REVIEW
Traditional Medicine Research 2023;8(4):23. https://doi.org/10.53388/TMR20220706001

The role of selected medicinal plants from Iranian traditional medicine for the treatment of fatigue in metabolic syndrome

Akram Alembagheri[1], Homa Hajimehdipoor[2], Rasool Choopani[3], Somayeh Esmaeili[2*]

[1]Student Research Committee, Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran 1516745811, Iran. [2]Traditional Medicine and Materia Medica Research Center, Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran 1516745811, Iran. [3]Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran 1516745811, Iran.

[*]**Corresponding to:** Somayeh Esmaeili, Traditional Medicine and Materia Medica Research Center, Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, No. 08, Shams Alley, Across from Shahid Abbaspour Street, Vali Asr Ave., Tehran 1516745811, Iran. E-mail: sesmaeili@sbmu.ac.ir.

Author contributions

Somayeh Esmaeili supervised the project. Somayeh Esmaeili and Akram Alembagheri were the executors of this study and wrote the manuscript. Akram Alembagheri, Homa Hajimehdipoor, Rasool Choopani and Somayeh Esmaeili designed the study and revised the manuscript. All authors read and agreed to the final text.

Competing interests

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

Acknowledgments

This study is related to the project No. 1399/60857 from Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We also appreciate the "Student Research Committee" and "Research & Technology Chancellor" in Shahid Beheshti University of Medical Sciences for their financial support of this study.

Peer review information

Traditional Medicine Research thanks Sadique Hussain and other anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

ITM, Iranian traditional medicine; ATP, adenosine triphosphate; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; MDA, malondialdehyde; SOD, superoxide dismutase; IL, interleukin; LPS, lipopolysaccharide; GLUT, glucose transporter; STZ, streptozotocin; HbA1c, hemoglobin A1c; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE, angiotensin converting enzyme; DPPH, 2,2-diphenyl-1-picrylhydrazyl; NF-κB: Nuclear factor kappa B; BHT, butylated hydroxytoluene; IC_{50}, half-maximal inhibitory concentration; TC, total cholesterol; GSH, glutathion; FRAP, ferric reducing antioxidant power method.

Citation

Alembagheri A, Hajimehdipoor H, Choopani R, Esmaeili S. The role of selected medicinal plants from Iranian traditional medicine for the treatment of fatigue in metabolic syndrome. *Tradit Med Res*. 2023;8(4):23. doi: 10.53388/TMR20220706001.

Executive editor: Guang-Ze Ma.

Received: 06 July 2022; **Accepted:** 06 September 2022; **Available online:** 02 December 2022.

Abstract

Background: Fatigue is a symptom of metabolic disorders such as metabolic syndrome, which is currently increasing in the world. There is no specific medication for fatigue, but in many cases, such as in metabolic disorders, it can be relieved by treating the underlying causes. Oxidative stress and inflammation are associated with fatigue and metabolic syndrome. Other mechanisms in metabolic syndrome are also involved in causing fatigue. **Objective:** The aim of this study was to investigate the role of selected medicinal plants from Iranian traditional medicine (ITM) in improving fatigue in patients with metabolic syndrome. **Methods:** ITM is one of the most ancient systems of medicine. In this article, we first explained fatigue, its types, and treatment from the perspective of ITM and then introduced a list of medicinal plants used in ITM to treat fatigue. Next, we reviewed the biological effects of these plants effective in treating the manifestations of the metabolic syndrome based on a search of electronic databases. **Results:** They have antioxidant, anti-inflammatory, and anti-diabetic activities. Among them, *Matricaria chamomilla* L., *Laurus nobilis* L., *Origanum majorana* L., *Vitex agnus-castus* L., *Lawsonia inermis* L., *Anethum graveolens* L., and *Pistacia terebinthus* L. improve the lipid profile and reduce dyslipidemia. Also, the antihypertensive effects of *Matricaria chamomilla*, *Laurus nobilis*, and *Origanum majorana* have been proven. **Conclusion:** These plants prevent fatigue and disease progression by countering oxidative stress and inflammation and affecting the properties of the metabolic syndrome.

Keywords: medicinal plants; fatigue; metabolic syndrome; Iranian traditional medicine; Persian medicine

Traditional Medicine Research 2023;8(4):23. https://doi.org/10.53388/TMR20220706001

Highlights

This article reviews the medicinal plants for reducing fatigue based on Iranian traditional medicine. There is no specific medication for fatigue, but in many cases, such as in metabolic disorders, it can be relieved by treating the underlying causes. Upon review, we got 10 medicinal plants with have considerable potential for treating fatigue in metabolic syndrome. These plants prevent fatigue and disease progression by countering oxidative stress and inflammation and affecting the properties of the metabolic syndrome.

Background

Fatigue is one of the most common symptoms in clinical medicine. It is defined as difficulty in initiating or maintaining voluntary activities [1]. Fatigue affects more than 20% of people worldwide, impacts the individual's abilities, motivation, memory, concentration, and social performance, and increases their excitability [2, 3]. Systemic and neurological causes induce fatigue, but its exact cause is not known yet in some patients. It is considered a common complaint in many conditions, such as multiple sclerosis, Parkinson's disease, some endocrine diseases, chronic heart failure, cancer, and pregnancy. Many metabolic disorders, including metabolic syndrome, are associated with fatigue [4]. Due to people's current sedentary lifestyle, metabolic syndrome is very common in today's societies, with characteristics such as obesity, hyperglycemia, insulin resistance, hypertension, and dyslipidemia [5]. Oxidative stress, decreased antioxidant potential, and inflammation play essential roles in developing metabolic syndrome and its complications [6].

Mitochondrial dysfunction is an early pathophysiological event in obesity and insulin resistance [7]. Mitochondria regulate cellular homeostasis and produce energy as adenosine triphosphate (ATP). Most reactive oxygen species (ROS) originate from the mitochondrial respiratory chain. Dysfunction of the respiratory chain increases ROS production, decreases ATP production and antioxidative capacity, and induces apoptosis [6]. The normal cellular antioxidants that usually neutralize these free radicals cannot neutralize all of them, and thus damage to cellular components occurs [8]. Membrane phospholipids and their unsaturated fatty acids are very sensitive to oxidative damage by ROS and reactive nitrogen species, resulting in the production of lipid peroxides, which are cytotoxic and lead to free-radical damage to other lipids, DNA, and proteins [9]. The accumulation of oxidized fatty acids in mitochondria can result in progressive oxidative damage [9]. High caloric consumption rises plasma glucose and free fatty acid levels, which are closely correlated with high ROS formation and worsening obesity [6]. On the other hand, lessened mitochondrial function caused by ROS/reactive nitrogen species membrane oxidation is linked to fatigue [9]. Indeed, moderate to severe fatigue has been correlated to impairment of mitochondrial function and diminished production or leakage of ATP [8, 10]. The failure in ATP production reduces physical and mental performance [8]. In addition to triggering metabolic syndrome, oxidative stress can lead to inflammation, change in vascular function, and vascular disease [5] (Figure 1).

The metabolic syndrome is associated with a state of chronic low-grade inflammation [4, 5]. One of the underlying causes of this situation is the presence of visceral obesity, which, in addition to causing insulin resistance, increases the production of inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) [5, 11]. An increase in the level of inflammatory cytokines such as IL-6 and TNF-α leads to behavioral changes, including fatigue, sleep disturbances, and depressive-like symptoms [4, 12, 13]. TNF-α is effective in producing insulin resistance and down-regulates muscle glucose uptake [14]. Muscle cells uptake glucose via insulin-stimulated translocation of glucose transporter (GLUT)-4; the enzyme glucokinase mediates the following phosphorylation of glucose and its incorporation into the glycogen synthesis pathway. Insulin resistance is defined as the inability of insulin to activate glucose transport in adipose tissue and skeletal muscle and insufficient suppression of hepatic glucose production. Therefore, in patients with insulin resistance, impaired insulin-stimulated glucose transport significantly influences reducing the rate of insulin-stimulated muscle glycogen synthesis [14, 15]. In normal physiological conditions, the energy for muscle contraction is provided mainly by glycogen. Consequently, the muscle which has a poor glycogen reservoir, the rapid exhaustion would be clinically expressed as fatigue and weakness, and finally muscle wastage [14] (Figure 2).

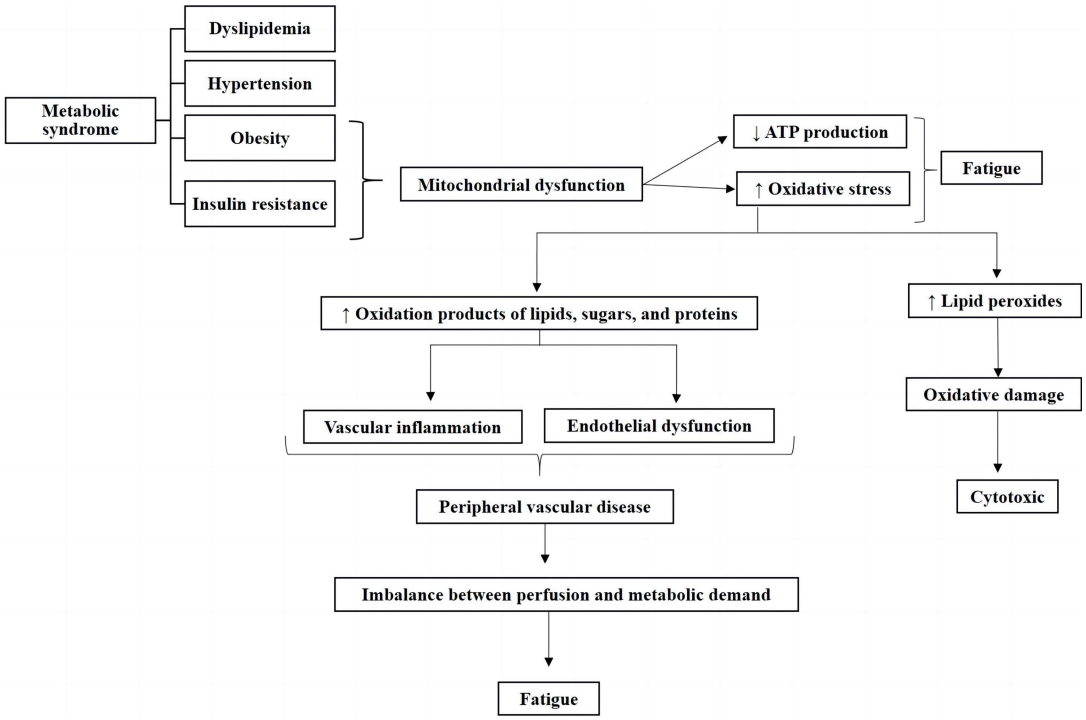

Figure 1 The mitochondrial dysfunction in metabolic syndrome causes fatigue through a variety of mechanisms. ATP, adenosine triphosphate.

Traditional Medicine Research 2023;8(4):23. https://doi.org/10.53388/TMR20220706001

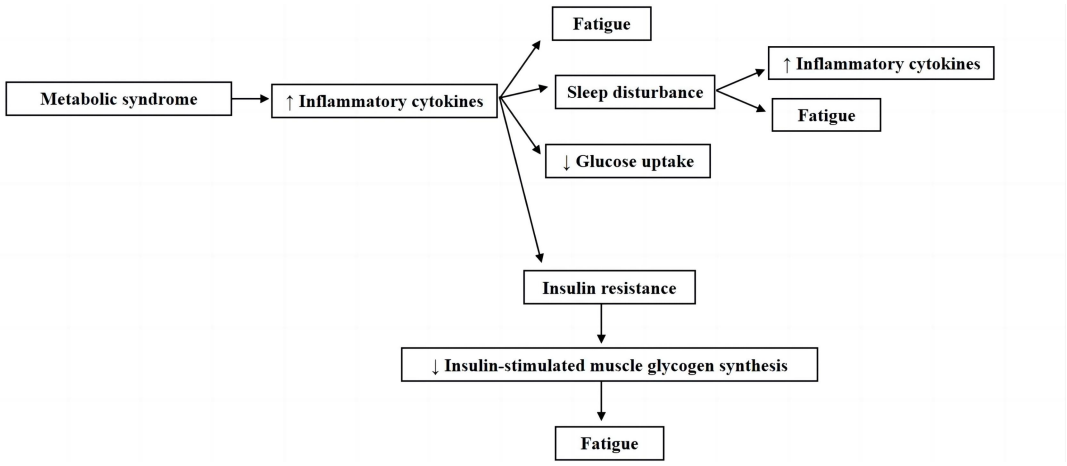

Figure 2 The metabolic syndrome is associated with a state of chronic low-grade inflammation, which causes fatigue via a variety of processes

There is an elevated risk for peripheral vascular disease in metabolic syndrome that fail to balance tissue perfusion with local metabolic demand. So the vascular networks can not deliver blood to working tissues in a suitable level and manner to meet the metabolic need effectively. In an increased metabolic amount, tissue and organ function becomes compromised due to an imbalance between perfusion and metabolic demand. This matter can create a compromised situation even at resting metabolic demands and is associated with a progressive decline in tissue perfusion, negatively affecting the skeletal muscle to resist fatigue. So muscle fatigue occurs faster during an increased metabolic demand [16, 17]. The presence of various factors in metabolic syndrome to cause fatigue can lead to a new approach to treating fatigue as a symptom of metabolic syndrome. There is no specific medication for fatigue [18]. Many researchers have shown an interest in medicinal plants and natural substances and their potential for curing fatigue, increasing physical strength, and eliminating fatigue-related metabolites [18, 19]. Modern pharmaceuticals and ethnopharmacology extensively use medicinal plants; nonetheless, traditional knowledge of medicinal plants in many societies merits further investigation [20]. Iranian traditional medicine (ITM), also known as Persian medicine, is rich in knowledge and information about the prevention, diagnosis, symptoms, and treatment of diseases and uses natural resources, including plants, animals, and minerals, to cure ailments and their symptoms [21–23]. According to ITM, health and disorder depend mainly on the temperament and balance of the humors. Each humor corresponds to a specific temperament. The humors are classified into four groups: “Dam” or blood (wet and hot temperament), “Balgham” or phlegm (wet and cold temperament), “Safraa” or yellow bile (dry and hot temperament), and “Soda” or black bile (dry and cold temperament). According to ITM, any imbalance in the humors leads to the onset of disease [21]. The present study aims to investigate the treatment of fatigue as a symptom of metabolic syndrome from the perspective of ITM.

Material and Methods

To investigate the types of fatigue and its treatment from the perspective of Iranian traditional medicine, three books *Al-Qanoon fi al-Tibb* (Avicenna, 970–1037 C.E.), *Eksir-e-Azam* (Azam Khan, 1857–1902 C.E.) and *Zakhire Kharazmshahi* (Jorjani, 1042–1136 C.E.) were consulted [21–23]. Furthermore, to identify medicinal plants that were used for easing or alleviating fatigue, this study used six books, including *Al-Qanoon Fi al-Tibb*, the *Makhzan-al-Adviah* (Aghili Khorasani, 12th AH century, 1771 C.E.) *Al-Havi* (Rhazes, 865–925 C.E.), *Al-Shamel fi Sena’ate Tabiee* (Ebn e Nafis Qarashi, 1210–1288 C.E.), *Al-abniye an- Hagha’egh-al- Adviah* (Heravi, 5th AH century), and *Tohfat-al- Mo’menin* (Hakim Mo’men, 11th AH century) [21 24–28]. Keywords such as “E’aya”, “Ta’ab”, “Mandegi” and “Khastegi”, which denote fatigue in Persian and Arabic, were selected. The matching and translation of traditional names into scientific terms were done using the following four books: matching the old medicinal plant names with scientific terminology, comparative description of ancient medicinal plants, encyclopedia of Traditional medicine (medicinal plants), and scientific names of medicinal plants used in traditional medicine [29–32]. Scientific names of the medicinal plants were searched in electronic databases, including PubMed, Science Direct, and Google Scholar. Data were collected from 2008 until December 2021. Only English and Persian language articles which have available full text were included. The study in electronic databases for each plant was performed as follow: “scientific name” (title/abstract) or “common name” (title/abstract) and “fatigue” (title/abstract) or “metabolic syndrome” (title/abstract) or “diabetes” (title/abstract) or “hypertension” (title/abstract]) or “antioxidant” (title/abstract) or “anti-inflammation” (title/abstract) or “oxidative stress” (title/abstract) or “hyperlipidemia” (title/abstract). We have considered in vitro, in vivo, and clinical studies.

Results

Fatigue and its treatment from the perspective of Iranian traditional medicine

Fatigue, with the keyword “E’aya”, is expressed as difficulty in moving and doing activities. According to the views of Iranian traditional physicians, fatigue may occur due to excessive physical activity or spontaneously in the absence of external factors [21–23]. They emphasized that fatigue caused by physical activity or exercise is less harmful than spontaneously occurring fatigue which can initiate a disease [21–23]. They categorized fatigue into four groups: “E’aya Ghoruhi” as ulcerous-sensed fatigue, “E’aya Tamaddodi”, which means tension-sensed fatigue, “E’aya Varami” as inflammation-related fatigue, and “E’aya Ghashafi” which means dry fatigue. The etiology and symptoms are different in each group. In general, the fatigue treatment depends on the type of fatigue and the person’s temperament, but some recommendations apply to all groups. The principles of treatment protocol comprise lifestyle changes, such as diet modification, sleeping regulation, emotional and mental relaxation, excretion of body wastes, and proper physical activity [21–23]. Massage with oils is also recommended. Here we give brief descriptions of all types of fatigue and their treatment.

E'aya Ghoruhi. E’aya Ghoruhi is a type of fatigue in which the person’s body feels sore and painful on the surface or inside the skin, especially when the skin is touched. It is difficult for the afflicted person to move, and while moving, they experience a painful sensation resembling stinging. With the increasing pain, fever and chills may also be present. It is believed that excessive hot humors (waste matter) are formed due to too much physical activity, causing fatigue. The cause must be considered in devising the treatment.

Physical activities that lead to fatigue should be moderated. To eliminate excess humors, abstaining from food or reducing food intake is recommended. Continued gentle massage with oil such as chamomile oil (*Matricaria chamomilla* L.) can disperse excess humors that are accumulated near the skin [21–23].

E'aya Tamaddodi. E'aya Tamaddodi is a type of fatigue in which the individual feels as if their body has been pounded and has a feeling of heat and tautness in the body. It is difficult for the person to move. This condition emanates from waste matter trapped in the muscles. Insufficient sleep is one of the causes of this type of fatigue. An important component of the treatment is relaxing the parts of the body that have become hard and rigid. Therefore, gentle massage with warm oil, prolonged bathing in lukewarm water, even two or three times a day, and rubbing oil onto the skin after each bath can help. Reducing food intake is even more important here. Exercise can break up and disperse the waste, resulting in the easing of this type of fatigue. The use of anise (*Pimpinella anisum* L.), cumin (*Cuminum cyminum* L.), and caraway (*Carum carvi* L.) can help in its treatment [21–23].

E'aya Varami. E'aya Varami is a type of fatigue in which a person's body is warmer than normal, and there is swelling on the skin that is irritated by touching and moving. There is also a sensation of tautness. The causes of this type of fatigue are similar to those of E'aya Tamaddodi. The treatment has three goals: relaxing and cooling the stretched and warm tissue and removing the waste. To achieve these goals, liberal use of warm oil, continued gentle massage, and long stays in the lukewarm bath are recommended. Modifying diet and eating less can help reduce waste [21–23].

E'aya Ghashafi. E'aya Ghashafi is a type of fatigue in which the person suffers from excessive dryness of humor, caused by too much activity, dry air, fasting, and low food intake [21–23].

We ranked the selected medicinal plants based on how many times their fatigue-reducing effects have been mentioned in the studied books. Plants mentioned three or more of in the six selected books are listed in Table 1.

Fatigue and its treatment from the perspective of conventional medicine

Fatigue is one of the most common complaints in clinical conditions [1]. It referred to a personal experience of physical and mental exhaustion and decreased energy levels [33, 34]. Studies show that if fatigue is left untreated, it can lead to chronic fatigue and chronic fatigue syndrome [34]. Chronic fatigue syndrome is a complex and debilitating condition in which fatigue does not improve with rest and is associated with mental and physical problems. It is strongly associated with immune system changes arising from physical and mental fatigue and lasts for six months or more [35]. Decreased antioxidant defense system, disruption of energy metabolism, and increased inflammatory factors are among the causes of chronic fatigue syndrome [36]. Obtaining a complete history from the patient is crucial to identify the underlying cause of the problem [1, 33]. Patient history should include a review of the lifestyle, diet, sleep schedule, daily activities, stress, depression, chronic illnesses, malnutrition, any medications used, and the time of the onset of fatigue [33]. Treatment is based on the diagnosis of the underlying cause of fatigue. In many cases, such as endocrine, nutritional, and metabolic disorders, fatigue is quickly relieved by treating the underlying cause. Antidepressants, graded exercise therapy, and cognitive behavioral therapy appear to be effective in treating chronic fatigue syndrome [33]. Because inflammatory cytokines, such as interleukin-1β and TNF-α are involved in fatigue, cytokine antagonists may be effective in treating fatigue [1].

Biological effects of selected medicinal plants from Iranian traditional medicine in fatigue treatment

The biological effects of selected medicinal plants related to fatigue and metabolic syndrome, retrieved from electronic databases, are summarized in Supplementary Table 1.

Chamomile (*Matricaria chamomilla* L.). Chamomile is the plant of the Asteraceae family. It contains various chemical compounds, such as phenolic compounds, flavonoids, sesquiterpenes, polyacetylenes, and coumarins, responsible for different pharmacological effects [37, 38]. Several studies have demonstrated its antioxidant activities. Chamazulene, a sesquiterpene, presents in essential oil scavenged free radicals [39]. The flower is rich in flavonoids and phenolic compounds. The ethanol and aqueous extracts of the flower decreased

Table 1 Medicinal plants with beneficial effects in reducing or curing fatigue based on Iranian traditional medicine

Scientific name	Common name	Traditional name	Family	Administration	Part used	Reference
Anethum graveolens L.	Dill	Shebet	Apiaceae	Topical	Leaf Seed	[21, 24, 27, 28]
Cymbopogon schoenanthus (L.) Spreng.	Camel grass	Ezkher	Poaceae	Topical	Fruit	[21, 25, 26, 27]
Dorema ammoniacum D. Don	Ammoniac gum	Oshagh	Apiaceae	Topical	Oelo-gum resin	[21, 25, 26]
Iris germanica L.	German Iris	Irsa	Iridaceae	Topical/Oral	Root	[21, 25, 26, 24, 28]
Laurus nobilis L.	Laurel	Ghar	Lauraceae	Topical	Leaf Seed	[21, 25, 26, 24, 28]
Lawsonia inermis L.	Henna	Henna	Lythraceae	Topical	Leaf	[21, 25, 26, 27]
Matricaria chamomilla L. Syn: *Matricaria recutita* L.	Chamomile	Babonaj	Asteraceae	Topical	Flower	[21, 26, 27, 24, 28]
Opopanax chironius (L.) W. D. J. Koch	–	Javshir	Apiaceae	Topical/Oral	Oelo-gum resin	[21, 25, 24, 26]
Origanum majorana L.	Sweet majoram	Marzanjosh/ Marzangosh	Lamiaceae	Topical/Oral	Leaf	[21, 25, 24, 26]
Pistacia terebinthus L.	Terebinth	Habbat-ol-khazra	Anacardiaceae	Topical	Fruit	[21, 25, 26]
Vitex agnus-castus L.	Chaste tree	Panj-angosht	Lamiaceae	Topical	Fruit	[21, 25, 26, 27]

oxidative stress and malondialdehyde (MDA) and improved the antioxidant system by increasing antioxidant enzymes such as superoxide dismutase (SOD) and catalase (Supplementary Table 1). The clinical trial results conducted by Zemestani et al. are in line with in vivo studies. The administration of chamomile tea to diabetic patients three times a day for eight weeks enhanced antioxidant status [40].

There are several in vitro studies on the anti-inflammatory effects of chamomile (Supplementary Table 1). Aqueous extracts of flower and apigenin (a flavonoid) have demonstrated anti-inflammatory effects. They reduced the production of TNF-α and IL-6 [41–44]. The aqueous extract inhibited cycloxygenase-2 enzyme activity and reduced lipopolysaccharide (LPS)-induced cycloxygenase-2 mRNA and protein expression in the model of LPS-stimulated macrophages. The sulindac, a non-steroidal anti-inflammatory drug, had similar effects in this study [42]. Also, short-term consumption of chamomile tea creates beneficial impacts on inflammatory markers, including high sensitive C-reactive protein and TNF-α in type 2 diabetic patients [45].

Moreover, chamomile tea reduced insulin resistance and the serum level of glucose, part of which is related to the reduction of inflammatory factors [45]. TNF-α is effective in creating insulin resistance by affecting several factors, including insulin signaling, GLUT-4, and adiponectin [45]. Ethanol and aqueous extracts of chamomile have reversed streptozotocin (STZ)-induced hyperglycemia in rats [46–48]. The aqueous extract, luteolin, and quercetin inhibited glycogen phosphorylase; furthermore, aqueous extract and quercetin inhibited hepatic glycogen degradation [47]. Rajagopalan et al. investigated the antihyperglycemic effects of an aqueous extract of chamomile in alloxan-induced diabetes in rats. The results revealed that administration of the extract at the dose of 300 mg/kg for six weeks reduced the glucose, hemoglobin A1c (HbA1c) level, and amylase activity, an enzyme involved in the release of glucose from food [49]. Also, chamomile tea demonstrated hypoglycemic and hypolipidemic effect in diabetic patients [50]. Heidary et al. evaluated the effects of the chamomile capsule (370 mg) on lipid profile in patients with the polycystic ovarian syndrome. The administration of chamomile capsule three times a day for 8 weeks did not have a significant effect on triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) level [51].

Chamomile beverages decreased systolic and diastolic blood pressures and heart rate in a clinical trial [52]. This result was in line with the in vivo study. Three different extracts of chamomile at the dose of 200 mg/kg and two doses of 100 and 200 mg/kg were administrated to the normotensive and hypertensive rats, respectively. The extracts significantly reduced blood pressure and heart rate and improved lipid profile. They also inhibited the angiotensin converting enzyme (ACE) at the concentration of 0.1 mg/mL [52].

Habibzadeh et al. evaluated the effect of foot massage with chamomile oil on the severity of fatigue in Hemodialysis patients. The results showed that foot massage with chamomile oil reduced fatigue and increased the quality of life [53].

Laurel (*Laurus nobilis* L.). Laurel is a plant that belongs to the Lauraceae family. The leaves contain chemical compounds such as alkaloids, flavonoids, terpenes, sesquiterpenic alcohols, polyphenols, vitamins, and minerals [54, 55]. Severina Pacific et al. investigated the antioxidant effect of alcohol extract and seven fractions using different in vitro antioxidant tests, including 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) scavenging activity and 2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonate tests. The results revealed that alcohol extract scavenged free radicals, but it was a weak scavenger of nitric oxide radicals. The aqueous fractions have shown weak scavenging ability than alcohol extract; in contrast, alcohol fractions were more active than parental extract [56]. The essential oil from the leaves of laurel is rich in 1,8-cineole, α-terpinyl acetate, sabinene, eugenol, linalool, and methyl eugenol [57, 58]. It has significant antioxidant activity that is more than butylated hydroxytoluene (BHT). The phenolic compounds in this plant directly correlate with antioxidant effects [57, 59].

Laurel also showed anti-inflammatory activity in several studies [60–64]. The aqueous extract of *Laurus nobilis* showed potent anti-inflammatory effects via inhibiting Nuclear factor kappa B (NF-κB)-dependent prostaglandin E2 production and cyclooxygenase-2 gene expression. Laurel affects the pathway responsible for transmitting the signals to cause inflammation [62]. Magnolialide, a sesquiterpene lactone, was isolated from the leaves of laurel. Magnolialide may be helpful in treating type-I IgE-mediated allergic inflammatory disease via inhibiting the production of IL-4 and suppressing the proliferation of IL-5-dependent Y16 early B cells [64]. Lindoldhamine, a bisbenzylisoquinoline alkaloid, was isolated from the leaves of laurel. It was administrated at a dose of 1 mg/kg in an animal model of Freund's adjuvant-induced inflammation. It decreased the paw edema [63]. Also, eucalyptol and *Laurus nobilis,* extract by affecting NF-κB signaling pathways, can reduce inflammatory cytokines, which ultimately suppress Propionibacterium acnes-induced skin inflammation [61].

The polyphenolic-rich fraction of leaves at half-maximal inhibitory concentration (IC_{50}) = 3.21 mg/mL inhibited α-glucosidase enzyme [59]. In addition, aqueous extract of leaves at IC_{50} = 25 ± 12 μg/mL inhibited human salivary α-amylase [65]. Inhibition of these two enzymes helps control blood sugar. Rafaat Mohammed et al. investigated the biological effects of laurel on STZ-induced diabetes in rats. The results confirmed the hypoglycemic effect of ethanol extract from leaves in which several mechanisms were involved, that is, increasing insulin secretion and decreasing the level of glucose. They suggested that the hypoglycemic effect of laurel may be similar to acarbose, a standard antihyperglycemic drug. Also, it reversed the pathological impacts of STZ in rat's pancreas and liver tissues [66]. In a clinical study, type 2 diabetic patients consumed capsules containing different amounts of laurel leaves for 30 days. The serum level of glucose, LDL, total cholesterol (TC), and TG decreased significantly in all three doses [67]. There was an increase in HDL in patients who took 1 or 2 g of leaves per day. In a group that consumed 3 g, the increase was not significant. Another clinical study confirms these results. It emphasized that consumption of leaves (2 g/d) for 30 days improves glucose and lipid profile, which ultimately reduces the cardiovascular risk in diabetic patients [68].

The polyphenolic fraction of laurel leaves also inhibited isolated pancreatic lipase [59]. As mentioned above, the lipid-lowering effect of this plant has been proven in some clinical studies. Chbili et al. evaluated the daily consumption of laurel tea on lipid profile. Daily consumption of laurel tea (5 g of dried leaves in 100 mL boiled water) for ten days in healthy volunteers significantly increased HDL, but the decreases in LDL and TG were not significant [69].

The polyphenolic fraction of laurel leaves have inhibitory activity against the ACE enzyme, which anti-hypertension effects should be further investigated in clinical trials [59].

Sweet majoram (*Origanum majorana* L.). The *Origanum majorana* L. commonly known as sweet majoram is a member of the Lamiaceae family. It contains tannic acid, coumarins, quercetin, flavonoids, chlorogenic acid, cinnamic acid, and rutin [70, 71].

The antioxidant effects of *Origanum majorana* have been confirmed in several in vitro and in vivo studies [70–77]. The methanolic extract of the seed with the maximum percent inhibition equal to 91.89% exhibited the best antioxidant activity in the DPPH test. The total antioxidant capacity and the antioxidant activity of the seed extracts in other tests were in the order: methanol > ethanol > acetone > chloroform [70]. Considering the β-carotene/linoleic acid assay, the essential oil of the aerial part showed better antioxidant activity compared to standard BHT, with IC_{50} 12.83 ± 1.04 and 75 ± 1 μg/mL, respectively [73]. The administration of the essential oil with the dose of 0.16 mL/kg twice daily for four weeks in the animal model of prallethrin induced oxidative damage and nephrotoxicity in the rats, attenuated the oxidative stress, and increased SOD and catalase activities [76]. The ethanol extract of the leaves of majoram significantly scavenged free radicals in the DPPH test and had remarkable reducing power. The total phenolic compounds were determined as 254 mg/g [72]. The comparison between the methanol, ethanol, diethyl ether, and hexane extracts of the leaves revealed that

the methanol extract with half maximal effective concentration 0.0013 ± 0.0001 had the best antioxidant activity, the antioxidant effects of other extracts were in the order: diethyl ether > ethanol > hexane [75]. The study results with Ghosian Moghaddam et al. revealed that adding marjoram leaves to animal food (6.25%) could reduce oxidative stress and glucose in the animal model of STZ-induced diabetes in the rats [77]. The methanol and aqueous extracts of the leaves and its essential oil with the dose of 400 mg/kg significantly elevated the SOD enzyme level in the animal model of STZ-nicotinamide induced non-insulin-dependent diabetes mellitus in the rats; also, the methanol extract and essential oil with both doses 200 and 400 mg/kg increased the catalase enzyme level [74].

M. Wahby et al. demonstrated the anti-inflammatory effects of the ethanol extract of the majoram leaves. The administration of 0.5 mg/kg of the ethanol extract for ten days in the animal model of the LPS-induced oxidative inflammation in rats decreased inflammation, peritoneal macrophages, and nitric oxide in the peritoneal fluid and liver. Furthermore, it improved the antioxidant system via increasing glutathion (GSH) and decreasing MDA [71].

Majoram, via several mechanisms, plays an essential role in regulating blood glucose. The essential oil of the majoram leaves, which contains sabinene, linalool, γ-terpinene, and α-terpinene, inhibited α-amylase enzyme [78]. Inhibiting the dipeptidyl peptidase IV enzyme helps reduce hyperglycemia and HbA1c levels. Also, reducing the protein tyrosine phosphatase 1B enzyme activity increases insulin sensitivity. The methanol extract of the majoram seed inhibited both dipeptidyl peptidase IV and protein tyrosine phosphatase 1B enzymes [79]. The methanol extract and essential oil of the leaves with the doses 100, 200, and 400 mg/kg and the aqueous extract with the dose of 400 mg/kg significantly reduced the glucose level in the animal model of STZ-nicotinamide induced non-insulin-dependent diabetes mellitus in the rats. The aqueous extract could not change the level of insulin. In contrast, all doses of essential oil and two doses of the methanol extract (200 and 400 mg/kg) increased the insulin level compared to glibenclamide. Each dose of the methanol extract and essential oil, and aqueous extract with the dose of 400 mg/kg significantly reduced the HbA1c level [74]. Pimple et al. demonstrated similar results, but in their study, the methanol, aqueous and essential oil with two doses of 200 and 400 mg/kg significantly reduced the HbA1c level. Furthermore, with these two doses, all extracts significantly improve lipid profile [80]. The administration of the ethanol extract of the majoram leaves with the doses 100, 200, and 400 mg/kg for three weeks exhibited hypoglycemic and hypolipidemic effects along with increasing HDL in STZ-induced diabetic rats [81, 82]. The administration of the aqueous extract of majoram leaves with a 20 mg/kg/day dose for two weeks resulted in improving dyslipidemia and hyperglycemia in the animal model of STZ-induced diabetes in rats with the high-fat diet. It up-regulated the gene expression, which is related to lipid and glucose metabolism, including GLUT-2, lipoprotein lipase, and adiponectin; also, it down-regulated the gene expression of leptin [83]. The aqueous extract also exhibited the hypoglycemic effect in alloxan-induced diabetic rats; decreasing oxidative stress plays an essential role [84].

The ethanol extract of majoram dose-dependently caused vasodilation which was effective in the anti-hypertensive activity [85].

Dill (*Anethum graveolens* L.). Dill is a member of the Apiaceae family. It contains various chemical compounds, including monoterpenoids, limonene, alkaloids, flavonoids, anthocyanins, tannins, carvone, and camphor [86–88].

The different extracts of dill exhibited antioxidant activity in the in vitro tests [87, 89–97]. Treatment of the diabetic rabbits with the ethanol extract of dill with a dose of 700 mg/kg for 45 days produced a significant increase in the GSH levels [86]. Furthermore, the ethanol extract inhibited lipid peroxidation in the dexamethasone-induced diabetic rats and enhanced antioxidant activity such as SOD, catalase, and GSH, and showed a hyperglycemic effect [98]. The methanol extract of dill restored the activity of antioxidant enzymes in the carbon tetrachloride-induced hepatotoxicity in rats, compared to the standard drug, silymarin [88, 99]. These results were also seen when using the aqueous extract in the paracetamol-induced hepatotoxicity in rats [100].

The isolated alkaloid from the aerial parts of dill (500 mg/kg) significantly increased total antioxidant capacity in the animal model of cholesterol-induced hypercholesterolemia in rabbits; also, it improved hyperlipidemia and decreased lipid peroxidation [101]. Bahramikia and Yazdanparast evaluated various fractions of dill in the animal model of hypercholesterolaemic rats. The results were consistent with previous studies. The diethyl ether, aqueous, and ethyl acetate fractions, in addition to the hypolipidemic effect, decreased lipid peroxidation and oxidative stress and improved the antioxidant system. The diethyl ether had the best activity, and the aqueous fraction was the least [102].

The chemical compounds including carvone, camphor, carveol, perillyl alcohol, and limonene in the dill essential oil have various antioxidant effects; among them, carveol showed the best free radical scavenging activity, while camphor showed the least [87]. The nanoemulsion of essential oil of dill at the doses of 0.125, 0.250, and 0.500 mg/L of drinking water inhibited the cadmium-induced oxidative stress in mice and down-regulated the iNOS gene that caused the anti-inflammatory activity [103]. The anti-inflammatory of the essential oil of dill has been reported previously. The essential oil at the concentration of 45 mg/mL inhibited LPS-induced nitric oxide secretion with an inhibition percentage equal to 82.0 ± 0.0 % [94].

The ethanol extract of dill seed (10–500 mg/kg) exhibited a hypoglycemic effect on glucose tolerance in rabbits [104]. Administration of capsules containing hydro alcohol extract of dill in patients with metabolic syndrome for 12 weeks did not have any significant effect on glucose level and blood pressure, but it lowered TG [105]. Mobasseri et al. conducted a clinical study that used dill tablets (1.1 g) three times a day for 8 weeks in diabetic patients. The results demonstrated the positive effects of dill in lowering insulin levels and improving lipid profile [106].

Two doses of the hydro alcohol extract of dill, 250 and 500 mg/L, were added to drinking water for 30 days in the NMRI mice. The hydro alcohol extract significantly lowered LDL, TG, and cholesterol and increased HDL [107]. The administration of hydro alcohol extract at the dose of 100 mg/kg for four weeks improved the lipid profile in the animal model of STZ-induced diabetes in rats. It did not significantly affect HDL level [108]. Masoume Mansouri et al. conducted a randomized, double-blind controlled trial to evaluate the effect of dill on metabolic parameters in patients with metabolic syndrome. The capsule containing the hydro alcohol extract of dill for 12 weeks was administrated. The dill capsule did not improve blood pressure and glucose level but significantly reduced TG from the baseline [105]. Consuming six dill tablets daily for two months in hyperlipidemic patients resulted in decreased TC and TG. The reduction of TC by dill tablet was more than gemfibrozil [109]. Also, administration of dill capsule containing 500 mg of a dill powder in hyperlipidemic patients twice a day for four weeks exhibited similar results and improved lipid profile [110].

Henna (*Lawsonia inermis* L.). *Lawsonia inermis* L., with the common name henna, is the Lythraceae family plant and contains various chemical compounds such as flavonoids, triterpenoids, aliphatic hydrocarbons, coumarin, and gallic acid derivatives. Several studies have proven the antioxidant activities of this plant [111–115]. That the ethanol extract of henna showned better free radical scavenging than the aqueous extract, his is due to the more phenolic substances in the ethanol extract [112]. The n-butanolic fraction of alcohol extract of henna leaves contains five phenolic glycosides. The n-butanolic fraction and its phenolic glycosides have antioxidant activity in b-carotene and DPPH tests. Among them, three compounds have potent antioxidant activity, and 1,2,4-trihydroxynaphthalene-1-J-b-D-glucopyranoside showed the highest antioxidant effect. It suggested that the antioxidant activity of phenolic compounds depends on the number of hydroxyl groups attached to the aromatic ring [113]. Also, the butanolic fraction has a

hepatoprotective effect in an animal model of 2-acetylaminofluorene induced hepatic damage in rats that were related to scavenging free radicals and inhibiting lipid peroxidation [111].

7-Hydroxy-3,5-dimethoxy-6,8-dimethylflavon (a flavone derivative) and eudesmane-4β,7α-diol (a eudesmane derivative) along with ten other compounds have been isolated from henna and evaluated anti-inflammatory effects in the LPS-stimulated macrophage. The results revealed that syzalterin, sideroxyline, and isoscopoletin had shown inhibitory effects on LPS-induced nitric oxide production [116]. In two animal models of formaldehyde-induced arthritis and Freund's adjuvant-induced arthritis in the rats, the hydro alcohol of henna decreased the inflammation via suppressing inflammatory mediators [117]. Daemi et al. evaluated the effect of topical use of an ointment containing 3% and 6% hydro alcohol extract of *Lawsonia inermis* leaves in rats' circular excisional wound model. Topical ointment decreased the edema score, inflammatory cell infiltration, and inflammatory phase, which finally improved wound healing. Furthermore, henna up-regulated the GlUT-1 and insulin-like growth factor I expression that increased the glucose uptake, an essential factor in wound healing [115].

The administration of the hydro alcohol extract of henna (400 mg/kg) significantly decreased the glucose in the animal model of alloxan-induced diabetes in rats. This reduction (39.08%) was comparable to metformin (46.30%) and glibenclamide (44.77%). The hydro alcohol extract increased the production of insulin. Also, it reduced the LDL, TG, very low density lipoprotein, and TC levels and increased HDL [118].

Ammoniac gum (*Dorema ammoniacum* D. Don). *Dorema ammoniacum* is a plant of the Apiaceae family. Based on ITM, the oleo-gum resin of this plant is called oshagh. The essential oil of the aerial part contains various compounds, including oxygenated non-terpenes, β-chamigrene, diterpenes, hydrocarbon sesquiterpenes, linalool, and α-pinene. The in vitro evaluation of the antioxidant effects of this plant showed that the ethyl acetate extracts of both aerial parts and roots, along with the chloroform extract of roots, were the best free radical scavenger in the DPPH test. In contrast, the essential oil of both parts of the plant showed the least antioxidant effects in the ferric reducing antioxidant power method (FRAP) and DPPH tests. In addition, the ethyl acetate extract of aerial parts and roots showed the highest ferric-reducing power in the FRAP test [119].

The aqueous solution of the gum exhibited dose-dependent anti-inflammatory activity in the animal model of carrageenan-induced edema in rats; the anti-inflammatory effect at a dose of 500 mg/kg was comparable to indomethacin [120].

The phytochemical investigation of the hydromethanol extract of *Dorema ammoniacum* root resulted in the isolation of six compounds. Among them, 1,5-dicaffeoylquinic acid at a concentration of 750 μM had a considerable inhibitory effect against the α-glucosidase enzyme, which was determined as 76.9% of the acarbose activity [121].

Camel grass (*Cymbopogon schoenanthus* (L.) Spreng.). *Cymbopogon schoenanthus* (L.) Spreng. is a member of the Poaceae family. The essential oil contains different chemical compounds such as oxygenated monoterpenes, monoterpene hydrocarbons, piperitone, limonene, and α-terpineol [122, 123]. Studying the essential oil from aerial parts of camel grass collected from the Illizi indicated weak antioxidant effects due to the low amount of phenolic substances [122]. The essential oil of dried and fresh leaves (67.3 ± 17.5% and 73.8 ± 2.1%, respectively) and dried roots (61.0 ± 5.6%) of *Cymbopogon schoenanthus* exhibited antioxidant activities that were comparable to standards: BHT (100.0 ± 0.0%), verbenone (77.1 ± 0.5%) and carvacrol (87.4 ± 1.5%) in DPPH test [124]. These results emphasize that the geographical origin and environmental conditions significantly impact the plant extracts' chemical components and biological activities [122, 124]. Furthermore, essential oil had significant metal chelating ability in the ferrous chelating test [123]. The hydro alcohol extract of the leaves with IC_{50} of 110 μg/mL had a dose-dependent antioxidant activity in the DPPH test, which was related to its flavonoid contents [125]. The aqueous extract also showed potent scavenging ability in the 2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonate test, making it effective like BHT [126].

The essential oil of the leaves inhibited the α-amylase enzyme, while it did not inhibit the α-glucosidase enzyme [1–3, 7, 8].

Golestaneh Talaei et al. evaluated the anti-inflammatory effect of the essential oil of camel grass. The essential oil at three doses, 50, 100, and 200 mg/kg, reversed the carrageenan-induced inflammation and reduced the inflammation and pain in the second phase of the formalin test due to the piperitone and other components of the essential oil [127]. The ethanol and aqueous extract of the aerial part showed an anti-inflammatory effect in an in vitro test. The inhibitory effect of the aqueous extract was more than the ethanol extract [128].

German Iris (*Iris germanica* L.). *Iris germanica* L., commonly known as german Iris, belongs to the Iridaceae family. The plant's phytochemical investigation has resulted in isolating different compounds, including triterpenes, ceramides, sterols, flavonoids, benzoquinones, and vitamins, especially ascorbic acid [129]. The antioxidant effects of this plant have been proven in various studies [129–133]. The ethanol extract of rhizome and aerial parts of *Iris. germanica* showed better antioxidant activity than BHT and ascorbic acid at similar concentrations in the β-carotene–linoleic acid method [132]. Sayyed et al. evaluated the antioxidant effects of methanol and dichloromethane extracts from different parts of the plant. The results revealed that the methanol extracts were significantly more potent than the dichloromethane extracts; such that methanol extract of rhizome, flower, and leaves showed the best antioxidant activity with half maximal effective concentration of 192.8, 174.4, and 106.8, respectively [130]. The isoflavonoids of the root, irilone, irigenin S, irisolidone, iridin, irilone 4'-O-β-D-glucopyranoside, and irigenin, had antioxidant activity in the DPPH test. Iridin A, an isoflavonoid glycoside with IC_{50} 8.91 μM, showed the best free radical scavenging activity among other compounds [129]. Also, 8-hydroxyirilone and 8-hydroxyirilone 5-methyl ether, with IC_{50} 9.23 and 12.92 μM, displayed noticeable antioxidant activities [131].

Iridin A, irigenin, and irisolidone, the isolated isoflavonoids, displayed inhibitory activity against α-amylase enzyme with % inhibition of 70.5, 67.5, and 70.8, respectively, compared the acarbose, a standard α-amylase inhibitor [129]. A study conducted with Sabrin et al. confirmed that irisolidone, 8-hydroxyirilone, 8-hydroxyirilone 5-methyl ether, and irilone inhibited α-amylase enzyme with % inhibition 70.1, 78.3, 66.1, and 67.3, respectively [131].

The mentioned isoflavonoids, irisolidone, irigenin S, irilone, irigenin, iridin, and irilone 4'-O-β-D-glucopyranoside, decreased paw edema and inflammation in an animal model of formalin-induced paw edema in rats. Studying the chemical structure of flavonoids showed that the presence of the C-2,3 double bond, the pyran ring, and a methoxyl group at C-5 and C-7 are effective in causing anti-inflammatory effects [134].

Chaste tree (*Vitex agnus-castus* L.). *Vitex agnus-castus* L. is a plant from the Lamiaceae family. The fruit contains several compounds, including sesquiterpenes, flavonoids, iridoids, diterpenoids, phenolic acids, and tannins [135, 136].

The aqueous extract of the fruit, rich in polar chemical compounds, exhibited the best antioxidant activities among the other extracts. The study emphasized that the polarity of the extract has an essential effect on antioxidant effects. In the β-carotene/linoleic acid test, the antioxidant activity of the aqueous extract was 94.07% ± 0.02, which is almost equal to BHT (94.68% ± 0.04). The essential oil was the weakest radical scavenger in the DPPH test, but it showed noticeable activity in the β-carotene/linoleic acid test [136]. The methanol extract has shown antioxidant activities and a significantly chelating ferrous ion in the ferric chelating antioxidant capacity test [137]. At the concentration of 0.5 mg/mL, the methanol extract had a higher scavenging ability of H_2O_2 than both standards, quercetin and rutin [137]. Also, casticin, a flavonoid isolated from the fruit of the chaste tree, exhibited antioxidant activity in different tests [135]. The administration of ethanol extract (600 mg/kg, twice daily) for one

week in the D-galactose-induced aging mouse model significantly attenuated oxidative stress, decreased MDA, and increased SOD and catalase activity as compared to the aging group [138].

Methyl 3,4-dihydroxybenzoate, p-hydroxybenzoic acid, and 3,4-dihydroxybenzoic acid have been isolated from the methanol extract aerial part. These compounds exhibited significant in vitro anti-inflammatory activity compared to both standards, indomethacin, and aspirin. Also, casticin and artemetin significantly inhibited lipoxygenase enzyme with IC_{50} 26.0 and 54.6 μM, respectively [139]. The other isolated compounds, 3,4-dihydroxybenzoic acid, 3,3'-dihydroxy-5,6,7,4'-tetramethoxy flavon, methyl 4-hydroxybenzoate, 5-hydroxy-2-methoxybenzoic acid, methyl 3,4-dihydroxybenzoate, and penduletin, did not inhibit this enzyme [139].

The hypoglycemic effects of the chaste tree have been confirmed in an animal model of STZ-induced diabetes in rats. The administration of the methanol extract of *Vitex agnus-castus* (300 mg/kg) for three weeks resulted in a gradually decreasing level of glucose, which represented a 66.52% reduction compared to the initial level. This amount for the glibenclamide-treated group was 72.87%. Furthermore, it improved the lipid profile, significantly decreased LDL and TG, and increased HDL [140]. Moreover, the hydro alcohol extract of this plant (600 mg/kg, bid, one week) improved homeostasis model assessment-estimated insulin resistance in the animal model of D-galactose-induced aging in female mice and showed pancreatic protection [141].

Terebinth (*Pistacia terebinthus* L.). *Pistacia terebinthus* L., commonly known as a terebinth is a member of the Anacardiaceae family. There are various chemical substances in this plant which are tannins, γ-tocopherol, quercetin, triterpenes, flavonoids, linoleic acid, α-pinene, sesquiterpene hydrocarbons, and limonene [142–145].

Considering the antioxidant effects, the ethanol and hydro alcohol extracts of the terebinth fruit exhibited better antioxidant activity than the dichloromethane and n-hexane extract in different in vitro antioxidant tests. The trolox equivalent antioxidant capacity, an indicator for antioxidant capacity, for the ethanol extract was equal to 0.985 ± 0.115 mmol/g, which was the best cupric-reducing activity [146]. While, the trolox equivalent antioxidant capacity for the crude extract of the leaf was 85.06 mmol/g, which was higher than synthetic antioxidants, BHT and butylated hydroxyanisole, and ascorbic acid [147]. The ethyl acetate and methanol extract of terebinth fruit also have shown their free radical scavenging in the DPPH test. In contrast, their N, N-dimethyl-p-phenylenediamine scavenging ability was lower as compared to DPPH. Neither of them could scavenge H_2O_2 radicals [143]. O¨ zcan et al. confirmed that pre-sonication could increase the terebinth extract's phenolic compounds and antioxidant capacity 142. Also, roasting the fruit can enhance the terebinth oil's antioxidant effects and oxidative stability [148]. In consistent with in vitro studies, the administration of an aqueous extract of flower (250 mg/kg) in an animal model of hydrogen peroxide-induced oxidative stress in rats reversed lipid peroxidation in the brain, kidney, and lungs; along with an increase in glutathione level and SOD and glutathione peroxidase enzyme activities [149].

Improving the antioxidant system plays an essential role in protecting β cells against oxidative stress. The *Pistacia terebinthus* oil has shown a hypoglycemic effect in STZ-induced diabetic rats. In addition to reducing MDA level and enhancing the antioxidant system, treatment of the diabetic rats with the terebinth oil with a dose of 2 mL/kg for 28 days resulted in decreasing glucose levels and improving lipid profile compared to the diabetic group without treatment [150]. Also, the aqueous extract of leaves and fruits of terebinth showed inhibitory effects against both α-glucosidase and α-amylase enzymes, which can help manage carbohydrate digestion and absorption [144]. The aqueous extract of leaves and fruits of terebinth inhibited pancreatic lipase with IC_{50} 9.0 ± 0.4 and 125.2 ± 12.1 μg/mL, respectively [144, 151].

Bahcecioglu et al. administrated terebinth coffee in water for the thioacetamide-induced liver injury in rats for eight weeks. The results demonstrated the protective effect of terebinth against hepatotoxicity. The terebinth coffee significantly reduced inflammation, fibrosis, and necrosis. It inhibited NF-κB activity and decreased TNF-α, IL-6, and transforming growth factor-beta [145].

Discussion

The metabolic syndrome comprises a constellation of metabolic defects such as insulin resistance, hypertension, dyslipidemia, and obesity [4]. There are various mechanisms in a metabolic syndrome that are effective in causing fatigue, including oxidative stress and inflammation, which have been recently introduced as underlying causes of metabolic syndrome [5]. The mitochondrial dysfunction due to obesity and insulin resistance increases oxidative stress and reduces ATP production, which causes fatigue [7]. Oxidative stress results in the accumulation of oxidation products of lipids, sugars, and proteins, which bring about changes in vascular function by causing vascular inflammation and endothelial dysfunction [6]. This condition leads to the elevated risk of peripheral vascular disease, which ultimately impaired tissue and organ function due to insufficient blood supply [16, 17]. On the other hand, inflammatory cytokines induced by visceral obesity, including IL-1, TNF-α, and IL-6, play an essential role in causing fatigue and sleep disturbances [12, 13]. That TNF-α and IL-6 by causing insulin resistance and, following that, reducing the glucose uptake, impairs insulin-stimulated muscle glycogen synthesis. So, the muscles get tired faster, shown as weakness and fatigue [4, 14, 15, 152].

From the perspective of ITM, the quality and quantity of the humors and the balances between them play an essential role in being healthy. Any changes in the quantity and quality of substances are called "So-e-Mizaj", which leads to changes in the blood contents, including sugar and fat, resulting in abnormal humor [21–23]. Weakness and fatigue are symptoms of the accumulation of abnormal humor in the body, which is also seen in the condition called "Emtela" [21]. The accumulation of abnormal humor, especially the dominancy of phlegm and moisture, is effective in causing fatigue [21–23, 153]. The amount of humor increases during Emtela, affecting the human metabolism [154]. Emtela leads to various symptoms and complications, such as high blood pressure, obesity, drowsiness, fatigue, and sluggish movement [21, 155]. The most common cause of Emtela is concentrated and viscous humor, such as viscous phlegm and significantly abnormal black bile, which are not readily excreted and increase blood viscosity. The increased blood viscosity reduces tissue blood flow and consequently reduces the function of the tissue and causes functional weakness and fatigue [156, 157].

Sleep deprivation is another cause of fatigue based on ITM. In other words, lack of sleep alters the function of the organs and changes the humor's quality and quantity, which results in So-e-Mizaj, Emtela, and their consequences [21, 158].

The scientific articles demonstrated that sleep deprivation increases the risk of metabolic defects and subsequent metabolic syndrome [159–166]. Regular sleep and circadian rhythm are crucial for metabolic and hormonal regulation, which control glucose and lipid metabolism. It is worth noting that circadian rhythm and sleep are the main factors for regulating energy metabolism [163]. The circadian rhythm disruption affects insulin and leptin secretion; also, it changes eating behaviors that contribute to obesity, especially abdominal obesity [162–165]. Besides, insufficient sleep leads to fatigue by increasing inflammatory cytokines such as IL-6 [167]. In general, short-term disruption of the circadian rhythm leads to fatigue, impaired concentration, and unwell being. Still, long-term disruption leads to impaired sugar and fat metabolism, obesity, diabetes, hypertension, dyslipidemia, depression, and mental disorders [163, 164]. Also, metabolic syndrome due to abdominal obesity is associated with obstructive sleep apnea syndrome, which is an important reason for excessive daytime sleepiness correlated with fatigue [1, 4, 165].

Mahjoub et al. compared the symptoms of E'aya with fatigue in conventional medicine. The results showed that E'aya has symptoms similar to chronic fatigue syndrome [153]. Given that some of the

mechanisms that cause fatigue in metabolic syndrome and chronic fatigue syndrome are similar, we can consider the recommendations suggested by ITM for treating E'aya.

The treatment of fatigue from the perspective of ITM and conventional medicine has common recommendations. One of the most important is to consider the underlying causes for planning the treatment. Both treatment systems recommend improving the quality of life, including modifications in diet, sleep pattern, and physical activity, as part of fatigue treatment [1, 21–23, 33]. A high-calorie diet raises blood glucose and lipid levels, leading to increased oxidative stress and obesity [6]. Several studies have demonstrated that caloric restriction with different fasting regimens can improve the glucose level as well as lipid profile and decrease blood pressure and body weight in patients with metabolic syndrome [168, 169]. Furthermore, 7-day fasting increased the quality of sleep and enhanced mode, resulting in decreasing fatigue [168]. This is in line with ITM suggestion for reducing food to eliminate excessive humor and prevent the Emtela from getting worse [21–23, 170]. In addition to changing sleep patterns and diet modification along with improving food timing, physical activity is important for enhancing sleep quality, decreasing mental stress, and preventing fatigue and obesity [14, 165, 171]. Overall, lifestyle modification must be designed based on the patient condition [153, 165].

Also, ITM has interventions to increase the catabolism of humor and its excretion [21–23, 153]. Massage with oils helps in this regard. It changes the viscosity of the humor, which accelerates its removal [153]. Scientific studies have confirmed that massage can reduce muscle tension, decrease swelling, enhance flexibility, and improve blood circulation and lymph flow. Therefore, massage has a good effect on recovering from exercise fatigue and injury [172, 173]. Clinical trials have explored the effectiveness of massage in reducing fatigue in various diseases such as cancer, chronic fatigue syndrome, and fibromyalgia [173–178]. The results showed that massage not only reduced fatigue but also relieved physical symptoms, depression, pain, and anxiety in patients with chronic fatigue syndrome [177].

Based on our review, 11 medicinal plants, frequently referred to in the most authoritative texts of ITM, were employed in fatigue treatment. In particular, their oils have been recommended topically. These plants have various biological activities. While the obvious, reducing oxidative stress, inflammation, and cardiovascular risk factors are important for treating metabolic syndrome and its complications, including fatigue [16]. Some biological effects related to the treatment of metabolic syndrome, including antioxidant, anti-inflammatory, anti-diabetic, antihypertensive, and anti-hyperlipidemic effects, have been established in several studies. Based of our knowledge, except for *Opopanax chironius*, all these plants have the biological effects on various components of metabolic syndrome or its side effects and underlying causes, such as oxidative stress and inflammation (Supplementary Table 1); in a way, they all show antioxidant, anti-inflammatory, and anti-diabetic activities, Their chemical substances, especially their flavonoids and phenolic compounds, have considerable effects in decreasing oxidative stress and increasing antioxidant enzymes such as SOD and catalase (Supplementary Table 1). Their anti-inflammatory effects are mediated through various mechanisms, such as reducing the macrophage numbers and inhibiting the production of pro-inflammatory cytokines such as IL-1 and TNF-α. These anti-inflammatory effects are in line with the therapeutic use of these plants in ITM for treating "Uram", swellings, some of which show symptoms of inflammation. It is also essential in relieving E'aya Varami, which is characterized by swelling [21–24]. Improving the antioxidant system and inhibiting α-glucosidase and α-amylase enzymes are involved in their anti-diabetic effects (Supplementary Table 1). Also, studies suggest that antioxidant administration improves hypertension through altering markers of oxidative stress, including enhancing FRAP, decreasing plasma lipid hydroperoxides and decreasing arterial stiffness, and enhancing brachial artery flow-mediated dilation. Additionally, considering the important role of the ACE in hypertension and metabolic syndrome, it has been shown that chamomile and laurel have inhibitory effects against ACE. Also, chamomile has been demonstrated to decrease systolic and diastolic blood pressures and the heart rate in clinical trials and hypertensive rats; besides, sweet majoram shows antihypertensive effects by vascular relaxation [52, 59, 85].

Another important feature of the metabolic syndrome is dyslipidemia which improves with the inhibition of pancreatic lipase. The polyphenolic-rich fraction of laurel and aqueous extract of terebinth inhibit this enzyme. In vivo studies have shown that extracts of several other plants, including chamomile, dill, henna, chaste tree, and sweet majoram, can improve dyslipidemia by decreasing TG, LDL, and TC and increasing HDL levels (Supplementary Table 1).

Numerous studies have proven the anti-fatigue effects of plants on physical fatigue and chronic fatigue syndrome [35, 36, 180–186]. Medicinal plants reduce fatigue by accelerating the elimination of metabolites caused by physical fatigue, improving the antioxidant system and inflammatory conditions [35, 36, 180–186].

Considering the pharmacological effects of the plants used in ITM to treat E'aya, these plants may effectively treat fatigue in patients with metabolic syndrome. Three species among them, chamomile, laurel, and sweet majoram, have remarkable effects on the underlying causes and characteristics of metabolic syndrome, such as diabetes, hypertension, and hyperlipidemia.

In conclusion, medicinal plants have considerable potential that makes them valuable candidates for the treatment of various diseases and complications based on the therapeutic approaches of ITM. The potentialities of *Matricaria chamomilla*, *Laurus nobilis*, and *Origanum majorana* have been confirmed through scientific studies. To further explore these plants' effects on curing fatigue in patients with metabolic syndrome, animal studies, and clinical trials should be performed.

References

1. Fauci AS. *Harrison's Principles of Internal Medicine*. New York, NY: McGraw-Hill Education; 2015. Available at: https://lib.hpu.edu.vn/handle/123456789/32524
2. Geng P, Siu KC, Wang Z, et al. Antifatigue Functions and Mechanisms of Edible and Medicinal Mushrooms. *BioMed Res Int* 2017;2017:1–16. Available at: http://dx.doi.org/10.1155/2017/9648496
3. Yu DS, Lee DT, Man NW. Fatigue among older people: A review of the research literature. *Int J Nurs Stud* 2010;47(2):216–228. Available at: http://dx.doi.org/10.1016/j.ijnurstu.2009.05.009
4. Kaltsas G, Vgontzas A, Chrousos G. Fatigue, Endocrinopathies, and Metabolic Disorders. *PMR* 2010;2:393–398. Available at: http://dx.doi.org/10.1016/j.pmrj.2010.04.011
5. Monserrat-Mesquida M, Quetglas-Llabrés M, Capó X, et al. Metabolic Syndrome Is Associated with Oxidative Stress and Proinflammatory State. *Antioxidants* 2020;9:236. Available at: http://dx.doi.org/10.3390/antiox9030236
6. Vona R, Gambardella L, Cittadini C, et al. Biomarkers of Oxidative Stress in Metabolic Syndrome and Associated Diseases. *Oxid Med Cell Longev* 2019;2019:1–19. Available at: http://dx.doi.org/10.1155/2019/8267234
7. Cheng Z, Almeida F. Mitochondrial alteration in type 2 diabetes and obesity: An epigenetic link. *Cell Cycle* 2014;13:890–897. Available at: http://dx.doi.org/10.4161/cc.28189
8. Nicolson GL, Rosenblatt S, et al. Clinical Uses of Membrane Lipid Replacement Supplements in Restoring Membrane Function and Reducing Fatigue. *Discoveries* (*Craiova*) 2016;4:e54. Available at: http://dx.doi.org/10.15190/d.2016.1
9. Nicolson GL. Metabolic syndrome and mitochondrial function: Molecular replacement and antioxidant supplements to prevent membrane peroxidation and restore mitochondrial function. *J Cell Biochem* 2007;100:1352–1369. Available at:

http://dx.doi.org/10.1002/jcb.21247
10. Filler K, Lyon D, Bennett J, et al. Association of mitochondrial dysfunction and fatigue: A review of the literature. *BBA Clin* 2014;1:12–23. Available at: http://dx.doi.org/10.1016/j.bbacli.2014.04.001
11. Kyrou I, Chrousos GP, Tsigos C. Stress, Visceral Obesity, and Metabolic Complications. *Ann N Y Acad Sci* 2006;1083:77–110. Available at: http://dx.doi.org/10.1196/annals.1367.008
12. Bower JE, Ganz PA, Irwin MR, et al. Inflammation and Behavioral Symptoms After Breast Cancer Treatment: Do Fatigue, Depression, and Sleep Disturbance Share a Common Underlying Mechanism? *JCO* 2011;29:3517–3522. Available at: http://dx.doi.org/10.1200/JCO.2011.36.1154
13. Lasselin J, Capuron L. Chronic Low-Grade Inflammation in Metabolic Disorders: Relevance for Behavioral Symptoms. *Neuroimmunomodulation* 2014;21:95–101. Available at: http://dx.doi.org/10.1159/000356535
14. Rojas-Rodríguez J, Escobar-Linares LE, Garcia-Carrasco M, et al. The relationship between the metabolic syndrome and energy-utilization deficit in the pathogenesis of obesity-induced osteoarthritis. *Med Hypotheses* 2007;69:860–868. Available at: http://dx.doi.org/10.1016/j.mehy.2007.01.075
15. Schinner S, Scherbaum WA, Bornstein SR, et al. Molecular mechanisms of insulin resistance. *Diabet Med* 2005;22:674–682. Available at: http://dx.doi.org/10.1111/j.1464-5491.2005.01566.x
16. Frisbee JC, Goodwill AG, Frisbee SJ, et al. Microvascular perfusion heterogeneity contributes to peripheral vascular disease in metabolic syndrome. *J Physiol* 2014;594:2233–2243. Available at: http://dx.doi.org/10.1113/jphysiol.2014.285247
17. Frisbee JC, Goodwill AG, Butcher JT, et al. Divergence between arterial perfusion and fatigue resistance in skeletal muscle in the metabolic syndrome. *Exp Physiol* 2011;96:369–383. Available at: http://dx.doi.org/10.1113/expphysiol.2010.055418
18. Tan W, Yu K, Liu Y, et al. Anti-fatigue activity of polysaccharides extract from Radix Rehmanniae Preparata. *Int J Biol Macromol* 2012;50:59–62. Available at: http://dx.doi.org/10.1016/j.ijbiomac.2011.09.019
19. Hsiao CY, Hsu YJ, Tung YT, et al. Effects of Antrodia camphorata and Panax ginseng supplementation on anti-fatigue properties in mice. *J Vet Med Sci* 2018;80(2):284–291. Available at: http://dx.doi.org/10.1292/jvms.17-0572
20. Ningthoujam SS, Talukdar AD, Potsangbam KS, et al. Challenges in developing medicinal plant databases for sharing ethnopharmacological knowledge. *J Ethnopharmacol* 2012;141:9–32. Available at: http://dx.doi.org/10.1016/j.jep.2012.02.042
21. Avicenna. *The Canon of Medicine (Al-Qanon fi al-Tibb). Beirut: Dar Ihyaa al-Turaath al-Arabi*; 2005. (Arabic)
22. Cheshti MA. Exir-e Azam (Azam's Elixir). Tehran: Iran University of Medical Science, Institute for Islamic and Complementary Medicine; 2007. (Persian)
23. Esmaeil J. *Zakhir-e-Kharazm Shahi*. Qom: Institute of Natural Medicine Rehabilitation; 2013.
24. Aghili MH. *Makhzan-al-Advia*. Tehran: Tehran University of Medical Sciences; 2009. (Persian)
25. Rhazes (Razi MZ). *Al-Hawi (The Continens)*. Tabatabaei SM. (Translator). Tehran: Al-Hawi Pharmaceutical Company Press. 1991. (Arabic)
26. Gharashi EN. *Al-Shamel Fe-Sena'at-e- Tabiee*. Tehran: Iran University of Medical Sciences; 2009.
27. Heravi M. *Al-Abniye an- Hagha'egh-Al- Adviah*. Tehran: University of Tehran Press; 1968.
28. Momen Tonekaboni M. *Tohfat-al- Mo'menin*. Qom: Noore Vahy, 2011. (Persian)
29. Ahmad Reza Okhovat AG. *Matching the Old Medicinal Plant Names with Scientific Terminology*. Tehran: University of Tehran Press; 2005.
30. Okhovat A, Ghahreman A. *Comparative Description of Ancient Medicinal Plants*. Tehran: University of Tehran Press; 2010.
31. Soltani A. *Encyclopedia of Traditional Medicine* (*Medicinal Plants*). Tehran: Arjmand press; 2006.
32. Dini M. *Scientific Names of Medicinal Plants Used in Traditional Medicine*. Tehran: Forests and Range lands Research Institute; 2006.
33. Dennis Kasper, Anthony Fauci SH. *Harrison's Manual of Medicine*. New York, NY: McGraw-Hill Education; 2016.
34. Wan J, Qin Z, Wang P, et al. Muscle fatigue: general understanding and treatment. *Exp Mol Med* 2017;49:e384. Available at: http://dx.doi.org/10.1038/emm.2017.194
35. Chi A, Kang C, Zhang Y, et al. Immunomodulating and antioxidant effects of polysaccharide conjugates from the fruits of Ziziphus Jujube on Chronic Fatigue Syndrome rats. *Carbohydr Polym* 2015;122:189–196. Available at: http://dx.doi.org/10.1016/j.carbpol.2014.12.082
36. Lee JS, Kim HG, Han JM, et al. Anti-fatigue effect of Myelophil in a chronic forced exercise mouse model. *Eur J Pharmacol* 2015;764:100–108. Available at: http://dx.doi.org/10.1016/j.ejphar.2015.06.055
37. Kolodziejczyk-Czepas J, Bijak M, Saluk J, et al. Radical scavenging and antioxidant effects of *Matricaria chamomilla* polyphenolic–polysaccharide conjugates. *Int J Biol Macromol* 2015;72:1152–1158. Available at: http://dx.doi.org/10.1016/j.ijbiomac.2014.09.032
38. Singh O, Khanam Z, Misra N, et al. Chamomile (*Matricaria chamomilla* L.): An overview. *Phcog Rev* 2011;5:82. Available at: http://dx.doi.org/10.4103/0973-7847.79103
39. Querio G, Antoniotti S, Foglietta F, et al. Chamazulene Attenuates ROS Levels in Bovine Aortic Endothelial Cells Exposed to High Glucose Concentrations and Hydrogen Peroxide. *Front Physiol* 2018;9. Available at: http://dx.doi.org/10.3389/fphys.2018.00246
40. Zemestani M, Rafraf M, Asghari-Jafarabadi M. Chamomile tea improves glycemic indices and antioxidants status in patients with type 2 diabetes mellitus. *Nutrition* 2016;32:66–72. Available at: http://dx.doi.org/10.1016/j.nut.2015.07.011
41. Gupta. Chamomile: An anti-inflammatory agent inhibits inducible nitric oxide synthase expression by blocking RelA/p65 activity. *Int J Mol Med* 2010;26. Available at: http://dx.doi.org/10.3892/ijmm_00000545
42. Srivastava JK, Pandey M, Gupta S. Chamomile, a novel and selective COX-2 inhibitor with anti-inflammatory activity. *Life Sciences* 2009;85:663–669. Available at: http://dx.doi.org/10.1016/j.lfs.2009.09.007
43. Miguel FG, Cavalheiro AH, Spinola NF, et al. Validation of a RP-HPLC-DAD Method for Chamomile (*Matricaria recutita*) Preparations and Assessment of the Marker, Apigenin-7-glucoside, Safety and Anti-Inflammatory Effect. *Evid Based Complement Alternat Med* 2015;2015:1–9. Available at: http://dx.doi.org/10.1155/2015/828437
44. Drummond EM, Harbourne N, Marete E, et al. Inhibition of Proinflammatory Biomarkers in THP1 Macrophages by Polyphenols Derived From Chamomile, Meadowsweet and Willow bark. *Phytother Res* 2012;27:588–594. Available at: http://dx.doi.org/10.1002/ptr.4753
45. Zemestani M, Rafraf M, Asghari-Jafarabadi M. Effects of chamomile tea on inflammatory markers and insulin resistance in patients with type 2 diabetes mellitus. *Trends Gen Pract* 2018;1. Available at: http://dx.doi.org/10.15761/TGP.1000117
46. Cemek M, Kağa S, Şimşek N, et al. Antihyperglycemic and antioxidative potential of *Matricaria chamomilla* L. in

streptozotocin-induced diabetic rats. *J Nat Med* 2008;62:284–293. Available at: http://dx.doi.org/10.1007/s11418-008-0228-1
47. Kato A, Minoshima Y, Yamamoto J, et al. Protective Effects of Dietary Chamomile Tea on Diabetic Complications. *J Agric Food Chem* 2008;56:8206–8211. Available at: http://dx.doi.org/10.1021/jf8014365
48. Najla OA, Olfat AK, Kholoud SR, Enas ND, Hanan ISA. Hypoglycemic and Biochemical Effects of *Matricaria Chamomilla* Leave Extract in Streptozotocin-Induced Diabetic Rats. *J Heal Sci*. 2012;2(5):43–48. http://dx.doi.org/10.5923/j.health.20120205.01
49. Prasanna R, Ashraf EA, Essam MA. Chamomile and oregano extracts synergistically exhibit antihyperglycemic, antihyperlipidemic, and renal protective effects in alloxan-induced diabetic rats. *Can J Physiol Pharmacol* 2017;95:84–92. Available at: http://dx.doi.org/10.1139/cjpp-2016-0189
50. Rafraf M, Zemestani M, Asghari-Jafarabadi M. Effectiveness of chamomile tea on glycemic control and serum lipid profile in patients with type 2 diabetes. *J Endocrinol Invest* 2014;38:163–170. Available at: http://dx.doi.org/10.1007/s40618-014-0170-x
51. Akbarzadeh M, Heidary M, Yazdanpanahi Z, et al. Effect of chamomile capsule on lipid- and hormonal-related parameters among women of reproductive age with polycystic ovary syndrome. *J Res Med Sci* 2018;23:33. Available at: http://dx.doi.org/10.4103/jrms.JRMS_90_17
52. Awaad AA, El-Meligy RM, Zain GM, et al. Experimental and clinical antihypertensive activity of*Matricaria chamomilla* extracts and their angiotensin-converting enzyme inhibitory activity. *Phytother Res* 2018;32:1564–1573. Available at: http://dx.doi.org/10.1002/ptr.6086
53. Habibzadeh H, Dalavan OW, et al. Effects of Foot Massage on Severity of Fatigue and Quality of Life in Hemodialysis Patients : A Randomized Controlled Trial. *IJCBNM* 2020;8(2):92–102. http://dx.doi.org/10.30476/IJCBNM.2020.81662.0.92
54. Stefanova G, Girova T, Gochev V, et al. Comparative study on the chemical composition of laurel (*Laurus nobilis* L.) leaves from Greece and Georgia and the antibacterial activity of their essential oil. *Heliyon* 2020;6:e05491. Available at: http://dx.doi.org/10.1016/j.heliyon.2020.e05491
55. Fidan H, Stefanova G, Kostova I, et al. Chemical Composition and Antimicrobial Activityof *Laurus nobilis* L. Essential Oils from Bulgaria. *Molecules* 2019;24:804. Available at: http://dx.doi.org/10.3390/molecules24040804
56. Paci S, Gallicchio M, Lorenz P, et al. Neuroprotective Potential of *Laurus nobilis* Antioxidant Polyphenol- Enriched Leaf Extracts. *Chem Res Toxicol* 2014;27(4):611–626. Available at: http://dx.doi.org/10.1021/tx5000415
57. Nabiha B, Abdelfateh EO, Faten K, et al. Chemical Composition and Antioxidant Activity of*Laurus nobilis* Floral Buds Essential Oil. *J Essent Oil Bearing Plants* 2009;12:694–702. Available at: http://dx.doi.org/10.1080/0972060X.2009.10643777
58. Caputo L, Nazzaro F, Souza L, et al. *Laurus nobilis*: Composition of Essential Oil and Its Biological Activities. *Molecules* 2017;22:930. Available at: http://dx.doi.org/10.3390/molecules22060930
59. Sakulnarmrat K, Konczak I. Composition of native Australian herbs polyphenolic-rich fractions and in vitro inhibitory activities against key enzymes relevant to metabolic syndrome. *Food Chem* 2012;134:1011–1019. Available at: http://dx.doi.org/10.1016/j.foodchem.2012.02.217
60. Bennett L, Abeywardena M, Burnard S, et al. Molecular Size Fractions of Bay Leaf (*Laurus nobilis*) Exhibit Differentiated Regulation of Colorectal Cancer Cell Growth In Vitro. *Nutr Cancer* 2013;65:746–764. Available at: http://dx.doi.org/10.1080/01635581.2013.796999
61. Lee EH, Shin JH, Kim SS, et al. Suppression of Propionibacterium acnes-Induced Skin Inflammation by *Laurus nobilis* Extract and Its Major Constituent Eucalyptol. *Int J Mol Sci* 2019;20:3510. Available at: http://dx.doi.org/10.3390/ijms20143510
62. Orlando RA, Gonzales AM, Hunsaker LA, et al. Inhibition of Nuclear Factor κB Activation and Cyclooxygenase-2 Expression by Aqueous Extracts of Hispanic Medicinal Herbs. *J Med Food* 2010;13:888–895. Available at: http://dx.doi.org/10.1089/jmf.2009.1128
63. Osmakov DI, Koshelev SG, Palikov VA, et al. Alkaloid Lindoldhamine Inhibits Acid-Sensing Ion Channel 1a and Reveals Anti-Inflammatory Properties. *Toxins* 2019;11:542. Available at: http://dx.doi.org/10.3390/toxins11090542
64. Lee T, Lee S, Ho Kim K, et al. Effects of magnolialide isolated from the leaves of *Laurus nobilis* L. (Lauraceae) on immunoglobulin E-mediated type I hypersensitivity in vitro. *J Ethnopharmacol* 2013;149:550–556. Available at: http://dx.doi.org/10.1016/j.jep.2013.07.015
65. Takács I, Takács Á, Pósa A, et al. HPLC method for measurement of human salivary α-amylase inhibition by aqueous plant extracts. *Acta Biol Hung* 2017;68:127–136. Available at: http://dx.doi.org/10.1556/018.68.2017.2.1
66. Mohammed RR, Omer AK, Yener Z, et al. Biomedical effects of *Laurus nobilis* L. leaf extract on vital organs in streptozotocin-induced diabetic rats: Experimental research. *Ann Med Surg* 2021;61:188–197. Available at: http://dx.doi.org/10.1016/j.amsu.2020.11.051
67. Khan A, Zaman G, Anderson RA. Bay Leaves Improve Glucose and Lipid Profile of People with Type 2 Diabetes. *J Clin Biochem Nutr* 2009;44:52–56. Available at: http://dx.doi.org/10.3164/jcbn.08-188
68. Aljamal A. Effects of Bay Leaves on the Patients with Diabetes Mellitus. *Res J of Med Plant* 2011;5:471–476. Available at: http://dx.doi.org/10.3923/rjmp.2011.471.476
69. Chbili C, Maoua M, Selmi M, et al. Evaluation of Daily *Laurus nobilis* Tea Consumption on Lipid Profile Biomarkers in Healthy Volunteers. *J Am Coll Nutr* 2020;39:733–738. Available at: http://dx.doi.org/10.1080/07315724.2020.1727787
70. Dhull SB, Kaur P, Purewal SS. Phytochemical analysis, phenolic compounds, condensed tannin content and antioxidant potential in Marwa (*Origanum majorana*) seed extracts. *Resour Effic Technol* 2016;2:168–174. Available at: http://dx.doi.org/10.1016/j.reffit.2016.09.003
71. Wahby MM, Yacout G, Kandeel K, et al. LPS-induced oxidative inflammation and hyperlipidemia in male rats: The protective role of *Origanum majorana* extract. *Beni Suef Univ J Basic Appl Sci* 2015;4:291–298. Available at: http://dx.doi.org/10.1016/j.bjbas.2015.11.004
72. Amarowicz R, Żegarska Z, Rafałowski R, et al. Antioxidant activity and free radical-scavenging capacity of ethanolic extracts of thyme, oregano, and marjoram. *Eur J Lipid Sci Technol* 2009;111:1111–1117. Available at: http://dx.doi.org/10.1002/ejlt.200800170
73. Hajlaoui H, Mighri H, Aouni M, et al. Chemical composition and in vitro evaluation of antioxidant, antimicrobial, cytotoxicity and anti-acetylcholinesterase properties of Tunisian *Origanum majorana* L. essential oil. *Microb Pathog* 2016;95:86–94. Available at: http://dx.doi.org/10.1016/j.micpath.2016.03.003
74. Pimple B, Kadam P, Patil MJ. Ulcer healing properties of different extracts of *Origanum majorana* in streptozotocin-nicotinamide induced diabetic rats. *Asian Pacific J Trop Dis* 2012;2:312–318. Available at: http://dx.doi.org/10.1016/S2222-1808(12)60068-1
75. Roby MHH, Sarhan MA, Selim KA-H, et al. Evaluation of antioxidant activity, total phenols and phenolic compounds in thyme (*Thymus vulgaris* L.), sage (*Salvia officinalis* L.), and marjoram (*Origanum majorana* L.) extracts. *Ind Crop Prod*

2013;43:827–831. Available at: http://dx.doi.org/10.1016/j.indcrop.2012.08.029
76. Refaie AAER, Ramadan A, Mossa ATH. Oxidative damage and nephrotoxicity induced by prallethrin in rat and the protective effect of *Origanum majorana* essential oil. *Asian Pacific J Trop Med* 2014;7:S506–S513. Available at: http://dx.doi.org/10.1016/S1995-7645(14)60282-0
77. Ghosian Moghaddam M, Ansari I, Roghani M, et al. The Effects of *Origanum Majorana* on Oxidative Stress and Histopathology of Renal Tissue among Streptozotocin-Induced Diabetic Rats. *Thrita J Med Sci* 2013;2:29–34. Available at: http://dx.doi.org/10.5812/thrita.9282
78. Capetti F, Cagliero C, Marengo A, et al. Bio-Guided Fractionation Driven by In Vitro α-Amylase Inhibition Assays of Essential Oils Bearing Specialized Metabolites with Potential Hypoglycemic Activity. *Plants* 2020;9:1242. Available at: http://dx.doi.org/10.3390/plants9091242
79. Bower AM, Real Hernandez LM, Berhow MA, et al. Bioactive Compounds from Culinary Herbs Inhibit a Molecular Target for Type 2 Diabetes Management, Dipeptidyl Peptidase IV. *J Agric Food Chem* 2014;62:6147–6158. Available at: http://dx.doi.org/10.1021/jf500639f
80. Pimple BP, Kadam PV, Patil MJ. Comparative antihyperglycaemic and antihyperlipidemic effect of *Origanum majorana* extracts in NIDDM rats. *Orient Pharm Exp Med* 2011;12:41–50. Available at: http://dx.doi.org/10.1007/s13596-011-0047-x
81. Tripathy B, Satyanarayana S, Abedulla Khan K, et al. A Comparative Study On Antidiabetic Effects Of Ethanol Extract Of *Origanum majorana* And Indigofera Linnaei Ali On Streptozotocin Induced Diabetic Rats. *Am J PharmTech Res* 2018;8:167–178. Available at: http://dx.doi.org/10.46624/ajptr.2018.v8.i1.011
82. Tripathy B, Satyanarayana S, Abedulla Khan K, et al. A Comparative Study On Antidiabetic Effects Of Ethanol Extract Of *Origanum majorana* And Indigofera Linnaei Ali On Streptozotocin Induced Diabetic Rats. *AJPTR* 2018;8:167–178. Available at: http://dx.doi.org/10.46624/ajptr.2018.v8.i1.011
83. Soliman MM, Nassan MA, Ismail TA. *Origanum Majoranum* Extract Modulates Gene Expression, Hepatic and Renal Changes in a Rat Model of Type 2 Diabetes. *Iran J Pharm Res* 2016;15(Suppl):45–54. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5242351/
84. Oaman HF, Abbas OA. Beneficial effects of *Origanum majorana* on some biochemical and histological changes in alloxan-induced diabetic rat. *Arab J Nucl Sci Appl* 2010;43:269–280. Available at: https://inis.iaea.org/search/search.aspx?orig_q=RN:41053670
85. Badran A, Baydoun E, Samaha A, et al. Marjoram Relaxes Rat Thoracic Aorta Via a PI3-K/eNOS/cGMP Pathway. *Biomolecules* 2019;9:227. Available at: http://dx.doi.org/10.3390/biom9060227
86. Shakir WA, Khalil LW. The protective role of alcoholic extract of (*Anethum graveolens*) seeds on renal function in alloxan induced diabetic rabbits. *Iraqi J Vet Med* 2015;39:1–6. Available at: http://dx.doi.org/10.30539/iraqijvm.v39i2.169
87. Kaur N, Chahal KK, Kumar A, Singh R, Bhardwaj U. Antioxidant activity of Anethum graveolens L . essential oil constituents and their chemical analogues. *J Food Biochem* 2019;e12782:1–11. Available at: http://dx.doi.org/10.1111/jfbc.12782
88. Oshaghi EA, Khodadadi I, Mirzaei F, et al. Methanolic Extract of Dill Leaves Inhibits AGEs Formation and Shows Potential Hepatoprotective Effects in CCl_4 Induced Liver Toxicity in Rat. *J Pharm* 2017;2017:6081374. Available at: http://dx.doi.org/10.1155/2017/6081374
89. Shyu YS, Lin JT, Chang YT, et al. Evaluation of antioxidant ability of ethanolic extract from dill (*Anethum graveolens* L.) flower. *Food Chem* 2009;115:515–521. Available at: http://dx.doi.org/10.1016/j.foodchem.2008.12.039
90. Leahu A, Damian C, Oroian M, Miclescu V, Ropciuc S. Variation in content of antioxidant and free radical scavenging activity of basil (*Ocimum Basilicum*), dill (*Anethum Graveolens*) and parsley (*Petroselinum Sativum*). *J Fac Food Eng* 2013;XII(4):347–353. Available at: https://www.academia.edu/58734717/VARIATION_IN_CONTENT_OF_ANTIOXIDANT_AND_FREE_RADICAL_SCAVENGING_ACTIVITY_OF_BASIL_Ocimum_Basilicum_DILL_Anethum_graveolens_AND_PARSLEY_Petroselinum_sativum_
91. Bahramikia S, Yazdanparast R. Antioxidant and Free Radical Scavenging Activities of Different Fractions of *Anethum Graveolens* Leaves Using in Vitro Models. *Pharmacologyonline*. 2008;2:219–233. Available at: https://pharmacologyonline.silae.it/files/archives/2008/vol2/21_Yazdanparast.pdf
92. Selen Isbilir S, Sagiroglu A. Antioxidant Potential of Different Dill (*Anethum Graveolens*L.) Leaf Extracts. *Int J Food Prop* 2011;14:894–902. Available at: http://dx.doi.org/10.1080/10942910903474401
93. Kazemi M. Chemical composition and antimicrobial, antioxidant activities and anti-inflammatory potential of Achillea millefolium L., *Anethum graveolens* L., and Carum copticum L. essential oils. *J Herbal Med* 2015;5:217–222. Available at: http://dx.doi.org/10.1016/j.hermed.2015.09.001
94. Kazemi M. Phenolic profile, antioxidant capacity and anti-inflammatory activity of *Anethum graveolens* L. essential oil. *Nat Prod Res* 2014;29:551–553. Available at: http://dx.doi.org/10.1080/14786419.2014.951934
95. Edziri H, Ammar S, Souad L, et al. In vitro evaluation of antimicrobial and antioxidant activities of some Tunisian vegetables. *S Afr J Bot* 2012;78:252–256. Available at: http://dx.doi.org/10.1016/j.sajb.2011.09.012
96. Dadashpour M, Rasooli I, Sefidkon F, et al. Lipid Peroxidation Inhibition, Superoxide Anion and Nitric Oxide Radical Scavenging Properties of Thymus daenensis and *Anethum graveolens* Essential Oils. *J Med Plants* 2011;10(37):109–120. Available at: https://pesquisa.bvsalud.org/portal/resource/pt/emr-123927
97. Kamkar AAF. The study of antioxidant activity of essential oil and extract of Iranian *Anethum graveloens*. *Ofogh-e-Danesh GMUHS J* 2009;15(2):11–16. Available at: https://www.sid.ir/paper/68691/en
98. Panda S. The effect of *Anethum graveolens* L. (dill) on corticosteroid induced diabetes mellitus: involvement of thyroid hormones. *Phytother Res* 2008;22:1695–1697. Available at: http://dx.doi.org/10.1002/ptr.2553
99. Tamilarasi R, Sivanesan D, Kanimozhi P. Hepatoprotective and antioxidant efficacy of *Anethum graveolens* linn in carbon tetrachloride induced hepatotoxicity in albino rats. *J Chem Pharm Res* 2012;4(4):1885–1888. Available at: https://www.semanticscholar.org/paper/Hepatoprotective-and-antioxidant-efficacy-of-linn-Tamilarasi-Sivanesan/d0056a709009434771e0a73ccba3f0f11234d73a
100. Ramadan M, Abd-Algader N, El-kamali H, et al. Volatile compounds and antioxidant activity of the aromatic herb *Anethum graveolens*. *J Arab Soc Med Res* 2013;8:79. Available at: http://dx.doi.org/10.4103/1687-4293.123791
101. Al-Fartosy AJM, Zearah SA, Alwan NA. Total Antioxidant Capacity and Antihyperlipidemic Activity of Alkaloid Extract from Aerial Part of Total Antioxidant Capacity and Antihyperlipidemic Activity of Alkaloid Extract from Aerial Part of *Anethum graveolens* L. plant. *Eur Sci J* 2013;9(33):413–423. Available at: https://doi.org/10.19044/esj.2013.v9n33p%25p
102. Bahramikia S, Yazdanparast R. Efficacy of Different Fractions of *Anethum graveolens* Leaves on Serum Lipoproteins and Serum and Liver Oxidative Status in Experimentally Induced

Hypercholesterolaemic Rat Models. *Am J Chin Med* 2009;37:685–699. Available at: http://dx.doi.org/10.1142/S0192415X09007168
103. Shafaei N, Barkhordar SMA, Rahmani F, et al. Protective Effects of *Anethum graveolens* Seed's Oil Nanoemulsion Against Cadmium-Induced Oxidative Stress in Mice. *Biol Trace Elem Res* 2020;198:583–591. Available at: http://dx.doi.org/10.1007/s12011-020-02093-z
104. Mudassir HA, Azmi MB, Qureshi SA. Phytochemical Investigation of Ethanolic Seed Extract of *Anethum Graveolens* and Its Effect on Glucose Tolerance in Rabbits. *FUUAST J BIOL* 2011;1(2):41–45. Available at: https://www.researchgate.net/publication/286296824
105. Mansouri M, Nayebi N, keshtkar A, et al. The effect of 12 weeks *Anethum graveolens* (dill) on metabolic markers in patients with metabolic syndrome; a randomized double blind controlled trial. *DARU J Pharm Sci* 2012;20. Available at: http://dx.doi.org/10.1186/2008-2231-20-47
106. Mobasseri M, Payahoo L, Ostadrahimi A, et al. *Anethum graveolens* Supplementation Improves Insulin Sensitivity and Lipid Abnormality in Type 2 Diabetic Patients. *Pharm Sci* 2014;20:40–45. Available at: https://ps.tbzmed.ac.ir/Article/PHARM_2038_20140717140626
107. Yousofvand N, Soltany A. Effects of Hydroalcoholic Extract of Dill (*Anethum graveolens*) on the serum levels of blood lipids (cholesterol, Triglycerides, LDL and HDL) in male NMRI mice. *J Pharm Chem Biol Sci* 2015;3(May):114–121. Available at: http://jpcbs.info/2015_3_1_12_Yousofvand.pdf
108. Askari M, Nazari H , Rahimizadeh SH, Sadeghimansorkhani H, Daneshpayeh NA. The Effect of the Hydroalcoholic Extract of Dill (*Anethum graveolens*) Seed on Lipid Profile in Diabetic Male Rats. *Armaghane danesh* 2016;21(5):446–454. Available at: http://armaghanj.yums.ac.ir/browse.php?a_code=A-10-423-2&slc_lang=en&sid=1
109. Mirhosseini M, Baradaran A, Rafieian-Kopaei M. *Anethum graveolens* and hyperlipidemia: A randomized clinical trial. *J Res Med Sci* 2014;19:758–761. Available at: https://pubmed.ncbi.nlm.nih.gov/25422662/
110. Sahib SA, Mohammad IH, Al-Gareeb AA. Effects of *Anethum graveolens* leave powder on lipid profile in hyperlipidemic patients. *Spatula DD* 2012;2:153–158. Available at: http://dx.doi.org/10.5455/spatula.20120907123553
111. Kumar M, Kaur P, Chandel M, et al. Antioxidant and hepatoprotective potential of *Lawsonia inermis* L. leaves against 2-acetylaminofluorene induced hepatic damage in male Wistar rats. *BMC Complement Altern Med* 2017;17. Available at: http://dx.doi.org/10.1186/s12906-017-1567-9
112. Ling LT, Radhakrishnan AK, Subramaniam T, et al. Assessment of Antioxidant Capacity and Cytotoxicity of Selected Malaysian Plants. *Molecules* 2010;15:2139–2151. Available at: http://dx.doi.org/10.3390/molecules15042139
113. Hsouna AB, Trigui M, Culioli G, et al. Antioxidant constituents from *Lawsonia inermis* leaves: Isolation, structure elucidation and antioxidative capacity. *Food Chem* 2011;125:193–200. Available at: http://dx.doi.org/10.1016/j.foodchem.2010.08.060
114. Guha G, Rajkumar V, Kumar RA, et al. Antioxidant Activity of *Lawsonia inermis* Extracts Inhibits Chromium(VI)-Induced Cellular and DNA Toxicity. *Evid Based Complement Altern Med* 2011;2011:1–9. Available at: http://dx.doi.org/10.1093/ecam/nep205
115. Daemi A, Farahpour MR, Oryan A, et al. Topical administration of hydroethanolic extract of *Lawsonia inermis* (henna) accelerates excisional wound healing process by reducing tissue inflammation and amplifying glucose uptake. *Kaohsiung J Med Sci* 2019;35:24–32. Available at: http://dx.doi.org/10.1002/kjm2.12005
116. Yang CS, Chen JJ, Huang HC, et al. New flavone and eudesmane derivatives from *Lawsonia inermis* and their inhibitory activity against NO production. *Phytochem* Lett 2017;21:123–127. Available at: http://dx.doi.org/10.1016/j.phytol.2017.06.012
117. Kore KJ, Shete RV, Desai NV, Dnyanpeeths R. Anti-Arthritic activity of Hydroalcoholic extract of *Lawsonia Innermis*. *Int J Drug Dev Res* 2011;3(4):217–224. Available at: https://www.itmedicalteam.pl/articles/antiarthritic-activity-of-hydroalcoholic-extract-of-lawsonia-innermis-101295.html
118. Singh S, Verma N, Karwasra R, et al. Safety and efficacy of hydroalcoholic extract from *Lawsonia inermis* leaves on lipid profile in alloxan-induced diabetic rats. *Ayu* 2015;36:107. Available at: http://dx.doi.org/10.4103/0974-8520.168999
119. Delnavazi MR, Tavakoli S, Rustaie A, Batooli H, Yassa N. Antioxidant and antibacterial activities of the essential oils and extracts of Dorema ammoniacum roots and aerial parts. *Res J Pharmacogn* 2014;1(4):11–18. Available at: https://www.rjpharmacognosy.ir/article_6331.html
120. Bakhtiarian A, Shojaii A, Hashemi S, Nikoui V. Evaluation of Analgesic and Anti-Inflammatory Activity of Dorema Ammoniacum Gum in Animal Model. *Int J Pharm Sci Res* 2017;8:3102–3106. Available at: http://dx.doi.org/10.13040/IJPSR.0975-8232.8(7).3102-06
121. Etemadi-Tajbakhsh N, Faramarzi MA, Delnavazi MR. 1, 5-dicaffeoylquinic acid, an α-glucosidase inhibitor from the root of Dorema ammoniacum D. Don. *Res Pharma Sci* 2020;15:429. Available at: http://dx.doi.org/10.4103/1735-5362.297845
122. Naima H, Mahfoud HM, Farah R, et al. Antimicrobial and antioxidant activities of Cymbopogon schoenanthus (L.) spreng. essential oil, growing in Illizi – Algeria. *J Med Plants Res* 2016;10:188–194. Available at: http://dx.doi.org/10.5897/JMPR2015.5985
123. Yagi S, Mohammed ABA, Tzanova T, et al. Chemical profile, antiproliferative, antioxidant, and enzyme inhibition activities and docking studies of *Cymbopogon schoenanthus* (L.) Spreng. and *Cymbopogon nervatus* (Hochst.) Chiov. from Sudan. *J Food Biochem* 2019;44(2):e13107. Available at: http://dx.doi.org/10.1111/jfbc.13107
124. Khadri A, Serralheiro MLM, Nogueira JMF, et al. Antioxidant and antiacetylcholinesterase activities of essential oils from Cymbopogon schoenanthus L. Spreng. Determination of chemical composition by GC–mass spectrometry and 13C NMR. *Food Chem* 2008;109:630–637. Available at: http://dx.doi.org/10.1016/j.foodchem.2007.12.070
125. Saggu S, Rehman H, Aziz AT, et al. Cymbopogon schoenanthus (Ethkher) ameliorates cadmium induced toxicity in swiss albino mice. *Saudi J Biol Sci* 2019;26:1875–1881. Available at: http://dx.doi.org/10.1016/j.sjbs.2017.01.002
126. Abu-Serie MM, Habashy NH, Maher AM. In vitro anti-nephrotoxic potential of Ammi visnaga, Petroselinum crispum, Hordeum vulgare, and Cymbopogon schoenanthus seed or leaf extracts by suppressing the necrotic mediators, oxidative stress and inflammation. *BMC Complement Altern Med* 2019;19. Available at: http://dx.doi.org/10.1186/s12906-019-2559-8
127. Golestaneh Talaei M, Mousavi Z, Jahandideh M. Anti-Inflammatory Activity of Cymbopogon schoenanthus Essential Oil in Animal Models. *Res J Pharmacogn* 2019;6. Available at: https://doi.org/10.22127/rjp.2019.89466
128. Rocchetti G, Alcántara C, Bäuerl C, et al. Bacterial growth and biological properties of Cymbopogon schoenanthus and Ziziphus lotus are modulated by extraction conditions. *Food Res Int* 2020;136:109534. Available at: http://dx.doi.org/10.1016/j.foodres.2020.109534
129. Ibrahim S, Al-Ahdal A, Khedr A, et al. Antioxidant α-amylase inhibitors flavonoids from Iris germanica rhizomes. *Rev Bras*

Farmacogn 2017;27:170–174. Available at: http://dx.doi.org/10.1016/j.bjp.2016.10.001
130. Sayyed K, Hdayed I, Tabcheh M, et al. Antioxidant properties of the Lebanese plant Iris x germanica L. crude extracts and antagonism of chlorpromazine toxicity on Saccharomyces cerevisiae. *Drug Chem Toxicol* 2020;45:1168–1179. Available at: http://dx.doi.org/10.1080/01480545.2020.1810261
131. Ibrahim SRM, Mohamed GA, Zayed MF, et al. 8-Hydroxyirilone 5-methyl ether and 8-hydroxyirilone, new antioxidant and α-amylase inhibitors isoflavonoids from Iris germanica rhizomes. *Bioorg Chem* 2017;70:192–198. Available at: http://dx.doi.org/10.1016/j.bioorg.2016.12.010
132. Basgedik B, Ugur A, Sarac N. Antimicrobial, antioxidant, antimutagenic activities, and phenolic compounds of Iris germanica. *Ind Crops* Prod 2014;61:526–530. Available at: http://dx.doi.org/10.1016/j.indcrop.2014.07.022
133. Asghar SF, Choudahry MI. Gas chromatography-mass spectrometry (GC-MS) analysis of petroleum ether extract (oil) and bio-assays of crude extract of Iris germanica. *Int J Genet Mol Biol* 2011;3(7):95–100. Available at: https://www.researchgate.net/publication/281398263
134. Ibrahim SRM, Mohamed GA, Al-Musayeib NM. New Constituents from the Rhizomes of Egyptian *Iris germanica* L. *Molecules* 2012;17:2587–2598. Available at: http://dx.doi.org/10.3390/molecules17032587
135. Ono M, Eguchi K, Konoshita M, et al. A New Diterpenoid Glucoside and Two New Diterpenoids from the Fruit of *Vitex agnus-castus*. *Chem Pharm Bull* 2011;59(3):392–396. Available at: http://dx.doi.org/10.1248/cpb.59.392
136. Sarikurkcu C, Arisoy K, Tepe B, et al. Studies on the antioxidant activity of essential oil and different solvent extracts of Vitex agnus castus L. fruits from Turkey. *Food Chem Toxicol* 2009;47:2479–2483. Available at: http://dx.doi.org/10.1016/j.fct.2009.07.005
137. Maltaş E, Uysal A, Yıldız S,Durak Y. Evaluation of Antioxidant and Antimicrobial Activity of *Vitex agnus castus* L. *Fresenius Environ Bull* 2010;19(12):3094–3099. Available at: https://www.researchgate.net/profile/Ahmet-Uysal-8/publication/256394211
138. Ahangarpour A, Najimi SA, Farbood Y. Effects of *Vitex agnus-castus* fruit on sex hormones and antioxidant indices in a d-galactose-induced aging female mouse model. *J Chin Med Assoc* 2016;79:589–596. Available at: http://dx.doi.org/10.1016/j.jcma.2016.05.006
139. Choudhary MI, Azizuddin, Jalil S, et al. Antiinflammatory and lipoxygenase inhibitory compounds from *Vitex agnus-castus*. *Phytother Res* 2009;23:1336–1339. Available at: http://dx.doi.org/10.1002/ptr.2639
140. Berrani A, Lrhorfi LA, Larbi OM, et al. Hypoglycemic Effect of Vitex agnus castus Extract in Diabetic Rats Induced by Streptozotocin. *Phytothérapie* 2018;16:S40–S47. Available at: http://dx.doi.org/10.3166/phyto-2018-0034
141. Ahangarpour A, Oroojan A, Khorsandi L, et al. Pancreatic protective and hypoglycemic effects of *Vitex agnus-castus* L. fruit hydroalcoholic extract in D-galactose-induced aging mouse model. *Res Pharma Sci* 2017;12:137. Available at: http://dx.doi.org/10.4103/1735-5362.202452
142. Özcan MM, Al Juhaimi F, Uslu N, et al. Effect of sonication process of terebinth (*Pistacia terebinthus* L.) fruits on antioxidant activity, phenolic compounds, fatty acids and tocopherol contents. *J Food Sci Technol* 2020;57:2017–2025. Available at: http://dx.doi.org/10.1007/s13197-019-04235-1
143. Orhan IE, Senol FS, Gulpinar AR, et al. Neuroprotective potential of some terebinth coffee brands and the unprocessed fruits of *Pistacia terebinthus* L. and their fatty and essential oil analyses. *Food Chem* 2012;130:882–888. Available at: http://dx.doi.org/10.1016/j.foodchem.2011.07.119
144. Foddai M, Kasabri V, Afifi FU, et al. In vitro inhibitory effects of SardinianPistacia lentiscusL. And *Pistacia terebinthus* L. on metabolic enzymes: Pancreatic lipase, α-amylase, and α-glucosidase. *Starch Stärke* 2014;67(1–2):204–212. Available at: http://dx.doi.org/10.1002/star.201400068
145. Bahçecıoğlu IH, Ispiroglu M, Tuzcu M, et al. *Pistacia Terebinthus* Coffee Protects against Thioacetamide-Induced Liver Injury in Rats. *Acta Medica* (*Hradec Kralove*) 2015;58:56–61. Available at: http://dx.doi.org/10.14712/18059694.2015.94
146. Hacıbekiroğlu I, Yılmaz PK, Ha¸imi N, et al. In vitrobiological activities and fatty acid profiles of *Pistacia terebinthus* fruits andPistacia khinjukseeds. *Nat Prod Res* 2014;29:444–446. Available at: http://dx.doi.org/10.1080/14786419.2014.947492
147. Kavak DD, Altıok E, Bayraktar O, et al. *Pistacia terebinthus* extract: As a potential antioxidant, antimicrobial and possible β-glucuronidase inhibitor. *J Mol Catal B: Enzym* 2010;64: 167–171. Available at: http://dx.doi.org/10.1016/j.molcatb.2010.01.029
148. Durmaz G, Gökmen V. Changes in oxidative stability, antioxidant capacity and phytochemical composition of *Pistacia terebinthus* oil with roasting. *Food Chem* 2011;128:410–414. Available at: http://dx.doi.org/10.1016/j.foodchem.2011.03.044
149. TÜRKOĞLU S, ÇELİK S, KESER S, et al. The effect of *Pistacia terebinthus* extract on lipid peroxidation, glutathione,protein, and some enzyme activities in tissues of rats undergoing oxidative stress. *Turk J Zool* 2017;41:82–88. Available at: http://dx.doi.org/10.3906/zoo-1508-41
150. Uyar A, Abdulrahman NT. A histopathological, immunohistochemical and biochemical investigation of the antidiabetic effects of the *Pistacia terebinthus*in diabetic rats. *Biotech Histochem* 2020;95(2):92–104. Available at: http://dx.doi.org/10.1080/10520295.2019.1612092
151. Noguera-Artiaga L, Pérez-López D, Burgos-Hernández A, et al. Phenolic and triterpenoid composition and inhibition of α-amylase of pistachio kernels (*Pistacia vera* L.) as affected by rootstock and irrigation treatment. *Food Chem* 2018;261: 240–245. Available at: http://dx.doi.org/10.1016/j.foodchem.2018.04.033
152. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. *Clin Dermatol* 2018;36(1):14–20. Available at: http://dx.doi.org/10.1016/j.clindermatol.2017.09.004
153. Mahjoub F, Salari R, Noras MR, et al. Are Traditional Remedies Useful in Management of Fibromyalgia and Chronic Fatigue Syndrome? A Review Study. *J Evid Based Complement Altern Med* 2017;22:1011–1016. Available at: http://dx.doi.org/10.1177/2156587217712763
154. Emaratkar E, Choopani R, Namdar H, et al. Avicenna's view on the prevention of thrombosis. *Int J Cardiol* 2013;168:3093–3094. Available at: http://dx.doi.org/10.1016/j.ijcard.2013.04.079
155. Emtiazy M, Choopani R, Khodadoost M, et al. Avicenna's doctrine about arterial hypertension. *Acta Med Hist Adriat* 2014;12(1):157–162. Available at: https://pubmed.ncbi.nlm.nih.gov/25310615/
156. Choopani R, Mosaddegh M, Gir AAG, et al. Avicenna (Ibn Sina) aspect of atherosclerosis. *Int J Cardiol* 2012;156(3):330. Available at: http://dx.doi.org/10.1016/j.ijcard.2012.01.094
157. Gooshah Gir AA, Namdar H, Emaratkar E, et al. Avicenna's view on the prevention of thrombosis. *Int J Cardiol* 2013;166(1): 274–275. Available at: http://dx.doi.org/10.1016/j.ijcard.2012.09.151
158. Soltani SS, Minaii B, Besharat M. Sleep and Wakefulness Correction in Different Seasons From Avicenna's Perspective. *Iran Red Crescent Med J* 2013;15:276–277. Available at: http://dx.doi.org/10.5812/ircmj.7677

159. Wolk R, Somers VK. Sleep and the metabolic syndrome. *Exp Physiol* 2007;92:67–78. Available at: http://dx.doi.org/10.1113/expphysiol.2006.033787
160. Kawada T. Sleep Duration, Physical Activity, and Metabolic Syndrome for Adolescents. *Ann Behav Med* 2013;46(3):401–402. Available at: http://dx.doi.org/10.1007/s12160-013-9531-5
161. Countryman AJ, Saab PG, Llabre MM, et al. Cardiometabolic Risk in Adolescents: Associations with Physical Activity, Fitness, and Sleep. *Ann Behav Med* 2012;45:121–131. Available at: http://dx.doi.org/10.1007/s12160-012-9428-8
162. Gozal D, Dumin M, Koren D. Role of sleep quality in the metabolic syndrome. *Diabetes Metab Syndr Obes* 2016;9:281–310. Available at: http://dx.doi.org/10.2147/DMSO.S95120
163. Serin Y, Acar Tek N. Effect of Circadian Rhythm on Metabolic Processes and the Regulation of Energy Balance. *Ann Nutr Metab* 2019;74(4):322–330. Available at: http://dx.doi.org/10.1159/000500071
164. Medic G, Wille M, Hemels ME. Short- and long- term health consequences of sleep disruption. *Nat Sci Sleep* 2017;9:151–161. Available at: http://dx.doi.org/10.2147/NSS.S134864
165. Borel AL. Sleep Apnea and Sleep Habits: Relationships with Metabolic Syndrome. *Nutrients* 2019;11(11):2628. Available at: http://dx.doi.org/10.3390/nu11112628
166. Koren D, Taveras EM. Association of sleep disturbances with obesity, insulin resistance and the metabolic syndrome. *Metabolism* 2018;84:67–75. Available at: http://dx.doi.org/10.1016/j.metabol.2018.04.001
167. Irwin MR, Olmstead RE, Ganz PA, Haque R. Sleep disturbance, inflammation and depression risk in cancer survivors. *Brain Behav Immun* 2013;30 Suppl(Suppl):S58–S67. Available at: http://dx.doi.org/10.1016/j.bbi.2012.05.002
168. Li C, Ostermann T, Hardt M, et al. Metabolic and Psychological Response to 7-Day Fasting in Obese Patients with and without Metabolic Syndrome. *Complement Med Res* 2013;20:413–420. Available at: http://dx.doi.org/10.1159/000353672
169. Zhang J, Wu Z, Cai Y, et al. L-carnitine ameliorated fasting-induced fatigue, hunger, and metabolic abnormalities in patients with metabolic syndrome: a randomized controlled study. *Nutr J* 2014;13. Available at: http://dx.doi.org/10.1186/1475-2891-13-110
170. Nozad A, Naseri M, Safari MB, et al. Food Reduction in Avicenna's View and Related Principles in Classical Medicine. *Iran Red Crescent Med J* 2016;18(6). Available at: http://dx.doi.org/10.5812/ircmj.25760
171. Su KY, Yu CY, Chen YW, et al. Rutin, a Flavonoid and Principal Component of Saussurea Involucrata, Attenuates Physical Fatigue in a Forced Swimming Mouse Model. *Int J Med Sci* 2014;11:528–537. Available at: http://dx.doi.org/10.7150/ijms.8220
172. Zhou KL, Dong S, Wang K, et al. Clinical massage therapy for patients with exercise-induced fatigue. *Medicine* 2020;99: e20870. Available at: http://dx.doi.org/10.1097/MD.0000000000020870
173. Kawabata N, Hata A, Aoki T. Effect of Aromatherapy Massage on Quality of Sleep in the Palliative Care Ward: A Randomized Controlled Trial. *J Pain Symptom Manage* 2020;59(6):1165–1171. Available at: http://dx.doi.org/10.1016/j.jpainsymman.2020.01.003
174. Kinkead B, Schettler PJ, Larson ER, et al. Massage therapy decreases cancer-related fatigue: Results from a randomized early phase trial. *Cancer* 2017;124:546–554. Available at: http://dx.doi.org/10.1002/cncr.31064
175. Alraek T, Lee MS, Choi TY, et al. Complementary and alternative medicine for patients with chronic fatigue syndrome: A systematic review. *BMC Complement Altern Med* 2011;11:87. Available at: http://dx.doi.org/10.1186/1472-6882-11-87
176. Yuan SLK, Matsutani LA, Marques AP. Effectiveness of different styles of massage therapy in fibromyalgia: A systematic review and meta-analysis. *Man Ther* 2015;20(2):257–264. Available at: http://dx.doi.org/10.1016/j.math.2014.09.003
177. Field TM, Sunshine W, Hernandezreif M, et al. Massage Therapy Effects on Depression and Somatic Symptoms in Chronic Fatigue Syndrome. *J Chronic Fatigue Syndr* 2001;8(1):1. Available at: http://dx.doi.org/10.1300/J092v08n01_01
178. Wang J, Chai T, Lin G, et al. Effects of the Intelligent-Turtle Massage on the Physical Symptoms and Immune Functions in Patients with Chronic Fatigue Syndrome. *J Tradit Chin Med* 2009;29:24–28. Available at: http://dx.doi.org/10.1016/S0254-6272(09)60026-1
179. Chi A, Li H, Kang C, et al. Anti-fatigue activity of a novel polysaccharide conjugates from Ziyang green tea. *Int J Biol Macromol* 2015;80:566–572. Available at: http://dx.doi.org/10.1016/j.ijbiomac.2015.06.055
180. Cao Y, Hu Y, Liu P, et al. Effects of a Chinese traditional formula Kai Xin San (KXS) on chronic fatigue syndrome mice induced by forced wheel running. *J Ethnopharmacol* 2012;139:19–25. Available at: http://dx.doi.org/10.1016/j.jep.2011.08.030
181. Xia F, Zhong Y, Li M, et al. Antioxidant and Anti-Fatigue Constituents of Okra. *Nutrients* 2015;7:8846–8858. Available at: http://dx.doi.org/10.3390/nu7105435
182. Qi B, Liu L, Zhang H, et al. Anti-fatigue effects of proteins isolated from Panax quinquefolium. *J Ethnopharmacol* 2014;153:430–434. Available at: http://dx.doi.org/10.1016/j.jep.2014.02.045
183. Zhang H, Li J, Li G, et al. Structural characterization and anti-fatigue activity of polysaccharides from the roots of Morinda officinalis. *Int J Biol Macromol* 2009;44:257–261. Available at: http://dx.doi.org/10.1016/j.ijbiomac.2008.12.010
184. Hong SS, Lee J, Lee JS, et al. The traditional drug Gongjin-Dan ameliorates chronic fatigue in a forced-stress mouse exercise model. *J Ethnopharmacol* 2015;168:268–278. Available at: http://dx.doi.org/10.1016/j.jep.2015.04.001
185. Mitra A, Sur TK, Upadhyay S, et al. Effect of Coelogyne cristata Lindley in alleviation of chronic fatigue syndrome in aged Wistar rats. *J Ayurveda Integr Med* 2018;9:266–271. Available at: http://dx.doi.org/10.1016/j.jaim.2017.06.011
186. Huang LZ, Huang BK, Ye Q, et al. Bioactivity-guided fractionation for anti-fatigue property of Acanthopanax senticosus. *J Ethnopharmacol* 2011;133:213–219. Available at: http://dx.doi.org/10.1016/j.jep.2010.09.032