Original Article

Study of Monoamine Oxidase Inhibitory Effects of Seven Iranian Medicinal Plant Extracts

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Abstract

Background: Monoamine oxidase (MAO) enzymes abundantly found in the central nervous system (CNS) play an essential role in CNS disorders, so monoamine oxidase inhibitors (MAOIs) have been used for the treatment of neurological ailments such as depression, Parkinson's, and Alzheimer's disease. Therefore, finding the new selective MAOIs is still on the focus of researchers' attention. This study aimed to evaluate MAO-A and MAO-B inhibitory effects of seven methanolic extracts of Iranian medicinal plants including *Sanguisorba minor, Cerasus microcarpa, Ferulago angulata, Stachys pilifera, Amygdalus scoparia, Rosa canina*, and *Alhagi pseudalhagi.* **Materials and Methods:** The dried aerial parts of the plants were extracted with methanol by the maceration method. The inhibitory effects of extracts on MAO-A and MAO-B enzymes of rat brain mitochondria were measured by the fluorimetric method by using kynuramine as a substrate. **Results:** Among the extracts, *S. minor* (IC50 = 7.133 µg/mL) and *C. microcarpa* (IC50 = 49.53 µg/mL) were the most potent MAO-A and MAO-B inhibitors, respectively. A comparison of the IC50 value indicated that *A. scoparia* and *S. pilifera* had a higher affinity for MAO-A inhibition, whereas *C. microcarpa* and *R. canina* selectively inhibited the MAO-B enzyme. Moreover, *F. angulata* was recognized as a non-specific MAO inhibitor. The *A. pseudalhagi* and *S. minor* extracts did not show any MAO-B inhibitory effect. **Conclusion:** Our study showed that studied extracts have different MAO-A and MAO-B inhibitory effects. Therefore, they can be used for the treatment of various CNS disorders; also, these extracts are an excellent source for finding new compounds with MAO-A or MAO-B inhibitory effects.

Keywords: *Medicinal plants, mitochondria, monoamine oxidase, neurodegenerative diseases, neuropsychiatric diseases*

Introduction

Monoamine oxidase (MAO) is a flavin-containing enzyme located at the outer membranes of mitochondria and catalyzes the oxidative deamination of biogenic amines such as dopamine, serotonin, and norepinephrine. It is found in the brain and peripheral tissue, including the gut, liver, placenta, lymphocytes, and platelets. Two isoforms are identified for MAO called MAO-A and MAO-B and distinguished by their differences in substrate and inhibitor selectivity. MAO-A is selectively inhibited by clorgyline, whereas MAO-B is inhibited by selegiline; also serotonin and norepinephrine have more affinity to MAO-A enzyme and are mostly metabolized by that, whereas MAO-B mostly catalyzes the oxidation of phenylethylamine and benzylamine.[1]

Abnormal MAO activity plays a significant pathological role in central nervous system (CNS) disorders. Increased MAO-B activity is involved in neurological disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD).[2] It is reported that the level of MAO-B enzyme in the brain is elevated by increasing age[3]; moreover, increased MAO-B activity has been reported in the brain of patients with AD.[2] MAO-B enzyme is mostly found in the astrocytes in the brain, and the oxidative deamination reaction catalyzed by this enzyme produces hydrogen peroxide (H_2O_2), which is the main source of reactive hydroxyl radical (OH) in the brain. Therefore, elevated MAO-B activity increases oxidative damage of neurons, thereby exacerbating neural cell death in neurodegenerative disease. So, MAO-B inhibition protects neurons from oxidative damage, and then MAO-B inhibitors have been used in the prevention and treatment of AD and PD.[4,5]

MAO-A plays a vital role in psychiatric conditions such as depression,[6] so MAO-A inhibitors have been used as antidepressants

How to cite this article: Shamsi M, Soodi M, Hajimehdipoor H, Ghazanfari A. Study of monoamine oxidase inhibitory effects of seven Iranian medicinal plant extracts. J Rep Pharm Sci 2021;10:187-93.

Received: 17 Mar 2020
Accepted: 01 May 2021
Published: 17 Dec 2021

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Access this article online

Website: www.jrpsjournal.com

DOI:10.4103/jrptps.JRPTPS_23_20

Quick Response Code:

since 50 years ago and improve depression by increasing the level of serotonin, dopamine, and norepinephrine in the brain.[7,8] Although monoamine oxidase inhibitors (MAOIs) are currently available for the treatment of CNS disorders, their adverse effects limit their usage. The development of new potent and selective MAOIs, which are more effective in CNS disorders, is still in the focus of researchers.[9,10]

Medicinal plants are important and valuable sources of phytochemicals with various pharmacological activities. Recently, many researches have been done to elucidate the pharmacological potential of medicinal plants and their isolated bioactive constituents having MAO inhibitory activity.[11,12] It has been shown that some of the important secondary plant metabolites such as flavonoids, alkaloids, xanthones, and coumarins have MAO inhibitory activity, and plants containing the MAOI compounds have been effective in improving the psychiatric condition such as depression and anxiety or neurological disorders such as the AD and PD.[13]

In contrast, CNS disorders have complex pathophysiology so that several mechanisms such as oxidative stress, inflammation, and excitotoxicity are involved, so a multitargeted drug strategy is more effective in CNS disorder therapy.[14,15] Recent studies have indicated that multifunctional compounds with anticholinesterase, anti-oxidant, and MAO-B inhibitory activities are more effective in improving AD.[16] Also, compounds with MAO-A inhibitory and antioxidant activity improve depression more effectively.[17]

In the present study, MAO inhibitory activity of seven methanolic extracts of Iranian medicinal plants includes *Alhagi pseudalhagi, Cerasus microcarpa, Amygdalus scoparia, Stachys pilifera, Sanguisorba minor, Ferulago angulate,* and *Rosa canina*, as has been investigated. Our previous study indicated the anticholinesterase and antioxidant activity of these extracts.[18] Therefore, we aim to find medicinal herb extracts with multifunctional properties to treat complex CNS disorders such as AD.

Materials and Methods

Chemicals

Kynuramine and clorgyline were purchased from Santacruz Biotechnology (USA), selegiline was purchased from Zahravi Pharmaceutical Company (Iran), and all other materials were obtained from Merck (Germany).

Plant material

Aerial parts of *Cerasus microcarpa* (Rosaceae), *A. pseudalhagi* (Fabaceae), *S. pilifera* (Lamiaceae), *A. scoparia* (Rosaceae), *F. angulate* (Apiaceae), and fruits of *R. canina* (Rosaceae) were collected from Kohgiluyeh and Boyerahmad province, Iran, and aerial parts of *S. minor* (Rosaceae) were collected from Hamedan province, Iran. The species were identified at the Herbarium of Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran. The voucher numbers were registered as 2870, 3281, 2175, 1998, 2800, 2343, and 3545, respectively.

Plant extraction

The plant materials were dried in shade and ground. About 10 g of each plant powder was macerated with methanol: water in the ratio 80:20 (1:10) for 3 days. Every 24 h, the mixture was filtered, and the fresh solvent was added to the plant powder. The combined extracts were concentrated by a rotary evaporator and dried by a freeze dryer.

Animals

Male adult Wistar rats (200 ± 20 g) were obtained from the Animal House of Tarbiat Modares University. Animals were maintained under standard condition, including temperature 25°C, 12 h light/dark cycle, and free access to water and food *ad libitum*. All ethical principles for the care and working with animals were according to the Ethical Committee of Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences.

Brain mitochondrial preparation

Rats were decapitated under ether anesthesia, and the whole brain was removed and rinsed in the ice-cold phosphate buffer, pH=7.4. After that the brain tissue was homogenized in mitochondrial extraction buffer (10% w/v) consisting of 10 mM KCl; 68 mM sucrose; 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES); 220 mM mannitol, and 0.1% bovine serum albumin (pH=7.4). The brain homogenate was centrifuged at 3000*g* for 10 min at 4°C and then the supernatant was centrifuged at 11,500*g* for 15 min at 4°C. After that, the supernatant was discarded, and the resultant pellet, which was a mitochondria-enriched fraction, was suspended in 2 mL phosphate buffer pH=7.4 and stored at −80°C.[19] The protein concentration was determined by the Bradford method.[20]

Measurement of MAO activity

MAO-A and -B enzyme activities in the rat brain mitochondria were measured by the fluorimetric method by using kynuramine as a non-selective substrate for the MAO enzyme. The oxidative deamination of kynuramine by the MAO enzyme produces a fluorescent 4-hydroxyquinoline metabolite that can be measured at excitation and emission wavelengths of 310 and 360 nm, respectively. The MAO-A inhibition assay was carried out in black polystyrene 96-well plates. The final volume of reaction mixture was 200 µL, consisting of 125 µL of phosphate-buffered saline, 5 µL of selegiline 10 µM (to get a final concentration of 250 nM at the well) as a selective MAO-B inhibitor, 20 µL of plant extract, 40 µL of mitochondrial suspension, and 10 µL of Kynuramine 1 mM (to get a final concentration of 50 µM at the well). After incubation at 37°C for 30 min, the reaction was stopped by adding 75 µL NaOH 2 M. Then the fluorescent intensity was measured by a microplate reader (Citation 3, Biotek). The MAO-B enzyme assay was carried out similar to the MAO-A assay except by using clorgyline as a selective inhibitor of MAO-A instead

of selegiline. The protein concentration of mitochondrial suspension was 0.5 mg/mL. Several dilutions of mitochondrial suspension based on protein concentration ranging between 0.1 and 2 mg/mL were tested to find appropriate mitochondrial suspension concentration in the linear range. The control wells contain all assay materials except extract. The blank wells contain all assay materials without mitochondrial suspension as an enzyme source.[19] We carried out a separate experiment to explore possible interaction between the extract's components and 4-hydroxyquinoline product that may affect its fluorescent intensity. The mitochondrial suspension was incubated with the reagent buffer without extract in different wells at the above-mentioned experimental condition. During this incubation period, the enzyme produced the 4-hydroxyquinoline product, and then the enzyme activity was stopped by adding NaOH 2 M; after that, the highest concentration of each extract was added to a separate well, and one well was left without extract as control. The reagent blank wells, which contained reagent buffer and plant extract without mitochondrial suspension, were also included. After 15 min incubation, the fluorescent intensity of wells was measured. Extract alone did not have florescence at measured EM/EX wavelength; besides, there were no differences between florescent intensity of control well (4-hydroxyquinoline product without extract) and extract-containing wells. These results indicated that extracts did not react with the 4-hydroxyquinoline product to change its fluorescent intensity.

The plant extracts were dissolved in dimethyl sulfoxide. At first, the inhibitory effect of extract at a concentration of 400 µg/mL was determined, and extracts that showed 50% inhibition or more were chosen for further inhibition assay and determination of IC50 value. To this end, six concentrations of each extract were tested, and the dose–response curve was established; then, the IC50 value was estimated by a non-linear regression method. The Graphpad Prism 8 software was used for statistical analysis and IC50 calculation.

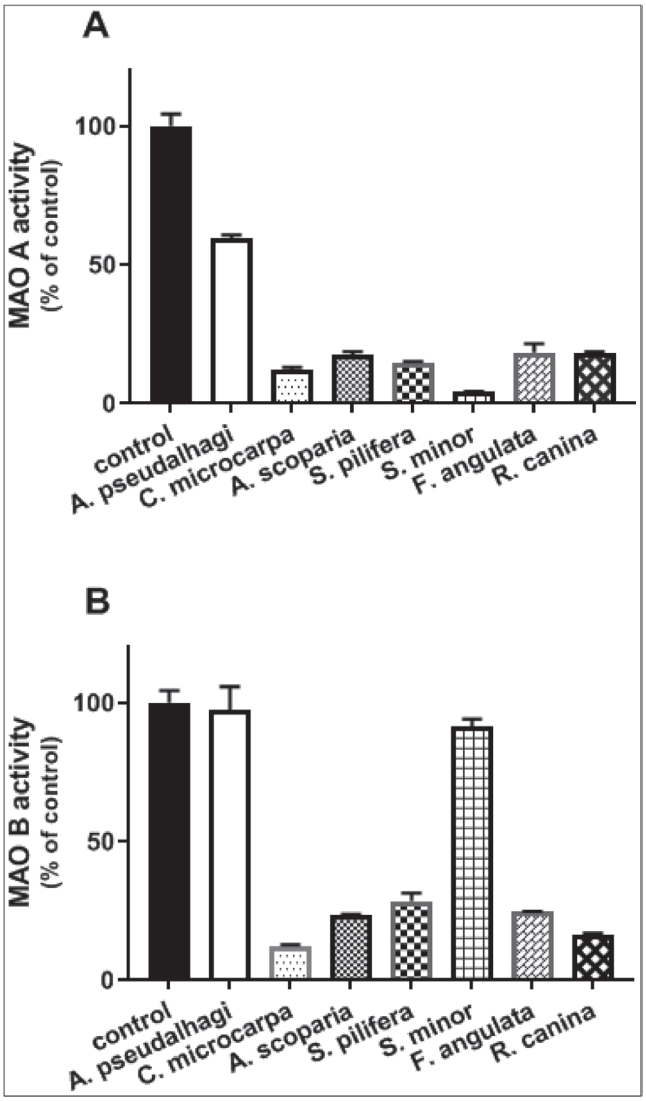

Figure 1: Effect of extracts at 400 µg/mL on activity of MAO-A (A) and MAO-B (B)

Results

The results of MAO-A and MAO-B inhibition by extracts at 400 µg/mL concentration have been shown in Figure 1A and B, respectively. All extracts had MAO-A inhibitory effect at this concentration, and MAO-A inhibition was more than 50% for all extracts except for *A. pseudalhagi* [Figure 1A]. Also, *C. microcarpa, A. scoparia, S. pilifera, F. angulate,* and *R. canina* inhibited MAO-B enzyme more than 50% at 400 µg/mL concentration, whereas *A. pseudalhagi* and *S. minor* did not have MAO-B inhibitory effect in this concentration [Figure 1B].

Figure 2 indicates the dose–response curve for MAO-A and MAO-B inhibitory effects of extracts. *C. microcarpa, A. scoparia, S. pilifera, R. canina*, and *F. angulate* dose-dependently inhibited both the MAO-A and MAO-B enzymes, whereas *S. minor* dose-dependently inhibited only the MAO-A enzyme. The IC50 values are presented in Table 1. The most potent MAO-A inhibitory effect was observed with *S. minor* extract with an IC50 value of 7.135 µg/mL, whereas the most potent MAO-B inhibitory effect was observed with *C. microcarpa* extract with an IC50 value of 49.53 µg/mL. *S. minor* did not show any MAO-B inhibitory effect; then, it is considered as a selective MAO-A inhibitor. The *C. microcarpa* and *R. canina* extracts, with the IC50 MAO-A/MAO-B inhibition ratios of 2.55 and 1.52, respectively, are more MAO-B selective inhibitors than MAO-A, whereas *A. scoparia* and *S. pilifera* extracts, with the IC50 MAO-A/MAO-B inhibition ratios of 0.55 and 0.58, respectively, are more MAO-A selective inhibitors. Beside, *F. angulate* was recognized as a non-specific inhibitor of MAO enzyme with the IC50 MAO-A/MAO-B inhibitory ratio of 0.82 [Table 1].

Discussion

In this study, the MAO-A and MAO-B inhibitory effects of seven Iranian medicinal plant extracts, including *S. minor,*

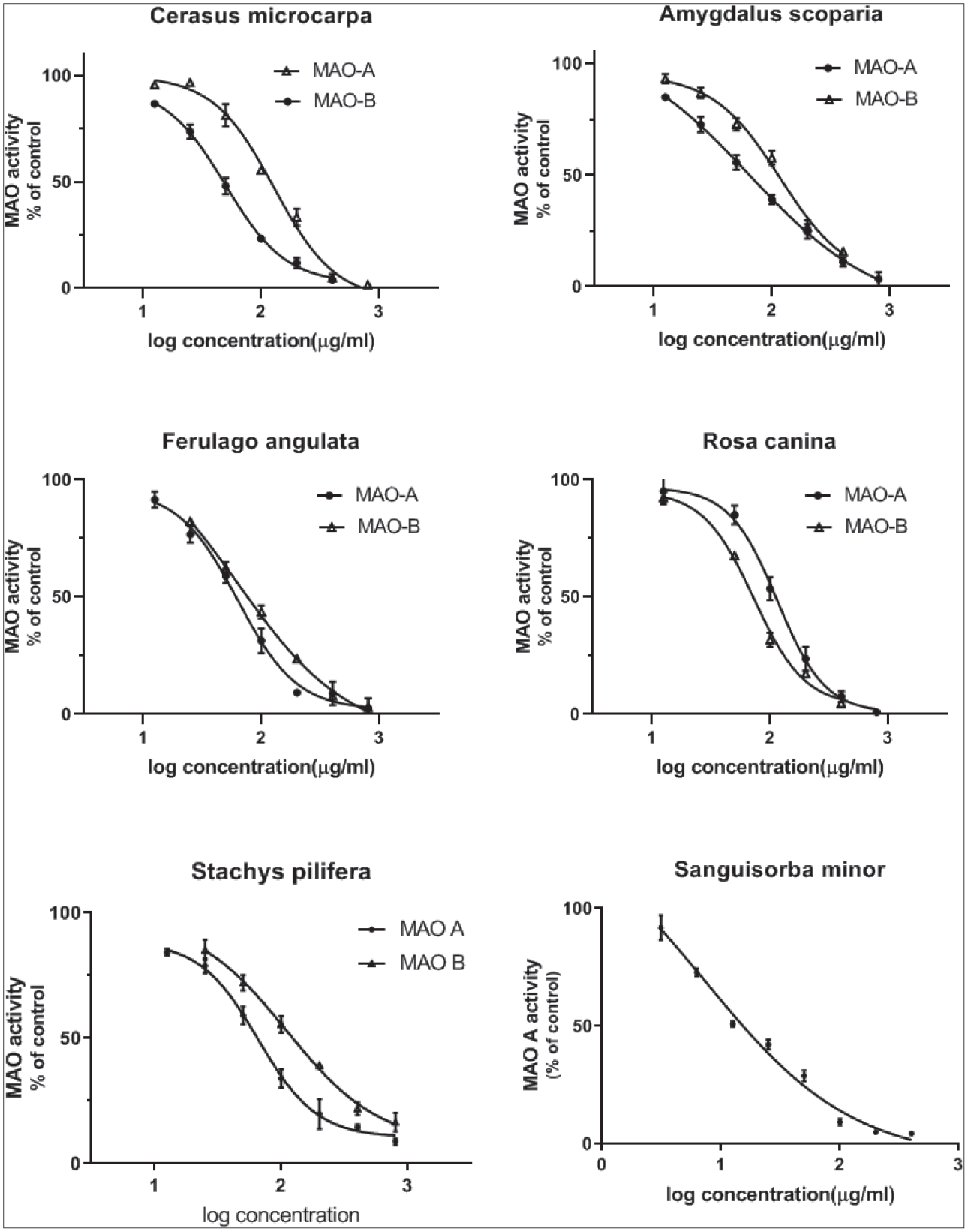

Figure 2: Dose–response curve of effective extract for MAO-A and MAO-B inhibitory effects

C. microcarpa, F. angulata, A. pseudalhagi, S. pilifera, A. scoparia, and *R. canina*, were investigated.

The MAO-A enzyme in the brain has a pivotal role in psychiatric disorders such as depression and anxiety, and MAO-A inhibitors

Table 1: The IC50 values of MAO-A and MAO-B inhibitory activity of extracts

Extract names	IC50 value (µg/mL) (MAO-A inhibition)	IC50 value (µg/mL) (MAO-B inhibition)	Selectivity index (MAO-A/ MAO-B inhibitory ratio)
Cerasus microcarpa	126.6	49.53*	2.55
Amygdalus scoparia	63.9.6	117.1*	0.55
Stachys pilifera	65.66	112.3*	0.58
Sanguisorba minor	7.313	—	—
Ferulago angulata	62.2	75.55	0.82
Rosa canina	112.3	73.68*	1.52
Clorgyline	113.8 (nM)		
Selegiline		288.8 (nM)	

*Represents significant difference between MAO-A and MAO-B inhibitory IC50 values

improve these diseases by increasing the level of serotonin and norepinephrine in the brain. Results of the present study indicated that all studied extracts have the MAO-A inhibitory effect with different potencies. The weakest effect was observed with the *A. pseudalhagi* extract, whereas *S. minor* showed the most potent MAO-A inhibitory activity. Besides, the *S. minor* extract did not have any MAO-B inhibitory effect; therefore, it was identified as the selective inhibitor of MAO-A enzyme. *S. minor* belongs to the Rosaceae family. It has antioxidant, antibacterial, antiviral, anti-inflammatory, and anti-cancer activities. It is reported that the methanolic extract of *S. minor* contains large amounts of phenolic compounds such as gallic acid, ellagic acid, and quercetin.[21,22] Studies have shown that secondary plant metabolites, mainly phenolic and flavonoid compounds, have inhibitory effects on MAO.[13] Gallic acid at doses of 10 and 20 mg/kg caused 40% inhibition of MAO-A enzyme in the mice brain and showed antidepressant effects in behavioral tests.[23] Also, ellagic acid and quercetin have the MAO-A inhibitory effect with the IC50 value of 1.5 µg/mL and18 µM, respectively.[24,25] Therefore, according to these studies, the MAO-A inhibitory effect of *S. minor* extract could be attributed to its phenolic and flavonoid compounds. Because of the potent MAO-A inhibitory effect of *S. minor*, it seems that this extract is a good source for the finding of new compounds with MAO-A inhibitory effect, which needs further studies. Besides, it may have antidepressant effects that it is recommended to be studied in the future.

Results of our study indicated that *A. scoparia* and *S. pilifera* extracts inhibited both MAO-A and MAO-B enzymes, but with more tendency to inhibition of MAO-A, then they are considered as MAO-A selective inhibitors and may have an antidepressant effect. *A. scoparia* and *S. pilifera* belong to the Rosaceae and Lamiaceae family, respectively. These plants are native to Iran, and there are not many studies on their pharmacological effects and chemical compositions; therefore, they need further investigations for the identification of their chemicals, which are responsible for their MAO inhibitory effects.

In the present study, the *F. angulata* extract was identified as a non-selective inhibitor of the MAO enzyme. *F. angulata* is a plant from the Apiaceae family with the local name called Chavir or Chevil. The plants in *Ferulago* species are rich in coumarin compounds.[26] Several coumarin derivatives such as osthole, psoralen, and umbelliferone have been identified in *Ferulago* species; moreover, the coumarin compounds such as xanthotoxin, isoimperatorin, oxypeucedanin, and oxypeucedanin hydrate were isolated from the dichloromethane extract of *F. angulate*.[27] Coumarin compounds have a wide range of pharmacological effects, including inhibition of MAO.[28] These compounds with different structures have different effects on the MAO-A and MAO-B isoenzymes. For example, scopoletin is a specially MAO-B inhibitor.[29] While osthole and psoralen are potent and selective inhibitors of MAO-A,[13,30] it is therefore suggested that the MAO inhibitory effect of *F. angulate* is due to its coumarin compounds, and the presence of diverse coumarin compounds with different effects on MAO-A and MAO-B isozymes in the total extract resulted in non-specific inhibition of the MAO enzyme. Hence, this plant is a good source for finding new MAO-A and MAO-B inhibitor compounds and required further studies.

MAO-B enzyme increases with aging in the brain, and studies have shown that it has a role in the pathophysiology of neurodegenerative diseases such as AD and PD. Monoamine oxidase type B inhibitors (MAO-BIs) such as selegiline and rasagiline are used in the treatment of PD and improve the symptoms of this disease.[5] Also, in AD, the elevated level of MAO-B in the brain is associated with increased beta-secretase activity, which potentiates the amyloidogenic pathway of amyloid precursor protein cleavage, leading to production and accumulation of beta-amyloid (Aβ) peptide.[31] It is reported that the selective MAO-B inhibitor reduces the production of Aβ plaques in the brain of the transgenic mice model of AD and improves memory impairment.[32] Also, in Aβ-injected mice, co-administration of selegiline and donepezil improves Aβ-induced memory impairment more effectively than donepezil or selegiline alone, which indicates the synergic effect of anticholinesterases and MAO-BIs in the treatment of AD.[33] Among the studied plants, the extract of *C. microcarpa* and *R. canina* showed a selective effect on the MAO-B enzyme. Both plants belong to the Rosaceae family. *C. microcarpa* is native of Iran, and its pharmacological effects and chemical composition have not been studied more. In one study, a moderate acetylcholinesterase inhibitory effect has been reported for *C. microcarpa* extract.[34] Plants in the Rosaceae family are rich in phenolic and flavonoid compounds. It is reported that some of these compounds have MAO-B inhibitory activity. For example, catechin and epicatechin inhibit the rat brain mitochondrial MAO-B enzyme selectively. Also, the MAO-B inhibitory effect has been reported for formononetin, kushenol, and naringenin.[13] Our previous study indicated that *C. microcarpa* contains a high amount of

phenolic compounds; therefore, the MAO-B inhibitory effect of *C. microcarpa* could be attributed to the phenolic compounds that it needs further studies. In the present study, the *C. microcarpa* extract had the most potent MAO-B inhibitory effect among the studied extract; therefore, it is recommended that its chemical compositions should be studied in detail for finding the new selective MAO-B inhibitor compounds.

In contrast, our previous study indicated that the *C. microcarpa* extract has neuroprotective activity and be able to prevent neural cells against Aβ toxicity. Regarding this issue, acetylcholinesterase inhibitory, MAO-B inhibitory, and antioxidant activity of *C. microcarpa* extract, it is a good candidate for investigation as a multitargeted agent in AD therapy. Further studies on the animal model of AD are needed to confirm this hypothesis, which is our plan in the future.

Another extract that showed a selective MAO-B inhibitory effect was *R. canina* fruit extract. The fruits of the plants from the Rosa genius called Rosehip have multiple compounds with different biological effects. Catechin and epicatechin are flavonoid compounds found in Rosehip, which are the selective MAO-B inhibitors.[35] *R. canina* fruit has antioxidant, anti-inflammatory, and neuroprotective properties.[36] The previous study indicated that a herbal compound that contains *R. canina* fruit extract improves memory impairment in an animal model of AD.[37] The MAO-B inhibitory effect of *R. canina* fruit extract reported for the first time in the present study may be contributed to the neuroprotective effects of this extract.

In conclusion, the present study showed that the *F. angulate* extract is a non-selective inhibitor of MAO enzyme and *S. minor*, *A. scoparia*, and *S. pilifera* extracts are selective inhibitors of MAO-A enzyme. Also *C. microcarpa* and *R. canina* extracts are selective inhibitors of MAO-B enzyme. These plants are an excellent source for finding the new MAO inhibitor compounds and may be useful in neurological disorders such as AD and PD or psychiatric conditions such as depression and anxiety.

Financial support and sponsorship

This work was supported by a grant from the Traditional Medicine and Materia Medica Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (grant no. 197).

Conflicts of interest

The authors declare no conflict of interest.

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