolia, Thymus vulgaris, Rosmarinus officinalis, Ginkgo biloba, Cynodon dactylon*, and *Vaccinium myrtillus*. The phytochemical analysis of the plants showed that compounds such as quercetin, anthocyanins, curcumin, phenolics, isoflavones glycosides, flavonoids, and saponins constitute the main active substances within these plants. These natural remedies have the potential to enhance the digestive system and alleviate pain and discomfort in patients. However, further research is imperative to comprehensively evaluate the benefits and safety of herbal medicines to use their active ingredients for the development of natural and effective drugs.

Keywords: Mediterranean diet, active compounds, digestive disorders

1 Introduction

Globally, digestive disorders are widespread, often frustrating, and occasionally life threatening. In 2019, digestive disorders accounted for 2276.27 million predicted prevalent cases, 2.56 million fatalities, and 88.99 million disability-adjusted life-years worldwide [1]. Some digestive disorders and ailments are acute, lasting only a short period, while others are chronic, persisting over the long term. Common symptoms of digestive disorders, including bleeding, bloating, constipation, diarrhea, heartburn, incontinence, abdominal discomfort, swallowing, weight gain or loss, nausea, and vomiting [2]. Regrettably, most people suffer from gut and digestive system issues virtually from birth. Common digestive disorders include gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colorectal cancer (CRC), peptic ulcer disease (PUD), as well as lactose intolerance, hiatal hernia, liver disease (LD), pancreatitis, heartburn, and cancer (Figure 1) [3]. While conventional medications are commonly used to treat digestive disorders, they come with inherent risks. These drugs often yield adverse effects such as nausea, vomiting, and diarrhea. Moreover, certain oral medications may negatively impact the digestive tract, leading to esophageal strictures, ulcers, bleeding, and constriction. When multiple medications are administered concurrently, the potential for interactions increases significantly. These interactions can lead to adverse effects, including food allergies, sensitivities, and exacerbation of existing conditions such as diabetes, renal illness, or LD [4,5]. Alternative medicine offers a wealth of treatment possibilities. Natural substances and their structural analogs have significantly influenced pharmacotherapy in the past. The quest for scaffolds exhibiting a wide range of bioactivities and substantial structural diversity remains feasible through the use of natural products. These scaffolds can be either directly produced or serve as building blocks for the development of novel drugs. However, natural products face persistent challenges due to high attrition rates in medication research. Factors such as sustainable supply, accessibility, and intellectual property restrictions add complexity to their utilization. Fortunately, recent scientific and technological advancements are addressing these concerns and opening up new opportunities [6].

The Mediterranean flora includes numerous aromatic and diverse medicinal plants that have long been an

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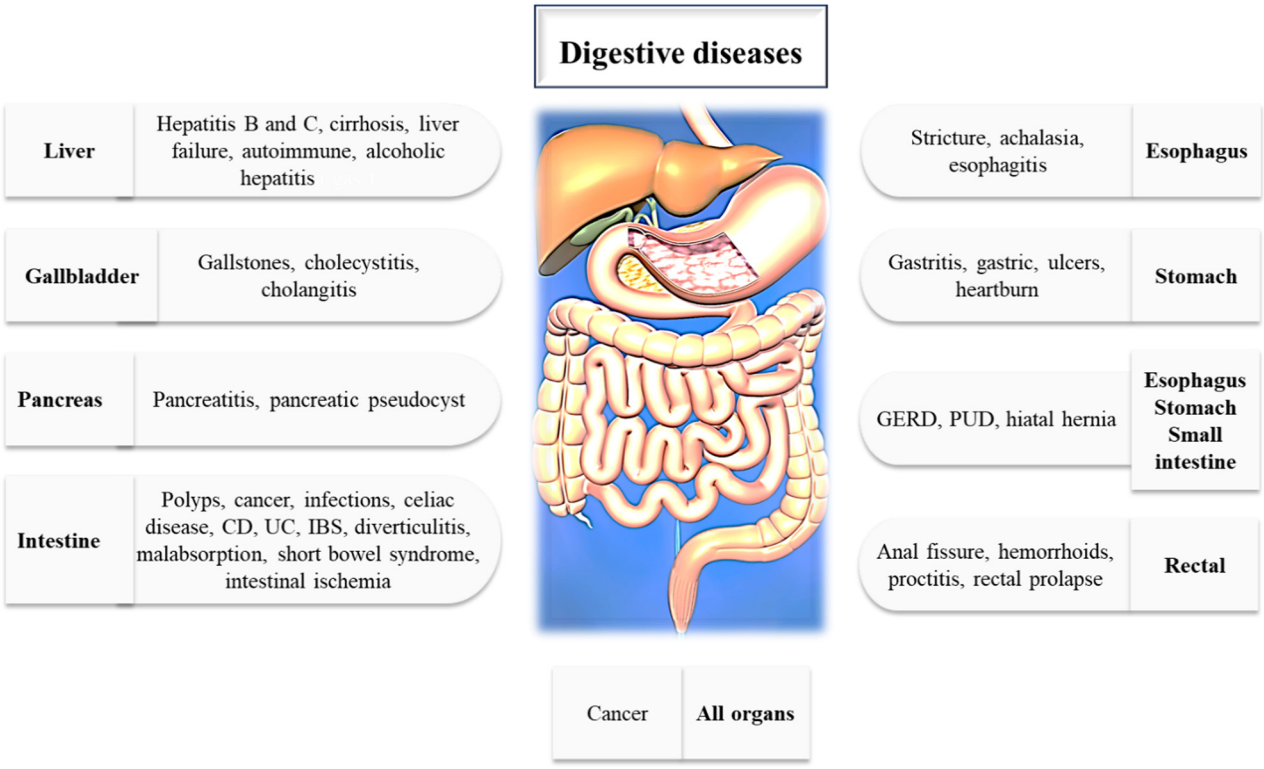

Figure 1: Common digestive disorders. CD: Crohn's disease; UC: ulcerative colitis; IBS: irritable bowel syndrome; GERD: gastroesophageal reflux disease; PUD: peptic ulcer disease.

integral part of local culture, representing a wide range of ecological contexts [7,8]. Among the plants that are traditionally used in the Mediterranean Basin, species from the Lamiaceae, Asteraceae, and Apiaceae families are the most prevalent. Notably, some of these plants have already been examined for their pharmacological properties, including sage, rosemary, thyme, oregano, lavender, and other Lamiaceae species [9]. Natural bioactive compounds have been used for food and medicine purposes since prehistoric times. People have employed plants in traditional recipes to improve nutrition and overall health. Interestingly, many contemporary medications are rooted in the traditional knowledge of plant-based medicinal potential. The overwhelming majority of the population (approximately 80%, particularly in developing countries) continues to rely on plant-based traditional medicines for basic health care needs [10]. These digestive plant preparations operate through various mechanisms, including healing the intestine lining, activating the mechanical and chemical digestion, as well as promoting smooth bowel movements, enhancing bowel frequency, detoxifying and eliminating toxins, and soothing upset stomach. Furthermore, they play a role in reducing gas, bloating, and other digestive problems. Medicinal plants likely represent the earliest form of medication, having been utilized by diverse societies throughout history. They have been utilized by many societies throughout history and continue to be an important element of our current technological advanced society. Plant-derived pharmaceuticals or natural compounds and their derivatives account for over than half of all clinically used medications [11].

Medicinal plants and phytomedicines offer several benefits, including their natural origin, minimal side effects, and avoidance of dissatisfaction associated with conventional medication [12]. A recent study provides compelling evidence that various functional food types such as probiotics, prebiotics, and herbs may have a favorable impact on the digestive tract [13]. Probiotics are likely to be beneficial in the prevention of IBD, whereas prebiotics include fibers that may inhibit the development of IBD [14–16]. Triangles, elm, and pie plant are herbs that may be associated with alleviating symptoms of IBDs. Mastic, herbal origin, may help manage heartburn, which is a common symptom of GERD [17]. Blueberries have been shown to lessen diarrhea, a frequent sign of gastrointestinal illnesses [18]. A double-blind experiment revealed that *Aloe vera* alleviated symptoms of persistent constipation [19]. In addition, *A. vera* syrup showed promise in managing GERD in a preliminary randomized positive-controlled experiment [20]. The bioactive

components of Mediterranean diet (MD) known for their health benefits found to reduce chronic inflammation by influencing C-reactive protein, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [21]. Recent analysis suggests that inflammation-induced platelet-activating factor plays a pivotal role in initiating cardiovascular diseases (CVD) rather than a mere rise in blood cholesterol levels [22]. Given the link between diet and gastrointestinal health, further research is needed to explore the potential impact of specific functional foods and bioactive substances synergistically present in the MD [23]. More clinical and epidemiological studies are essential to unravel the intricate role of nutrition and bioactive chemicals in gastrointestinal illnesses to promote the consumption of functional foods [23].

The purpose of the current review is to explore the diverse mechanisms of action associated with herbal-based medicine and the MD, along with their active components, specifically concerning the digestive system. In addition, we highlight their potential advantages for human health, particularly in the prevention and treatment of digestive disorders such as GERD, IBS, IBD, CRC, and PUD. Our focus lies on identifying the most prevalent and effective active compounds and compiling a list of important medicinal herbs.

2 MD

The traditional MD emerged in the nations of the Mediterranean Basin, where a warm and pleasant environment supports the cultivation of a wide variety of fruits and vegetables all year. Consequently, the MD is characterized by an abundance of these fruits and vegetables, along with the prominent use of extra virgin olive oil as the primary source of fat. Legumes, whole grains, nuts, seeds, and fragrant herbs also play a vital role in this dietary pattern [24,25]. Today, the phrase “MD” broadly refers to the typical eating practices of nations bordering the Mediterranean Sea. However, it is essential to recognize that historically, the Greek term “diaita” referred to more than just daily dietary habits. It encompassed a complete way of life, aligning with modern concepts of lifestyle and well-being [26]. Recent studies demonstrate that these components may have health advantages such as protection against and prevention of significant health issues such as diabetes, CVD, skin disease, digestive disease, and aging [10,27]. Active substances derived from MD such as polyphenols, omega-3 fatty acids, carotenoids, vitamins, folate, magnesium, aromatic compounds (e.g., rosmarinic acid), and curcumin are proven for their protective as well as therapeutic effects on the aforementioned disorders (Table 1).

Table 1: Active compounds from MD with their target mechanisms in various diseases

Active compound	Plant source	Disease	Target	References
Polyphenols	Olive oil, fruits, vegetables, nuts, legumes, cereals	Obesity, diabetes, CVD, cancer, neurodegenerative disease, digestive diseases, skin diseases	Antioxidant, anti-inflammatory, anti-diabetic, anti-atherogenic, anti-cancer, neuroprotective, gastroprotective, dermatoprotective	[30,31]
Omega-3 fatty acids	Fish, nuts, seeds	Obesity, diabetes, CVD, cancer, neurodegenerative disease, digestive diseases, skin diseases	Anti-inflammatory, anti-diabetic, anti-atherogenic, anti-cancer, neuroprotective, gastroprotective, dermatoprotective	[30]
Fiber	Fruits, vegetables, nuts, legumes, cereals	Obesity, diabetes, CVD, cancer, digestive diseases	Prebiotic, satiating, anti-diabetic, anti-atherogenic, anti-cancer, gastroprotective	[32]
Carotenoids	Fruits, vegetables	Obesity, diabetes, CVD, cancer, skin diseases	Antioxidant, anti-inflammatory, anti-diabetic, anti-atherogenic, anti-cancer, dermatoprotective	[33]
Vitamin C	Fruits, vegetables	Obesity, diabetes, CVD, cancer, skin diseases	Antioxidant6, anti-inflammatory, anti-diabetic, anti-atherogenic, anti-cancer, dermatoprotective5	[32,33]
Vitamin E	Olive oil, nuts, seeds	Obesity, diabetes, CVD, cancer, skin diseases	Antioxidant, anti-inflammatory, anti-diabetic, anti-atherogenic, anti-cancer, dermatoprotective	[32,33]
Folate	Fruits, vegetables	CVD	Anti-atherogenic	[32,33]
Magnesium	Nuts, seeds	CVD	Anti-hypertensive	[33,34]
Aromatic compounds	Rosemary	Obesity, cancer, skin diseases	Anti-obesity, anti-cancer, antimicrobial	[35]
Curcumin	Turmeric	Obesity, diabetes, CVD, cancer, neurodegenerative disease	Antioxidant, anti-inflammatory, anti-diabetic, anti-atherogenic, anti-cancer, neuroprotective	[35]

Interestingly, plants synthesize an estimated 100,000 of these organic compounds, yet only 10% of them have been identified. These metabolites fall into three categories: terpenes, phenolics, and alkaloids (nitrogen-containing chemicals), each with therapeutic effects. Flavonoids, found in blueberries, strawberries, grapes, melons, citrus fruits, apricots, onions, cabbage, fennel, tomatoes, lettuce, broccoli, spinach, and other foods, as well as frequent yogurt eating appear to reduce the probability of developing several tumors [24,25]. The active compounds found in medicinal and aromatic plants vary greatly based on the portion of the plant (inflorescence, bracts, leaves, stems), the developmental stage, the season, the time of day, and the environmental factors that influenced the cultivation or natural growth of an aromatic-medicinal plant [28,29].

It is challenging to trace the origins of Mediterranean cuisine, although it most likely evolved alongside cultures inhabiting the Mediterranean Basin since the birth of civilization. Over time, this culinary tradition absorbed influences from various invaders while preserving many local customs. The Fertile Crescent, the Near East geographical region, lies between the eastern tip of the Mediterranean Sea and the Persian Gulf, and it encompasses areas such as Mesopotamia, Canaan, and some argue, Northern Egypt. These regions may well had contributed to the rich tapestry of Mediterranean cuisine [36].

3 Digestive diseases

According to a recent survey published involving 73,000 adults across 33 countries on six continents, more than 40% of the global population experiences functional gastrointestinal disorders (FGIDs). Among these individuals, 49.5% of females and 36.6% of males meet eligibility for at least one of the FGIDs [37]. Digestive disorders influence approximately 40 million people in the United States leading to millions of clinical visits annually. The associated costs reached a staggering $119.6 billion in the year 2018 [38,39]. Furthermore, the burden of digestive disorders is elevating in developing countries [39]. These common digestive diseases that affect millions of people worldwide significantly affect the quality of life and contribute to morbidity and mortality. Accurate diagnosis and appropriate management, both pharmacological and nonpharmacological, are of utmost importance. Some of the main digestive diseases, their impact on work activities, and why they are important are addressed here.

3.1 GERD

GERD is a digestive disease characterized by the backflow of stomach acid or bile into the esophagus, leading to irritation and inflammation of its lining. The disrupting mechanism in the lower esophageal sphincter ordinarily prevents stomach contents from refluxing. Common symptoms of GERD include heartburn, chest discomfort, regurgitation, and trouble swallowing. GERD is a prevalent condition that affects people of all ages and genders, with global rates ranging from 8 to 33% [40]. GERD is mainly associated with proton pump inhibitor (PPIs) management [41]. PPI medications are often prescribed as an initial empirical diagnostic strategy for patients with typical GERD symptoms (such as heartburn and regurgitation) and atypical symptoms (such as noncardiac chest pain, chronic cough, hoarseness, throat clearing, and wheezing) [42,43]. Functional esophageal problems are mainly treated with neuromodulators, which alter the neuronal activity without acting as neurotransmitters. Various notable neuromodulators explored for managing functional esophageal issues, particularly noncardiac chest discomfort, such as tricyclic antidepressants, trazodone, selective serotonin reuptake inhibitors, and serotonin norepinephrine, reuptake inhibitors [44]. In addition, many Mediterranean plants, such as *Artemisia absinthium*, *Humulus lupulus*, *Matricaria recutita*, *Foeniculum vulgare*, and *Thymus vulgaris*, are well-known for their effects on GERD therapies. These plants contain active constituents that contribute to their therapeutic properties are listed in Table 2.

3.2 PUD

PUD arises from acid peptic damage to the gastrointestinal tract, leading to the loss of the protective mucosal barrier. While peptic ulcers most commonly occur in the stomach or proximal duodenum, they can also be found in the esophagus or Meckel's diverticulum [64]. The primary cause of PUD includes *Helicobacter pylori* infection and nonsteroidal anti-inflammatory medications (NSAIDs) [65]. The lifetime prevalence of PUD in the general population is estimated to be around 51%, with an annual incidence of 01–03% [64–67]. Due to the increasing frequency of antibiotic resistance, effective treatment of *H. pylori* infection has become an international concern [65]. The typical first-line therapy of PUD involved PPIs along with antibiotics, such as clarithromycin plus amoxicillin or metronidazole. However, the efficacy of this regimen in eradicating *H. pylori* has declined from over 90% two decades ago to less than 70% currently in many countries due to antibiotic resistance [65]. Table 2 highlights examples of Mediterranean plants, such as *T. vulgaris, Rosmarinus officinalis, Salvia officinalis, Origanum vulgare*, and *Mentha piperita*. These botanicals are well known for their therapeutic effects in managing PUD.

Table 2: Mediterranean plants and their active compounds used to treat specific digestive diseases, with their mechanisms of action

Plant	Active compound	Digestive disease	Mechanism of action	Reference
Artemisia absinthium (Wormwood)	Sesquiterpene lactones, flavonoids, phenolic acids	GERD, PUD	Antacid, anti-inflammatory, antibacterial, antispasmodic, cytoprotective	[45]
Humulus lupulus (Hops)	Alpha and beta acids, flavonoids, prenylated chalcones	GERD, PUD, IBS	Antacid, anti-inflammatory, antibacterial, antispasmodic, anxiolytic	[46]
Ginkgo biloba (Ginkgo)	Flavonoids, terpenoids	IBS, IBD, CRC	Anti-inflammatory, antioxidant, immunomodulatory, anticancer	[47]
Panax spp. (Ginseng)	Ginsenosides, polysaccharides, phenolic compounds	IBS, IBD, CRC, LD	Anti-inflammatory, antioxidant, immunomodulatory, anticancer, hepatoprotective	[48]
Ganoderma lucidum (Reishi mushroom)	Triterpenoids, polysaccharides, phenolic compounds	IBS, IBD, CRC, LD	Anti-inflammatory, antioxidant, immunomodulatory, anticancer, hepatoprotective	[49]
Gynostemma pentaphyllum (Jiaogulan)	Gypenosides, flavonoids, saponins	IBS, IBD, CRC, LD	Anti-inflammatory, antioxidant, immunomodulatory, anticancer, hepatoprotective	[46]
Matricaria recutita (Chamomile)	Flavonoids, terpenoids, coumarins, phenolic acids	GERD, PUD, IBS, IBD	Antacid, anti-inflammatory, antibacterial, antispasmodic, sedative	[50]
Foeniculum vulgare (Fennel)	Monoterpenes, phenylpropanoids, flavonoids, coumarins	GERD, PUD, IBS, IBD	Antacid, anti-inflammatory, antibacterial, antispasmodic, carminative	[51]
Thymus vulgaris (Thyme)	Phenolic monoterpenes, flavonoids, phenolic acids	GERD, PUD, IBS, IBD	Antacid, anti-inflammatory, antibacterial, antispasmodic, antioxidant	[52]
Rosmarinus officinalis (Rosemary)	Phenolic diterpenes, flavonoids, phenolic acids	GERD, PUD, IBS, IBD, CRC	Antacid, anti-inflammatory, antibacterial, antispasmodic, antioxidant, anticancer	[51]
Salvia officinalis (Sage)	Phenolic diterpenes, flavonoids, phenolic acids	GERD, PUD, IBS, IBD, CRC	Antacid, anti-inflammatory, antibacterial, antispasmodic, antioxidant, anticancer	[53]
Origanum vulgare (Oregano)	Phenolic monoterpenes, flavonoids, phenolic acids	GERD, PUD, IBS, IBD, CRC	Antacid, anti-inflammatory, antibacterial, antispasmodic, antioxidant, anticancer	[54]
Cynodon dactylon (Bermuda grass)	Flavonoids, phenolic acids, triterpenoids, steroids	PUD, IBD, CRC	Anti-ulcer, anti-inflammatory, antioxidant, anticancer	[55]
Borago officinalis (Borage)	Gamma-linolenic acid, rosmarinic acid, flavonoids	GERD, PUD, IBS, IBD	Antacid, anti-inflammatory, antibacterial, antispasmodic	[56]
Lavandula angustifolia (Lavender)	Linalool, linalyl acetate, terpenoids, flavonoids	GERD, PUD, IBS, IBD	Antacid, anti-inflammatory, antibacterial, antispasmodic, sedative	[50]
Mentha piperita (Peppermint)	Menthol, menthone, flavonoids, phenolic acids	GERD, PUD, IBS, IBD	Antacid, anti-inflammatory, antibacterial, antispasmodic, carminative	[56]
Calendula officinalis (Marigold)	Flavonoids, triterpenoids, carotenoids, phenolic acids	PUD, IBD, CRC	Anti-ulcer, anti-inflammatory, antioxidant, anticancer	[57]
Aloe vera (Aloe)	Anthraquinones, polysaccharides, phenolic compounds	PUD, IBD, CRC	Anti-ulcer, anti-inflammatory, immunomodulatory, anticancer	[58]
Curcuma longa (Turmeric)	Curcumin, curcuminoids, turmerones	PUD, IBD, CRC, LD	Anti-ulcer, anti-inflammatory, antioxidant, immunomodulatory, anticancer, hepatoprotective	[59]
Zingiber officinale (Ginger)	Gingerols, shogaols, zingerone	PUD, IBD, CRC, LD	Anti-ulcer, anti-inflammatory, antioxidant, immunomodulatory, anticancer, hepatoprotective	[60]
Daucus carota (Carrot)	Carotenoids, flavonoids, phenolic acids, polyacetylenes	GERD, PUD, IBS, IBD, CRC	Antacid, anti-inflammatory, antioxidant, anticancer, prebiotic	[61]
Nerium oleander (Oleander)	Cardiac glycosides, flavonoids, phenolic acids	PUD, IBD	Anti-ulcer, anti-inflammatory, immunomodulatory, cytoprotective	[45]
Amaranthus viridis (Amaranth)	Betalains, flavonoids, phenolic acids, saponins	PUD, IBD, CRC	Anti-ulcer, anti-inflammatory, antioxidant, anticancer, prebiotic	[62]
Vaccinium myrtillus (Bilberry)	Anthocyanins, flavonoids, phenolic acids	GERD, PUD, IBS, IBD, CRC	Antacid, anti-inflammatory, antioxidant, anticancer, anti-diarrheal	[47]
Taraxacum officinale (Dandelion)	Sesquiterpene lactones, flavonoids, phenolic acids, coumarins	GERD, PUD, IBS, IBD, LD	Antacid, anti-inflammatory, antibacterial, antispasmodic, hepatoprotective	[63]

(Continued)

Table 2: *Continued*

Plant	Active compound	Digestive disease	Mechanism of action	Reference
Punica granatum (Pomegranate)	Anthocyanins, flavonoids, tannins, organic acids, and xanthonoids	CRC, UC, IBS, BUD, IBD	Anti-ulcer, anti-inflammatory, antioxidant, anticancer, Anxiolytics	[46]

GERD: gastroesophageal reflux disease; PUD: peptic ulcer disease; IBS: irritable bowel syndrome; IBD: inflammatory bowel disease; CRC: colorectal cancer; UC: ulcerative colitis.

3.3 IBD

IBD is a chronic and recurrent gastrointestinal condition. The immune regulatory system, responsible for maintaining a delicate balance between tolerance and reactivity to gut microorganisms, becomes compromised in IBD. Common symptoms of IBD include diarrhea, stomach discomfort, weight loss, and fever. In addition, IBD can lead to severe physical and mental distress, significantly impacting both individuals and society, resulting in substantial health-care expenses [68]. The global prevalence of IBDs, including Crohn's disease (CD) and UC, is increasing, notably in the Mediterranean area [69]. Approximately 2 million Europeans and 15 million North Americans are affected by IBD, with medical costs constituting a significant portion of healthcare expenditures. Recent large-scale genome-wide association studies have identified more than 200 genetic loci linked to IBD, some of which are shared with other chronic autoimmune illnesses [70]. Clinically, anti-inflammatory agents (such as aminosalicylates and corticosteroids), immunosuppressants (such as azathioprine and methotrexate), and biologics (such as anti-TNF antibodies and anti-integrin antibodies) are the most commonly used drugs to treat IBD [68]. Many Mediterranean plants, including as *Curcuma longa, Zingiber officinale, Daucus carota, Amaranthus viridis*, and *Vaccinium myrtillus*, have prospective effects on IBD therapies. These plants contain active constituents that contribute to their therapeutic properties are listed in Table 2.

3.4 CRC

CRC remains a significant global health concern, with over 1.85 million cases and 850,000 deaths reported annually. As the third most common cause of cancer-related mortality worldwide, CRC poses substantial challenges for patients and healthcare systems. Notably, 25% of individuals initially diagnosed with localized disease will eventually develop metastases, while 20% of newly diagnosed CRC patients already present with metastatic disease. For patients with metastatic CRC that is not curable, treatment options primarily include cytotoxic chemotherapy and biologic therapy. The latter includes immunotherapy and antibodies treating cellular growth factors. Although extended lifespans remain relatively rare, there is a growing expectation of increased longevity. Genomic profiling makes it possible to select therapies, maximizing benefits for a broader population while minimizing exposure to the adverse effects of ineffective medications [71]. Despite advances in our understanding of CRC etiology, precursor lesions, and risk factors, a clear

explanation for the recent rise in cancer cases among young people remains elusive. [72]. Further research is essential to unravel the underlying mechanisms driving this concerning trend. Table 2 includes examples of Mediterranean plants, such as *A. vera, Calendula officinalis, Gynostemma pentaphyllum, Ganoderma lucidum,* and *Cynodon dactylon*, as well as their active constituents that may have effects on CRC medication.

3.5 IBS

IBS is characterized by the abdominal discomfort during defecation or a change in bowel behavior [73]. Common symptoms include abdominal discomfort, bowel difficulty, and bloating, as well as the elimination of potentially dangerous symptoms such as unexpected weight loss, rectal bleeding, or a recent change in bowel function. Studies from Southeast Asia and the Middle East report a prevalence of 7.0%, that from North America, Europe, and Australasia report a prevalence of 11.8–14.0%, and that from South Europe, Africa, and South America report a prevalence of 15.0–21.0%. [74]. A meta-analysis of 56 global studies revealed that the prevalence of IBS tends to be slightly but considerably greater in women compared to men [75]. In general, IBS has a significant impact on the individual, affecting their quality of life and imposing significant societal and economic burdens [76]. Many Mediterranean plants such as *H. lupulus, Panax* spp., *Borago officinalis, Lavandula angustifolia,* and *Taraxacum officinale* are well known for their effects on IBS therapies. These plants contain active constituents that contribute to their therapeutic properties are listed in Table 2.

3.6 Liver digestive associated diseases

The liver, a vital organ, performs multiple essential functions such as blood filtration, bile production, nutrition metabolization, and blood volume regulation. However, the liver is susceptible to various disorders that impair its function and give rise to digestive complications. Liver malfunction inhibits normal nutrient digestion and absorption, potentially leading to gastrointestinal inflammation and bleeding. Some treatments of gastrointestinal LDs include medications (e.g., antibiotics, steroids, immunosuppressants, antivirals, chelating agents, anticancer drugs, and lifestyle modifications such as avoiding alcohol, losing weight, eating a healthy diet) [77–79]. Globally, LDs claim the lives of over 2 million people annually, and among these fatalities, cirrhosis accounts for approximately 1.16 million deaths. Alcohol and nonalcoholic fatty liver disease (NAFLD) are currently the main causes of cirrhosis in Western developed nations [80]. Liver damage is often associated with oxidative damage, an increase in tissue lipid peroxidation, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase, total bilirubin, total protein, and cell necrosis [81,82]. Hepatic disease treatment is significantly affected by conventional therapies derived from natural sources. Active chemicals found in Mediterranean medicinal plants (Table 3) are utilized to treat digestive problems related to the liver. One such compound is silymarin, known for its antioxidant properties and its impact on enzyme systems involved in fibrosis and cirrhosis. Clinical trials have demonstrated that silymarin treatment significantly reduces liver-related mortality in patients with cirrhosis [83].

Recent research has highlighted the potential of several natural compounds in mitigating liver damage. Among these compounds, resveratrol, glycyrrhetinic acid, phytolanthin, curcumin, and silymarin have demonstrated to possess both anti-inflammatory and antioxidant activities in animal models of LDs. These compounds show promise in reducing liver damage. Milk thistle silymarin, in particular, enhances hepatic glutathione and may contribute to the antioxidant defense of the liver [92,93]. In a randomized study involving 97 patients with histologically diagnosed mild, acute, and subacute LD caused by alcohol abuse, silymarin treatment for 4 our weeks resulted in a significantly greater improvement in liver function. This improvement was evidenced by a decrease in ALT and AST levels, compared with placebo [94]. Moreover, a double-blind controlled trial [94] demonstrated the efficacy of silymarin therapy in reducing elevated liver enzymes in patients with ALD, cirrhosis, and NAFLD. Silymarin has been significantly improved liver aminotransferases in patients with NAFLD without causing any particular negative effects, as shown in a randomized, double-blind, placebo-controlled trial [95]. Due to its anti-inflammatory properties, silymarin was found to downregulate the expression of NF-κB, IL-6, MMP-2, MMP-13, transforming growth factor beta-1, tumor-suppressor Krueppel-like factor, collagen α1 expression, and platelet-derived growth factor signaling in an alcoholic fatty liver model in rats [96,97].

Recent research has explored the therapeutic potential of curcumin in improving NAFLD, and it reduces the production of triglycerides (TG) [98] by inhibiting HMG-COA reductase [99]. In mice models, curcumin effectively reduces hepatic steatosis and lowers elevated hepatic TG [100]. When curcumin was supplemented to adult patients with metabolic syndrome, their body mass index values as well as their serum glucose levels, glycated hemoglobin, AST, ALT, TG, and total cholesterol were all below those of the placebo group [101]. Patients with NAFLD who received daily low-dose phospholipid curcumin supplementation for two months show a substantial decrease in their hepatic steatosis and enzyme

levels when compared to placebo [102]. In addition, glycyrrhetinic acid showed to promote the growth of liver cells by binding to the epithelial growth factor receptor, enhancing the hepatic antioxidant defense, acting as an anti-inflammatory agent (Table 3), and activating the extracellular signal-regulated kinases (ERK2) pathway, along with stimulating DNA synthesis in liver cells [103,104]. 18β-glycyrrhetinic acid further reduces oxidative stress and the expression of inflammatory markers by downregulating of NF-κB and upregulating nuclear factor erythroid 2–related factor 2 (Nrf2) target genes. These effects were observed in both *in vitro* cel models and *in vivo* animal models with hepatic injury [105,106]. Furthermore, ethanolic extracts of *Phyllanthus amarus* exhibits strong hepatoprotective properties in both *in vitro* and *in vivo* settings. Recent studies have shed light on the potential benefits of Phyllanthus extract in the treatment of both acute and chronic hepatitis in children [38]. In addition, phytolanthin, a compound found in Phyllanthus, has demonstrated protective effects on rat livers exposed to galactosamine and carbon tetrachloride-induced cytotoxicity [107]. Another intriguing compound, resveratrol, plays a crucial role in safeguarding the liver following hepatocyte injury by modulating the expression of the nuclear transcription factors Nrf2 and NF-κB and downregulating the expression of HO-1 and iONS genes. Resveratrol effectively protects the liver following hepatocyte injury by reducing oxidative stress [108]. Furthermore, the Mediterranean foods, particularly plants, are thought to be rich in various kinds of chemical compounds that deserve clinical investigation to figure out their importance in treating digestive system-related liver illnesses.

Table 3: Common LDs. The main Mediterranean plants' active compounds used to treat LDs and their target mechanism of action

LD	Cause	Active compound	Plant source	Mechanism of action	References
Alcohol-related liver disease	Excessive alcohol consumption	Silymarin	Milk thistle (*Silybum marianum*)	Antioxidant, anti-inflammatory, antifibrotic and anti-apoptotic effects	[84]
Fatty liver disease	Excess fat accumulation	Curcumin	Turmeric (*Curcuma longa*)	Modulation of lipid metabolism, inflammation, oxidative stress, and insulin resistance	[85]
Hemochromatosis	Genetic, absorption too much iron	Phyllanthin	Bhumyamalaki (*Phyllanthus amarus*)	Chelation of iron and inhibition of iron absorption	[86]
Wilson disease	Genetic, preventing removal excess copper	Tetrathiomolybdate	Brassica spp.	Reduction of copper levels and inhibition of copper-dependent enzymes	[87]
Liver cancer	chronic viral infections, cirrhosis, exposure to toxins, and genetic factors	Betulinic acid	White birch (*Betula alba*)	Induction of apoptosis, inhibition of angiogenesis, and modulation of signaling pathways	[88]
Autoimmune hepatitis	Autoimmunity, attacks the liver cells	Glycyrrhizin	Licorice (*Glycyrrhiza glabra*)	Suppression of immune response, reduction of inflammation, and protection of hepatocytes	[89]
Primary sclerosing cholangitis	Bile ducts become inflamed and scarred	Silymarin	Milk thistle (*Silybum marianum*)	Antioxidant, anti-inflammatory, antifibrotic, and anti-apoptotic effects1, reduced hepatic TIMP-1/2	[90]
Primary biliary cholangitis	Autoimmunity, attacks the small bile ducts	Oleanolic acid	Olive (*Olea europaea*)	Anti-inflammatory, immunomodulatory, and hepatoprotective effects	[91]

4 MD importance in digestive diseases

Functional foods, enriched with specific minerals, vitamins, fatty acids, and dietary fibers, contain biologically active substances. These include phytochemicals, antioxidants, and probiotics, which have the potential to improve health and reduce disease risk [109–111]. Polyunsaturated fatty acids (found in olive oil and nuts) and antioxidative bioactive substances such as flavonoids, phytosterols, terpenes, and polyphenols exhibit anti-atherogenic and anti-inflammatory functions. Similarly, a perfect balance of micronutrients, including vitamins and minerals, which are rich in this diet, aids in the prevention of malnutrition and immunodeficiencies [112]. Concerning digestive disorders, high intakes of mono- and disaccharides, along with total lipids, for example, continuously increase the risk of developing IBD. Higher vegetable consumption may lower

the incidence of UC, whereas higher fruit and/or dietary fiber consumption may offer protection against CD. Probiotics and prebiotics may influence gut microbiota and lessen the chance of IBD relapse. Previous studies have linked depression and emotional stress with the appearance of FGIDs such as functional dyspepsia and IBS [113,114]. Dietary patterns and the overall diet may be more relevant in illness risk than particular meals or nutrients [115]. Malnutrition impairs the clinical course of underlying disorders and is linked to poor clinical outcomes. Dietary control of gastrointestinal illness pathophysiology by manipulation of intestinal permeability and inflammation [116,117]. The individuals living in the Mediterranean Basin had underneath death rate with the prevalence of cardiovascular and cancer disorders than other populations, according to Ancel Benjamin. MD is marked by an excessive amount of grains, vegetables, fruit, olive oil, and tiny amounts of dairy products, pastry, sweets, and meat-based foods all simultaneously [118,119].

5 Mechanism of action of Mediterranean plants active compounds used to treat specific digestive diseases

There is still much to learn about the exact mechanism of action by which the active chemicals in medicinal plants and MDs accomplish their therapeutic effects. Figure 2 shows the potential target mechanisms by which gastrointestinal tract diseases can be managed through medicinal herbs and their active phytocompounds.

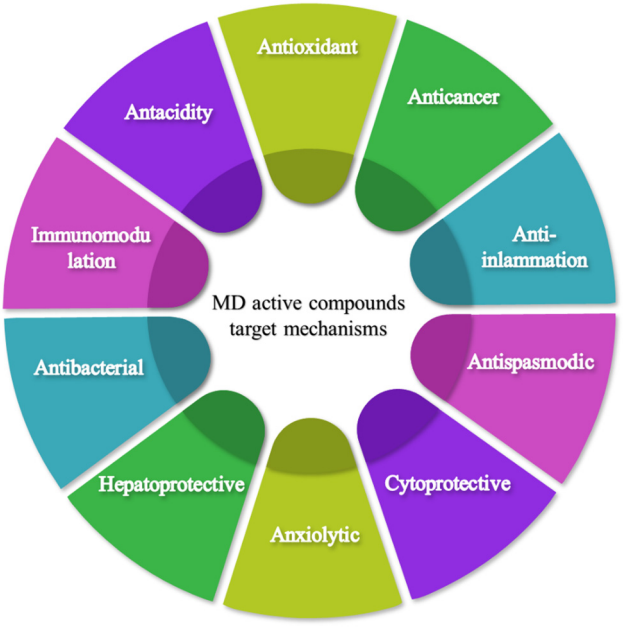

Figure 2: Mediterranean active compounds target mechanisms.

5.1 Antacidity

The release of gastric acid by parietal cells in the stomach plays a crucial role in regulating the acidity of the digestive tract. However, an overabundance of acid, on the other hand, can cause a variety of digestive illnesses such as GERD, PUD, and nonulcer dyspepsia. Notably, peptic ulcers can result in severe complications such as excessive bleeding due to erosion of blood vessels [120]. To avoid excessive acid production, H2 antagonists, such as ranitidine, bind to H2 receptors, thereby inhibiting histamine binding and reducing acid output [121]. In addition, the hydrogen potassium ATPase enzyme, which is responsible for the final step of acid secretion into the stomach, is inhibited by PPI. Remarkably, PPI are prodrugs become active only after cleaving in the acidic secretory canaliculi of parietal cells by an acid. In the liver, P450 enzymes break down PPIs, with cytochrome P450 2C19 being the most common P450 enzyme involved in the breakdown of the different PPIs, albeit the specific P450 enzymes involved, although specific P450 enzymes may vary slightly [122,123]. Beyond conventional pharmaceutical approaches, antacid effects have been observed in phytochemicals. Flavonoids, alkaloids, tannins, and saponins are some phytochemicals that have been studied for their antacid characteristics. Notably, Mediterranean medicinal herbs such as *A. absinthium* and *H. lupulus* are two major Mediterranean medicinal herbs have been used as antacids [45,46,118,121]. However, while certain medicinal herbs have been demonstrated to have antacid characteristics, they should not replace standard medical therapy [124]. Table 2 provides an overview of 14 Mediterranean plants and their active constituents, which are well known for their antacid effects.

5.2 Anti-inflammation

Inflammation is the body's complicated biological respond to various stimuli such as germs, damaged cells, or irritants [125]. In the context of health, understanding inflammation and its modulation is crucial. Mediterranean medicinal plants rich in phytocompounds such as curcumin, resveratrol, anthocyanins, quercetin, and gingerol (Table 2) play a crucial role in reducing toll-like receptor (TLR) 4 receptor

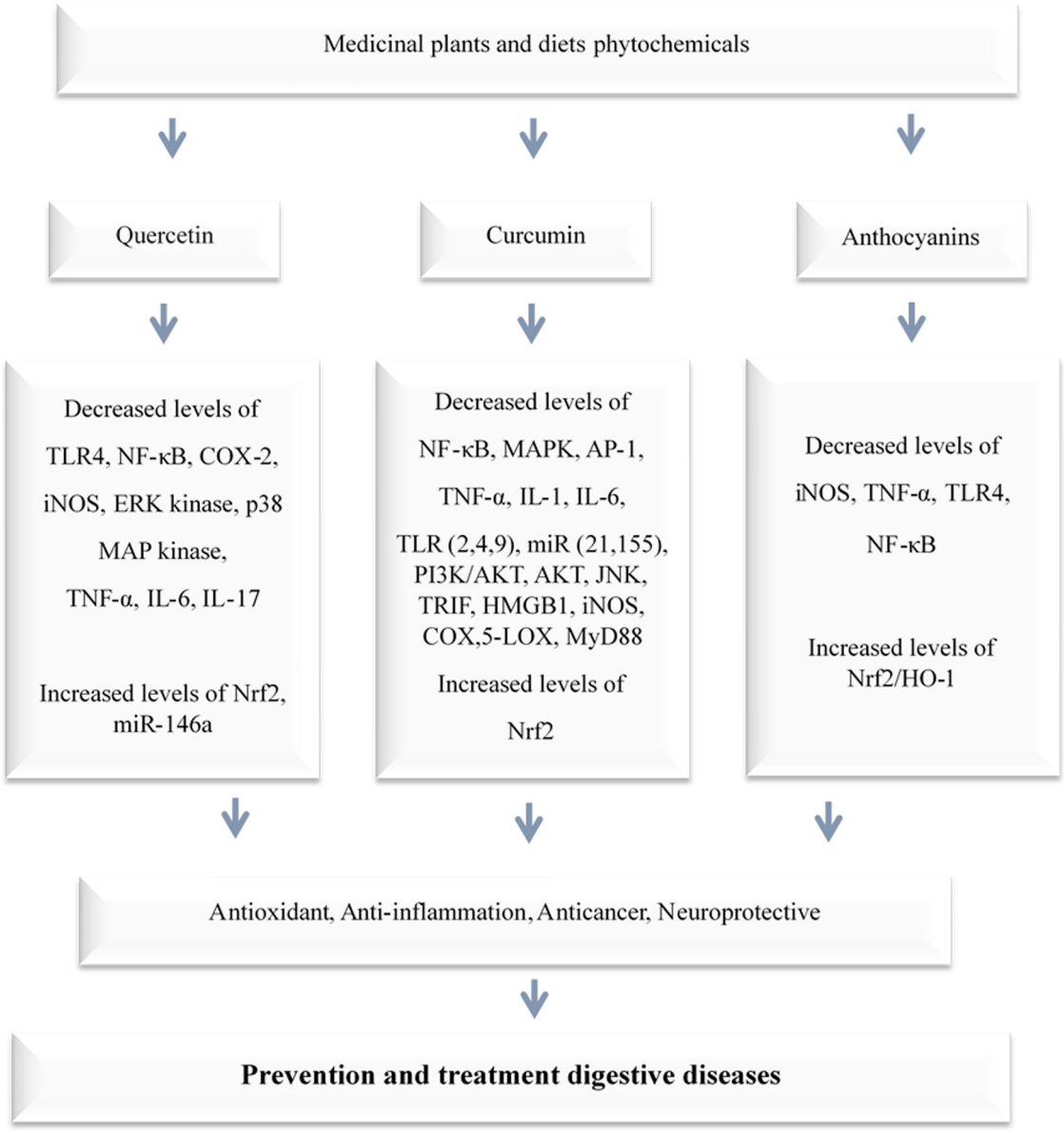

Figure 3: Major phytochemicals of Mediterranean medicinal plants and their antidigestive mechanisms. TLR: Toll-like receptor; NF-Kb: nuclear factor kappa B; COX: cyclooxygenase; iNOS: nitric oxide synthases; ERK2: extracellular signal-regulated kinases; MAPK: mitogen-activated protein; TNF-α: tumor necrosis factor alpha; IL: interleukin; Nrf2: nuclear factor erythroid 2–related factor 2; mIR: microRNA; AP-1: activator protein 1; PI3K: phosphoinositide 3-kinases; AKT: Protein kinase B; JNK: Jun N-terminal kinase; TRIF: TIR-domain-containing adapter-inducing interferon-β; HMGB1: high mobility group box 1; LOX: lysyl oxidase; MYD: myeloid differentiation primary response.

expression along with NF-κB transcription factor operation, hence minimizing the synthesis of downstream pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, as well as free radicals such as nitric oxide and reactive species (ROS). Furthermore, these phytochemicals stimulate the Nrf-2 signaling pathway, which falls oxidative stress [126]. Some plant chemicals can reduce inflammation by affecting miRNAs and genes that control it. For example, miR-155 and miR-21 are two miRNAs that increase inflammation by activating NF-κB and its target genes such as TNF-α, IL-6, and mitogen-activated proteins (MAPKs). Many plant chemicals mentioned earlier (Figure 3) can lower the levels of these miRNAs and reduce inflammation [125,127]. These plant chemicals can also change the activity of enzymes that modify the DNA and histones, such as histrone acetyl transferases and HDACs, and affect the expression of inflammatory genes [125]. Inflammation within the digestive system can cause problems like IBD, IBS, and GERD [125]. Following MD, which is rich in plant

chemicals, can improve the symptoms and markers of inflammation in children and teens with mild to moderate IBD. After 12 weeks of therapy, the majority of the participants in a clinical investigation achieved recovery. Participants who followed the MD protocol had a substantial decrease in both clinical ratings (PCDAI and PUCAI) and most inflammatory markers (CRP, calprotectin, TNF-α, IL17, IL12, and IL13) when compared to those in the control group, with faster recovery in both PCDAI and CRP [128]. Mediterranean medicinal plants offer a natural arsenal against inflammation, providing valuable insights for therapeutic strategies.

5.2.1 Quercetin

Quercetin is a flavonoid abundant in various dietary sources, including citrus fruits, apples, onions, red grapes, and tea [125]. This phenolic molecule exhibits a remarkable array of health-promoting issues and serves as anti-inflammatory, antioxidant, chemopreventive, and neuroprotective [129]. In macrophages and human PBMCs, quercetin decreases the production of TLR4 and hinders NF-κB trafficking to the nucleus, which alleviates the inflammatory response [125]. It also suppresses cyclooxygenase (COX)-2 and nitric oxide synthases (iNOS) gene expression *in vitro* and greatly lowers the generation of proinflammatory cytokines in LPS-activated macrophages via the MAP kinases and NF-κB pathway [130]. In LPS-treated RAW 264.7 macrophages, quercetin inhibits NF-κB activation via regulating the NF-κB/IB complex and reduces phosphorylated ERK kinase and p38 MAP kinase [130]. It has been observed that quercetin and its metabolite can also suppress the NF-κB pathway indirectly by activating the Nrf2 signaling cascade [131]. Furthermore, quercetin has been demonstrated to upregulate miR-146a, which is followed by a reduction in NF-κB, TNF-α, IL-6, and IL-17 levels. The quercetin content of Mediterranean plants may have cytoprotective properties in digestive diseases such as IBD, IBS, and GERD [125].

5.2.2 Curcumin

Curcumin, a polyphenol derived from the ginger plant *C. longa* [132,133] plays a pivotal role in managing various inflammatory conditions, including rheumatoid arthritis, IBD, nephropathies, and certain malignancies [125]. Curcumin has a strong anti-inflammatory effect, which is attributed to its regulation of the TLR4 and MyD88 pathways in macrophages, and it effectively prevents NF-κB activation [134,135]. In addition, curcumin suppresses MAPK and AP-1 transcription factor activation along with inhibiting IB-phosphorylation and degradation [136,137]. These antagonistic effects on TLR4 signaling pathways and downstream mediators are followed by suppression of proinflammatory cytokines such as TNF-α, IL-1, and IL-6 [125]. A research indicates that curcumin pretreatment protects against T cell-mediated hepatitis in mice. The strong impact of curcumin may be attributed in part to decreasing the expression levels of TLR2, TLR4, and TLR9 in the liver [138]. Moreover, curcumin was found to downregulated miR-155 levels *in vivo* and *in vitro* following LPS stimulation via depleting the phosphoinositide 3-kinase PI3K/AKT pathway [139]. Regular consumption of curcumin reduces the expression of miR-21 and miR-155 in clinical investigations. Consequently, this was followed by a reduction of the proliferative kinases AKT and JNK, as well as the transcription factor AP-1, which reduced inflammation by decreasing NF-κB activation, TNF-α, and IL-6 production [140,141]. Curcumin is typically taken three times per day at doses ranging between 400 and 600 mg. Remarkably, it exhibits no adverse effects on the kidney or liver when taken up to 12 g/day [142,143]. However, extremely high dosages may lead to stomach distress and gastric ulcers [144]. Hence, curcumin, which is a key ingredient in Mediterranean traditional medicine, may be a safer compared with NSAIDs for inflammation. A study indicates that curcumin can decrease the development of TLR2, TLR4, and HMGB1 in rats suffering from fibrogenesis expression of ligand molecules, suggesting that curcumin's hepatoprotective mechanism may be attributed to its antioxidant activity [145,146]. In addition, curcumin may lower other ROS-producing enzymes such as iNOS, the COX system, and arachidonate 5-lipoxygenase, as well as reducing the action of numerous pyoderma gangrenosums [144].

5.2.3 Anthocyanins

Anthocyanins, flavonoids present in many fruits and vegetables, particularly in the Mediterranean area, represent a part of the traditional diet [147]. They may aid in the prevention or treatment of digestive illnesses such as IBD, UC, CD, and CRC. Anthocyanin has recently been shown to be beneficial in the treatment of fatty liver and inflammation (125). Anthocyanins, in particular, reduce proinflammatory mediators like as iNOS and TNF-α by lowering TLR4 expression and inactivating NF-κB [148]. They also help to protect against oxidative stress by stimulating the Nrf2/HO-1 signaling pathway [149]. Anthocyanins have been shown to inhibit proinflammatory TNF-α signaling and gene expression in murine livers [150]. A clinical investigation, including individuals with UC for example, found that supplementation with anthocyanin-rich bilberry extract improved patients' activity

and quality of life. A recent study shed the light on the health-promoting effects of anthocyanins derived from purple sweet potato extracts. It decreased colonic inflammation and inhibited the development of carcinogenesis in a rat model of colitis-associated CRC. Furthermore, a meta-analysis of epidemiological data supports the potential benefits of anthocyanin consumption. Increased intake of anthocyanin was associated with a decreased risk of CRC [147,151].

5.3 Antibacterial

Bacterial infections of the gastrointestinal system are most commonly caused by bacteria or bacterial toxins of contaminated food or drink. Dental caries, periodontal disease, shigellosis, salmonellosis, and typhoid fever exemplify bacterial disorders of the digestive system [152–154]. However, plants such as *A. absinthium*, *H. lupulus*, *F. vulgare*, *T. vulgaris*, *T. officinale,* and their derived metabolites of different Mediterranean habit (Table 2) inhibit damaging factors of pathogenic microorganisms. There have been reports of phytochemical components that provide a fascinating defense mechanism against predation by a variety of Gram-positive and Gram-negative bacteria, along with antibiotic-resistant bacteria. These constituents include tannins, flavonoids, alkaloids, glycosides, cyanogenetic glycosides, reducing sugar, and several other aromatic compounds [155,156]. Reports suggest that flavonoids and polyphenolic chemicals may have antibacterial activity because of their capacity to bind to bacterial cell walls and impede microbial development [157]. In addition, antivirulence phytochemical research has mostly focused on *in vitro* quorum quenching with their antibiofilm characteristics. Notably, myristic acid, which reduces virulence *in vitro*, paradoxically acts as a signal molecule that increases *Pseudomonas aeruginosa* pathogenicity in a dermonecrotic animal model. Moreover, certain mouse models have revealed that type three secretion systems play a pivotal role as virulence determinants [158]. Anthocyanins, abundant in various foods, may help the digestive tract by reducing oxidative stress, alleviating inflammation, and modulating gut flora [159].

5.4 Antispasmodic

Medicines with antispasmodic properties are frequently used to lessen excessive smooth muscle contractility, which often leads to stomach pain and cramping associated with various gastrointestinal, biliary, or genitourinary tract conditions [160]. A significant portion of the population experience conditions such as IBS, biliary colic brought on by gallstones, gastritis, colitis, pancreatitis, or dysmenorrhea, all of which commonly require antispasmodic medication to reduce symptoms [161–164]. Antispasmodic drugs are also employed to alleviate the pain during medical procedures such as colonoscopy [165]. Multiple Mediterranean medicinal herbs, including *Zanthoxylum armatum*, *Matricaria chamomilla*, *F. vulgare*, *Pycnocycla spinosa*, *Atropa belladonna*, *L. angustifolia*, *Mentha pulegium*, *Glycyrrhiza ularensis*, *Anethum graveolens*, and *Origanum majorana* contribute to symptom relief through their antispasmodic properties [161]. Phytochemicals have been demonstrated to have antispasmodic characteristics, particularly secondary metabolites such as terpenes, phenolics, and alkaloids, are responsible for these plants' pharmacological actions [162].

5.5 Cytoprotective

The capacity of cells to endure damaging stimuli while maintaining structural and functional integrity is referred to cytoprotecting. Cytoprotective drugs prevent or minimize damage to the gastrointestinal mucosa caused by different variables such as acid, pepsin, and *H. pylori* in the setting of digestive illnesses [166]. Various Mediterranean medicinal herbs, including *Olea europaea*, *Rosmarinus officinalis*, *T. vulgaris*, *O. vulgare*, and *Salvia officinalis*, have cytoprotective action [167]. Phytochemicals including curcumin, resveratrol, quercetin, and gingerol that target TLR4/NF-κB-mediated inflammatory mechanisms have cytoprotective activities [167].

5.6 Anxiolytics

Anxiolytics, a class of medications, exert their effects by targeting the gamma-aminobutyric acid (GABA) receptor. This receptor regulates chloride ion entry into neurons, leading to neuronal hyperpolarization [168]. However, the precise mechanism of action of anxiolytics is yet unknown [169]. Several medicinal herbs have been explored for their anxiolytic properties including pomegranate, lavender, hops, maypop, lemon balm, valerian, and peppermint [170]. Pomegranate contains various phytochemicals, such as anthocyanins, flavonoids, tannins, organic acids, and xanthonoids, and have demonstrated anxiolytic properties [171]. Phytochemicals in pomegranate likely exert their effects through multiple ways, including inhibition of GABAergic receptors, modulation of N-methyl-D-aspartate and CaMKII/CREB pathways, reduction of oxidative stress via TLR4 and iNOS inhibition, control of cytokines and NF-kB generation, and

activation of Nrf2 and AMPK. While anxiolytics offer relief, they may come with undesirable side effects, including addiction, depression, suicidal tendencies, seizures, sexual dysfunction, and headaches [172]. Exploring the anxiolytic potential of medicinal herbs provides valuable insights for managing anxiety while minimizing adverse effects associated with conventional medications.

5.7 Antioxidant

Antioxidants are molecules that have the potential to neutralize free radicals and prevent them from causing cell injury. In digestive diseases, oxidative stress can trigger inflammation and mucosal damage [173]. According to scientific studies, antioxidant properties are the key mechanism for phytochemicals to alleviate various disease pathways by increasing the antioxidant defense mechanisms of cells, scavenging free radicals, decreasing lipid peroxidation, boosting anti-inflammatory potential, and further protecting hepatic cell damage [84]. Terpenoids (such as monoterpenes and carotenoids) and polyphenols (such as quercetin and other flavonoids) are significant phytochemicals having antioxidant properties. In this context, lavender, hops, maypop, lemon balm, valerian, and peppermint are among the therapeutic herbs used to treat antioxidant-related illnesses [174]. In addition, bioactive phytochemicals from *Hypericum* species exhibit both anti-inflammatory and antioxidant properties [175]. Numerous antioxidant compounds have been found to be abundant in *Rosmarinus officinalis*, *Z. officinale*, *F. vulgare*, *C. longa*, and fragrans. Because these foods are antioxidant rich, regular consumption of these foods offers additional health benefits [176]. Quercetin is a strong antioxidant that suppresses the generation of lipid peroxides and lysosomal enzymes like the acid phosphatase and cathepsin D [177,178]. On the other hand, curcumin reduces oxidative damage during inflammation by stimulating the Nrf2-Keap1 pathway and enhancing antioxidant enzyme efficiency [179].

5.8 Immunomodulatory

Immunomodulators are chemicals that alter or control the immune system to improve the body's response to a medical condition and diseases. Immunomodulators can help regulate symptoms and preserve immune system homeostasis in the context of digestive diseases [180]. Several Mediterranean medicinal herbs, including *Echinacea purpurea*, *Panax ginseng*, *C. longa*, and *Allium sativum*, are used to treat immunomodulatory-related disorders [181]. Medicinal plants and isolated compounds with immunomodulatory properties are prospective treatments for digestive diseases and viral infections such as COVID-19. Polysaccharides, terpenoids, flavonoids, alkaloids, glycosides, and lactones are plant phytochemicals that play a crucial role in immunomodulation [182].

5.9 Anticancer

The intricacies of cancer pathobiology are strongly linked to the primary challenges in developing target-specific anticancer medications. Autophagy, alongside apoptosis, plays a critical role in cellular mechanisms related to cancer genesis and treatment. However, due to the abnormalities in signaling pathways, notably apoptosis, many tumor types developed resistance against treatment. Autophagy might be investigated as another cell fate mechanism for the exploration of target-specific antitumor medicines [183]. Growing evidence suggests that phytochemicals, which alter various signaling targets, including both autophagy and apoptosis, exhibit anticancer outcome [184]. Phytocompounds anticancer actions were shown to be selective and specific to cancer cells, involving the control of autophagy and apoptosis [183]. Numerous studies have documented the protective effects of curcumin against UC, CD, pancreatic, and colorectal malignancies [185]. In addition, researchers have explored phytochemicals derived from Mediterranean plants across a range of cancer cell lines to uncover their critical biological pathways in cancer genesis and control (Table 4) [183].

5.10 Hepatoprotective

Based on experimental validation, natural bioactive substances derived from plants are promising options for predicting and alleviating hepatotoxic effects and chronic problems [84]. Several in silico investigations and molecular networking substances have also highlighted active phytochemicals derived from natural sources as potential hepatoprotective agents [84]. Plant products contain a range of phytochemicals that exhibit the hepatoprotective effect against CCl4-induced toxicity by downregulating liver marker enzymes and activating the antioxidative capability of the liver cells, resulting in liver repair [88]. Despite the fact that these drugs show significant hepatoprotective benefits in animal and cell culture models, a lack of clinical research continues to be a barrier to their official recognition. Therefore, controlled clinical studies are required to establish the therapeutic effectiveness of possibly hepatoprotective substances. Understanding the fundamentals of phytochemical hepatoprotective action might guide future medication development and

Table 4: Phytochemical compounds from Mediterranean plants and their *in vitro* biological regulatory pathways in the genesis and control of cancer

Active compound	Cell line	Biological pathway
Resveratol	Human colon carcinoma	Activate apoptosis-3 and 8/FADD
Eriocalyxin	Human pancreatic cancer	Activate caspase 8 and 9 inhibit caspases 3 and 7
Apigenin	CRD	Activate NAG-1, p53, cleave caspase 3
Allicin	Human gastric cancer	Inhibit p38 expression and cleave caspase 3
Evodiamine	Human gastric cancer	Activate beclin-2, Bax, downregulate Bcl-2
Gingerol	Human colon cancer	Inhibit JNK, ERK1-2, P38 MAPK
Toxicarioside O	CRD	Inhibit Akt/Mtor
Oleanolic acid	Human pancreatic	Modulate JNK, mTOR pathway
Oridonin	Human hepatocellular carcinoma	Activation caspase-3 downregulate Bcl-2 and upregulate Bax
Thymoquinone	Oral cancer	Increase expression of LC3-II, Bax expression
Tetrandrine	Hepatocellular carcinoma	inhibit Wnt/Beta-catenin
Quinacrine	Human colon cancer	Activation p53, p21, inhibit topoisomerase
Chloroquine	Pancreatic cancer	Decrease the level of O_2
Isorhamnetin	Colon cancer	Increase ROS
Benzylisothiocyanates	Pancreatic cancer	Decrease phosphorylation of PI3K/Akt/FOXO1/PDK1/mTOR/FOXO3a
Kaempferol	CRD	Generates ROS and p53 signal
Triptolide	Human pancreatic	Inhibit Akt-mTOR-p70S6K

NAG-1: nonsteroidal anti-inflammatory drug-activated gene 1; Bax: Bcl-2-associated X protein; JNK: Jun *N*-terminal kinase; ERK2: extracellular signal-regulated kinases; MAPK: mitogen-activated protein; AKT: protein kinase B; mTOR: mammalian target of rapamycin; JNK: Jun *N*-terminal kinase; LC3-II: phosphatidylethanolamine conjugate II; ROS: reactive species; PI3K: phosphoinositide 3-kinases; PI3K/Akt/FOXO1/PDK1/mTOR/FOXO3a; signaling pathway, p70S6K: p70 ribosomal S6 kinase.

aid in the prevention of clinical trial failure. Furthermore, the development of innovative delivery methods that improve the bioavailability of weakly water-soluble drugs may improve the findings that have previously been obtained. Most significantly, published data indicate that phytochemicals modulate distinct signaling pathways to varying degrees, highlighting the necessity for the use of mixtures of numerous hepatoprotective substances in both experimental research and clinical trials [186]. Many plants, such as the roots of *T. officinale* and the leaves of *Mentha longifolia*, are utilized in various herbal formulations as hepatoprotectives. It has been discovered that curcumin prevents the hepatitis C virus from entering by changing the fluidity of the membrane and the way the virus binds and fuses [185]. In addition, total saponins from *Panax notoginseng* have been shown to have a promising effect on fatty LD [187]. Dietary polyphenols and their metabolites have been also found to be crucial for preserving the microbial balance and overall health of the gut [185].

6 Challenges of MD for health and well-being

The MD has been demonstrated to be an appropriate dietary regimen that may lower the risk of noncommunicable diseases [188]. Promoting the MD as a healthy dietary pattern, on the other hand, offers obstacles that require the involvement of all levels of society [188]. One difficulty is the lack of a uniform definition and scoring system for the MD [189]. Another problem is the effect of nutritional transition, which encourages the move of traditional foods to Westernized diets, complicating adherence to the MD [189]. Despite its growing global appeal, adherence to the MD model is declining due to a variety of variables such as lifestyle changes, food globalization, economic, and sociocultural considerations [190]. These alterations endanger the maintenance and transfer of the Mediterranean food legacy to future generations [190]. Interestingly, middle-aged and older Hispanic or Latino people who adhere to the MD experience improved cognitive function and reduced 7-year learning and memory loss. MD that is culturally adjusted may minimize the risk of cognitive decline and Alzheimer's disease [191]. More cross-disciplinary research on the environmental, economic, sociocultural, and sustainability components of the MD is expected to be extremely important [190]. MD containing plenty of plant foods with limited processing has been associated with increased life expectancy and a decreased risk of developing a number of chronic diseases [192]. Moreover, a Mediterranean-style diet may reduce the prevalence of gestational diabetes mellitus in pregnant women with metabolic risk factors [193]. A Mediterranean-style diet has also been shown to reduce the likelihood of GERD symptoms [194]. Unfortunately, as life and the drug

industry have advanced, this knowledge has become steadily less communicated and is on the verge of extinction, necessitating the need to preserve and integrate traditional medicine into the current health system through ethnobotany and ethnopharmacology [195]. As the diet is contributing mainly in obesity, it raised the risk of a variety of benign digestive disorders. Obesity-induced mechanical and humoral variables are implicated in the development of esophageal illnesses, whereas obesity-induced proinflammatory and inflammatory cytokines appear to be involved in the pathophysiology of other digestive disorders. Furthermore, excess weight and obesity increase free fatty acid, TNF-α, and resistin levels while decreasing adiponectin. This causes insulin resistance and changes in the IGF-1 pathway, as well as inhibiting apoptosis and increasing cell proliferation on target cells. Obesity elevates free fatty acids and modifies adipocytokines. This metabolic change results in metabolic syndrome, which includes insulin resistance, dyslipidemia, and hypertension. In addition, metabolic changes and metabolic syndrome have a role in both benign and malignant digestive disorders. Obesity's mechanical impact may lead to esophageal disease and other digestive disorders [196].

7 Conclusion

Disorders affecting the digestive system have a substantial impact on global health, resulting in elevated rates of illness and mortality. These challenges are particularly pronounced in rural areas where knowledge about sanitation and disease prevention is limited. In less developed countries, plant-based therapies frequently serve as the primary approach for preventing and treating gastrointestinal diseases. Numerous studies have validated the traditional use of these therapies by investigating their pharmacological effects on various diets and plants. These effects include reducing gas, relieving spasms, slowing intestinal transit, influencing gut motility, stimulating absorption, or decreasing electrolyte secretion. The MD, renowned for its rich variety of plant-based foods, is acknowledged as a dietary pattern that promotes overall health and well-being. This diet incorporates foods high in polyphenols, such as olive oil, walnuts, vegetables, fruits, legumes, wild edible plants, and whole grains, all of which are known to provide digestive benefits. Phytochemicals derived from plants and diet, particularly polyphenols, can function independently or synergistically to mitigate digestive system complications. Present scientific assessments of plant-based products primarily aim to validate and identify active components in extracts and other preparations. However, certain herbal preparations or active ingredients can cause severe side effects under specific conditions. As a result, it is crucial to establish a scientific foundation for their activity and to better evaluate the quality, effectiveness, and safety of traditionally used diets and medicinal plant-based preparations. Well-designed clinical trials are required to verify herbal medicines and offer the proof that's needed to justify their efficacy. The safety and tolerability of traditional and herbal medications used to treat problems of the digestive system have not been well studied in clinical trials, but those that have been performed have generally shown minimal adverse effects. To create alternative treatments for digestive disorders, more research on traditional plant-based remedies is necessary given the promising results of previous studies.

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Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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