

# *Pistacia* Genus as a Potential Source of Neuroprotective Natural Products

## Authors

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## ABSTRACT

Neuroprotective agents are able to defend the central nervous system against acute or chronic neuronal injuries. Even with the progress made over the last decades, most of the medications prescribed for the management of neurodegenerative diseases can only reduce their symptoms and slow down their progression. Based on natural product research, there are potential effective medicinal plants and phytochemicals for modulating neuronal functions and protecting against neurodegeneration. Plants in the genus *Pistacia* are also among valuable natural resources for neuroprotection research based on experiences in traditional medicine. Studies have supported the value of bioactive compounds of the genus *Pistacia* for central nervous system disorders such as Alzheimer's, Parkinson's, multiple sclerosis, cerebral ischemia, depression, and anxiety. Related literature has also revealed that most of the evidence on neuroprotection in the genus *Pistacia* is in the form of preliminary studies, mainly including models of behavior, motor function, and memory impairments in animals, neural toxicity, cerebral ischemia and seizure models, evaluation of their effects on antioxidant and inflammatory biomarkers, amyloid  $\beta$  aggregation, and acetylcholinesterase as well as investigations into some cellular pathways. Along with the phytonutrients in kernels such as pistachios, various phytochemicals, mostly terpenes, and phenolic compounds have also been identified in different plant parts, in particular their oleoresins, of species in the genus *Pistacia*. In this review, the pharmacology of neurological effects and related molecular mechanisms of the plants belonging to the genus *Pistacia* and its active constituents, as well as pharmacokinetics aspects, are discussed.

## Introduction

As one of the remarkable modalities of complementary medicine, natural products create a potential platform for drug discovery and development, especially for chronic diseases and major health problems associated with aging. Concentrating on neuroprotective activity of natural products to control or prevent neurodegenerative diseases (NDs) is relatively a new research area [1]. It should be noted that neuroprotective agents are able to defend the CNS against acute (e.g., stroke or trauma) or chronic (e.g.,

AD and PD) neuronal injuries [2] resulting from the breakdown and deterioration of neurons [3]. Despite differences in anatomic distribution of NDs, leading to various manifestations, it seems that their pathologies have numerous similarities at subcellular levels [4]. In this respect, aggregation of proteins, inflammation, oxidative stress, as well as loss of neurotransmitters are considered among common pathologies of NDs [3]. Even with the progress made over the last decades, most of the clinically prescribed medications for the management of NDs can merely reduce ND

## ABBREVIATIONS

6-OHDA	6-hydroxydopamine
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
AD	Alzheimer's disease
BDNF	brain-derived neurotrophic factor
CAT	catalase
CNS	central nervous system
COX-2	cyclooxygenase-2
DCF-DA	2',7'-dichlorofluorescein diacetate
DPPH	2,2-diphenyl-1-picrylhydrazyl
GABA	gamma-aminobutyric acid
GPx	glutathione peroxidase
IL	interleukin
NF- $\kappa$ B	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide
Nrf2	nuclear erythroid 2-related factor 2
PC12	pheochromocytoma cells
PD	Parkinson's disease
PPAR	peroxisome proliferator-activated receptor
PTZ	pentylentetrazole
SOD	superoxide dismutase
TBARS	thiobarbituric acid reactive substances

symptoms and slow down their progression, and, conversely, lead to unavoidable adverse effects [5].

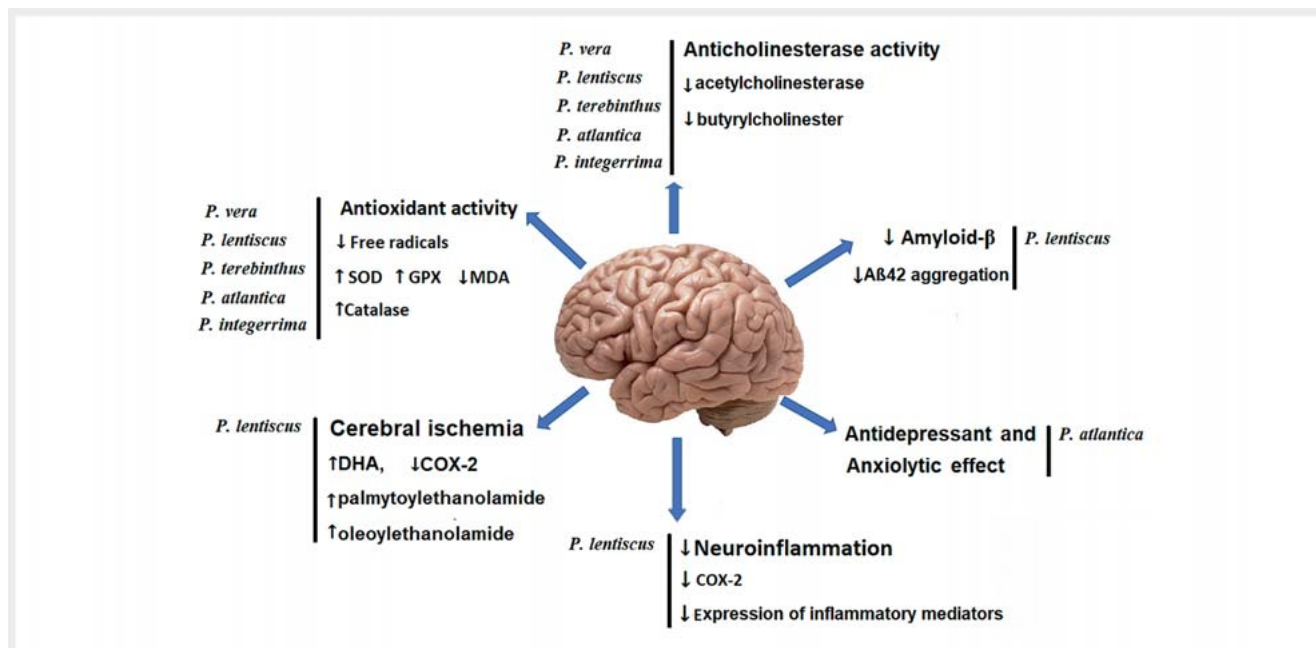
In recent years, plant-based products have received considerable attention. Hence, there is a strong tendency towards research on phytochemicals for modulating neuronal functions and protecting against neurodegeneration [6]. Numerous medicinal plants have also been recommended for the prevention and treatment of various diseases of the CNS in traditional medicine across the world [7]. Many of these herbs have been extensively studied regarding their neuroprotective effects. In addition, they have been reported to modulate multiple signal transduction pathways through direct effects on enzymes such as kinases, regulatory proteins, and receptors [8]. *Panax ginseng* C. A. Mey., *Ginkgo biloba* L., *Curcuma longa* L. and *Bacopa monnieri* (L.) Pennell. are among the most prominent plants examined in this field [7]. Plants in the genus *Pistacia*, belonging to the family Anacardiaceae [9], are also considered one of the valuable natural resources for neuroprotection research based on experiences in traditional medicine. This genus consists of at least 10 species in which *Pistacia vera* L., *Pistacia lentiscus* L., *Pistacia terebinthus* L., *Pistacia atlantica* Desf., and *Pistacia integerrima* J.L. Stewart ex Brandis. [*Pistacia chinensis* subsp. *integerrima* (J. L. Stewart ex Brandis) Rech. f.] are regarded as the most known ones. Among them, pistachios are more widely known because of the edible nature of their seeds. Although some others may also be suitable for eating, they are most often recognized for their oleoresin with industrial, pharmaceutical, and cosmetic uses [10]. In this study, along with elucidating traditional usage and evidence related to neuroprotective effects of these herbs, their major active ingredients and possible mechanisms of action as well as pharmacokinetic aspects were reviewed.

## Traditional Medicinal Usage of the *Pistacia* Genus

Hippocrates, Dioscorides, and Galen reported the distinctive characteristics of mastic gum (*P. lentiscus* oleoresin), such as taste and odor as well as therapeutic properties. Based on historical documents, this substance was the first natural chewing gum of the ancient world of Europe that was used to clean the teeth and to freshen the breath [11]. *P. lentiscus* has traditionally been used for memory improvement, as well as the treatment of stomachache, burn skin, asthma, and bronchitis in Algeria [12]. Even though the most important use of this oleoresin was the treatment of digestive problems such as gastric pains, it was introduced as a brain booster and protector in Greek and Persian traditional medicines, both having the same roots according to historical references. Its oleoresin, especially with olibanum, has also been prescribed orally for this purpose, especially for memory improvement. It has similarly been recommended for treating some types of headaches, psychiatric disorders, and management of stroke [13]. Leaves of the plant are traditionally used for toothaches, mycosis, herpes, abdominal and intestinal pain, rheumatism, antiseptic, cicatrizing, and as an astringent in Italy [14, 15]. The fruits have been used in Tunisia as a condiment and also for the treatment of scabies, rheumatism, and diarrhea [16].

Most therapeutic applications and reported uses of *P. atlantica* are related to traditional Persian medicine since the western region of Iran is one of the largest centers for producing this species, and its oleoresin is being used as chewing gum [17]. This oleoresin has therapeutic uses similar to mastic gum according to the written documents in traditional Persian medicine [18, 19]. In fact, in these documents, it has been prescribed to strengthen the stomach and the teeth, and also to cleanse the brain from waste materials interfering with brain activity such as memory. Its processed trunk exudate is used to clear mouth, gum, and teeth diseases, improving memory, and reducing stress [20]. In the western regions of Iran, the fruit of this plant, named bane, is also used as a nut, usually after grinding [21].

Records of the consumption of fruits of *P. vera* (pistachio) as a food date back to 7000 BC. Now it is cultivated in the Middle East, especially in Iran and Mediterranean countries as well as Turkey and the United States [22]. The oleoresin is used in folkloric medicine as chewing gum in Europe and the Middle East. In India, pistachios have been reported as a remedy for liver disorders, abscesses, and poor circulation [23]. In Turkey, pistachio gum has been used as a treatment for asthma, stomachaches, and hemorrhoids [24]. The fruits and fruit kernel of *P. vera* are used for strengthening the liver, heart, and stomach and as a brain tonic in traditional Persian medicine, as well [18]. In some areas of Jordan, the oil of the fruit has been used as a facial skin cleanser [25]. *P. integerrima* (*P. chinensis* subsp. *integerrima*) is known as kakra shingi in India. Its gall is currently being utilized to treat hepatitis and liver problems in Pakistan [26]. It is also known as an aromatic, astringent, expectorant, sedative, and spasmolytic agent in Ayurveda, and is being employed to treat asthma and chronic bronchitis, dysentery, and fever, as well as skin diseases [27]. The fruit of *P. terebinthus* has been recommended for the treatment of



► Fig. 1 Pharmacological aspects of the *Pistacia* genus on the brain.

colds, flu, stomachaches, rheumatism, and urinary inflammations. It has also been used as a diuretic, stimulant, antitussive, and appetizer, and as coffee in Turkey [28–30].

## Evidence Related to the Neuroprotection in the *Pistacia* Genus

### Search strategy

To obtain articles that directly assessed the neuroprotective activity of the plants in the *Pistacia* genus, databases including Scopus, PubMed, and Google Scholar were searched from 2000 to February 2019. Key words included “brain”, “memory”, “neuron”, “nootropic”, “neuroprotective”, “neurodegenerative”, “cognition”, “dementia”, “Alzheimer”, “Parkinson”, “amyotrophic lateral sclerosis”, “stroke”, “seizure”, “anxiety”, and “depression” along with the word “*Pistacia*” and also with each full scientific name of the plants. All studies that were in English and had full text were selected. The strategy was run by two researchers and then the findings of both were combined and duplicates were deleted. Obtained studies are classified in ► **Table 1** regarding the details of each study, including plant part, type of study, dose, duration, and results.

Most of the evidence related to neuroprotection activity in the genus *Pistacia* is in the form of preliminary *in vitro/vivo* studies; mainly including models of memory, motor function, and behavioral impairments in animals, neural toxicity, cerebral ischemia, and seizure models, evaluation of their effects on antioxidant and inflammatory biomarkers, amyloid- $\beta$  ( $A\beta$ ) aggregation, acetylcholinesterase (AChE), as well as investigations into some cellular pathways (► **Figs. 1** and **2**).

Even with the widespread presence of pistachios as the most commonly used phytonutrient-dense species of this genus, no clinical studies have directly aimed at investigating their effects on neurodegenerative disorders. In the following, studies on the neuroprotective effects of each individual plant are presented.

### *Pistacia vera*

In this domain, most of the studies have been carried out on pistachio’s kernel, hull, and its gum (oleoresin). In this respect, the neuroprotective effects of *P. vera* kernel was specified in a study through its administration for 5 weeks in rats, which could inhibit cognitive and motor impairments caused by cisplatin or vincristine and specifically reverse spatial memory disturbances by these neurotoxic anticancer drugs. However, pistachio has not indicated any effects on anxiety as monitored by the open field test. Its cognitive improvement effects might have been also related to high flavonoids and phenolic content of the pistachio fruit [31]. *P. vera* seed oil has been further reported to improve memory and cognitive impairment, as suggested by Y-maze test results in rats. However, it has not revealed any effects on spatial memory parameters in the Morris water maze test [32]. Moreover, one study found that the hydroalcoholic extract of pistachio nut (orally; 14 days) had significantly caused improved learning and memory in rats through the avoidance learning test [33]. In parallel, the aqueous-methanolic extract of *P. Vera* hull has been able to inhibit AChE activity to a certain extent. In this case, the  $IC_{50}$  of  $204.1 \pm 6.33 \mu\text{g/mL}$  was compared with physostigmine ( $IC_{50}$  of  $0.093 \mu\text{M}$ ) [34]. Moreover, the AChE inhibitory activity of its fruit hull methanol extract was proven in another study by a percentage of 5.5% in enzyme inhibition [35]. The anxiolytic effect of the hydroalcoholic extract of its hull (10 mg/kg) has been shown in female rats, which

► **Table 1** Pharmacological evidence related to the neuroprotection in the *Pistacia* genus.

Scientific name	Plant part	Extract/essential oil/active compound	In vivo/ in vitro	Animal species	Dose/duration	Assay/method/model	Results	Ref
<i>P. vera</i>	Hull	Aqueous-methanolic extract	<i>In vitro</i>	–	100 µg/mL	AChE inhibitory assay.	AChE inhibitory activity	[34]
	Kernel	Oil	<i>In vivo</i>	Male rats	1 and 4 mL/kg; p. o.; 21 days	Morris water maze (MWM) and Y-CAT maze.	Improved memory performance in Y-CAT maze test. The extract did not affect spatial learning and memory parameters in MWM.	[32]
	Oleo-resin	Hydroalcoholic extract	<i>In vivo</i>	Mice	0.25, 0.5, and 1 g/kg; i. p.	Pentobarbital model of sleep induction. Traction and rotarod tests. Elevated plus maze and open field tests.	Hypnotic, antianxiety, and muscle relaxant activities.	[40]
	Fruits	Pistachio suspension	<i>In vivo</i>	Male rats	10% dietary pistachio daily; 5 weeks	Model of motor and cognition impairments induced by cisplatin or vincristine. Rotarod and grasping tests; open field test. MWM	↓ Some learning, memory, and motor impairments.	[31]
	Hull	Methanolic extract	<i>In vitro</i>	–	–	AChE inhibitory assay.	AChE inhibitory activity.	[35]
	Kernel	Hydroalcoholic extract	<i>In vivo</i>	Rats	10, 50, and 100 mg/kg/day; p. o.; 14 days	Avoidance learning test using the shuttle box.	↑ The latency to enter the dark room. ↓ Time spent in the dark room improved learning and memory.	[33]
	Leaves	Aqueous and ethanolic extracts	<i>In vivo</i>	Mice	0.4 g/kg and 0.5 g/kg; i. p.	Hot plate and writhing tests. Xylene-induced ear edema. The cotton pellet test.	Antinociceptive.	[194]
	Ripe pistachio hulls	Hydroalcoholic extract	<i>In vivo</i>	Female Wistar rats	Single dose of 0.1, 1, 10, 50, 100, 250, 500 mg/kg; i. p.	Elevated plus maze model of anxiety.	Percentage of time spent in the open arms (%OAT), percentage of the number of entries into the open arms (%OAE).	[36]
	Seed	Hexan extract	<i>In vitro</i>	–	PC12 cells were pretreated with extract for 48 h (10%, v/v).	Measurement of intracellular oxidative stress. DPPH assay with Trolox. Measurement of cell viability by the MTT reduction assay.	↑ Cell viability. ↓ Intracellular ROS.	[37]
	Kernel	Hydroalcoholic extract	<i>In vivo</i>	Male rats	50 and 100 mg/kg, p. o.; every day (30 days)	Convulsive model induced by PTZ injection.	↓ Seizure scores, stage 4 latency and stage 5 duration.	[41]
	Gum	Hydroalcoholic extract	<i>In vivo</i>	Male NMRI rats	0.1, 0.25, 0.5 g/kg; i. p.	Thiobarbituric acid (TBA) and ferric reducing antioxidant power (FRAP) tests.	↓ Brain MDA. ↑ Antioxidant power of brain.	[38]

cont.

might be concluded due to the role of GABA and estrogen receptors in its antianxiety effect [36].

The protective potency of the hexane extract of the pistachio nut against oxidative stress has also been confirmed in a neuronal cell line via MTT and DCF-DA assays through focusing on its fatty acid composition [37].

With regard to antioxidant activity, the neuroprotective effects of *P. vera* gum extract have also been shown in rats with oxidative damage following cerebral ischemia. In this respect, the given extract could reduce the malondialdehyde (MDA) level and increase

antioxidant capacity of the brain in comparison with those in the control group [38, 39]. In another study, the hydroalcoholic extract of *P. vera* gum had been suggested to prolong sleep duration (at all doses: 0.25, 0.5, and 1 g/kg) and to shorten sleep onset latency (1 g/kg). In addition, the administration of the extract in mice demonstrated its antianxiety effects and consequently suppressed locomotor activity in the open field test [40]. The anti-epileptic effects of the hydroalcoholic extract of *P. vera* fruit have also been validated to be comparable with diazepam in a chronic PTZ-induced model of epilepsy in rats [41].

► Table 1 Continued

Scientific name	Plant part	Extract/essential oil/active compound	In vivo/in vitro	Animal species	Dose/duration	Assay/method/model	Results	Ref
<i>P. atlantica</i>	Leaves, flowers	Essential oil	<i>In vitro</i>	–	500 µg/mL	β-Carotene-linoleic acid assay; DPPH and ABTS assays; AChE inhibitory assay.	Antioxidant activity. Anticholinesterase activity against acetylcholinesterase and butyrylcholinesterase.	[52]
	Fruits	Hydroalcoholic extract	<i>In vivo</i>	Gonadectomized rats	100 mg/kg of bane extract; p. o., daily for 20 days	Elevated plus maze model of anxiety.	↑ The percentage of time spent and entries in the open arms.	[53]
	Fruits	Hydroalcoholic extract	<i>In vivo</i>	Male rats	400 mg/kg/bw pistachio + fluvoxamine 120 mg/kg/bw	Immobilization stress radial arm maze test.	↓ The time of reaching to target. ↓ MDA, corticosterone and blood glucose level. ↑ CAT.	[54]
	Leaves	Aqueous extract	<i>In vitro</i>	–	–	AChE inhibitory assay. Radical scavenging activity.	AChE inhibitory activity. ↓ Hydroxyl, DMPD, superoxide and ABTS.	[50]
	Leaves	Methanolic extract, ethyl acetate extract	<i>In vitro</i>	–	–	Total antioxidant and free radical scavenging activity. β-Carotene bleaching test. AChE inhibitory assay.	Considerable antioxidant property. Slight AChE inhibitory activity.	[51]
	Oleo-resin	Methanol and dichloromethane extracts	<i>In vitro</i>	–	–	AChE inhibitory assay.	Dichloromethane extract: AChE inhibitory activity.	[45]
	Fruit	Essential oil	<i>In vivo</i>	Rats, mice	200, 300, and 500 mg/kg	Hole-board, rotarod, catalepsy, hypnotic, light/dark tests.	CNS depressant, anxiolytic, sedative and anti-inflammatory properties.	[195]
	Leaves	Aqueous, ethyl acetate, and butanol extracts	<i>In vitro</i>	–	–	DPPH; AChE inhibitory assay.	Antioxidant activity (maximum in the ethyl acetate extract). AChE inhibitory activity (ethyl acetate and aqueous extracts).	[49]
	Leaves	Aqueous extract	<i>In vitro</i>	–	–	AChE inhibitory assay	AChE inhibitory activity.	[43]
<i>P. lentiscus</i>	Leaves	Essential oil	<i>In vivo</i>	Rats	200 mg	Bilateral common carotid artery occlusion model. Analysis of levels of the enzyme COX-2, as assessed by Western blot.	↑ DHA. ↓ COX-2s. ↑ Palmitoylethanolamide and oleoylethanolamide levels in plasma.	[48]
	Leaves	Alcoholic extract	<i>In vitro</i>	–	25, 50, 100 µg/mL	SK-N-BE (2)-C cells injury induced by H <sub>2</sub> O <sub>2</sub> , and Aβ (25–35) by the MTT assay.	Protected the cells against Aβ (25–35) and H <sub>2</sub> O <sub>2</sub> -induced toxicity.	[47]
	Oleo-resin	Ethanollic extract	<i>In vitro</i>	–	2, 4, 6, 8, 10 µg/mL	AChE inhibitory assay.	Competitive inhibitor of acetylcholinesterase.	[44]
	Fruits	Methanolic extract	<i>In vitro</i>	–	–	DPPH; ABTS. Thioflavine T assay (ThT); dynamic light scattering (DLS); transmission electron microscopy analysis (TEM).	Antioxidant activity. Inhibited Aβ <sub>42</sub> aggregation and related neurotoxicity.	[46]
	Leaves	Aqueous extract	<i>In vitro</i>	–	–	AChE inhibitory assay.	AChE inhibitory activity	[43]
	Fruit	Oil	<i>In vivo</i>	Male rats	3.3 mL/kg orally, daily for 15 days	Model of memory dysfunction and oxidative stress induced by lipopolysaccharide. Open field and spatial object recognition tests. AChE inhibitory assay.	↓ Spatial memory deficit. ↓ Brain acetylcholinesterase activation. ↓ Brain MDA, H <sub>2</sub> O <sub>2</sub> . ↑ Brain CAT, SOD.	[42]
	Oleo-resin	Methanol and dichloromethane extracts	<i>In vitro</i>	–	–	AChE inhibitory assay.	Dichloromethane extract: AChE inhibitory activity	[45]

cont.

► **Table 1** Continued

Scientific name	Plant part	Extract/essential oil/active compound	In vivo/ in vitro	Animal species	Dose/duration	Assay/method/model	Results	Ref
<i>P. integerrima</i>	Gall	Crude extract, ethyl acetate, aqueous, <i>n</i> -hexane and chloroform fraction; quercetin, pyrogallol	<i>In vitro</i>	–	1000, 500, 250, 125, 62.5 µg/mL	DPPH; ABTS; AChE inhibitory assay.	Ethyl acetate fraction: the most powerful radical scavenging activity. Quercetin and pyrogallol: antioxidant properties. Crude extract and ethyl acetate fraction: highly inhibited acetyl cholinesterase activity.	[57]
	Galls	Ethanollic extract	<i>In vivo</i>	Rats and mice	0.5 mL/kg; i. p.	Five behavioral experimental models. Convulsion experimental models induced by PTZ, strychnine. Maximal electroshock seizures (IVIES).	↑ Pentobarbitone-induced sleeping. ↑ Time of loss of righting reflex. ↑ Reaction time of 24 h fasted rats placed in a Hebb-William maze.	[56]
	Galls	Essential oil	<i>In vitro</i>	–	10 and 50 µg/mL	Pharmacological assays on rabbit jejunum spontaneous contractions, guinea pig ileum.	↑ Isoprenaline induced relaxation of rabbit jejunum, relaxation of basal tone of K <sup>+</sup> induced contraction, ↓ Ca <sup>2+</sup> induced contraction of isolated guinea pig ileum in Ca <sup>2+</sup> free medium. ↑ The reversal of a KCl-induced tonic contraction observed in Ca <sup>2+</sup> free medium.	[196]
<i>P. terebinthus</i>	Flowers	Aqueous extract	<i>In vivo</i>	Male rats	250 mg/kg every other day by gavage	Measuring the lipid peroxidation (LPO), total protein, glutathione, and enzyme activities in blood.	↓ Lipid peroxidation in brain. ↑ Glutathione and total protein. ↑ GSH-Px and SOD.	[197]
	Fruits	Ethyl acetate and methanolic extracts	<i>In vitro</i>	–	–	AChE inhibitory assay. Tyrosinase activity assay. DPPH, DMPD, FRAP and metal chelation tests and PRAP test as radical scavenging activity assay.	Methanolic extract moderately inhibited butyrylcholinesterase activity. The extracts did not inhibit acetyl cholinesterase and tyrosinase enzymes. Both extracts: DPPH and DMPD scavenging activity and antioxidant activity.	[59]

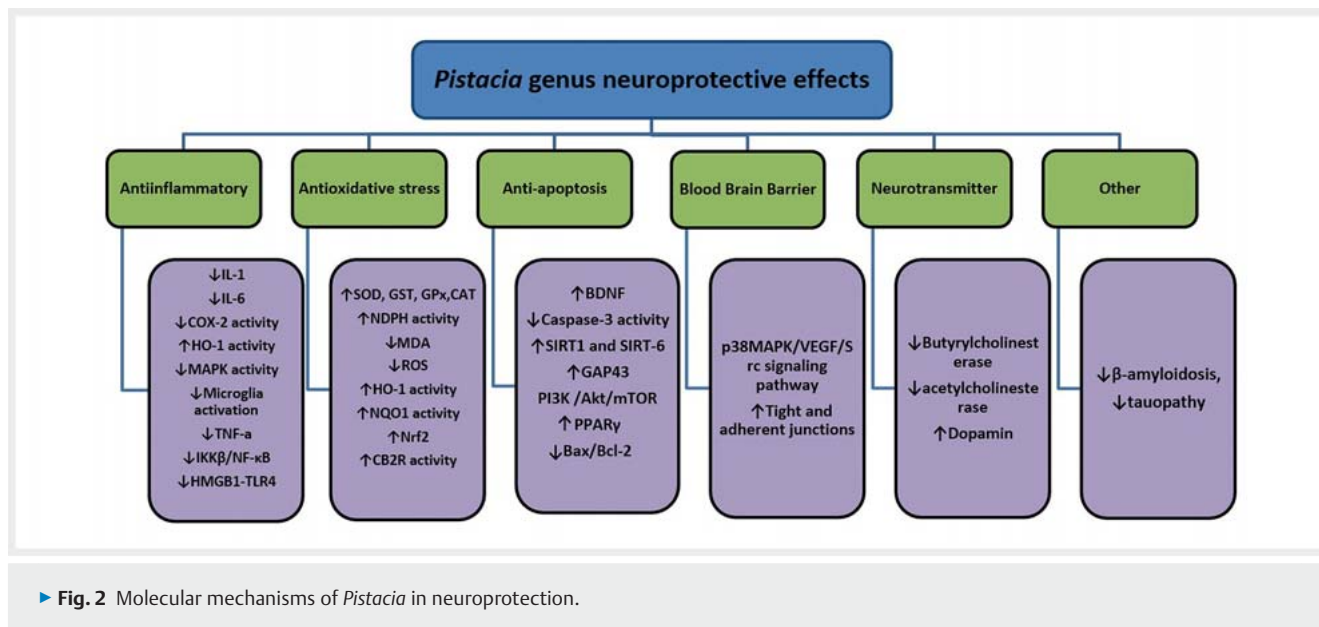
AChE: Acetylcholinesterase; i. p.: intraperitoneal; DPPH: 2,2-diphenyl-1-picrylhydrazyl; PTZ: pentylenetetrazol; MDA: Malondialdehyde; ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); DMPD: N,N-dimethyl-p-phenylenediamine; SOD: Superoxide dismutase; CAT: catalase; GSH: Glutathione

### *Pistacia lentiscus*

It has been reported that pretreatment by the essential oil of *P. lentiscus* fruit can attenuate lipopolysaccharide-induced memory impairment in rats in the open field and spatial object recognition tests. It can also induce a decrease in AChE activity as well as oxidative stress markers in brain tissues. The major components of the essential oil identified in this domain have been 4-(3-[(2hydroxybenzoyl) amino] aniline)-4-oxobut-2-enoic acid, β-myrcene, 3-pentadecylphenol, *P*-tolyl ester, aminofornic acid, and β-sitosterol [42]. Other studies have also demonstrated that the aqueous extract of *P. lentiscus* leaves and the ethanollic extract of its oleoresin possessed AChE inhibitory activity with IC<sub>50</sub> values of 13.67 ± 0.69 µg/mL and 6.5 µg/mL, respectively [43,44]. Additionally, the dichloromethane extract of *P. lentiscus* oleoresin has also been shown to inhibit AChE activity [45]. In this respect, Dhouafli et al. [46] investigated *P. lentiscus* for its ability to coun-

teract amyloid (Aβ<sub>42</sub>) aggregation, commonly considered a pathological hallmark of AD [47]. The results of this study indicated that pretreatment in SH-SY5Y cells with 100 µg/mL of defatted methanol extract of *P. lentiscus* (10 µg/mL) for 24 h could increase cell viability and reduce Aβ-mediated cellular toxicity. However, *P. lentiscus* extract did not have a significant cytoprotective effect. In contrast, cells treated with the same amount of Aβ<sub>42</sub> aggregates grown in the presence of the extract showed significant retention of viability, reaching 81.65% for *P. lentiscus* [46]. The alcoholic extract obtained from *P. lentiscus* leaves has also been demonstrated to contain substantial amounts of phenolic components as effective agents for preventing disorders induced by oxidative damage. This extract could significantly protect SK-N-BE (2)-C neuronal cells against oxidative injury by H<sub>2</sub>O<sub>2</sub> and Aβ (25–35) and almost entirely protect the given cells against Aβ-induced neuronal toxicity with the dose of 100 µg/mL [47]. Besides, ische-





mia of the brain causes free radical formation, neuroinflammation, and neuronal injury. In an ischemic model of bilateral common carotid artery ligation, the essential oil of *P. lentiscus* leaves was able to reverse ischemia-induced decrease of docosahexaenoic acid (DHA) and COX-2 expression in the frontal cortex. It is noteworthy that DHA is the predominant fatty acid of neuronal cell membrane affected by oxidative damage. It also acts through stimulating PPAR- $\alpha$ , which results in diminishing neuroinflammation. Moreover, COX-2 overexpression induced by ischemia can contribute to neuronal injury. Additionally, the essential oil increases the amount of palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) as well as DHA biosynthesis in plasma, which counteract neuroinflammation. The increase in DHA biosynthesis can be induced by elevated levels of PEA and OEA followed by PPAR- $\alpha$  activation. This potential mechanism eventually leads to a neuroprotective effect of *P. lentiscus* essential oil against ischemia/reperfusion brain injury [48].

### *Pistacia atlantica*

The most effective AChE inhibitory activity of the extracts of *P. atlantica* leaves has been reported by ethyl acetate and aqueous extracts, probably due to the high phenolic components in these substances [49]. The results of two studies in this domain demonstrated that the aqueous extract of *P. atlantica* leaves possessed remarkable AChE inhibitory activity with an  $IC_{50}$  of  $0.87 \pm 0.55 \mu\text{g/mL}$  [43] and  $58.05 \pm 0.12 \mu\text{g/mL}$  [50], respectively. It should be noted that *P. atlantica* consists of large amounts of phenolic compounds, possibly associated with the strong AChE inhibitory effect [43, 50]. In addition, anticholinesterase and antioxidant activities of methanolic and ethyl acetate extracts of *P. atlantica* leaves have been assessed. In this regard, powerful antioxidant properties have been observed by both extracts compared with known synthetic antioxidants. It should be noted that the antioxidant properties of *P. atlantica* leaf extracts can be attributed to their constituents, including total phenols, total flavo-

noids, anthocyanins, chlorophyll, and carotenoid contents. In addition, the extracts have demonstrated slight inhibitory activity against AChE. However, ethyl acetate extract could inhibit the enzyme much stronger than the methanolic extract [51].

Essential oils obtained from *P. atlantica* leaves and flowers have further been found to be protective against free radicals and oxidative stress. They can also inhibit the AChE enzyme. It is worth noting that the essential oils consist of large amounts of monoterpenes and oxygenated sesquiterpenes contributed to the antioxidant and anticholinesterase properties. Moreover, the effects of *P. atlantica* leaf essential oil on both free radical scavenging and anticholinesterase activities have been reported to be, to some degree, better than its flower oil. *P. atlantica* leaf oil has also shown an  $IC_{50}$  of  $18.5 \pm 0.5$  compared with *P. atlantica* flower oil, which has an  $IC_{50}$  of  $20.5 \pm 0.5 \mu\text{g/mL}$  against AChE [52].

In one animal study, anxiety-like behaviors were assessed using the elevated plus maze (EPM) test in intact and gonadectomized rats submitted to a chronic unpredictable stress (CUS) paradigm and treated with hydroalcoholic extracts of *P. atlantica* fruit (100 mg/kg, orally for 20 days). The results of this study revealed that *P. atlantica* treatment increased the percentage of both time spent and entries in the open arms of EPM in intact and gonadectomized rats. Moreover, the effects of chronic stress were reversed by *P. atlantica* treatment [53]. Administration of the hydroalcoholic extract of *P. atlantica* fruit (400 mg/kg) in combination with fluvoxamine in rats under immobilization stress also improved spatial memory via decreasing the time of reaching the target as well as reducing the MDA, corticosterone, and blood glucose levels and increasing the catalase level [54].

Pretreatments with noncytotoxic *P. atlantica* extract at  $100 \mu\text{g/mL}$  have similarly been reported to reduce starvation-induced apoptosis *in vitro*. Pretreatments with *P. atlantica* have also been demonstrated to be neuroprotective against PD-inducing neurotoxins, including 6-OHDA and rotenone [55].

## *Pistacia integerrima*

In this domain, Ansari et al. [56] found that pretreatment of rats with the ethanolic extract of *P. integerrima* galls could possess a CNS-depressant activity once administered (0.5 mL/kg; i.p.) in rats. It could also extend the duration of sleeping in a pentobarbition-induced sleeping model. Moreover, its extract could remarkably inhibit aggressive behaviors in isolated mice. As well, the administration of the given extract had significantly protected the mice against tonic-clonic convulsion and death induced by PTZ. Its major identified constituents were  $\alpha$ -terpineol,  $\beta$ -terpineol,  $\alpha$ -pinene,  $\beta$ -pinene, A3-carnene,  $\alpha$ -phellandrene,  $\beta$ -phellandrene,  $\delta$ -pinene,  $\alpha$ -terpinene, limonene  $\alpha$ -ocemene, and  $\beta$ -ocemene.

In another study, several types of *P. integerrima* gall extracts had been studied in order to identify radical scavenging and cholinesterase inhibitory activity. Among them, ethyl acetate extract demonstrated the best radical scavenging activity in both DPPH and ABTS assays as well as the most potent AChE and butyrylcholinesterase inhibitory activities compared with other tested extracts. *P. integerrima* crude extract also showed both AChE inhibitory and radical scavenging activities, which were approximately closer to the ethyl acetate extract. Free radical scavenging activity of quercetin and pyrogallol as pure compounds isolated from *P. integerrima* was also confirmed, with higher antioxidant properties for pyrogallol [57].

It has also been reported that the petroleum ether extract of *P. integerrima* gall could display anticonvulsant activity in zebrafish through prolonging the onset of hyperactivity and tonic-clonic seizure in PTZ-induced seizures (50, 100, 200 mg/kg). Additionally, anticonvulsant effects of the petroleum ether extract have been confirmed in mice at doses of 100 and 150 mg/kg. Besides, petroleum ether extract delayed or prevented hind limb extension onset in maximal electroshock models of epilepsy in a dose-dependent manner. In contrast, methanolic extract proved to have no protection against seizures in both PTZ and MES models [58]. The essential oil of *P. integerrima* gall also revealed relaxant and spasmolytic effects in one study, probably mediated by modulating  $\beta$ -adrenoceptors and calcium channels [27].

## *Pistacia terebinthus*

The anticholinesterase and antioxidant properties of ethyl acetate and methanolic extracts of *P. terebinthus* fruit and four terebinth coffee brands were investigated in an *in vitro* study. The results showed that both extracts had moderate inhibitory effects on butyrylcholinesterase activity (at the concentration of 200  $\mu$ g/mL). Moreover, they showed radical scavenging activity at a higher concentration (2000  $\mu$ g/mL) without inhibiting the activity of AChE and tyrosinase enzymes. It has been reported that phenolic and flavonoid contents of terebinth coffee brands are higher than *P. terebinthus* fruit, which results in higher antioxidant and neuroprotective activities. The increase in phenolic and flavonoid content may be due to the roasting process, which implies that the roasting process of fruit may improve the antioxidant properties of the extracts. It has also been reported that oleic acid is the major fatty acid found in *P. terebinthus* fruits, while  $\alpha$ -pinene is the main constituent in the essential oil followed by  $\beta$ -ocimene and limonene [59].

## Neuroprotective Phytochemicals in *Pistacia* Genus

Herbal medicine or phytotherapy generally refers to the medicinal usage of plant parts with their secondary metabolites for their curative properties. Different usable plant parts in the *Pistacia* genus also contain a variety of bioactive phytochemicals [9]. Phytochemicals are biologically active compounds that are not considered essential nutrients but seem to contribute to protection against degenerative disease [60].

Among the edible parts of the herbs in this genus, pistachio fruits (i.e., kernels) are the most extensively used nuts as food. From a nutritional point of view, *Pistacia* species have fruits with remarkable contents of fatty acids. The main fatty acid in kernels of *P. vera*, *P. atlantica*, *P. lentiscus*, and *P. terebinthus* fruits is oleic acid [22], which has been proven to be protective as an unsaturated fatty acid against AD as well as other neurological disorders [61]. Besides the other fatty acids identified in these species, linolenic has been known as the precursor of DHA and eicosapentaenoic acids (EPAs) and it has been reported to possess antioxidative and neuroprotective effects [62]. Polyunsaturated fatty acids (PUFAs) have been shown to play a central role in the maintenance of neuronal functions and brain development, contributing to neurogenesis and neuroplasticity. Moreover, these PUFAs also exert significant protective effects against inflammatory damage to the neurons and glial cells. Omega-3 fatty acids have also been reported to show promising effects as antidepressant agents [63].

The presence of other nutrients such as glutamic and aspartic acids, vitamins (vitamin E), choline, and phytosterols (i.e.,  $\beta$ -sitosterol, campesterol, and stigmasterol) could also emphasize the potential of these seeds (especially pistachios) in the prevention and control of neurological diseases [64]. Along with the nutrient dense kernels, various groups of phytochemicals, mostly terpenes (mono-, sesqui-, and triterpenes) and phenolic compounds, have been identified in different plant parts of *Pistacia* species. Many studies have shown a neuroprotective effect of *Pistacia* chemical constituents. Selected studies examining the key components in this domain are summarized in ► **Table 2** and are shown in ► **Fig. 2**.

### Terpenes

Terpenes and terpenoids (modified terpenes) are the principal constituents of the essential oils in many types of plants. Their classification is commonly based on isoprene units. Essential oils mostly contain mono- (with two isoprene units) and sesquiterpenoids (with three isoprene units) [65]. Monoterpenes are the predominant constituents of the essential oil obtained from leaves, oleoresin, and fruits of different *Pistacia* species [22]. The galls are also rich in terpenes. The galls usually contain higher levels of total terpene, especially monoterpenes like  $\alpha$ -pinene and limonene, while the healthy leaves possess higher contents of sesquiterpenes with a predominance of caryophyllene, germacrene D, and d-cadinene [66].



► **Table 2** Selected phytochemicals in the *Pistacia* genus and their neuroprotective activity.

Scientific name	Plant parts [22]	Constituents	Experimental model	Observation/mechanism
<i>P. vera</i>	Leaf, unripe fruit, resin	$\alpha$ -Pinene	H <sub>2</sub> O <sub>2</sub> -induced oxidative stress in rat PC12	↑ Cell viability ↓ Intracellular ROS ↑ CAT, SOD, GPx, GR, HO-1 ↓ Apoptosis ↓ Capase-3 ↑ Nrf2 [71]
<i>P. terebinthus</i>	Fruit, aerial part, leaf, gall		6-OHDA-induced PD in rat	Improvement of the movement disorder and avoidance memory ↓ MDA in striatum and hippocampus [73]
<i>P. lentiscus</i>	Resin, leaf fruit, aerial part		Inhalation of $\alpha$ -pinene in mouse	↓ Anxiety Accumulation of $\alpha$ -pinene in the brain and liver [198]
<i>P. atlantica</i>	Leaf, fruit, gall, resin		Inhalation of $\alpha$ -pinene in mouse	↑ BDNF in the olfactory bulb and in the hippocampus [74]
			Scopolamine-induced cognitive dysfunction in mouse	↑ Choline acetyltransferase ↑ Nrf2 Improvement of cognitive dysfunction [72]
<i>P. lentiscus</i>	Mastic water	Linalool	Dizocilpine-induced schizophrenia-like behavior	↓ Behavioral alteration ↓ Total distance travelled in the Y-maze test ↓ Activity of mice in the spontaneous locomotor activity test [75]
			Acrylamide-induced neurotoxicity in rat	↑ GSH ↓ Lipid peroxidation [77]
			OGD/R-induced cortical neuronal injury in microglial cell	↓ Cells death ↓ Intracellular ROS ↑ SOD, CAT ↓ Microglial migration [78]
			Triple transgenic model of AD (3 × Tg-AD) in aged mouse	Improvement of learning and spatial memory ↓ Extracellular $\beta$ -amyloidosis, tauopathy, astrogliosis and microgliosis ↓ p38 MAPK, NOS2, COX2, IL-1 $\beta$ [76]
			MCAO-induced ischemic neurodegeneration in rat Glutamate induced toxicity in glial cell	↓ Infarct volume Better neurological and motor skills and relearning performance ↓ Microgliosis, COX-2, IL-1B and Nrf2 markers ↓ NF- $\kappa$ B, IL1- $\beta$ , COX-2, and Nrf2 immunostaining and microglial changes under glutamate toxicity [79]
Expression of recombinant T-type Ca <sup>2+</sup> channels (Ca <sub>v</sub> 3.2) in HEK-293 T cells using whole-cell patch-clamp technique	↓ Ca <sub>v</sub> 3.2 Inhibition of TTCCs [199]			

cont.

## $\alpha$ -Pinene

$\alpha$ -Pinene is a bicyclic monoterpene widely found in nature, especially in essential oils with a strong turpentine odor [67, 68]. This substance forms a large part of the essential oil of the *Pistacia* genus from 57.06% [69] in *P. atlantica* to 75.6% in *P. vera* [70].

Antioxidant activity of  $\alpha$ -pinene has been shown through its beneficial effect on the equilibration of oxidant/antioxidant to protect against H<sub>2</sub>O<sub>2</sub>-induced oxidative stress in rat PC12 cells. Reactive oxygen species scavenging and induction of the Nrf2 were determined as the main mechanisms of action [71]. In another study,  $\alpha$ -pinene was administered in C57BL/6 mice with scopolamine-induced cognitive dysfunction. Increasing mRNA expression of choline acetyltransferase, hemeoxygenase-1 (HO-1) and activation of Nrf2 were the main mechanisms of the  $\alpha$ -pinene beneficial effect for management of dementia [72]. In addition, in mice with 6-OHDA-induced PD, administration of  $\alpha$ -pinene im-

proved the movement disorder and avoidance memory. It led to a reduction in the MDA level in the striatum and hippocampus [73]. This substance has been shown to exert anxiolytic effects as well. Inhalation of  $\alpha$ -pinene in mice increased BDNF mRNA and tyrosine hydroxylase mRNA in the olfactory bulb and in the hippocampus. It also increased locomotor activity and acted as an anxiolytic agent based on the elevated plus maze test [74]. Another animal study evaluated the effects of  $\alpha$ -pinene inhalation on mice with dizocilpine-induced schizophrenia-like behavior. Inhalation of  $\alpha$ -pinene suppressed the dizocilpine-induced increased total distance travelled in the Y-maze test, whereas it did not alter the MK-801-induced reduced threshold of antinociception in the hot plate test. Inhalation of  $\alpha$ -pinene suppressed the activity of mice in the spontaneous locomotor activity test and although it did not suppress the dizocilpine-induced increased locomotor activity in the open field test, it remarkably decreased the time that the mice

► **Table 2** *Continued*

Scientific name	Plant parts [22]	Constituents	Experimental model	Observation/mechanism
<i>P. terebinthus</i>	Leaf	$\beta$ -caryophyllene	OGD/R-induced ischemia in human neuroblastoma SH-SY5Y	Significant neuroprotection effect (more than MK 801, the positive control) [93]
<i>P. lentiscus</i>	Leaf, galls		LPS-induced toxicity in a proliferative oligodendrocyte cell line (OLN-93)	↓ Toxicity Involvement of CB2R through different pathways including Nrf2/HO-1/antioxidant axis, and PPAR- $\gamma$ [200]
			High-fat/fructose diet-induced neurobehavioral changes in rats	↓ OS ↓ Neuroinflammation and behavioral changes Involvement of CB2R in antidepressant and memory improvement by upregulation of PGC-1 $\alpha$ and BDNF Involvement of PPAR- $\gamma$ and CB2R in anxiolytic, antioxidant, and anti-inflammatory effects [87]
			CI/R injury in C57BL/6 mice. OGD/R-induced ischemia <i>in vitro</i>	↓ Necroptotic neurons and MLKL protein ↓ Infarct volumes, neuronal necrosis, RIPK1 and RIPK3 expression, and MLKL phosphorylation. ↓ HMGB1, TLR4, IL-1 $\beta$ , and TNF- $\alpha$ levels [91]
			CI-R injury in rat	↓ Neurological deficit scores, infarct volume, MDA, LPO, NO, Bax ↑ SOD, CAT and Bcl-2 ↑ Nrf2, HO-1 [92]
			MPTP-induced murine model of PD	↓ Motor dysfunction ↓ Glia activation ↓ Dopaminergic neuronal losses ↓ Inflammatory cytokines in the nigrostriatal system. Involvement of the CB2R [88]
			Rotenone-induced oxidative stress and neuroinflammation in a rat model of PD	↓ Dopaminergic neurons death ↓ Microglia and astrocyte activation ↓ Iba-1 and GFAP expression ↓ COX-2, iNOS, lipid peroxidation, glutathione depletion ↑ Antioxidant enzymes [201]
			Kainic acid-induced seizure activity in mouse	↓ Seizure activity score ↓ Mortality ↓ MAO, TNF- $\alpha$ , and IL-1 $\beta$ ↑ GPx, SOD, CAT [202]
			Pentylentetrazol-induced seizures in mouse	↑ Latency to myoclonic jerks Improvement of recognition index No behavioral changes in open field, rotarod, or forced swim tests No effect on TBAR and NPT [203]
			Transgenic APP/PS1 model of AD in mouse	↓ Cognitive impairment ↓ $\beta$ -amyloid ↓ Astroglia and microglial activation ↓ COX-2 protein and the mRNA levels of TNF- $\alpha$ and IL-1 $\beta$ in the cerebral cortex [84]
			MCAO-induced ischemia OGD/R in cerebral cells	↓ Neurological deficits ↓ iNOS, IL-1 $\beta$ , IL-6, and COX-2 in C6 microglial cells ↓ NO and PGE <sub>2</sub> [90]
			Animal model of vascular dementia in rat	↓ Learning and memory deficits ↑ Recovery of cerebral brain flow ↑ Expression of CB2 ↑ Expression levels of PI3K and Akt [82]
			Glutamate-induced cytotoxicity in the C6 glioma cell line	↓ ROS Reestablishing $\Delta\psi_m$ ↑ Nuclear translocation of Nrf2 ↑ GSH Involvement of CB2R activation [85]

cont.

► **Table 2** Continued

Scientific name	Plant parts [22]	Constituents	Experimental model	Observation/mechanism
<i>P. lentiscus</i>	Fruit, resin, leaves, twigs	Myrcene	Global CI/R by carotid occlusion in C57BL/6 mouse	↑ GSH, GPx, and SOD ↓ TBARs ↓ Histopathological damage and apoptosis in brain tissue [96]
<i>P. atlantica</i>	Fruit, resin, leaves			
<i>P. vera</i>	Fruit, leaves, hulls			
<i>P. atlantica</i>	gum	Limonene	Corticosterone-induced neurotoxicity in PC12	↓ Neurotoxicity ↓ MDA, NO, NADPH oxidase, iNOS, COX-2, IL-6, IL-1 $\beta$ , and TNF- $\alpha$ , ↓ Bax and cleaved caspase-3 ↑ SOD1, HO-1, Bcl-2 ↓ Number of TUNEL-positive cells ↑ AMPK $\alpha$ and ↓ of NF- $\kappa$ B nuclear translocation through upregulation of SIRT1 [97]
<i>P. terebinthus</i>	fruit			
<i>P. lentiscus</i>	Resin, fruit		Chronic immobilization stress-induced high anxiety in male rat	↑ Percentage of open arm entries and stay in these arms ↓ Stress-induced damage in CA1 pyramidal neurons [98]
			Transient cerebral ischemia in stroke-prone spontaneously hypertensive rats	↓ Cerebral infarct size ↓ mRNA expression of IL-1 $\beta$ , MCP-1, and COX-2 ↑ mRNA expression of VEGF in the brain ↑ SOD, CAT ↑ Glutathione ↓ MDA Improvement of behavior [99]
			Scopolamine-induced dementia	Improvement of associative and non-associative memory ↑ Dopamine ↓ AChE activity [100]

cont.

remained in the central area. In the tail suspension and grip strength tests, there was no effect on mouse behavior by administration of MK-801 (dizocilpine) and inhalation of  $\alpha$ -pinene [75].

### Linalool

Linalool (3,7-Dimethyl-1,6-octadien-3-ol) refers to two enantiomers of a naturally occurring terpene alcohol that is a major volatile component of over 200 essential oils of several aromatic plants. It has remarkable effects as a sedative, antinociceptive, anticonvulsant, and anxiolytic natural product [76]. Linalool administration in rats that were exposed to acrylamide, as a neurotoxic agent, led to an increase of glutathione content and reduction of acrylamide-induced lipid peroxidation in rat brain tissue [77].

In an *in vitro* study, (-)-linalool also demonstrated neuroprotective effects against neuronal injury induced by oxyglucose deprivation/reoxygenation (OGD/R). Antioxidant and anti-inflammatory properties of (-)-linalool might be related to this effect [78].

Oral administration of this monoterpene led to an improvement in learning and spatial memory and greater risk assessment behavior in old triple transgenic AD mice. A significant reduction in microgliosis, astrogliosis, extracellular  $\beta$ -amyloidosis, and tauopathy were detected in hippocampi and amygdalae from linalool-treated mice. Proinflammatory markers p38 mitogen-activated protein kinase (MAPK), NOS2, COX-2, and IL-1 $\beta$  also decreased [76]. Moreover, intranasal administration of linalool after focal-in-

duced ischemia in rats led to a reduction in infarct volume, and better neurological and motor skills. In this study, attenuation of microgliosis and COX-2, IL-1 $\beta$ , and Nrf2 markers in the cerebral cortex and hippocampus was detected [79].

### $\beta$ -Caryophyllene

$\beta$ -Caryophyllene, also known as caryophyllene or (-)- $\beta$ -caryophyllene, is a natural bicyclic sesquiterpene that is a constituent of many essential oils. It is usually found in nature as a mixture with small amounts of isocaryophyllene (the *cis* double bond isomer) and  $\alpha$ -humulene ( $\alpha$ -caryophyllene) isomers [80]. Various studies have shown neuroprotective effects of  $\beta$ -caryophyllene in animal models of cerebral ischemia, PD, and AD. It has also been shown as an anxiolytic, anticonvulsant, analgesic, immunomodulator, and antispasmodic agent. Machado et al. [81] have recently reviewed the neuroprotective perspective of this natural product.  $\beta$ -Caryophyllene appears to act as a neuroprotective agent by controlling inflammation and oxidative stress as well as various effects on cannabinoid receptor 2 (CB2) [80–82]. In a vascular dementia rat model study, Lou et al. [82] reported that  $\beta$ -caryophyllene-hydroxypropyl- $\beta$ -cyclodextrin inclusion complex could alleviate cognitive deficits by increasing the expression of CB2 in the brain, along with the expression levels of phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt).  $\beta$ -Caryophyllene also acted as agonist for CB2 and PPAR- $\alpha$  receptors in an animal hypoperfusion-reperfusion model of oxidative stress, and modulated activation of the endocannabinoid system and lipoperoxidation as well

► **Table 2** *Continued*

Scientific name	Plant parts [22]	Constituents	Experimental model	Observation/mechanism
<i>P. lentiscus</i>	Resin [103]	Ursolic acid	Transient MCAO-induced focal cerebral ischemia in the mouse	Improvement of neurological deficit ↓ Infarct size ↓ Lipid peroxidation ↑ Nrf2 pathway ↓ TLR4, NF-κB More severe neurologic deficits, infarct size and inflammatory damage [125]
<i>P. vera</i>	Kernel [104]		Aβ (25–35)-induced toxicity in PC12 cells	↓ iNOS and COX-2 through inhibition of NF-κB activity ↓ ERK1/2, p-38, and JNK phosphorylation [117]
	Resin		Aβ-induced neurotoxicity in PC12 cells	↓ ROS, LPO ↓ Caspase-3, apoptosis [118]
			Aβ memory impairment in the mouse	↓ Memory impairment ↓ MDA ↑ Glutathione in hippocampus ↓ IL-1β, IL-6, TNF-α [115]
			Spinal cord injury model in the mouse	↑ Motor functions and axonal regrowth ↓ Astrogliosis ↓ IL-6, TNF-α ↑ Activation of MAPK and PI3K/PKB/mTOR pathways in the injured spinal cord [123]
			D-galactose-induced neurotoxicity and learning and memory impairment in the mouse	Improvement of memory ↑ SOD, CAT, GPx, and GR ↓ MDA, caspase-3 ↑ Neural growth-associated protein GAP43 [119]
			Model of aging mice (C57BL/6)	↑ SIRT1 and SIRT-6 Enhancement of α-Klotho and PGC proteins levels [120]
			Ellman's assays for evaluating acetylcholinesterase and/or butyrylcholinesterase inhibitory activity	↓ Butyrylcholinesterase [121]
			MPTP-induced PD in mouse	Improvement of behavioral deficits ↑ Dopamine ↑ Dopaminergic neurons [122]
			High-fat diet-induced cognitive impairment in C57/BL6J mouse	Improvement of behavioral performance ↓ Endoplasmic reticulum stress and IKKβ/NF-κB-mediated inflammatory signaling ↑ Insulin signaling and PI3K/Akt/mTOR pathway ↑ Memory-related protein expression in the hippocampus [124]
			Traumatic brain injury-induced cerebral ischemia in wild-type (WT) and Nrf2(-/-) mouse	↓ Brain edema and the neurological insufficiencies ↑ Nuclear translocation of Nrf2 protein ↑ Expression of NQO1 and HO1 ↑ Expression of AKT Involvement of Nrf2-ARE signaling pathway No effect on Nrf2(-/-) mice [126]
			Endovascular puncture model of subarachnoid hemorrhage	↓ Expressions of TLR4 pathway-related agents, such as ICAM-1, TLR4, NF-κB, P65, IL-1β, TNF-α, IL-6, iNOS, and MMP-9 ↓ Apoptosis [127]
			MCAO and reperfusion model in rats	Improvement in neurological deficit score ↓ Infarct volume ↑ Intact neurons ↑ PPARγ protein and PPARγ-positive cells ↓ Protein levels of MMP2, MMP9, and activated MAPKs ↑ TIMP1 [128]
			Pentylentetrazole-induced seizures in the mouse	Positive modulation of α1β2γ2 L GABA-A receptors Anticonvulsant, antidepressant, and anxiolytic activities [129]
			Pentobarbital-mediated sleeping model in the mouse	Enhances sleep duration through GABA-A receptor activation [130]

cont.

► Table 2 Continued

Scientific name	Plant parts [22]	Constituents	Experimental model	Observation/mechanism	
<i>P. lentiscus</i>	Resin	Oleanolic acid	Cobalt chloride-induced focal cortical hypoxia in rats	↓ Neuronal degeneration and cytoskeleton changes ↓ Astroglial and microglial reaction ↑ Brain tissue recovery [112]	
<i>P. terebinthus</i>	Resin		Neural stem cells	↑ Proliferation and neural differentiation ↑ MAP2 expression ↓ Nestin ↑ Phosphorylation of GSK3 $\beta$ at Ser9 and expression of active forms of $\beta$ -catenin [111]	
<i>P. atlantica</i>	Resin			6-OHDA induced Parkinsonian in rats 6-OHDA-induced intracellular ROS in PC12	↓ Microglial activation Improved motor symptoms ↑ Striatal dopamine ↓ Amount of intracellular ROS in PC12 cells [110]
				Experimental mouse model of MS (experimental autoimmune encephalomyelitis)	↓ Encephalomyelitis ↓ Activation of microglial cells, BBB disruption and infiltration of inflammatory cells within the CNS ↓ Proinflammatory cytokines and chemokines ↑ Anti-inflammatory ones (modulatory role in Th1/Th2 polarization) ↓ Anti-MOG antibodies [106]
				SAH induction by a standard intravascular puncture model in rats	↓ Permeability of BBB ↓ Brain edema by protein expression of TJs and AJs ↓ SAH grades ↑ Protein expression of HO-1 ↓ Upregulation of VEGF and the phosphorylation of p38 MAPK, ↓ p38MAPK/VEGF/Src signaling pathway [107]
<i>P. integerrima</i>	Bark	Pistagremic acid	<i>In vitro</i> $\beta$ -secretase, AChE, and butyrylcholinesterase inhibition assay	↓ $\beta$ -secretase No obvious AChE activity [131]	
<i>P. vera</i>	Seed and skin	Gallic acid	Oxidative stress induced with 6-OHDA in PD model in rats	↑ Passive avoidance memory, total thiol, and GPx contents ↓ MDA in the hippocampus and striatum [144]	
<i>P. lentiscus</i>	Leaf, fruit		$A\beta$ -induced toxicity in neuronal cells $A\beta$ -induced cognitive dysfunction in mouse	↓ NF- $\kappa$ B ↓ Cytokine production in microglia cells ↓ Neuronal cell death ↓ Expression of cytokines ↓ NF- $\kappa$ B acetylation Improvement of cognitive dysfunction [141]	
<i>P. atlantica</i>	Gall, leaf			Traumatic brain injury in rat (Marmarou's method)	Improvement of neurological score, memory, and long-term potentiation from hippocampal dentate gyrus ↓ Brain lipid peroxidation and cerebral proinflammatory cytokines [145]
				Glutamate-induced neurotoxicity in primary rat cortex neurons culture	↓ Neurotoxicity ↓ Cortex neurons antioxidant profile ↓ Proinflammatory cytokine Maintenance of Ca <sup>2+</sup> homeostasis, IGF-1 expression [146]

cont.

as COX-2 in brain tissue [83]. The role of CB2 was revealed in another study as well. In a mouse model of AD,  $\beta$ -caryophyllene ameliorated the Alzheimer-like phenotype in mice with reducing  $A\beta$  in brain tissue. It also reduced astrogliosis and microglial activation as well as the levels of COX-2 and proinflammatory cytokines in the cerebral cortex; its protective effect was associated to CB2 receptor activation and the PPAR $\gamma$  pathway [84]. The cytoprotective effect of this sesquiterpene has also been indicated to be mediated through the amelioration of cellular antioxidant re-

sponses via Nrf2 activation, which is, in part, dependent on CB2R activation [85]. Similar results were obtained after evaluating the effect of  $\beta$ -caryophyllene against lipopolysaccharides-induced oligodendrocyte toxicity *in vitro*. There were remarkable correlations between  $\beta$ -caryophyllene concentration and selective modulation of CB2, Nrf2, sphingomyelinase (SMase), and PPAR $\gamma$  c pathways [86]. Moreover,  $\beta$ -caryophyllene was shown to alleviate high-fat/fructose-diet-induced neurobehavioral changes in rats. The role of PPAR- $\gamma$  and CB2R in the anxiolytic, antioxidant, and anti-inflam-



► **Table 2** *Continued*

Scientific name	Plant parts [22]	Constituents	Experimental model	Observation/mechanism
<i>P. vera</i>	Seed, skin	Catechin	Doxorubicin-induced memory deficit in Wistar rats Doxorubicin-induced neurotoxicity in IMR-32 neuroblastoma cells	↑ Viability of undifferentiated IMR-32 cells ↑ Neurite length of differentiated cells ↓ OS ↓ Neuroinflammation ↓ AChE [152]
<i>P. lentiscus</i>	Leaf		Aβ-induced BACE-1 upregulation in neuronal culture	↓ ROS and beta-sheet structure formation ↓ Aβ-induced BACE-1 upregulation [142]
			Traumatic brain injury model in rats	Protection of BBB integrity ↑ Junction proteins ↓ Local inflammatory reactions [153]
			Streptozotocin-induced diabetes in rats	Improvement of alternation score and retention and recall in passive avoidance test ↓ MDA and nitrite [155]
			Streptozotocin-induced model of dementia in rats	Improvement of cognitive deficit, S100B content and secretion, AChE activity, GPx activity, NO metabolites, and ROS content [156]
			MPTP-induced PD in mice	Prevention of neurotoxicity ↓ Dopaminergic neuron loss in substantia nigra [157]
<i>P. vera</i>	Skin, nuts	Cyanidin-3-O-glucoside	Aβ-induced neurotoxicity in a human neuronal cell line (SH-SY5Y).	↓ Apoptosis and Necrosis ↓ Aβ oligomer binding to plasma membrane, ↓ Membrane integrity loss [158]  <i>cont.</i>

matory effects of  $\beta$ -caryophyllene was proven in this study as well. Its memory-enhancing and antidepressant effects are probably mediated via CB2R, mainly by the upregulation of BDNF and peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) [87].

$\beta$ -Caryophyllene might exert its neuroprotective effects in PD via multiple mechanisms as well. It showed an ameliorative effect in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced murine model of PD by decreasing the levels of inflammatory cytokines in the nigrostriatal system and involvement of the CB2 receptors [88]. In a rotenone-induced oxidative stress/neuroinflammation rat model of PD,  $\beta$ -caryophyllene reversed the loss of dopaminergic neurons and decreased microglia and astrocyte activation, as evidenced by reduced ionized calcium-binding adaptor molecule-1 (Iba1) and glial fibrillary acidic protein (GFAP) expression. Attenuation of proinflammatory cytokines and inflammatory mediators such as COX-2 and inducible nitric oxide synthase (iNOS), restoration of antioxidant enzymes, and inhibition of lipid peroxidation and glutathione depletion were also reported [89].

It has been reported that  $\beta$ -caryophyllene alleviates cerebral ischemia injury through its potent neuroprotective activity *in vivo* via inhibiting neuronal death and inflammatory responses [90]. It has been shown to reduce necroptotic cell death via the downregulation of receptor-interaction protein kinase (RIPK)1, RIPK3, and mixed lineage kinase domain like pseudokinase (MLKL) expression *in vivo*, as well as alleviation of inflammation through inhibiting the high-mobility group box 1 (HMGB1)-toll-like receptor (TLR4) signaling pathway [91]. This compound also reduced the mRNA expression of iNOS, IL-1 $\beta$ , IL-6, and COX-2 in microglial cells, and

decreased the levels of NO and prostaglandin E2 [90]. In another study, Nrf2/HO-1 was introduced as an involved pathway in  $\beta$ -caryophyllene protection against cerebral ischemia injury *in vivo* [92]. Chang et al. [93] investigated the neuroprotective effect of different terpenoids on human neuroblastoma SH-SY5Y, *in vitro*, by using a simulated ischemia model, and *trans*-caryophyllene was identified as the most potent neuroprotective agent. In the mentioned study, terpinen-4-ol, one of the other terpenes of the *Pistacia* genus, was also found as a neuroprotective substance.

### Myrcene

$\beta$ -Myrcene is a monoterpene that forms about 40% of the essential oil of *P. lentiscus* leaves [94] and has been notably (41%) identified in the methanolic extract of *P. atlantica* fruits [95]. In an animal model of cerebral ischemia/reperfusion-induced oxidative stress, myrcene treatment protected against neurotoxicity, which occurred via an increase in TBARS formation and a decrease in the antioxidant defense systems, including glutathione (GSH), CAT, GPx, and SOD. Myrcene also eliminated the histopathological damage and apoptosis in brain tissue [96].

### Limonene

Limonene, another monoterpene, which has a cyclic structure, forms about 10% of essential oil obtained from *P. lentiscus* leaves [94], and 4–5% of the methanolic extract of *P. atlantica* fruits [95]. Evaluation of the effects of d-Limonene on a PC12 cellular model of corticosterone-induced neurotoxicity showed that it has antioxidant and anti-inflammatory effects via decreasing the levels of MDA and NO, activities of NADPH oxidase, and expression of

► Table 2 Continued

Scientific name	Plant parts [22]	Constituents	Experimental model	Observation/mechanism
<i>P. vera</i>	Seed, skin	Quercetin	Radiation-induced brain injury in rats	↓ Cellular degeneration and infiltration parameters ↓ OS [171]
			MPTP-induced PD in mice	Improvement of the motor balance and coordination ↑ Activities of GPx, SOD, and Na/K-ATPase, AChE, dopamine ↓ 4-Hydroxy-2-nonenal immunoreactivity in the striatum of brains [204]
			Aged triple transgenic AD model in mice	↓ Extracellular $\beta$ -amyloidosis, tauopathy, astrogliosis and microglia ↓ PHF, $\beta$ A 1–40 and $\beta$ A 1–42 levels ↓ BACE1-mediated cleavage of APP antibody Improvement of performance in learning and spatial memory [162]
			Cadmium-induced memory impairment and anxiogenic-like behavior in rats	↓ Impaired memory and anxiogenic effect ↑ Na/K-ATPase activity ↓ ROS, TBARS, protein carbonyl content, dsDNA fractions ↑ T-SH, GSH, and GR activities and the rise of GST activity ↓ AChE activity [163]
			$A\beta$ (1–42)-induced oxidative cell toxicity in cultured neurons	↓ $A\beta$ (1–42)-induced cytotoxicity, protein oxidation, lipid peroxidation and apoptosis [164]
			Mouse model of AD, hippocampal neuronal culture	↑ Cell proliferation in the hippocampal neurons ↑ Neurogenesis, synaptogenesis and cell proliferation ↓ $A\beta$ -induced synaptic loss ↑ Phosphorylation of CREB ↑ BDNF ↑ Dendritic processes in hippocampal neurons [166]
			Perphenazine and reserpine-induced catalepsy in rats	↓ Catalepsy ↓ Activity of COMT and MAO ↑ Bioavailability of L-dopa in the brain [168]
			MPPT-induced oxidative stress in PC12 cells	↓ Apoptotic death ↓ Phosphorylation of STAT Modulation of mRNA levels and protein expression of Bax and Bcl-2 Release of cytochrome c and nuclear translocation of the AIF [169]
			Rotenone-induced hemi-Parkinson in rats	↓ Amphetamine- or apomorphine-induced unilateral rotations ↓ Rotenone-induced loss in striatal dopamine, and nigral oxidized ↓ Glutathione ↑ CAT and SOD ↑ Mitochondrial complex-I activity [170]
Transient bilateral common carotid artery occlusion and reperfusion in rats	↓ Microvascular permeability, leukocyte adhesion and ROS Protection of capillary perfusion. ↓ Arteriolar dilation [172]			

6-OHDA: 6-Hydroxydopamine;  $\Delta\psi$ m: Mitochondrial membrane potential; AChE: Acetylcholinesterase; AD: Alzheimer's disease; AIF: Apoptosis-inducing factor; Akt: Protein kinase B; AMPK $\alpha$ : AMP-activated protein kinase; BAX: BCL2 associated X; BBB: Blood-brain barrier; Bcl-2: B-cell lymphoma 2; BDNF: Brain-derived neurotrophic factor; CAT: Catalase; CAV: Caveolin; CB2: Cannabinoid receptor type 2; CI-R: Cerebral ischemia-reperfusion; COMT: catechol-O-methyltransferase; COX2: Cyclooxygenase 2; CRBE: Cyclic-AMP response element binding protein; DHE: Dihydroethidium; DMPD: N,N-dimethyl-p-phenylenediamine; ERK1: Extracellular signal-regulated kinases 1; GFAP: Glial fibrillary acidic protein; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: Glutathione; GSK3 $\beta$ : Glycogen synthase kinase 3 $\beta$ ; HMGB-1: High-mobility group box 1. HO-1: heme-oxygenase 1; Iba-1: Ionized calcium binding adaptor molecule 1; ICAM-1: Intercellular adhesion molecule-1; IGF-1: Insulin-like growth factor 1; IL-1 $\beta$ : Interleukin 1 beta; IKK: I $\kappa$ B kinase  $\beta$ ; JNK: c-Jun N-terminal kinases; MAP-2: Microtubule-associated protein 2; MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; MCAO: Middle cerebral artery occlusion; MDA: Malondialdehyde; MLKL: Mixed lineage kinase domain-like pseudokinase; MMP: Matrix metalloproteinase; MOG: Myelin-oligodendrocyte glycoprotein. MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NADPH: Nicotinamide adenine dinucleotide phosphate; mTOR: Mammalian target of rapamycin; NF- $\kappa$ B: Nuclear factor kappa B; NO: Nitric oxide; NOS2: Nitric oxide synthase 2; NPT: Nonprotein thiols content; NQO1: NAD(P)H quinone dehydrogenase 1; Nrf2: Nuclear factor erythroid 2-related factor 2; OGD/R: Oxygen glucose deprivation/reoxygenation; OS: Oxidative stress; PC12: pheochromocytoma cells; PD: Parkinson's disease; PGC-1 $\alpha$ : peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PGE2: Prostaglandin E2; PHF: Paired helical filament; PI3K: phosphoinositide 3-kinase; PKB: protein kinase B; PPAR: Peroxisome proliferator-activated receptors; PTZ: pentylenetetrazol; RIPK: Receptor-interaction protein kinase; ROS: Reactive oxygen species; SAH: Subarachnoid hemorrhage; Ser9: Phospho-GSK-3 $\beta$ ; SIRT: Sirtuins; SOD: Superoxide dismutase; TBAR: Thiobarbituric acid-reactive. TIMP1: Tissue inhibitor of metalloproteinases; TLR: Toll-like receptor; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling; VEGF: Vascular endothelial growth factor; WT: Wild type

proinflammatory markers such as iNOS, COX-2, IL-6, IL-1 $\beta$ , and TNF- $\alpha$ . It also reduced the expression of BCL2-associated X protein (Bax), cleaved caspase-3, and increased antiapoptotic protein Bcl-2. d-Limonene significantly activated AMP-activated protein kinase (AMPK $\alpha$ ) and inhibited nuclear translocation of NF- $\kappa$ B through upregulating sirtuin (SIRT)1 [97]. In an animal model of high anxiety induced by chronic immobilization stress, limonene reduced stress-induced damage in CA1 pyramidal neurons and reversed adverse effects of anxiety [98]. Moreover, impairment in cognitive and memory functions following cerebral ischemia was reversed by D-limonene in rats. It decreased the cerebral infarct size following stroke, along with decreasing mRNA expression of IL-1 $\beta$ , monocyte chemoattractant protein-1 (MCP-1), and COX-2, and increasing the activities of antioxidant enzymes in rats following stroke [99]. In another *in vivo* study, administration of s-limonene attenuated the memory deficits resulting from scopolamine. It improved dopamine reduction induced by scopolamine [100]. s-Limonene has shown also AChE inhibitory activity *in vitro* [100].

### Triterpenoids

Some triterpenoid derivatives have recently been identified as potential neuroprotective agents with their ability to protect the brain against neurodegenerative and neuroinflammatory processes [101, 102]. Some triterpenes such as oleanolic acid (OA), masticadienonic acid, morolic acid, ursolic acid [22], and ursolic acid (UA) [103, 104] have been identified in different *Pistacia* species, and pistagremic acid has been isolated from galls of *P. integerrima* [22].

### Oleanolic acid

OA is a pentacyclic triterpenoid compound with a widespread occurrence either as a free acid or as an aglycone precursor for triterpenoid saponins throughout the plant kingdom. Besides its anti-inflammatory and antioxidant activities, OA has been shown to possess neuroprotective effects in several studies [105]. In an experimental mice model of multiple sclerosis, OA inhibited the development of autoimmune encephalomyelitis (EAE), and reduced activation of microglial cells, blood-brain barrier (BBB) disruption, and infiltration of inflammatory cells within the CNS [106]. Its effect in protecting the integrity of the BBB has been shown to be associated with an increase in protein expression of tight and adherent junctions in a rat model of subarachnoid hemorrhage. This compound also suppressed the p38MAPK/VEGF/Src signaling pathway, which is involved in BBB disruption [107]. In a mice model of MS, OA also showed a modulatory role in T helper cell polarization [106]. EAE mice treated with OA had a decrease in the cytokine osteopontin level and TNF- $\alpha$  in CNS tissue. Moreover, EAE mice treated with OA had lower levels of anti-myelin-oligodendrocyte glycoprotein (anti-MOG) antibodies than untreated animals [106]. *In vitro*, OA decreased the inflammatory stimuli-induced proliferative response, phagocytic properties, and synthesis of proinflammatory mediators in microglia; it also inhibited extracellular signal-regulated kinases (ERK) and ribosomal protein S6 (rS6) phosphorylation as key factors of the MAPK and mammalian target of rapamycin (mTOR) pathways, which play a crucial role in the regulation of cell growth and proliferation [108].

As a beneficial natural product in PD, OA ameliorated forelimb use asymmetry in a 6-OHDA-induced PD rat model and inhibited the reduction of dopamine in the striatum of PD animals. It also decreased membrane depolarization and attenuated mitochondrial apoptosis [109]. OA exerted its neuroprotective effects in 6-OHDA-induced PD in rats by attenuating microglial activation [110]. *In vitro*, it inhibited the accumulation of intracellular ROS in PC12 cells, resulted in promoting cell survival [110]. In another study, migration, proliferation, and differentiation of neural stem cells (NSCs) were elevated by OA. The mechanism of action was determined as suppressing glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) activity, which has a role in peripheral and CNS inflammation in various neurological disorders [111].

Pretreatment of rats with OA before focal cortical hypoxia induced by brain injection of cobalt chloride resulted in a reduction of neuronal damage and glial reaction as well as recovery of brain tissue after injury [112]. OA mitigated cognitive deficits in a rat model of A $\beta$ -induced AD. Related to this, in a model of beta-amyloid-stimulated astrocytes, OA ameliorated primary neuron death and neuroinflammation (via inhibiting transcription and secretion of IL-6, TNF- $\alpha$ , and IL-1 $\beta$ ) in secretory phospholipase type A2 (sPLA2)-IIA-mediated calcium signals [113].

### Ursolic acid

UA as another naturally derived pentacyclic triterpene acid derives from a hydride of an ursane. It is widely found in fruits, spices, and medicinal herbs [114] such as in the *Pistacia* genus [103, 104]. Several studies have evaluated the neuroprotective effects of this compound against A $\beta$  to show the therapeutic potential of this phytochemical for AD. It has been reported that A $\beta$ -induced memory and learning deficits in mice were reversed by UA, along with a decrease/increase in MDA/glutathione levels in the mouse hippocampus. Besides its antioxidant effect, UA also reduced the levels of inflammatory markers (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) [115]. *In vitro*, UA was also shown to attenuate A $\beta$ -induced neurotoxicity in PC12 neuronal cells through modulation of the NF- $\kappa$ B signaling pathway [116]. In these cells, it has also been shown to inhibit the A $\beta$ -induced expression of iNOS and COX-2 through inhibition of NF- $\kappa$ B activity, along with reduced ERK1/2, p-38, and Jun N-terminal kinases (JNK) phosphorylation [117]. Moreover, UA reversed the increase in ROS, LPO, and apoptosis induced by A $\beta$  via inhibiting caspase-3 activity [118].

Treatment with UA in aged mice subjected to D-galactose-induced neurotoxicity resulted in improved memory as well as elevated the levels of antioxidant enzymes SOD, CAT, GPx, and glutathione reductase (GR) and decreased the level of MDA. In addition, the activation of caspase-3 was inhibited by UA, while the level of neural growth-associated protein GAP43 was elevated [119]. Anti-aging effects of UA might also be considered through increasing the levels of anti-aging biomarkers such as SIRT1, SIRT-6,  $\alpha$ -Klotho, and PGC-1 $\beta$  protein [120].

UA has also been reported as an AChE inhibitor, which is one of the characterized targets in a therapeutic approach to AD. The synthetic hydroxyl-propinyl derivatives of UA were shown as more potent AChE/butyrylcholinesterase inhibitors [121].

In an experimental PD mouse model, UA was shown to protect dopaminergic neurons in MPTP-intoxicated mice. It also improved

behavioral deficits and restored the altered dopamine level. UA mitigated the MPTP-induced increase of MDA and NO levels [122].

UA has been shown to mimic the human natural killer (HNK)-1 and promote the regaining of motor functions and axonal regrowth in mice with a spinal cord injury via activation of MAPK and PI3K/Akt/mTOR pathways. It also reduced astrogliosis and levels of proinflammatory markers (IL-6 and TNF- $\alpha$ ) in the acute phase of inflammation in injured spinal cords [123]. Additionally, UA administration has been indicated to reverse high-fat diet-induced cognitive impairment via inhibition of endoplasmic reticulum stress and NF- $\kappa$ B signaling and activating the PI3K/Akt/mTOR pathway in the mouse hippocampus [124].

UA treatment in mouse models of cerebral ischemia [125] and traumatic brain injury [126] led to a decrease in oxidative stress [125, 126] by enhancing the expression of antioxidant enzymes (NQO1 and HO1) as well as Akt, as an Nrf2 upstream factor, suggesting a possible mechanism via activation of the Nrf2-ARE pathway [126]. It also decreased inflammatory factors (TLR4 and NF- $\kappa$ B) after stroke in the mouse brain [125]. In a subarachnoid hemorrhage rat model, UA treatment reduced early brain injury via reducing apoptosis and suppressing TLR4-mediated inflammatory factors, such as intercellular adhesion molecule-1 (ICAM-1), TLR4, NF- $\kappa$ B, IL-1 $\beta$ , TNF- $\alpha$ , IL-6, iNOS, and matrix metalloproteinase (MMP)-9 [127]. It also showed neuroprotective effects as an activator of PPARs in a rat model of cerebral artery occlusion and reperfusion and modulated the metalloprotease/anti-metalloprotease balance, possibly by inhibiting the MAPK signaling pathway [128]. UA has also been shown to have anxiolytic, anticonvulsant, and antidepressant activities in mice via affecting the GABA-A receptor, especially acting on the benzodiazepine binding site of GABA receptors [129, 130].

### Pistagremic acid

Pistagremic acid, another triterpenoid compound isolated from *P. integerrima*, was evaluated for b-secretase (BACE 1) enzyme inhibition and showed significant activity against BACE1, which plays an important role in APP (amyloid precursor protein) cleavage and subsequent formation of A $\beta$  40–42. However, the effect of pistagremic acid was selective for BACE1 and its inhibitory activity was insignificant against acetylcholinesterase and butyrylcholinesterase enzymes [131].

### Masticadienonic acid

Although masticadienonic and masticadienolic acids are among specific triterpenoids identified in the resins of the *Pistacia* genus [22], there are limited studies on the neuroprotective activity of these natural products. In one study, these triterpenoids showed anti-inflammatory effects *in vivo* by preventing PMA-induced ear edema, and also the synthesis of lipoxygenase products [132]. In a recently published clinical study, Hazan et al. [133] reported the safety and tolerability of RPh201 in a phase 1, placebo-controlled, double-blinded trial in healthy subjects. RPh201 has been introduced as a botanical formulation, mainly containing masticadienonic acid and isomasticadienonic acid from mastic gum. They also reported that based on their previous *in vivo* studies, RPh201 promoted neurogenesis and synaptogenesis, and increased functional recovery of cognition, memory, and sensorimotor impair-

ments (unpublished data) [133]. Next they designed a phase 2 clinical trial (NCT02045212) for the assessment of the effect of RPh201 in subjects with previous non-arteritic anterior ischemic optic neuropathy, which is a neurodegenerative disease resulting in vision loss. As a result, improvement in visual acuity was reported in the RPh201 group compared to placebo. The phase 3 clinical trial is in recruiting status (NCT03547206) [134].

## Phenolic Compounds

### Gallic acid

Gallic acid, a phenolic compound, is a well-known trihydroxybenzoic acid found abundantly in free and conjugated (hydrolysable tannins) or esterified forms in many plants [135]. Gallic acid and its derivatives have also been isolated from different *Pistacia* species [22]. As a polyphenolic compound in dietary and medicinal plants, its pharmacokinetic characteristics have been partially studied [136, 137]. It has been shown that when 50 mg gallic acid was orally administered to healthy volunteers, its metabolites concentration in plasma reached 4  $\mu$ M and the urinary level was about 37% of the ingested amount [136]. One animal study also indicated that gallic acid exhibited slower absorption in myocardial infarcted rats than those in normal rats. However, there is still uncertainty about its pharmacokinetic profile under pathological conditions [138].

As a phytochemical with antioxidant and anti-inflammatory activities, the neuroprotective effect of gallic acid against neuroinflammation, neurodegeneration, and neurotoxicity has been reviewed in some studies [135, 139, 140]. It has been indicated that gallic acid inhibits A $\beta$ -induced neurotoxicity via suppressing microglial-mediated neuroinflammation and decreasing cytokine generation and levels of NF- $\kappa$ B acetylation [141]. The ester derivative of gallic acid, epigallocatechin gallate, also plays a positive role in the modification of AD through suppressing A $\beta$ -induced beta-site APP cleaving enzyme-1 upregulation [142]. Furthermore, it has been shown to regulate the amyloid precursor protein and increase the transferrin receptor in H-SY5Y neuroblastoma cells. These findings seem to be related to its metal (especially iron) chelating activity [143]. Gallic acid has been demonstrated to reduce memory deficit and cerebral oxidative stress in a 6-OH-DA-induced Parkinson's disease model in rats [144]. Also, its neuroprotective effect has been shown in models of traumatic brain injury [145], and glutamate-induced neurotoxicity [146] in rats, which was due to improvement of the antioxidant profile and inhibition of proinflammatory cytokine generation [145, 146].

### Catechin

Catechin (a flavan-3-ol) belongs to the flavonoids and is well recognized as an antioxidant [147]. Catechin isomers and their gallic acid conjugates are naturally occurring constituents in various plants [148], in which the *Pistacia* genus is also among them [22]. Despite their therapeutic effects, catechins have been shown with low systemic bioavailability, poor membrane permeability, and rapid metabolism. In this regard, some strategies have recently been used for their structural modifications to improve pharmacokinetic properties [149].

There have been several reviews to date on the neuroprotective properties of catechins, which were mostly through antioxidant and anti-inflammation effects mainly involving Nrf2 and NF- $\kappa$ B signaling pathways [147, 150, 151]. One *in vivo* study has revealed that it can improve cognitive impairment induced by doxorubicin via increasing antioxidant defense, preventing neuroinflammation, and inhibiting AChE [152]. Another study showed that catechin has neuroprotective activity in a rat model of traumatic brain injury. An anti-inflammatory effect and intervention in the self-perpetuating procedure of BBB disruption were underlying mechanisms [153]. Catechin has also been indicated to inhibit the late stages of A $\beta$ -soluble aggregate growth change in the fibrillar form of A $\beta$  [154]. In streptozotocin-induced diabetes [155] and dementia [156] models in rat, catechin treatment resulted in the improvement of behavioral alternations, along with a decrease in the levels of MDA and nitrite [155], and reduction in cognitive deficit, S100B content, AChE activity, NO, and ROS content [156]. It also prevented neurotoxin-induced dopamine neuron loss in substantia nigra in a mouse model of PD [157].

### Cyanidin 3-O-glucoside

Cyanidin 3-O-glucoside has also been shown to inhibit the formation of A $\beta$  oligomers in a human neuronal cell line (SH-SY5Y) [158].

### Quercetin

The well-known and widespread flavonoid quercetin has frequently been reviewed as a neuroprotective polyphenol in several studies [159–161]. Various evidence showed that quercetin can exert neuroprotection, mostly via countering oxidative stress, which is known as one of the important causes of neurodegenerative conditions [161]. Also, quercetin protects neuronal cells through modifying some of the main features involved in AD including A $\beta$  aggregation, and the APP cleaving enzyme (BACE1) [162], as well as AChE inhibition [163]. It has been reported that quercetin attenuated A $\beta$  (1–42)-induced cytotoxicity, lipid peroxidation, and protein oxidation as well as apoptosis in primary hippocampal neuron cultures [164]; it also improved the emotional and cognitive impairments in AD models [165]. Quercetin treatment in the hippocampal neurons resulted in the elevation of neurogenesis, synaptogenesis, and cell proliferation as well as restoration of A $\beta$ -induced synaptic loss. It also increased phosphorylation of the cAMP response element-binding protein (CREB) in these cells and enhanced the levels of pCREB in the mouse brain [166].

Furthermore, as a potential effective natural product in PD [167], quercetin has been shown to possess inhibitory activity on catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) enzymes, which can lead to an increase of the bioavailability of L-dopa in the brain [168]. It has been able to inhibit the phosphorylation of the signal transducer and activator of transcription (STAT) and prevent apoptosis in dopaminergic cells via the down/upregulation of Bax/Bcl-2, respectively [169]. Considering its free radical scavenging activity, quercetin also adjusted the electron transport defect of mitochondria and upregulated Complex I in a rotenone-induced rat model of PD [170]. Its protective effect in an animal model of radiation-induced brain injury was also reported through the antioxidant mechanism [171]. Moreover, quercetin decreased rat pial microvascular permeability, leuko-

cyte adhesion, and ROS production during transient bilateral common carotid artery occlusion and reperfusion [172]. The neuroprotective effects of quercetin are manifested through different signaling pathways, including regulation of cytokines via Nrf2, JNK, protein kinase C, MAPK signaling cascades, and PI3K/Akt pathways [173]. Moreover, quercetin has been indicated to be effective in attenuating diabetes-induced neurodegeneration and inflammation due to inhibition of the STAT [150].

## Phytochemistry and Pharmacokinetics

### Terpenes

Terpenes are derived from isoprene units with five carbons, and based on the number of isoprene units, terpenes can be classified as hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and tetraterpenes (C40) [174]. Triterpenoids are mostly found as tetra- or penta-cyclic structures, but acyclic, mono-, bi-, tri- and hexa-cyclic triterpenoids also exist. The pentacyclic triterpenes are divided into three major classes: lupane, oleanane, and ursane [175].

Various pharmacological activities of terpenes have been reported so far, but the clinical relevance of these effects depends on the systemic availability of these natural compounds. However, for monoterpene compounds, more pharmacokinetic data in humans are needed. In addition, based on studies supporting the effects of volatile compounds of essential oils on cognitive function via aromatherapy, it is important to evaluate their absorption through the skin, or following inhalation, and crossing the BBB [176, 177]. (+)- $\alpha$ -Pinene, (+)-limonene, and (-)-linalool have been shown to be transported to the brain in different amounts following inhalation in mice, indicating that even their low concentrations are capable of exerting effects on the brain [177]. Bicyclic monoterpenoids easily transport to the brain both by inhalation and through blood.  $\beta$ -Caryophyllene is a volatile bicyclic sesquiterpene with extensive biological activities, occurring in the essential oil of numerous plants. However, its poor water solubility and physicochemical sensitivity might decrease its bioavailability. These potential complications have resulted in the use of various drug delivery systems for  $\beta$ -caryophyllene, mostly including inclusion complexes and nanoemulsions, which have been shown to improve its oral bioavailability and neuropharmacological activity *in vivo* [178].

Various studies on the bioavailability of pentacyclic triterpenes showed that several factors can affect the oral bioavailability of these natural products. Their bioavailability can be improved by increasing the low solubility in the gastrointestinal fluid for better absorption, and, in some cases, by inhibiting their metabolism. It has been shown that high-fat meals enhance triterpene absorption [179]. As a triterpenoid compound, oral administration of OA in rats resulted in low gastrointestinal absorption and hepatic microsomal metabolism [174]. UA is also known to be almost insoluble in water, with a low oral bioavailability. These compounds require some modifications to improve their bioavailability. For example, in the form of self-micro/nano emulsion, the intestinal absorption and bioavailability of UA/OA has been improved. After



absorption, OA is transported to the liver where it is converted to its glucuronic acid conjugate. Conjugated OA is transported via the bile to the gut. Then it is hydrolyzed to OA again. UA is mostly distributed in the liver, spleen, stomach, and kidney after intravenous administration, and is rapidly removed by metabolism and in small amounts through the excretion of the kidneys [180].

## Phenolic compounds

Studies revealed that (poly)phenols and their metabolites can enter the brain at detectable levels in mammals, which supports their direct neurological action [181]. As a hydroxybenzoic acid, gallic acid has been shown to be effectively accumulated in the brain. It has been detected in trace amounts in the mouse brain after repeated oral administration of a polyphenolic grape extract [182]. Some studies focusing on the bioavailability of gallic acid in humans also showed that compared with other polyphenols, this compound is relatively well absorbed [182].

The chemical structures of flavonoids are based on a diphenylpropane (C6-C3C6) skeleton with two aromatic rings as part of a six-member heterocyclic ring. These compounds can be divided into three classes, including flavonoids, neoflavonoids, and isoflavonoids, based on the connection of the aromatic ring to the heterocyclic ring. Depending on the degree of oxidation and saturation in the heterocyclic C-ring, flavonoids might be divided into different subclasses and minor subclasses [183, 184]. Among different dietary flavonoids, flavanols, flavanones, and flavonol glycosides have intermediate rates of absorption and bioavailability, while proanthocyanidins, flavanol gallates, and anthocyanins have the lowest absorption [183]. Dietary flavonoids occur mainly as glycosides and need to undergo enzymatic deglycosylation before absorption. The only subclass of flavonoids that could be present in the non-glycosylated form in the diet are flavan-3-ols [i.e., (+)-catechin, (-)-epicatechin], which are absorbed mainly in the small intestine [184]. (-)-Epicatechin and quercetin as flavan-3-ol and flavonol compounds, respectively, enter the circulatory system after ingestion, in only trace amounts, and appear mostly as phase II glucuronide, sulfate, and methyl metabolites [185]. Based on limited animal studies, (-)-epicatechin metabolites seem to reach the brain of rodents at levels that might be physiologically effective [186]. Some conjugated forms of quercetin can also accumulate in the brain after oral administration, while aglycone quercetin is scarcely distributed in the CNS [187, 188].

Anthocyanins are the glycosides of 2-phenyl-benzopyrylium or flavylum salts, which have different hydroxy or methoxy groups. As major anthocyanin flavonoids, glycosides of cyanidin (particularly cyanidin-3-glucoside) are primarily present in most of the herbs [189]. Several *in vitro/in vivo* studies have shown the pharmacokinetic characteristics of anthocyanins and their passage through the BBB. Studies showing that anthocyanins and some of their metabolites are able to cross the BBB have recently been reviewed in detail by Manolescu et al. [190]. Cyanidin-3-glucoside has been shown as the most absorbed anthocyanin through the jejunum and ileum in rats followed by cyanidin-3-galactoside and cyanidin-3-rutinoside [191]. Anthocyanins are hydrolyzed to anthocyanidins through removal of the 3-O-glycosidic part by colon microbiota. Phase I and II reactions mainly occur in the small intestine and liver, and the anthocyanidins become glucuronide, sul-

phate, or methyl derivatives. Anthocyanins metabolites are eliminated from the body by urine, bile, feces, and breath [192, 193].

## Conclusion

The genus of *Pistacia* has demonstrated various activities such as antioxidant, anti-inflammatory activities, and inhibitory effects on the progression of neurodegeneration together with promoting neuronal growth. These mentioned bioactivities along with their modulatory roles in functions of neurotransmitters, and modulation of signaling pathways as well as maintenance of BBB integrity support promising action of the plants for development in neuroprotective approaches. Phenolic compounds and terpenes as the two main groups of phytochemicals have been identified in different species of the genus *Pistacia*.  $\alpha$ -Pinene,  $\beta$ -caryophyllene, and oleanolic, ursolic, and masticadienonic acids as well as gallic acid, quercetin, and catechins are among the most abundant compounds in *Pistacia*. They demonstrated notable neuroprotective effects against different neurotoxic agents. The characteristic feature of these species is the production of remarkable essential oils from different parts of plants as well as large quantities of oleoresin. The obtained oleoresins are rich in terpenes, which have been supported by substantial evidence for their antioxidant, anti-inflammatory, and neuroprotective effects.

In this study, we reviewed the neuroprotective efficacy of the genus *Pistacia* and the related molecular mechanisms of these herbs in various *in vitro* and *in vivo* models. The supporting scientific evidence shows that the *Pistacia* genus might be considered a potential source as a therapeutic agent for the treatment of NDs due to the multitargeted mechanism of action. However, further detailed investigations are essential to assess their safety, efficacy, bioavailability, and probable molecular evaluation experiments.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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