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Nepeta menthoides Boiss. & Buhse, an endemic species in Iran: A review of traditional uses, phytochemistry and pharmacology

Zahra Memariani[1,2], Atena Rahimi[3*], Mohammad Hosein Farzaei[4,5], Niloofar Zakaria Nejad[1]

[1]Traditional Medicine and History of Medical Sciences Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[2]Department of Persian Medicine, School of Persian Medicine, Babol University of Medical Sciences, Babol, Iran
[3]Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[4]Pharmaceutical Sciences Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[5]Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

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ABSTRACT

Nepeta menthoides Boiss & Buhse is one of the endemic species in Iran. Named Ostokhodus, it is almost used as substitute of the *Lavandula stoechas* –the original Ostokhodus- in traditional Persian medicine (TPM) over the time and widely used for the management of some ailments such as anxiety, depression, dementia and chronic pain. The aim of this study is to review the pharmacological and phytochemical evidence on *Nepeta menthoides* for the assessment of the recommended traditional indications of this herb. In this review, all the relevant articles that met our inclusion criteria [English or Persian articles, having full text, evaluating therapeutic effects of *N. menthoides* and dated mainly from the year 1980 to 2018] were included by searching studies in PubMed, Scopus, Google Scholar, Web of Science, and SID. The search terms were "*Nepeta menthoides*, "Ostokhodus". Triterpenes and monoterpenes were the most chemicals reported from essential oil of *N. menthoides*. Several pharmacological properties via *in vitro*, *in vivo* and clinical studies have been reported including antioxidant, anti-inflammatory, anti-nociceptive, antidepressant and anxiolytic, anticholinesterase, neuroprotective, memory enhancing, anti-Alzheimer's disease, anticancer and effect on opioid dependence. Some proposed traditional indications of this herb in TPM books are in accordance with pharmacological evidence like anti-nociceptive, anti-seizure, anti-Alzheimer's disease, memory enhancing, neuroprotective, antidepressant, anxiolytic activity and anti-infective properties**.** Although some properties in TPM, such as anti-tussive and gastrotonic effects are not supported by scientific evidence, they need more investigations.

Implication for health policy/practice/research/medical education:
As one of the endemic species in Iran, *Nepeta menthoides* is widely used as medicinal plant by the vernacular name "Ostokhodus" in traditional Persian medicine. Reviewing the scientific evidence via collecting, classifying and summarizing published studies on the medicinal properties and possible side effects of this plant can be helpful for therapists and researchers in traditional medicine. It also provides basic information for further research as a coherent herbal monograph.

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Introduction

Plants have long been used for the treatment of various conditions and many researches are being done in pharmaceutical industries because of the belief that these natural remedies might have lesser side effects than current drugs (1). Lamiaceae family is one of the largest and specific flowering plants with about 220 genera and 4000 species all around the world (2,3). The genus *Nepeta* L. is one of the genera of Nepetoideae subfamilies and consists of about 300 species widely distributed in Europe, Asia and some areas of Africa (3,4). Iran is one of the major sources of this genus with 79 species (5). Various species of the genus *Nepeta* have been used traditionally for their therapeutic effects including anticonvulsant, antitussive,

***Corresponding author**: Atena Rahimi,
Email: atena.rahimi@yahoo.com

anti-microbial and anti-asthma properties (6). *Nepeta menthoides* is one of the endemic species distributed in different areas of Iran including Azarbaijan, Tabriz, Sabalan, and Marand (7,8). *Nepeta menthoides* is a herbaceous, perennial, climbing plant with the height about 15-45 cm with the purple flowers (8). Archaeological excavation evidence suggests that some species of the Lamiaceae family were widely cultivated in the past locally (9). Many species of this family have been shown to possess similar essential oils (2,3). Many studies have been conducted on the chemical composition of the *Nepeta* sp. essential oils in Iran and other countries; based on these studies the main components of these species are nepetalactone, 1,8-cineole, β-pinene and geranyl acetate. Phenolic compounds such as flavonoids have also been reported as the main component of this genus (10). *Nepeta menthoides* is one of the plants named "Ostokhodus" through the time in TPM and widely used for the treatment of neurological disorders including seizure, chronic pain, depression and anxiety disorder (11,12). The original Ostokhodus (*Lavandula stoechas*) was used in Persia for a long time as an imported drug (13). As an endemic medicinal plant and a common substitute of *L. stoechas* in Iran, this herb is of importance in traditional Persian medicine (TPM). Some researches on *N. menthoides* have been carried out to evaluate scientifically the traditional uses of this herb. The aim of this study is to review the pharmacological and phytochemical scientific evidence on *N. menthoides*. This review presents a comprehensive assessment report on phytochemical aspects, pharmacological activities, and toxicity of *Nepeta menthoides* by focusing on the data from the year 1980 until the May 30th 2018 via papers on databases including PubMed, Scopus, Google Scholar, Web of Science, and SID (a Persian scientific database). The keywords "*Nepeta menthoides*" and "Ostokhodus" were used for the search.

Nepeta menthoides in traditional medicine

Nepeta menthoides is an endemic species of the genus *Nepeta* in Iran which is distributed in the northwest of the country. *Nepeta menthoides* is named "ostokhodus" in Persian traditional medicine and herbal stores (10). Ostokhodus or stoechas is one of the oldest herbs mentioned in TPM books and has been represented by several herbs during the time. Today *Nepeta menthoides* is used as ostokhodus in herbal markets of Iran and traditional medicine because its therapeutic effects are similar to those of ostokhodus in TPM books (13, 14).

Ostokhodus has been mentioned in TPM books for reinforcing the major organs including brain, heart and liver, and considered as one of the brain-targeted medications based on TPM concepts. There are TPM indications of ostokhodus including amnesia, sadness and depression, obsession, epilepsy and melancholy. In addition, based on TPM theories some ailments of the other organs such as gastric disorders and respiratory problems including cough and catarrh are related to the brain disorders, and with this viewpoint, ostokhodus has also been recommended for these diseases in TPM (12,15).

Pharmacological profile

Different pharmacological effects of *N. menthoides* have been reported in *in vitro, in vivo* and clinical studies. These pharmacological activities have been summarized in Table 1.

Phytochemistry

Various types of chemical constituents such as monoterpene derivatives, sesquiterpenes, diterpenes, triterpenes, phenolic compounds such as flavonoids, phenolic acids, and some other constituents have been identified in *Nepeta* species (16-18). Phytochemical screening tests of *N. menthoides* have been shown to be positive for triterpene, sterol, saponin and flavonoid (10,19,20). The names, chemical structure and sources of identified compounds are collected in Table 2. As can be seen from the Table, terpenoids and flavonoids are dominant constituents within this plant.

Anti-infective properties

A number of reports have been published on the antibacterial effects of *N. menthoides* extracts or its oil. Methanol extract from aerial parts of *N. menthoides* showed significant antibacterial activity against the gram-positive bacteria: *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus aureus* and *Bacillus cereus*. However, aqueous extracts of the plant had no antibacterial activity (20). A poor inhibitory activity of methanol extracts from *N. menthoides* root and leaves was observed against *Bordetella bronchiseptica* and *Staphylococcus aureus* respectively. (21, 22). In addition, *N. menthoides* essential oil from aerial parts and its crude methanolic extract have been shown to have larvicidal activity against *Anopheles stephensi* with LC50=234.3 ppm and LC50=69.5 ppm, respectively. The authors indicated that nepetalactone isomers and 1,8 cineol must be mentioned as effective compounds related to larvicidal activity (8). Moreover, the antibacterial activity of the essential oil of *N. menthoides* and its 2 main constituents, 1,8-cineol (57%) and 4aα, 7α, 7aα- nepetalactone, was evaluated against *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Klebsiella pneumonia*, and *Escherichia coli* (23).

Antioxidant activity

The antioxidant effect of the essential oil from *N. menthoides* was investigated by Kahkeshani et al (24). The authors demonstrated its effects by two different methods: DPPH and FRAP assays and concluded that the antioxidant activity of the essential oil may partly be

Table 1. Pharmacological evidence of *Nepeta menthoides*

Pharmacological activity	Plant part	Assay	Extract/ essential oil/ isolated component	Dose or concentration	Observations	Ref.
Anti-infective properties	Aerial parts	Disc diffusion	Methanolic extract	ND	Noticeable activity against the gram-positive bacteria: Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus aureus and Bacillus cereus (DIZ: 36 mm, 35 mm, 40 mm, and 21 mm respectively). No effect on *Pseudomonas aeruginosa, Escherichia coli,* and *Klebsiella oxytoca* Positive controls: vancomycin and gentamycin	(20)
			Chloroform extract	ND	Activity against *Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus* aureus and *Klebsiella oxytoca* (DIZ: 13 mm, 11 mm, 12 mm, and 10 mm respectively) No effect on *Pseudomonas aeruginosa, Escherichia coli,* and *Bacillus cereus* Positive controls: vancomycin and gentamycin	
			Aqueous extract	ND	Had no antibacterial activity	
	Root	Agar well diffusion	Methanolic extract	20 mg/mL	Activity against *Bordetella bronchiseptica* (MIC: 15 µg/mL) *Micrococcus luteus, Klebsiella pneumonia,* and *Serratia marcescens* were resistant to *N. menthoides*	(21)
	Leaf	Agar well diffusion	Methanolic extract	20 mg/mL	Poor activity against *Staphylococcus aureus* (PTCC No: 1337) , DIZ: mm No activity against *Staphylococcus aureus* (PTCC No: 1112 and 1113)	(22)
	Aerial parts	WHO method	Methanolic extract	12.5, 25, 50, 100, 200 ppm	In concentration of 200 ppm showed 100% mortality LC_{50}: 69.5 ppm, LC_{90}: 175.5 ppm	(8)
		WHO method	Essential oil	80, 120, 180, 270, 405 ppm	In concentration of 405 ppm showed 100% mortality LC_{50}: 234.3 ppm, LC_{90}: 419.9 ppm	
	Aerial parts	Disc diffusion	Essential oil	10 µL/disc	Activity against seven bacteria (*Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Klebsiella pneumonia, Escherichia coli*) with MIC values in the range of 1.8 - 7.2 mg/mL Positive control: Ampicillin	(23)
			1,8-Cineole	10 µL/disc	Activity against seven bacteria (*Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Klebsiella pneumonia, Escherichia coli*) with MIC values in the range of 0.9 - 7.2 mg/mL Positive control: Ampicillin	
			4aα-7α-7aα-Nepetalactone	10 µL/disc	Activity against seven bacteria (*Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Klebsiella pneumonia, Escherichia coli*) with MIC values in the range of 1.8 - 15 mg/mL Positive control: Ampicillin	

Table 1. Continued

Pharmacological activity	Plant part	Assay	Extract/ essential oil/ isolated component	Dose or concentration	Observations	Ref.
Antioxidant activity	Aerial parts	DPPH and FRAP method	Essential oil	10, 20, 40, 80, 100 µg/mL	IC_{50} of DPPH test and FRAP value were 28.363 µg/mL and 68.902±1.37 µmol Fe2+/g dry plant	(24)
Anti-Inflammatory and anti-nociceptive activity	Aerial parts	Formalin test, Xylene test, Hot water tail-immersion test	Hydro-alcoholic extract	70, 350, 700, 1400, 2800 mg/kg	Anti-inflammatory effect at all doses, particularly at dose of 2800 mg/kg Anti-nociceptive effect in chronic phases	(25)
Antidepressant and anxiolytic activity	Aerial parts	Beck and Hamilton depression inventories	Crystalline powder	400 mg (capsule)	*N. menthoides* could be effective in depressed patients	(26)
		Beck Depression Inventory-II	Freeze-dried powder of aqueous extract	400 mg (capsule)	*N. menthoides* had benefit effects in the control of mood in major depression and showed a significant lower recurrence rate	(27)
		Beck anxiety inventory	Freeze-dried powder of aqueous extract	400 mg (capsule)	*N. menthoides* could be effective in the treatment of anxiety in patients with depression and had lower symptom recurrence rate	(28)
Sedative-hypnotic effects	Aerial parts	Righting reflex test Open field test	Ethanolic extract	100-800 mg/kg	*N. menthoides* could reduce the locomotor activity	(29)
		Pittsburgh Sleep Quality Index (PSQI), sleep diary, and Insomnia Severity Index (ISI)	Freeze-dried aqueous extract	400 mg (capsule)	*N. menthoides* could decrease in the mean difference of ISI and total PSQI and increase total sleep time based on the sleep diary	(30)
Anticholinesterase activity	Aerial parts	Mata method	Essential oil	25, 50, 75, 100 µg/mL	The essential oil had desirable activity with IC50 value of 64.870 µg/mL	(24)
	Flowering part	Ellman's method	Methanol extract, Dichloromethane extract	10 mg/mL	Showed AchE inhibitory activity	(32)
	Aerial parts	Ellman's method	Essential oil, 1,8-cineole	25 µL	Showed AchE inhibitory activity	(33)
Neuroprotective effect	Aerial parts	TUNEL assay	Ethanolic extract	250, 500, 1000 mg/kg	*N. menthoides* showed neuroprotective effects in a dose-dependent manner	(37)
		TUNEL assay	Ethanolic extract	250, 500, 1000 mg/kg	Administration of *N. menthoides* before neural injury causes no more neuroprotective effect.	(38)
		TUNEL assay	Ethanolic extract	250, 500 mg/kg	*N. menthoides* induced neuroprotective effect on axotomized sensory neurons in dorsal root ganglion	(39)

Table 1. Continued

Pharmacological activity	Plant part	Assay	Extract/ essential oil/ isolated component	Dose or concentration	Observations	Ref.
Memory enhancing effects	Aerial parts	Y-maze task	Aqueous extract, Hydro-alcoholic extract	50,100,150 mg/kg	*N. menthoides* had memory enhancing effect in mice	(34)
	Leaf	Passive avoidance down step model	Aqueous extract	100, 200, 400, 800 mg/kg	*N. menthoides* had memory enhancing effect in mice	(35)
	Aerial parts	Morris water maze task	Aqueous extract	100, 500 mg/kg	*N. menthoides* reversed the destructive effect of chronic cold-water-induced hypothermia on learning and memory in rats	(36)
Anti-Alzheimer's	Aerial parts	MMSE inventories	Hydro-alcoholic extract	500 mg (capsule)	*N. menthoides* had positive influence on the treatment of Alzheimer disease	(31)
Cytotoxic activity	Aerial parts	MTT test	Essential oil	50, 100, 250, 500, 1000 µg/mL	*N. menthoides* showed a significant effect against T47D, HT-29 and Caco-2 cell lines	(24)
			Essential oil, 1,8-cineole	25 µL	Essential oil and 1,8-cineole showed a significant effect against three breast cancer cell lines (MCF-7, T47D and MDA-MB-231)	(33)
Effect on opioid dependence and tolerance	Aerial parts	Chimney test	Hydro-alcoholic extract	200, 400 mg/kg	*N. menthoides* could dose-dependently attenuate the development of dependence in morphine-treated mice and potentiated morphine anti-nociceptive effect	(40)

AchE: acetylcholinesterase; DIZ: Diameter of inhibition zone (mm); DPPH: 2,2-diphenyl-1-picrylhydrazyl; FRAP: Fluorescence recovery after photobleaching; ISI: Insomnia Severity Index; IC50: half maximal inhibitory concentration; LC50: half maximal lethal concentration; MIC: Minimum inhibitory concentration; MMSE: Mini–Mental State Examination; ND: Not determined; PSQI: Pittsburgh Sleep Quality Index; PTCC: Persian type culture collection; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling; WHO: World Health Organization

Table 2. Chemical compounds of *Nepeta menthoides*

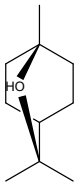
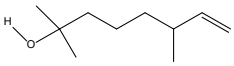
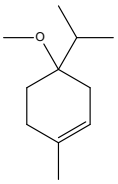
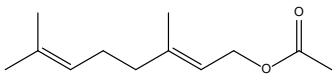
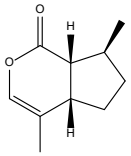
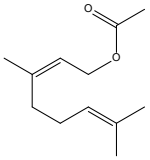
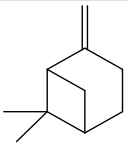
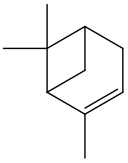
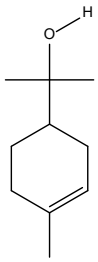
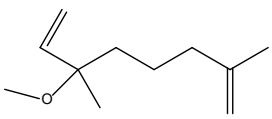
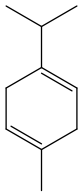
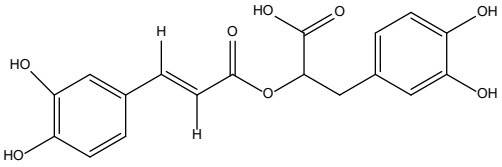
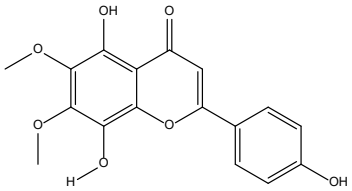
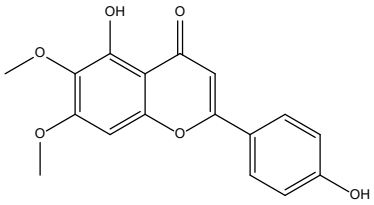
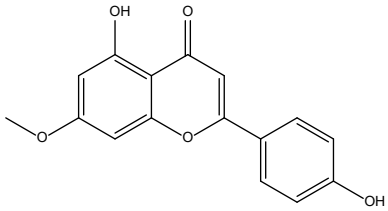
Name of compound	Chemical structure	Plant part	References
1, 8-cineole		Leaves and flowers Flowering shoots Aerial parts	(4,7,8,10,18,19,23, 37,42,43)
Dihydromyrcenol		Leaves and flowers	(4)
4-terpineol (Terpinen-4-ol)		Leaves and flowers Flowering shoots	(4,7)
Geranyl acetate		Leaves and flowers Flowering shoots aerial parts	(4,7,10,19)
4aα, 7α, 7aα- nepetalactone		Flowering shoots aerial parts	(7,8,10,18,23)
Neryl acetate		Flowering shoots	(7)
β-Pinene		Flowering shoots leaves and flowers aerial parts	(7,19,40)
α-Pinene		Aerial parts	(40)
α-Terpineol		leaves and flowers aerial parts	(7,40)
α-Linalool		aerial parts	(18)

Table 2. Continued

Name of compound	Chemical structure	Plant part	References
γ-Terpinene		Aerial parts	(40)
Rosmarinic acid		Aerial parts	(44)
Isothymusin		Aerial parts	(18)
6-Methoxy-7-O-methyl apigenin (cirsimaritin)		Aerial parts	(18)
7-O-Methyl apigenin (genkwanin)		Aerial parts	(18)

attributed to its components like myrcene, 1,8-cineole, limonene, α-terpinene and α-terpinolene. Moreover, this activity may play a crucial role in protecting cells from oxidative stress and disease prevention.

Anti-Inflammatory and anti-nociceptive activities

A hydroalcoholic extract of *N. menthoides* was reported to possess anti-nociceptive and anti-inflammatory activities as evidenced by effects in formalin test, hot water tail-immersion test and xylene induced ear oedema in mice. The study reported that *N. menthoides* aerial parts had anti-inflammatory effect at all tested doses, particularly at dose of 2800 mg/kg. Also, it caused a significant reduction of pain in the formalin test (acute and chronic phases) and the dose of 2800 mg/kg had the highest anti-nociceptive effect in chronic phases. Meanwhile, *N. menthoides* hydroalcoholic extract showed an acceptable analgesic effect in the tail immersion test. These effects might be due to its constituents: Nepetalactone and 1,8 cineole (25).

Antidepressant and anxiolytic activities

Nepeta menthoides aerial parts have been shown to possess antidepressant activity in an 8-week triple-blind randomized controlled trial study. In this study, fifteen patients received only *N. menthoides* capsules (400 mg) and fifteen patients treated with *N. menthoides* capsules and conventional drugs. Pharmaceutical capsules of *N. menthoides* could be potentially effective in depressed patients (26). In parallel, Kolouri et al assessed the effectiveness of *N. menthoides* in the treatment of major depression (MD). The results of this double blind randomized controlled trial study showed that in a short-term therapy, patients with MD receiving capsules containing 400 mg freeze-dried powder of *N. menthoides* aqueous extract experienced a significant reduction in their Beck Depression Inventory (BDI) scores after four

weeks of treatment compared with the standard treatment group (sertraline). Furthermore, two weeks follow up after intervention showed a statistically significant lower recurrence rate in the *N. menthoides* group (27). The anxiolytic activity of *N. menthoides* was investigated by evaluating its influence on the Beck anxiety inventory (BAI) score in patients with depression. The *N. menthoides* group who received freeze- dried aqueous extract formulation (400 mg/BID) demonstrated a greater reduction of BAI score and lower symptom recurrence rate as compared to the sertraline group. Moreover, the prevalence of reported side effects was lower in the *N. menthoides* than the SSRI group (28). These studies demonstrated the effects of *N. menthoides* on depression and anxiety induced by monoterpenes, sesquiterpenes, polyphenolic compounds and flavonoids. The findings of these studies suggested that *N. menthoides* might be an effective and safe treatment for depression and anxiety along with conventional medications.

Sedative-hypnotic effects

In an effort to find new effective substances that relieve insomnia while avoiding side effects, numerous studies tending to focus on herbal medicines have been done. In 2012, Bozorgmehr et al reported a sedative effect for the ethanolic extract of *N. menthoides* (29). *N. menthoides* (freeze-dried aqueous extract) has been shown to possess hypnotic effect. In this triple-blind randomized placebo controlled study, the subjects received three 500 mg capsules containing 1000 mg *Melissa officinalis* plus 400 mg of *N. menthoides* nightly for four weeks. The results showed that the Insomnia Severity Index (ISI) significantly decreased in treatment group and the patients who received herbal treatment experienced a significant improvement in their total sleep time as compared to the placebo group (30).

Effect on cognition and memory

The efficacy of *N. menthoides* extract in the treatment of patients with Alzheimer's disease was assessed in a clinical trial. The study was performed on two groups of AD patients. While the first group was prescribed the oral capsule (500 mg) of *Nepeta* extraction, the second group was given the placebo capsules (500 mg). Both groups were prescribed the conventional Alzheimer medications as the primary drugs. The remarkable improvement in the MMSE (Mini–Mental State Examination) scores in patients who received oral capsule of *N. menthoides*, three times daily, emphasized the potential of this plant accompanied by the conventional medications in decreasing the AD symptoms (31). Furthermore, some pharmacological evidence has been indicated the anticholinesterase activity, and memory enhancing effects of *N. menthoides in vivo* and *in vitro*.

Essential oil from *N. menthoides* aerial parts was found to inhibit the acetylcholinesterase enzyme (AChE). In AchE inhibitory test, the essential oil had desirable anticholinesterase activity with IC50 value of 64.870 µg/mL. 1,8-cineol, the greatest percentage composition of *N. menthoides* essential oil, is a potent inhibitor of AchE which plays a major role in inhibiting the enzyme (24). Moreover, AchE inhibitory activity of *N. menthoides* was also measured in a study conducted by Adhami et al. Both the methanol and dichloromethane extract showed significant AchE inhibitory effect (32). More recent studies showed the significant inhibition of AchE activity by essential oil and 1,8-cineole from *N. menthoides*. 1,8-Cineole exhibited higher inhibitory than the essential oil and both of them were more potent than rivastigmine (33). Taken together, these findings implicate that *N. menthoides* would be excellent candidate for future Alzheimer's disease therapy.

Behavioral studies have demonstrated that *N. menthoides* extract affects learning and memory in experimental animals. Hydroalcoholic extract of *N. menthoides* was reported to improve scopolamine-induced impairments of memory retention and retrieval in Y-maze task in mice (34). In similar work, Sarahroodi et al (35) demonstrated that the aqueous extract of *N. menthoides* leaves had promising memory enhancing effects at dose of 800 mg/kg using passive avoidance down step model. The presence of antioxidants such as rosmarinic acid, luteolin, cinnamic acid derivatives, caffeic acid, tocopherols, phenolic acids and coumarins can be a major contributor to the memory-enhancing effects of *N. menthoides* extract. Moreover, the water extract of *N. menthoides* was found to reverse the destructive effect of chronic cold-water-induced hypothermia on learning and memory in rats. The results showed that lower dose of *N. menthoides* neutralized learning and memory impairment, but higher dose had adverse effects on learning. Moreover, the extract could reduce hyperphosphorylation of tau protein that seems to be one of the mechanisms of its anti-dementia activities (36).

Neuroprotective effects

Different doses of *N. menthoides* were investigated for neuroprotective activity. It was observed that intraperitoneal administration of axotomized rats with ethanolic extract of *N. menthoides* resulted in an increased survival of axotomized motoneurons and a decreased apoptotic rate in a dose-dependent manner which was most prominent with the dose of 500 mg/kg (37). However, the study on prophylactic capacity of *N. menthoides* revealed that administration of *N. menthoides* ethanolic extract before neural injury causes no more neuroprotective effect on axotomized motoneurons (38). In another study, alcoholic extract of *N. menthoides* aerial parts by virtue of its anti-apoptotic effects induced neuroprotective effect on axotomized sensory neurons in dorsal root ganglion

(DRG) of neonate rats by attenuating the apoptotic cell death (39). The results confirm the traditional use of this plant for the treatment of neural disorders such as epilepsy and melancholia (12).

Cytotoxic activity

The anti-proliferative effects of essential oil of *N. menthoides* were investigated in colon carcinoma (HT-29), colorectal adeno-carcinoma (Caco-2), breast ductal carcinoma (T47D) cell lines and the Swiss mouse embryo fibro blast (NIH-3T3) as a normal cell line using the MTT method. As the IC50 value for the normal cell line was low, the MTT test showed that the essential oil exhibited the highest cytotoxic activity against T47D followed by HT-29 and Caco-2 cell lines with the IC50 values of 19.37±4.92, 30.7±7.36 and 32.24±5.98 µg/mL, respectively. This cytotoxic activity of *N. menthoides* might be observed due to specific components like α-terpineol, terpinolene, 1,8-cineole and limonene (24). In 2018, Kahkeshani et al studied the inhibitory effects of the essential oil and 1,8-cineole isolated from *N. menthoides* against three breast cancer cell lines (MCF-7, T47D and MDA-MB-231). Both compounds displayed inhibitory activity, but the essential oil was more cytotoxic than 1,8-cineole to breast cancer cell lines (33).

Effect on opioid dependence and tolerance

Chronic pretreatment with *N. menthoides* hydro-alcoholic extract could dose-dependently attenuate the development of dependence in morphine-treated mice. Furthermore, *N. menthoides* prevented the acquisition of morphine tolerance and potentiated morphine analgesic effect in a synergistic manner. It appears that inhibition of the nitric oxide (NO) overproduction is the main mechanism responsible for these effects of *N. menthoides* (40).

Toxicity and safety

Nepeta menthoides has been widely used in Persian traditional medicine. Although previous clinical studies on this herb have reported no significant adverse effects, some clinical and experimental studies have shown that *N. menthoides* has mild to moderate side effects. In one clinical trial anorexia, bulimia, xerostomia, emesis, impotence, and drowsiness were the most commonly side effects reported by the patients and one patient stopped *N. menthoides* capsules due to severe dermal irritation [16, 28]. Moreover, *N. menthoides* was found to increase susceptibility to seizures (41).

Discussion

Ostokhodus, one of the oldest herbs in Iran, had been widely introduced in TPM textbooks for treating various ailments. This herb has been substituted with other herbs with similar therapeutic effects over the time. Since 20 century the plant *N. menthoides* has been utilized as ostokhodus in Iran by people for different medicinal effects. This review collected findings about phytochemical and pharmacological properties of *N. menthoides* and presented comprehensive analysis of researches published since the year 2000. Ethnopharmacological published data about this herb is rare because of limited distribution as an endemic plant in Iran. Despite the lack of comprehensive pharmacological studies on *N. menthoides*, this plant is widely used in traditional medicine as anti-nociceptive, anti-Alzheimer's disease, memory enhancer, neuroprotective, antidepressant and anxiolytic agent. It seems that more preclinical studies are needed to assess this herb clinically specially in the field of seizure because one study indicated the increased susceptibility to seizures. Moreover, there are several medicinal properties discussed in Persian medicine such as anti-tussive, gastrotonic and gastrointestinal effects which are not supported by any modern scientific evidence and *N. menthoides* should also be assessed in these fields.

Despite high consumption of this plant, little phytochemical and quality control studies have been done on it. However, with respect to the limited published phytochemical assays, triterpenes and monoterpenes are the most abundant constituents of the essential oil of *N. menthoides*.

Conclusion

Considering the medicinal properties of isolated components, it can be concluded that terpenoids might be associated with anti-inflammatory and antimicrobial activities. Also, antioxidant and anticancer activities could be related to its phenols and flavonoids. Many of the phytochemical studies on this herb are based on essential oil analysis; hence there is still a huge need for extensive analysis on its different extracts.

Authors' contributions

All the authors contributed in data collection and preparation of the manuscript. All authors read the final version and confirmed for the publication.

Conflict of interests

The authors declare that they have no conflict of interests.

Ethical considerations

Ethical issues have been observed by the authors.

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