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Pharmacological Investigation of Genus *Pistacia*

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Abstract

Several plants in the genus *Pistacia* are used in the treatment of various pathogenic and non-pathogenic disorders. Especially important are the major species belonging to this genus such as *Pistacia lentiscus*, *Pistacia atlantica*, *Pistacia vera*, *Pistacia terebinthus*, and *Pistacia khinjuk*, among others; these have been reported for their potential benefits both in medical and commercial purposes. In addition, members of this genus exhibit numerous ethnomedicinal uses, such as analgesic, anti-inflammatory, anticancer, antimicrobial, antihypertension, antihyperlipidemic, antiviral, and antiasthma. In light of these potential uses, the present chapter aimed to collect and summarize the literature about all of this medicinal information. Accordingly, this chapter focuses on the pharmacological uses and benefits of the genus *Pistacia*, especially those related to health issues.

Keywords: *Pistacia*; *Pistacia lentiscus*, *Pistacia atlantica*, *Pistacia vera*, *Pistacia terebinthus*, *Pistacia khinjuk*, pharmacological activities

1. Introduction

Pistacia, a genus that belongs to the family and order of Anacardiaceae and Sapindales, respectively, includes almost twenty species five of which have been classified and characterized as significant and economically important [1]. Flowers of this genus are in panicles or racemes, unisexual, small, apetalous, subtended by 1–3 small bracts and wind-pollinated, and 2–7 bracteoles. Deciduous, alternative or evergreen leaves are typically pinnate, sometimes simple or trifoliate, leathery, or membranous [2]. *Pistacia vera*, *P. khinjuk*, *P. atlantica*, *P. terebinthus*, and *P. lentiscus* are the foremost species of the genus *Pistacia*, where studies carried out by numerous researchers showed that the *Pistacia vera* L. as the utmost economically valuable species [3]. Cultivated pistachio, which is scientifically known as *Pistacia vera* has continued to rise to an annual estimated value of around \$2 billion over the last two decades [4]. It has comestible seeds and a commercially important influence. Pistachios, often utilized in the shell, are fresh to consume; baked products, fruit, and ice cream are used for manufacturing purposes. Their applications as traditional, medical, and non-food products, such as toothache relief, are also

available. In addition, Pistachio has been documented as a solution for sclerosis and scirrhous of the liver, abscesses, impaired circulation, and other health-related issues [2, 5]. Furthermore, the *Pistacia* genus has been tested for multiple ethnomedicinal ailments, including inflammation, cancer, microbial attack, hypertension, and asthma, among others. The frequent usage of representatives of this genus rendered it as core plants in natural medicines. For instance, several health problems and disorders caused by free radicals may be can be mitigated by means of antioxidants.

Antioxidants are the strongest protective agents against free radicals. In this respect, members of genus *Pistacia* have been documented to display variable degrees of free radical scavenging potential. Leaf extracts obtained from *Pistacia lentiscus* and *P. atlantica* exert antioxidant effects with 14.16% and 19.3%, respectively [6]. In addition, research findings indicated that genus *Pistacia* genus has been established as natural antimicrobial agents. Fungal growth was substantially decreased by the crude leaf extract of *P. atlantica* and *P. lentiscus*, but the growth of bacteria was not significantly suppressed [6]. Similarly, the mouthwash of *P. atlantica* has an impressive antimicrobial effect on the microorganism of gingivae and has been recommended as reliable and effective [7]. In addition, essential oil from *P. vera* with an effective effect against some pathogenic bacteria particularly *S. aureus* and *E. coli* [8]. On the other hand, the lipophilic extract of *P. vera* demonstrated potential antiviral effect [9]. In addition, *P. lentiscus*, *P. atlantica*, *P. palaestina*, and *P. vera*, among others exhibited anticancer activity in numerous experimental studies. In this context, the crude extract of leaves and fruits of *P. lentiscus* substantially suppressed the growth in the cell line of the growing melanoma [10], where inhibitory potential against BHK21 cell line has been identified in the seed oil of *P. lentiscus* [11]. Furthermore, the ethanol extract of *P. atlantica* showed significant activity against gastric and cervical carcinoma [12]. Besides, the essential oil obtained from *P. palaestina* is efficient in inhibiting malignant colorectal cancer [13]. Mansouri et al. [79] evaluated in vivo the neuroprotective effect of *P. vera* L. gum extract on oxidative damage during cerebral ischemia–reperfusion in rats and concluded that the neuroprotective potency may be due to cumulative antioxidant defense as well as suppression of free radical production [14]. Besides, anthelmintic role has been observed for different extract and essential oil of *P. khinjuk* particularly against *Echinococcus granulosus*, which develops hydatid cyst [15]. Except for all of these biological activities, members of genera *Pistacia* exert high therapeutic activity against numerous health issues, including peptic ulcer, colitis, Hypoglycemia, obesity, hypertension, Nephritic disorders, hepatic disorders, and other toxicological problems. Based on the previous discussion, the aim of the present work is to collect and summarize the medicinal information along with recent references pertaining to members of the genus *Pistacia*, which would be helpful to and further researchers in the field. Below are details about documented biological activities related to the members of the genus *Pistacia*.

2. Biological activity

2.1 Antioxidant effect

Free radicals are responsible for ample of disorder in human medicines. Blockage, neutralization or complexation of these noxious radicals can prevent or mitigate numerous health issues. In this respect, synthetic antioxidants might be

responsible for several side effects; therefore, natural antioxidants are preferred. Antioxidants are the best preventive agents against free radicals responsible for various diseases. Within this context, different members of the genus *Pistacia* demonstrated variable degree of free radicals scavenging potential. The leaf extracts of *P. lentiscus* and *P. atlantica* showed a weak antioxidant effect (14.16 and 19.3% respectively) [1]. On the other hand, the methanol extract of *P. lentiscus* at the flowering season was tested for antioxidant effect using DPPH and PRAP assays; results showed a high significant antioxidant (131 mmol/L) effect [2]. Similarly, the crude leaf extract of *P. lentiscus* demonstrated significant antioxidant potential [3]. The methanol leaf extracts of *P. atlantica* of 34 collected samples were tested for antioxidant effect, and results revealed significant antioxidant [4]. In a similar fashion, the seeds and skin of pistachio (*P. vera* L) were subjected to antioxidant effect (DPPH, TEAC, and SOD mimetic assays), and the phenolic contents quantification (HPLC) were determined. The best antioxidant effect of skin as compared to seeds was attributed to the highest phenolic contents [5]. Additionally, the hydrophilic extract of pistachio nut showed antioxidant effects due to the presence of polyphenolic compounds [6]. The acetone and methanol extracts of *P. terebinthus* demonstrated good antioxidant effects, attributed to the presence of various phenolic contents and flavones [7]. *P. weinmannifolia* is a shrub and widely distributed in the Yunnan area of China. The leaves of this plant are used traditionally by the herbalist. The leaves are rich in phenolic constituents, among which Gallotannins, Pistafolin A and B were confirmed. The protection of lipid, proteins and DNA damage from the reactive oxygen species (ROS) by Pistafolin A and B through antioxidant effect was reported. The free radical scavenging effect of Pistofoli A was more potent than Pistofolin B due to structural changes [1]. Taken all together, *Pistacia* plants could be excellent free radical scavengers, which could help to cure or mitigate several diseases. The ROS or RNS etc., as free radicals interact with the cell membrane, such as the free radicals interact with hemoglobin and making them denatured, the denatured hemoglobin accumulating at the surface of RBC and making the cell membrane non-flexible, which leads to the rupturing of RBC known as hemolytic anemia. The use of antioxidant, especially the plants-based antioxidants, can prevent a lot of health problems.

2.2 Anti-microbial effect

The list of antibiotics is supplementing day by day due to antimicrobial resistance issues. These antibiotics are helpful and have extended spectrum but are responsible for various adverse effects. These adverse effects minimize the patient compliance, and, therefore, the search for new, effective and affordable antibiotic is a big challenge to phytochemical researchers. In this respect, natural antibiotics could have multiple uses in addition to the antibiotic effect; therefore, the use of natural antibiotic can minimize the polypharmacy. Within this context, research findings indicated that the crude leaf extract of *P. lentiscus* and *P. atlantica* significantly reduce the fungal growth, whereas weak bacterial inhibitory effect was reported [1]. Roozegar investigated the effect of *P. atlantica* leaf extract against mouth and saliva bacterial load, and reported a significant effect against *S. mutans* and *S. mitis* in disk diffusion method with zone of inhibition of 19 and 25 mm, respectively; no significant effect was observed against *S. salivarius* [8]. The mouthwash of *P. atlantica* exhibited excellent antimicrobial effect against gingival microorganism. Therefore, this mouthwash was recommended as effective and safe [9].

Similarly, the hydro extract of *P. atlantica* was tested against different bacteria *in vitro* and was found effective against *E. coli*, *P. aeruginosa* and *S. aureus*, except for *H. pylori* [10]. Additionally, the hydro distilled essential oil from the stem of *P. vera* was tested against some pathogenic bacteria, and exhibited significant effect against *E. coli* and *S. aureus* [11]. Furthermore, the antibacterial potential of *P. lentiscus* extract was tested against gram positive and gram-negative bacteria. Results demonstrated that the extract exerts significant effect against gram positive as compared to gram negative bacteria [12]. The leaf extract of *P. khinjuk* when screened for the antibacterial and antifungal potential exhibited significant activity [13]. On the other hand, the essential oil of *P. khinjuk* was found to contain, through GC–MS analyses γ -terpinene (81.14%) (w/w), β -pinene (3.93%) (w/w), and α -terpinolene (2.38%) (w/w). This essential oil was tested for activity against *P. aeruginosa* and *S. subtilis*. Chemical constituents of the essential oil might be responsible for the antibacterial effect against the tested pathogenic bacteria [14]. Similarly, the essential oil from the leaves of *P. lentiscus* was also tested against different gram positive and gram negative pathogenic bacteria. The major chemical constituents in essential oil were α -pinene and β -pinene, and a variable degree of antibacterial effects were observed [15]. Volatile compounds from the essential of leaves and fruits of *P. lentiscus* exhibited best antibacterial effect [16]. Likewise, the antimicrobial effect of *P. integerrima* has been reported against various pathogenic microbes. The oil was found rich in 1-terpinen-4-ol (28.82%), p-menth-1-en-8-ol, (43.38%), n-octyl acetate (19.91%), and β -farnesene (7.88%). The concentration of α -terpinolene, limonene and α -thujene were less than 1%. The tested oils exhibited promising antibacterial activities. The zone on inhibition against *E. coli*, *S. aureus*, *K. pneumoniae*, *Straptodirimu*, *B. stearothermophilus* and *S. typhimurium* was 16, 18, 26, 22, 18 and 20 mm, respectively [17]. The essential oil of *P. terebinthus* (collected from Tunisia and Italy) was reported along with chemical composition (GC and GC–MS). The oil was isolated through hydrodistillation. The oil consisted of monoterpene hydrocarbons (86.3% and 90.9%, respectively), α -pinene (62.4 vs. 35.0)%, camphene (3.0 vs. 2.4)%, β -pinene (12.1 vs. 4.5)%, terpinolene (1.7 vs. 35.2)% and β -phellandrene (3.8 vs. 4.5)% as the main components. The oil demonstrated significant effect against *T. rubrum*, *M. canis* and *E. floccosum*, with MIC and MLC values in the range (0.16–0.32) μ L/mL [18]. In view of the above discussion, these plants might help against different pathogenic infections. Plants accumulate numerous phytochemicals that interact with the micro-organisms. The inhibition or the killing of these micro-organisms might be due to cell wall inhibition or protein synthesis inhibition or might be due to the antimetabolite action of constituents. These plants' use for the above infections needs to explore the exact mechanism on related microbes and clinical trials.

2.3 Antiviral effect

The antiviral effect of natural products cannot be ignored. The non-polar extract of *P. vera* is antiviral. *Herpes simplex* (DNA) and *Parainfluenza virus* (RNA) was used for confirmation of antiviral effect [19]. The extracts demonstrated antiviral effect at a concentration of 128–256 μ g/mL. Different antiviral compounds have been identified in *P. lentiscus*. The HSV-2, Coxsackievirus-3 and adenovirus-5 were used. The methanolic extract of *P. lentiscus* demonstrated antiviral action against HSV-2 [20]. The polyphenolic rich extract at concentration range of 0.4, 0.6, 0.8 mg/mL of *P. vera* has been used against the HSV-1 with significant results [21]. Further study is needed to confirm the antiviral action of *Pistacia* against a wide range of viruses, including coronavirus.

2.4 Antiemetic effect

Emesis is one of the common side effects of numerous drugs. Emesis is also a common problem of other associated diseases. Natural products used for this purpose are well developed traditionally. The copper sulfate and ipecac-induced emesis has been blocked by the *P. vera* leaves and nut extract [22]. Copper sulfate induces emesis through GIT irritation, and ipecac induces emesis through GIT irritation and chemically stimulated the CTZ. The chemical constituents of ipecac get readily absorbed and interact with 5HT₃ and dopamine receptors. A mechanistic study is needed to confirm the extract mode of action.

2.5 Anticancer effect

The crude extract of *P. lentiscus* leaves and fruits significantly inhibited the growth of melanoma cell line (B16F10 cells). The leaves and fruits significantly inhibited the B16F10 cells (IC₅₀ = 56.40 and 58.04 µg/mL, respectively) [3], whereas the seed oil and phenolic compounds fraction of *P. lentiscus* showed inhibitory potential against BHK21 cell line. The IC₅₀ was 0.029 g/mL and the percent effect was 42.4 at the concentration of 0.09 g/mL [23]. The essential oils extracted from the fruits and leaves of *P. lentiscus* were tested for anticancer effect. The oil of leaves exhibited interesting anticancer activity as compared to fruits [16] on RD and L20B cell lines with IC₅₀ values of 26.43 ± 2.18 and 33.02 ± 2.84 µg/mL, respectively. A protective effect of the oil of *P. lentiscus* has been reported in bleomycin-induced lung fibrosis and oxidative stress in rats [24]. A significant anti-proliferation potential of *P. atlantica* against COLO205 has been noticed along with good antioxidant effect [25]. Colorectal cancer is one of the major malignant forms of cancer, which has been blocked by the essential oil from the *P. palaestina* [26]. The ethanol extract of *P. atlantica* demonstrated a significant effect against the gastric and cervical carcinoma along with antioxidant effect, which is attributed to the presence of phenolic compounds in the extract [27]. The ethyl acetate extract of *P. vera* L. also attenuated the growth of MCF-7 human breast cancer [28]. The anticancer effect of these plants against various cells line is well established. Interestingly, the antiemetic effect of these plants is very good regarding the anticancer effect because most anticancer drugs have emesis as a significant side effect. If a natural remedy has anticancer and antiemetic potential, it might be one of the best therapeutic mixtures.

2.6 Cytotoxic effect

The crude extract and fractions of *P. integerrima* of gall, root, bark, and leaves have been reported with cytotoxic effect against brine shrimp [29]. The extract and fractions were tested at various concentrations (10, 100, and 1000 ppm). This preliminary study is a pathway toward anticancer potentials.

2.7 Antiparasitic effect

The essential oil (EO) from the leaves and fruits of *P. lentiscus* were tested against leishmanial species (*L. infantum*, *L. major*, and *L. tropica*) using MTT assay. Both of the tested samples demonstrated a variable degree of cytotoxic effect. The major constituents of leaves were myrcene, α pinene, while limonene and α-pinene constituted fruits essential oil. The EO of leaves demonstrated significant effect against *L. major* (IC₅₀ = 17.52 ± 1.26 µg/mL) as compared to the EO of fruits (IC₅₀ = 21.42 ± 2.92 µg/mL), while the EO of fruits exhibited more effect than

leaves against *L. infantum* ($IC_{50} = 08 \pm 0.83 \mu\text{g/mL}$) than *P. lentiscus* leaves essential oils ($IC_{50} = 11.28 \pm 1.63 \mu\text{g/mL}$) [16]. The extract of *P. khinjuk* demonstrated a significant *in vivo* and *in vitro* effects against *L. major* and *L. tropica* [30]. The fruits and leaves extract of *P. atlantica* and *P. vera* demonstrated a significant inhibition against hydatid cyst protoscolices [31, 32]. The essential oil of *P. vera* inhibited *in vitro* and *in vivo* leishmanial effect [33]. The essential oil of *P. lentiscus* also demonstrated *anti-trichomonas vaginalis* trophozoites. The EO were tested at concentration range of 15, 10 and 5 mg/mL with different time duration of incubation. The morphological changes were monitored through TEM [34, 35]. A new antiparasitic agent (pistagremic acid) has been reported from the *P. integerrima* with IC_{50} : $6.71 \pm 0.09 \mu\text{M}$ against *Leishmania major* [36].

2.8 Antidiarrheal effect

The crude methanolic extract of *P. integerrima* significantly reduces the castor oil-induced diarrhea in mice, where maximum relaxation of smooth muscle was noticed. The induced contraction was exerted through calcium and muscarinic receptor agonist. Contraction was inhibited by the plant extract, and this inhibition reflects the plant's antimuscarinic action as well as the calcium channel blocking properties [37]. The crude methanolic effect of *P. integerrima* bark has been tested for its GIT motility effect and showed a significant reduction in induced loos motion [38].

2.9 Antispasmodic effect

The crude methanolic extract of *P. integerrima* demonstrated a significant inhibition in spontaneous contraction of rabbit jejunum [37]. This calcium-induced contraction was reversed by the plant extract. This relaxing effect on GIT smooth muscle reflects the constipating effect of plant extract.

2.10 Bronchodilator effect

The induced contraction of tracheal section was completely relaxed with the application of methanolic extract of *P. integerrima* [37]. The essential oil of *P. integerrima* has been reported with antiasthematic effect [39].

2.11 Analgesic effect

P. integerrima bark's methanolic extract significantly reduced the induced writhing in mice representing the painkiller potential in this plant. This attenuation of acetic acid-induced writhing at the dose of 100 mg/kg reflects the peripheral analgesic effect of plant extract [38]. *P. integerrima* gall's extract demonstrated significant analgesic effect against acid-induced writhing, formalin-induced pain, and thermal-induced central algisia. The extract also attenuated the thermal-induced pain [40]. The gall analgesic effect was due to the presence of analgesic flavonoids [41]. The *P. vera* leaves extract proved central and peripheral analgesic in animal models [42]. The oil of *P. atlantica* fruits attenuated acetic acid-induced writhing in rats [43]. The *P. atlantica* was also reported to have a good painker in another study [44, 45]. Pestagremic acid is one of the potential analgesic constitutes of the *P. integerrima* bark [46]. The oleoresin demonstrated the anti-inflammatory effect while rest of the samples were devoid of analgesic potential [47]. The gold nanoparticles *P. integerrima* gall have been tested for analgesic effect at the tested doses of 10 and 20 in acetic acid-induced pain model. Results

demonstrated significant analgesic potential [48]. These research data reflect that this genus has central and peripheral analgesic potential. The opioids receptors mediate the central pain, while peripheral pain receptors or COX inhibition are responsible for the peripheral analgesic effect. The available synthetic drugs having a good analgesic effect but are associated with side effects like a peptic ulcer. To find the analgesic remedy free of side effects is a big challenge to the researcher in the current modern era. The above-tested extract or constitutes needs to inter in the clinical trial to find more useful analgesic drugs.

2.12 Anti-osteoarthritis effect

Osteoarthritis (OA) is one of the chronic health problems around the globe. The patient of OA commonly uses NSAID as self-medication, especially in developing countries. To develop or discover new effective and safe medication for OA, plants' screening is essential. The oleoresin from *P. atlantica* demonstrated a comparable effect with diclofenac in knee osteoarthritis [49]. The *P. atlantica* cream might inhibit various enzymes involved in inflammation. The formulated cream significantly inhibited the OA induced condition. The topical anti-OA is far better than systemic use for the elimination of severe side effects.

3. Anti-inflammatory activity

The fraction of the leaves of *P. lentiscus* significantly attenuated the induced edema as compared to acetylsalicylic acid [3]. The crude extract of the gall of *P. integerrima* also demonstrated anti-inflammatory effect in various doses [40]. In another study, the anti-inflammatory effect of gall was attributed to the presence of flavonoids. The isolated flavonoids were tested for carrageenan-induced edema and provided significant anti-inflammatory [41]. The EO from the fruits of *P. lentiscus* attenuated the carrageenan-induced edema (inflammation) at various tested doses [50]. The crude leaves extract of *P. vera* demonstrated anti-inflammatory effect both in acute and chronic inflammatory models [42]. The *P. atlantica* has been proven significant anti-inflammatory in animal model [44, 51]. The bark of *P. integerrima* accumulated anti-inflammatory constituents like pectagremic acid [46, 52]. The nano particles of *P. integerrima* gall also showed significant anti-inflammatory effect [48]. The ethanolic and aqueous extracts of different parts of *P. vera* as its oleoresin have been tested for anti-inflammatory effect. The oleoresin demonstrated the anti-inflammatory effect while the rest of the samples were devoid of anti-inflammatory potential [47]. In another study, the significant anti-inflammatory effect (*in-vivo* and *in-vitro*) of *P. vera* has been reported [53]. The extract and triterpene from the *P. terebinthus* gall demonstrated significant acute and chronic anti-inflammatory effects [54]. The aqueous extract of *P. khinjuk* demonstrated anti-inflammatory effect [54, 55]. The above data mean that the genus has the best anti-inflammatory plants. Inflammation is caused by prostaglandin (PG) production. The PGs are the product of arachidonic acid through COX. Inhibition of COX is responsible for the anti-inflammatory effect. These COX are widely distributed in the body. The extract or constitutes blocking COX are considered as anti-inflammatory drugs.

3.1 Anti-gout effect

The leaves of *P. integerrima* demonstrated uric acid (UA) lowering effect in fructose induced hyperuricemia animal model [56]. The chemical constituents

such as quercetin-3-*O*- β -*D*-glucopyranoside, kaempferol-3-*O*- β -*D*-glucopyranoside, quercetin-3-*O*-(6''-*O*-syringyl)- β -*D*-glucopyranoside, kaempferol-3-*O*-(4''-*O*-galloyl)- α -*L*-arabinopyranoside, rutin together with aglycons, quercetin, kaempferol and apigenin inhibited the XO up to a variable degree. The inhibition of XO is a strong indicator of *P. integerrima* as a significant anti-gout. Hyperuricemia is also a chronic pain condition and needs to prolong treatment.

3.2 Anti- epileptic effect

Epilepsy is one of the most common, serious neurological conditions, affecting more than 50 million people worldwide. The hydroalcoholic extract of *P. vera* demonstrated a significant anti-epileptic effect in pentylenetetrazole (PTZ) chronic induced kiding in male rats [57]. The epileptic condition was induced by PTZ (40 mg/kg, IP), and the induced condition was significantly inhibited by the extract of *P. vera* at the tested doses of 50 and 100 mg/kg. The inhibition of chronic induced seizure indicate that *P. vera* is a significant antiepileptic. The petroleum ether extract of *P. integerrima* attenuated the PTZ-induced jerks in zebrafish and mice models at the dose of 50 and 100 mg/kg. The antiepileptic effect was further confirmed through maximum electroshock (MES) in a rat model. The tested extract significantly attenuated various aspects of induced jurks [58].

4. Sedative and hypnotic activity

Insomnia is a worldwide health issue with different etiology. This condition is treated as self-medication through benzodiazepines, which have a potential side effect of addiction. Once the patient gets addicted, then these medicines are used for life. The natural plant's based tranquilizers might be free of such addiction due to the accumulation of agonist and antagonistic chemical constituents. The hydroalcoholic extract of *P. vera* gum showed a sedative effect in the locomotor test. The extract at the dose of 0.25, 0.5, 1 g/kg showed the increased duration of sleep and shortened sleep latency hypnotic effect in phenobarbital-induced sleep [59].

4.1 Muscle relaxation

The hydroalcoholic extract of *P. vera* gum acted as muscle relaxant in traction and rotarod test. When tested at 0.25, 0.5, 1 g/kg and only the higher dose (1 g/kg) demonstrated this muscle relaxation effect [59]. No further syudies are available.

4.2 Effect on memory

The essential oil of *P. lentiscus* attenuated memory dysfunction in rats. *P. lentiscus* oil (P_{Lo}) at a dose of 3.3 mL/kg for 15 days reversed LPS-induced memory deficits in rats. Besides, the increased acetylcholinesterase activity in brain structures of LPS-treated rats was reduced by P_{Lo}. Additionally, P_{Lo} significantly attenuated the increased oxidative stress in the brain of LPS-treated rats [60]. The chemical induced memory impairment was regulated with *P. vera* fruit [61].

4.3 Anti-fatigue effect

The hydro-alcoholic extract of *P. vera* seed is significant anti-fatigue. The extract was tested at the dose of 10, 100 and 1000 mg/kg in male rats. Animals were

allowed to run at the speed of 20 m/min on treadmills. The extract tested animals demonstrated less fatigue as compared to a negative control [62].

4.4 Anxiolytic effect

A significant population of the world is affected by anxiety and depression. The chronic use of anxiolytics is responsible for the physical dependence and withdrawal syndrome. To minimize or avoid such harmful effects, the natural plants based treatment might be helpful. The fruits extract of *P. atlantica* demonstrated significant anxiolytic effect in intact and gonadectomized rates [63]. In elevated puls maze animal model the extract of *P. vera* gum showed anxiolytic effect at higher dose (1 g/kg) [59].

5. Wound healing

The treatment of wounds is directly related to the use of antibiotics. The systemic use of antibiotics is associated with various side effects in addition to resistance. The topical use is far better than systematic use to avoid side effects. The natural products based topical application have more positive aspects as compared to the available synthetic chemical molecules. The beauty of plant-based topical wound healing dosage form is that these remedies accumulated various synergetic chemicals in addition to phytosterols. The development of the natural product-based topical dosage might provide analgesic, anti-inflammatory and antibiotic effects. The wound-healing effect of these valuable plants is also outstanding. The fruits oil of *P. lentiscus* has been reported with significant healing of laser burn [64]. In another study the fruits oil of *P. lentiscus* has accelerated the cutaneous wound healing [65]. The *P. lentiscus* resin also shorten the duration of skin burn in rats in a dose-dependent manner [66]. The *P. atlantica* and *P. khinjuk* extracts increased the curing rate of skin wound in experimental animals [67]. The methanolic extract of *P. khinjuk* is also a worthy topical anti-wound agent [68]. The mastic extract, seed oil and resin oil of *P. lentiscus* have been tested as significant wound healing agent in different experimental models [69–71]. Bioassay-guided isolation and identification of various chemical constituents of *P. vera* has been reported [72]. The topical wound healing gel has been formulated with significant effect of *P. atlantica* [73].

5.1 Diabetic wound healing effect

Healing of the diabetic wound is a big problem around the globe. There is no specific treatment for a diabetic foot or wound. Therefore, medicinal plants are the best option to screen for the said action. The *P. atlantica* resin oil is the best wound healing agent in STZ-induced diabetic experimental rat [74]. No more studies are available for this activity.

5.2 Anti-second degree burn

The curing of second-degree burns is also not so much easier by standard antibiotic treatment. Therefore, the search for a new, effective and safe anti-burn therapeutic agent is essential. The topical application of *P. vera* oil on the second-degree burn accelerated the wound healing effect [75].

5.3 Anti-colitis effect

The oil of *P. lenticus* has been reported as a significant curative and preventive agent in colitis induced animals [76]. In addition to this plant, no further work is perform in this regard.

5.4 Anti-peptic ulcer effect

H. pylori is the main cause of peptic ulcer. The ulcer duration is shortened by the triple therapy of metronidazole, clarithromycin and omeprazole for 15 days. But the complete eradication of peptic ulcers takes years. The anti-peptic ulcer effect of oil of *P. atlantica* is also worth mentioning [77]. A limited study is available of this genus on anti-peptic ulcer action.

5.5 Neuroprotective effect

The *Pistacia* genus is one of the best neuroprotective natural products [78]. The neuroprotective effect of *P. vera* gum in induced ischemia animal is worth mentioning [79]. The significant inhibition of acetylcholinesterase and related enzymes is responsible for the neuroprotective effect of *P. terebinthus* [80]. The leaf extract and its major phenolic compounds of *P. lenticus* reversed the aluminum-induced neurotoxic effect in mice [81]. The toxic effect of mercury on brain was regulated by the *P. atlantica* indicating the neuroprotective role [82].

5.6 Hypoglycemic effect

The antidiabetic effect of *P. atlantica* has been reported [44]. In a study, the *n*-hexane extract of *P. atlantica* significantly improved the streptozotocin (STZ)- induced hyperglycemic condition. The same extract also improved the beta cell of pancreas [83]. The leaf extract of this plant also inhibited the α -amylase and α -glucosidase enzymes responsible for the diabetic disorders [84]. The leaf and fruit extract of *P. lenticus* significantly attenuated the induced diabetic condition [85]. The alloxan-induced diabetic condition has been normalized by *P. lenticus* crude extract [86]. The STZ induced hyperglycemic condition in experimental animal was normalized by the crude extract of *P. terebinthus* [87]. The crude methanolic extract of *P. vera* fruit stem metabolites are week antidiabetic [88]. The potential inhibition of 11β -hydroxysteroid dehydrogenase 1 by the oleoresin of *P. lenticus* demonstrate a good antidiabetic property [89]. Pistagremic acid, one of the potential constitutes of *P. integerrima*, is also α -glucosidase inhibitor [90]. Interestingly, the plants in this genus can cure diabetic patients mostly suffering from diabetic neuropathy as well as from wounds. So the treatment of all these conditions at a time resulting from the polypharmacy situation. This polypharmacy situation leads to poor patient compliance. These plants at a time are antidiabetic, antidiabetic wound healers and neuroprotective. So further work is highly recommended to test these plants on such patients who suffer from all these conditions.

5.7 Effect on GLUT

This effect is also directly linked with the anti-diabetic effect. The body has different types of glucose transporters (GLUT). These GLUT are responsible for the influx of glucose molecules and keeping glucose concentration in the blood flow. Among these transporters, the GLUT-II is bi-directional, and the rest are unidirectional. The extract of *P. thlantica* improved the GLUT-IV transporter expression

indicating the improved function of insulin [91]. Other plants of this genus are highly recommended to be tested on these GLUTs.

5.8 Lipid lowering effect

The genus looks quite interesting with a particular aspect of diabetic treatment. Because the lipid-lowering activity is highly adjuvant to diabetic patients, only two genus-species have been tested on the lipid-lowering effect, and it is highly recommended to test the rest of the spp. For this effect, *P. atlantica* subsp. *kurdica* has been reported as the best lipid lowering medicinal plant in STZ-induced diabetic animals. The lipid-lowering effect is helpful in diabetic condition [92]. This effect has been shown by the *P. lentiscus* fatty oil in egg yolk fed rabbit [93].

5.9 Anti-obesity effect

The bioactive compounds mainly protocatechuic acid (452 µg/g dw) and quinic acid (960 µg/g dry weight dw) derived from *P. atlantica* root have been established to possess a notable lipase inhibition effect on porcine pancreatic lipase [94]. No further studies are available.

5.10 Antihypertensive effect

The genus is very limitedly explored for the antihypertensive (HTN) effect. The leaf extract of *P. atlantica* strongly inhibited the angiotensin-converting enzyme-I (ACE-I), indicating the antihypertensive effect [84]. The HTN is mostly associated with DM. So if a clinical trial is conducted on patients suffering from HTN and DM, it will be very fruitful.

5.11 Acetyl cholinesterase

P. atlantica exhibited a significant acetylcholinesterase inhibition effect [44]. The crude extract and different fractions and fruit stem metabolites of *P. vera* caused the significant acetylcholinesterase inhibition [88]. The inhibition of acetylcholinesterase by the *P. khinjuk* has also been reported [95].

5.12 Nephroprotective effect

Nephrotoxicity is related to chronic consumption of NSAID, DM, and even with HTN. The plants are analgesic, anti-inflammatory and nephroprotective. This is the beauty of natural products that they have multiple indications at a time. Ehsani et al. [96] established the protective effects of *Pistacia vera*-derived hydroalcoholic extract against rat nephrotoxicity induced by gentamicin. Nephrotoxicity in rats was caused by intraperitoneal gentamicin injection at a dose of 100 mg/kg/day. Pistachio hydroalcoholic extracts (10, 50, and 100 mg/kg) were administered for seven days. The findings from this study reported that treatment with pistachio could ameliorate renal failure and structural damage by mitigating inflammation and oxidative stress in the kidney [96].

5.13 Hepatoprotective effect

A significant hepatoprotective effect was observed in carbon tetrachloride-induced hepatitis by the hydroalcoholic extract of *P. vera*. Hepatoprotective effects were observed against CCl₄-triggered liver damage in 40 male rats when treated

with *P. vera* hydroalcoholic extract. The antioxidant properties of hydroalcoholic extract potentially supported hepatic cells to suppress inflammation and necrosis caused by CCl_4 . Findings from this study along with earlier studies confirm that Pistachio extract can act as a potential candidate for liver damage treatment [97]. Another study has been undertaken to ascertain the hepatoprotective effect of the fruit and leaf extracts of *P. lentiscus* on acute hepatitis induced by paracetamol, as evidenced by lowering tissue necrosis, reducing transaminase as well as MDA serum levels. Hepatoprotective capacity against paracetamol (165 mg/kg body weight) toxicity was found in mice pretreated with the same dosage of PL (*Pistacia* leaves) or PF (*Pistacia* fruits) extract (125 mg/kg) or a mixture of both. These findings were verified via histological analysis of the liver, which revealed substantial defense against hepatic necrosis triggered by paracetamol [85].

5.14 Anti-melanogenic effect

The methanol extract derived from seeds of *P. vera* has been documented to have anti-melanogenic effects against human Melanoma SKMEL-3 cells. The consequence of MPH on the content of melanin, the activity of cellular tyrosinase as well as cytotoxicity (MTT assay) of the SKMEL-3 human melanoma cell was assessed, followed by 72 hours incubation. Findings demonstrated that MPH has powerful radical DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) scavenging activity and low anti-tyrosinase function in comparison with the prominent antioxidant (BHT) and tyrosinase (kojic acid) inhibitors, respectively. MPH demonstrated substantial cytotoxic activity (~63 percent) with a large dose (0.5 mg/mL) and powerful anti-melanogenic influence (~57 percent) in SKMEL-3 cells. The consequence of MPH on melanin reduction may be attributed to its cytotoxicity. Thus it can be concluded from the findings that MPH may be used as a potential agent to treat hyperpigmentation conditions such as melanoma [98].

5.15 Anti-nipple fissure effect

Painful nipple fissure is a severe concern for breastfeeding mothers. In breastfeeding mothers, nipple fissures are typically induced by improper positioning when breastfeeding or complications with latching or suction. They may also be triggered by breast engorgement. In athletes, nipple fissures are started by nipple chaffing to assess the effectiveness of saqez (*Pistacia atlantica*) on breastfeeding women's improvement of nipple fissure. A randomized clinical trial was performed on 100 suitable women who accessed the health centers in their post-partum period at Shahid Beheshti University of Medical Sciences in Tehran, Iran. A total of 100 participants were divided randomly into two equal groups of 50 women, divided into breast-milk and saqez ointments group. The findings revealed that the demographic and obstetric characteristics of the two classes were matched. Additionally, it can be concluded that saqez ointment is comparatively effective than breast milk in curing and managing nipple fissures during one-month follow-up, without culminating in any adverse effects [99].

5.16 Anti-oral mucositis effect

Oral mucositis refers to the ulcerative and lesions of the oral mucosa found in people having cancer when treated with chemotherapy and radiation therapy of

areas, including the oral cavity. Oral mucositis lesions also are extremely painful and impair diet and oral health and raise the severity of the local and systemic infection. An experimental analysis conducted by Tanideh et al. [100] verified that the essential oil of *P. atlantica* (bene) accelerated the healing status of oral mucositis induced by 5-fluorouracil in hamsters. The healing influence of bene oil could predominantly be local and due to possessing antioxidants and fatty acids in saponified and non-saponified fractions, respectively [100].

5.17 Anthelmintic effect

Different extract and essential oil of *P. khinjuk* are significant anthelmintics, especially against *Echinococcus granulosus*, which causes hydatid cyst [101]. The *P. lentiscus* is also the best anthelmintic [102]. The exsheathment of gastro-intestinal nematode larvae is impaired by polyphenols of *Pistacia lentiscus* [103]. Additionally, The *P. lentiscus* along with other plants in mixture form killed the nematodes in naturally infected sheep [104].

5.18 Toxicological effect

In an acute toxicity study, the methanolic extract of *P. integerrima* bark proved to be safe [38]. Besides, the *P. atlantica* fruits also proved safe in acute toxicological studies where the acute toxicity was evaluated for two days. Antinociceptive action was conducted with tail-flick, hot plate, and rotarod test. The *P. atlantica* fruit extract levels for LD50 were 1.66 g/kg with a cumulative non-lethal dosage of 0.93 g/kg. The fruit extract derived from *P. atlantica* at the doses range of 50–350 mg/kg conferred analgesic effects dose-dependently 30 minutes after administration during the hot plate and tail-flick tests so that a substantial difference between the groups obtaining saline and the extract was observed ($p < 0.05$). Results also revealed no significant differences in a sensory-motor assessment with *P. atlantica* fruit extract's administration at doses ranging from 50 to 350 mg/kg. Additionally, findings revealed robust antinociceptive behavior of the *P. atlantica* fruit extract in mice [45].

6. Conclusions and future perspectives

Medicinal plants are potential source of various chemical constituents which are responsible for the cure of different diseases. Scientific work of these plants is based on the ethnopharmacological use, largely based on trial and error, which may cause harm to humans. In addition, there is a false public perception that natural remedies are free of side or toxic effects. Although this claim is correct to some extent due to the presence of agonist and antagonist molecules in the same plant or extract, however, use of such chemical constituents without scientific knowledge could lead to serious health problems. For this reason, researchers have tested these alternative medicines for various disorders. Within this context, the genus *Pistacia* has been screened for different diseases based on ethnomedicinal uses. In the present work, we tried to collect all pharmacological data related to *Pistacia*. The wide spread use of members of this genus made it a key source of natural medicines. Furthermore, the purpose of this data collection was to encourage researchers for development and commercialization of these valuable members into various dosage forms.

The genus *Pistacia* accumulated many potential plants with significantly correlated activities such as analgesic, anti-inflammatory, nephroprotective, hepatoprotective, and anti-peptic ulcers. These activities are positively correlated because most of the NSAIDs cause hepatic, renal and stomach problems. So plants in this genus are tested on such an experimental model. The same animal is subjected to pain, inflammation, peptic ulcers, hepatitis and nephrotic damages and then treated with these plants individually or in a mixture with the hope to cure with time. If the researcher succeeded in such a study, it would be a breakthrough in pharmaceutical sciences to minimize polypharmacy. It is worth mentioning that the plants of this genus are anti-diabetic, neuroprotective, anti-diabetic wound, GLUT enhancer, lipid-lowering and anti-HTN. All these conditions have a significant correlation. A substantial number of patients worldwide suffered at times with these conditions. Therefore, we strongly recommend these plants be tested up to the clinical trial level for curing such diseases. The significant curing of such correlated disorders can abolish the problem of polypharmacy. Polypharmacy is one of the major factors leading to poor patient compliance. Moreover, chronic toxicological profiling of these plants is needed on all vital organs.

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