PHARMACEUTICAL BIOLOGY, 2016
VOL. 54, NO. 6, 1071–1076
http://dx.doi.org/10.3109/13880209.2015.1102949

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

The monoamine oxidase inhibitory activity of essential oils obtained from *Eryngium* species and their chemical composition

Luiz Carlos Klein-Júnior[a], Carolina dos Santos Passos[a], Tiago Juliano Tasso de Souza[a], Fernanda Gobbi de Bitencourt[a], Juliana Salton[a], Sérgio Augusto de Loreto Bordignon[b] and Amélia Teresinha Henriques[a]

[a]Laboratory of Pharmacognosy and Quality Control of Phytomedicines, Faculty of Pharmacy, Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil; [b]Laboratory of Applied Biology, Centro Universitário La Salle – UNILASALLE, Canoas, Brazil

ABSTRACT

Context Monoamine oxidase (MAO) inhibitors are used in the treatment of depression, anxiety disorders, and the symptomatic treatment of Parkinson's disease. *Eryngium*, the most representative of the Apiaceae family, is well known for the presence of essential oils (EOs), which have already demonstrated MAO inhibitory potential.

Objective The objective of this study is to evaluate the MAO inhibitory capacity of the EOs obtained from *Eryngium floribundum* Cham. & Schlecht. (EF), *E. eriophorum* Cham. & Schlecht. (EE), *E. nudicaule* Lam. (EN), *E. horridum* Malme (EH), and *E. pandanifolium* Cham. & Schlecht. (EP).

Materials and methods EOs were obtained from fresh whole plants by hydrodistillation (3 h). Chemical analyses were performed by GC/MS using apolar and polar columns, with oven temperature from 60 to 300 °C at 3 °C/min. The MAO-A and -B activities were evaluated *in vitro* by an end-point method using kynuramine as the substrate and mitochondrial suspension or human recombinant enzymes as the enzymatic source. DMSO 2%, clorgyline 10^{-7} M, and pargyline 10^{-6} M were used as controls.

Results and discussion EFEO, EEEO, ENEO, EHEO, and EPEO GC/MS analysis showed (E)-caryophyllene (4.9–10.8%), germacrene D (0.6–35.1%), bicyclogermacrene (10.4–17.2), spathulenol (0.4–36.0%), and globulol (1.4–18.6%) as main constituents. None of the EOs inhibited MAO-A activity (4 and 40 μg/mL). However, EHEO inhibited MAO-B activity with an IC_{50} value of 5.65 μg/mL (1–200 μg/mL). Pentadecane (10 μM), its major constituent (53.5%), did not display significant MAO-B inhibition.

Conclusion The study demonstrates the promising application of *Eryngium* species as a source of potential central nervous system bioactive secondary metabolites, specially related to neurodegenerative disorders.

ARTICLE HISTORY
Received 28 July 2015
Accepted 27 September 2015
Revised 9 September 2015
Published online 21 January 2016

KEYWORDS
Neurodegeneration; Parkinson's disease; pentadecane

Introduction

Monoamine oxidase (MAO; EC1.4.3.4) is an enzyme responsible for the oxidative deamination of monoamines, involved with many mental disorders and behavioural effects of some psychotropic drugs. MAO exists in two isoforms: A and B. MAO-A is inhibited by clorgyline and is responsible for the oxidation of serotonin, while MAO-B is inhibited by L-deprenyl; benzylamine and 2-phenylethylamine are substrates. Both isoforms are able to oxidize dopamine, noradreanline, adrenaline, tryptamine, and tyramine. Taking into account their substrates, MAO have been focus of extensive studies in the development of new and effective inhibitors. Inhibition of MAO-A is related to antidepressant effect, while MAO-B inhibitors are associated with the treatment of Parkinson's disease. However, it is well known that MAO inhibitors are responsible for a series of adverse effects, as liver toxicity and hypertensive crises (Youdim & Bakhle 2006; Youdim et al. 2006).

Traditionally, plants are an important source of psychoactive substances. As demonstrated by Adams et al. (2007), several plant families are able to demonstrate central nervous system (CNS) effects, such as Lamiaceae, Polygalaceae, and Apiaceae. *Eryngium* L. is the largest genus in the Apiaceae family, accounting for about 75% of species diversity of the subfamily Saniculoideae. It comprises approximately 250 species distributed in temperate regions of every continent. There are four known centres of diversity in the world, including western Mediterranean, southwest Asia, central-west Mexico, and central-east South America (Calviño et al. 2008). In fact, there are more than 100

CONTACT Luiz C. Klein-Júnior lcarlosk@gmail.com Laboratory of Pharmacognosy and Quality Control of Phytomedicines, Faculty of Pharmacy, Universidade Federal do Rio Grande do Sul, Av. Ipiranga, 2752, 90610-000 Porto Alegre – RS, Brazil

species distributed in the western hemisphere, mainly concentrated in southern Brazil, Paraguay, Uruguay, and northern Argentina (Mathias et al. 1972).

There are several pharmacological activities described for the genus. Küpeli et al. (2006) demonstrated the anti-inflammatory activity of ethanolic and aqueous extracts obtained from the aerial parts and roots of eight Turkish *Eryngium* species. It was observed that *E. maritimum* L. and *E. kotschyi* Boiss. possess the most promising results, also exhibiting antinociceptive effect. The anti-mutagenic capacity of the ethanolic extract of *E. creticum* Lam. was also described, inhibiting the mutagenicity induced by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, mainly attributed to an increased recovery at the chromosomal level (Khader et al. 2010). Beside the activity of the extracts of *Eryngium* species, Cavaleiro et al. (2011) also demonstrated the antifungal effect of the essential oil of *E. duriaei* subsp. *juresianum* (Laínz) Laínz, with MIC values ranging from 0.16 to 0.32 µL/mL against several dermatophyte species. Indeed, *Eryngium* species are known for the essential oil production (Palá-Paúl et al. 2007; Flamini et al. 2008; Thiem et al. 2011).

Considering that essential oil constituents had already demonstrated the capacity to inhibit MAO (Tao et al. 2005), this study aims to assess the MAO inhibitory effect of the essential oils obtained from South-Brazilian *Eryngium* species, namely *E. floribundum* Cham. & Schlecht., *E. eriophorum* Cham. & Schlecht., *E. nudicaule* Lam., *E. horridum* Malme and *E. pandanifolium* Cham. & Schlecht., as well as to chemically characterize these essential oils.

Materials and methods

Chemicals

Kynuramine dihydrobromide, pargyline hydrochloride, clorgyline hydrochloride, pentadecane, and DMSO were purchased from Sigma Chemical Co. (St. Louis, MO). Human MAO-A and MAO-B Supersomes ™ were acquired from BD Gentest (Woburn, MA). Diethyl ether was acquired from Tedia Company, Inc. (Fairfield, OH). All remaining chemicals used were of analytical grade and were purchased from Sigma-Aldrich (Darmstadt, Germany).

Plant material

Eryngium floribundum, E. horridum, and *E. pandanifolium* were collected from Guaíba, Rio Grande do Sul, Brazil, in April 2012. *Eryngium eriophorum* and *E. nudicaule* were collected from Santo Antônio da Patrulha, Rio Grande do Sul, Brazil, in July 2012. The species were identified by Dr. Sérgio Augusto de Loreto Bordignon and vouchers were deposited at the herbarium of the Departmento de Botânica of the Universidade Federal do Rio Grande do Sul under the numbers ICN 190623, 190628, 190627, 190631, and 190632, respectively.

Essential oil extraction

Fresh materials were reduced and submitted to hydrodistillation in a Clevenger-type apparatus for 3 h. The oils were collected and the sample yields were based on dry weight. All the samples were stored at 4 °C in the dark. Before the analysis, the oils were diluted with diethyl ether.

Analysis by GC-MS

The GC-MS was carried out on a Shimadzu mass spectrometer (GC/MS-QP5000, Shimadzu Corp, Tokyo, Japan) connected with cylindric quadrupole and operated at 70 eV ionization energy. An apolar Durabond-DB5 column (Agilent Technologies, Inc., Atlanta, GA) (30 m × 0.25 mm × 0.25 µm) was used. To confirm, a polar column was also used (LM-120). The temperature was programmed from 60 to 300 °C at 3 °C/min and the injector and detector temperatures were set at 220 °C and 250 °C, respectively. CG-FID was used for quantification (Limberger et al. 2004; Simões-Pires et al. 2005). The relative composition of the oils was obtained by electronic integration and the identification of the compounds was based on the comparison with retention indices, determined relatively to the retention times of a homologous series of *n*-alkanes, and mass spectra of commercial database (NIST) and literature (Adams 2007).

MAO inhibitory assay

MAO inhibitory assay was performed with two different sources of enzyme. First, essential oils were evaluated using a mitochondrial suspension as source of MAO. Later, the IC_{50} value of the most active oil and the pentadecane activity was obtained using human recombinant MAO-A or MAO-B. Both assays were carried out in black polystyrene 96-well microtiter plates in a final volume of 200 µL. For the first method, 140 µL of PBS (pH 7.4), 10 µL of pargyline 10 µM (for MAO-A) or clorgyline 10 µM (for MAO-B), 20 µL of kynuramine 0.5 mM, and 10 µL of the samples (in DMSO) were preincubated for 20 min at 37 °C. 20 µL of the mitochondrial suspension 0.5 mg/mL (obtained as described by Passos et al. 2013) was added and the plate was

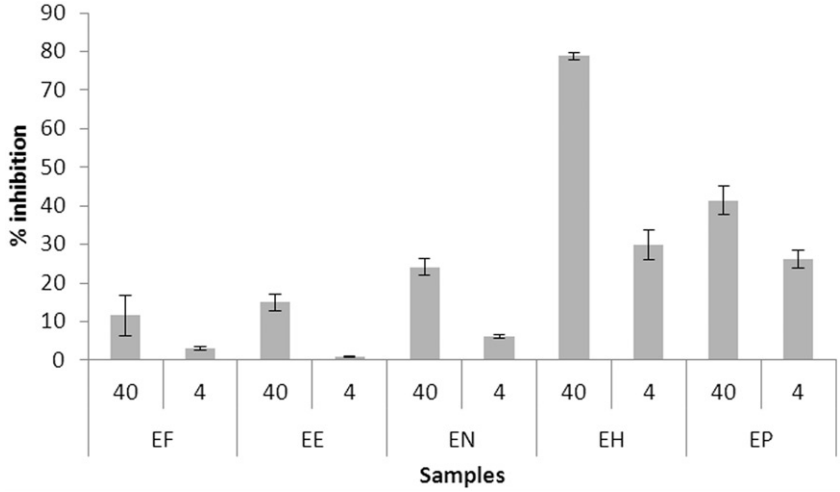

Figure 1. Inhibitory effect (%) of *Eryngium floribundum* (EF), *Eryngium eriophorum* (EE), *Eryngium nudicaule* (EN), *Eryngium horridum* (EH), and *Eryngium pandanifolium* (EP) on monoamine oxidase B activity. The samples were evaluated at 40 and 4 μg mL^{-1}. Error bars represent standard deviation ($n = 3$).

incubated for 30 min at the same temperature. Finally, 75 μL of NaOH 1M was used to stop the reaction. DMSO 2%, clorgyline 10^{-7} M (MAO-A inhibitor), pargyline 10^{-6} M (MAO-B inhibitor), and both clorgyline and pargyline (as 100% of inhibition) were used as controls. In the second method, the plate was preincubated as described above, however with 158 μL of potassium phosphate buffer pH 7.4, 2 μL of the sample diluted with DMSO and 20 μL of kynuramine 0.5 mM. Later, it was added 20 μL of the enzyme (MAO-A 0.09 mg mL^{-1} or MAO-B 0.15 mg mL^{-1}) and, after the incubation (30 min at 37 °C), 25 μL of NaOH 1 M was used to stop the reaction. DMSO 1% and clorgyline 10^{-6} M (100% of inhibition) and 10^{-8} M (50% of inhibition) for MAO-A, or pargyline 10^{-5} M (100% of inhibition) and 10^{-7} M (50% of inhibition) for MAO-B were used as controls. The fluorescence of both experiments were measured on a Wallac EnVision high-throughput screening microplate reader (PerkinElmer Life and Analytical Sciences, Turku, Finland), at an excitation wavelength $\lambda = 310$ nm and an emission wavelength $\lambda = 400$ nm. The oils were first tested at the concentrations of 4 and 40 μg mL^{-1} and, to obtain the IC_{50} value the doses were ranged from 1 to 200 μg/mL. Pentadecane was evaluated at the doses of 1 and 10 μM.

Statistical analysis

Data analysis was performed using Prism 5.0 (GraphPad Software, Inc., San Diego, CA) and the IC_{50} value was calculated by adjusting the experimental data (% of inhibition versus concentration) to non-linear regression curves.

Results and discussion

GC-MS analysis

None of the *Eryngium* species are known for containing large amounts of oil, as pointed out by Palá-Paúl et al. (2005a). In the present study, the yields obtained for *Eryngium* species were about 0.1%, corroborating with the results previously reported.

All the compounds identified for the essential oils, retention indices and their relative percentages are presented in Table 1. The main components observed were (E)-caryophyllene, germacrene D, bicyclogermacrene, spathulenol, and globulol. Germacrene D and bicyclogermacrene have already been extensively described as main constituents for other species of the genus, such as *E. rosulatum* P.W. Michael (Palá-Paúl et al. 2006), *E. amethystinum* L. (Flamini et al. 2008), and *E. bourgatii* Gouan (Palá-Paúl et al. 2005b). However, the detection of pentadecane as the main constituent of *E. horridum* is very atypical. In fact, the presence of aliphatic components in essential oils of *Eryngium* species is not common and, if they occur, it is usually in low concentrations.

It is also worth mentioning the great difference between the constituents of the oils. Actually, none of the compounds is common for all the essential oils. This great variability in the metabolic constitution of the oils had already been suggested by other authors (Flamini et al. 2008). Palá-Paúl et al. (2005a,b) verified that phyllocladene and derivatives are the principal components for *E. bourgatii* and *E. glaciale* Boiss., which grow under the same climatic conditions. However, 2,4,5- and 2,4,6-trimethylbenzaldehyde are detected in low quantities in these species and are present as the main

Table 1. Chemical composition of the essential oils obtained from *Eryngium floribundum* (EF), *Eryngium eriophorum* (EE), *Eryngium nudicaule* (EN), *Eryngium horridum* (EH), and *Eryngium pandanifolium* (EP).

Compound	RI[a]	EF%	EE%	EN%	EH%	EP%
α-Pinene	927	–	t	–	–	–
β-Pinene	970	–	t	–	–	–
Limonene	1024	–	t	–	–	–
cis-Chrysanthenyl acetate	1255	6.0	–	–	–	–
Bornyl acetate	1278	–	–	–	–	t
n-Tridecane	1294	–	–	–	t	–
α-Terpinyl acetate	1341	–	–	–	t	–
2,3,6-Trimethyl benzaldehyde	1351	15.7	–	–	–	–
α-Copaene	1364	–	t	t	–	t
β-Bourbonene	1373	0.8	–	–	–	–
β-Elemene	1381	3.3	5.4	0.9	–	4.0
n-Tetradecane	1390	–	–	–	t	–
2-epi-β-Funebrene	1399	–	–	0.1	–	1.4
β-Funebrene	1400	2.9	–	–	–	
(E)-Caryophyllene	1406	4.9	7.1	10.8	–	5.2
β-Copaene	1415	0.1	–	–	–	t
α-Cedrene	1416	–	–	–	t	–
cis-Thujopsene	1417	–	1.2	–	–	–
α-*trans*–Bergamotene	1424	–	–	t	–	–
Aromadendrene	1424	0.2	–	–	9.1	–
(*Z*)-β-Farnesene	1432	–	–	t	–	–
α-Humulene	1439	0.4	2.7	4.7	–	0.3
allo-Aromadendrene	1446	–	–	–	1.6	–
(*E*)-β-Farnesene	1447	t	–	1.6	–	–
Dauca-5,8–diene	1457	–	–	t	–	–
β-Acoradiene	1460	t	–	–	–	–
γ-Decalactone	1460	–	–	–	7.4	–
10-*epi*-β-Acoradiene	1462	–	–	5.6	–	–
γ-Muurolene	1465	t	–	1.8	–	–
Germacrene D	1469	0.6	35.1	5.4	–	28.9
β-Selinene	1473	–	1.8	–	–	3.3
Viridiflorene	1481	t	–	–	–	–
Bicyclogermacrene	1486	–	10.4	17.2	–	12.8
α-Muurolene	1487	–	–	–	–	t
trans-β-Guaiene	1489	–	–	5.0	–	–
Cuparene	1490	t	–	–	–	–
Pentadecane	1490	–	–	–	53.5	–
Germacrene A	1492	–	3.8	1.0	–	2.2
β-Bisabolene	1496	0.2	2.9	7.5	–	–
(*Z*)-γ-Bisabolene	1503	–	–	1.4	–	–
γ-Amorphene	1509	–	1.3	–	–	–
δ-Cadinene	1511	–	–	1.3	–	3.0
Dauca-4(11),8-diene	1514	–	t	–	–	–
Silphiperfol-5-en-3-one B	1535	–	0.8	–	–	–
epi-Longipinanol	1538	t	–	–	–	–
Germacrene B	1543	–	t	–	–	4.4
(*E*)-Nerolidol	1554	–	t	0.1	–	t
Longipinanol	1567	–	–	4.6	–	–
Spathulenol	1568	36.0	6.2	–	0.4	6.4
Caryophyllene oxide	1570	–	3.3	–	–	4.3
Globulol	1576	7.0	1.4	–	18.6	1.8
Salvial-4(14)-en-1-one	1581	–	1.5	–	–	2.0
Viridiflorol	1582	5.0	–	0.3	4.6	–
Cedrol	1590	–	–	1.2	–	–
Rosifoliol	1592	2.7	–	–	t	–
Guaiol	1595	–	–	t	–	–
Khusimone	1596	t	–	–	–	–
Humulene epoxide II	1597	–	–	t	–	–
Junenol	1605	–	–	–	–	t
cis-Cadin-4-en-7-ol	1621	–	–	–	–	t
allo-Aromadendrene epoxide	1625	–	t	–	–	t
3-iso-Thujopsanone	1637	–	1.2	–	–	–
Cubenol	1637	–	–	–	–	t
α-Muurolol	1638	–	–	t	–	t
α-Cadinol	1645	4.9	4.9	–	–	11.1
γ-Dodecalactone	1668	1.8	–	–	–	–
Khusinol	1670	–	–	–	–	t
α-Bisabolol	1675	0.1	2.9	–	–	1.0
Germacra-4(15),5,10(14)-trien-1-α-ol	1677	t	–	–	–	–
Eudesma-4(15),7-dien-1-β-ol	1678	–	t	0.9	–	–
(*E*)-Nerolidol acetate	1692	–	–	t	–	–
Mint sulfit	1723	–	–	1.4	–	–
Isobicyclogermacrenal	1724	t	0.2	1.8	–	–
Cyclocolorenone	1730	–	–	14.7	–	–
α-Sinesal	1743	–	–	1.4	–	–
Hexadecanal	1803	–	–	–	t	–
Total		**92.5**	**94.1**	**90.7**	**95.2**	**92.1**

[a]Relative retention index experimentally determined against *n*-alkanes on Durabond-DB5 column; t = trace.

components for *E. foetidum* L., *E. maritimum*, *E. yuccifolium* Michx., and other species. As suggested by the authors, many factors, such as geographical origin, climatic conditions, and others, may affect the metabolic constitution of essential oils of *Eryngium* species.

MAO inhibition

Tao et al. (2005) demonstrated that volatile oil constituents, as eugenol, have the capacity to inhibit monoamine oxidase *in vitro*. Taking this into account, in the present study, we aimed to evaluate the MAO inhibitory capacity of the essential oils obtained from *Eryngium* species.

First, we performed a screening with all essential oils, using two different concentrations (4 and 40 μg mL^{-1}). The results are represented in Figure 1. It was observed that none of the essential oil was able to significantly inhibit rat MAO-A activity. However, with respect to the effect on rat MAO-B, the oil of *E. pandanifolium* inhibited the enzyme in the order of 26 ± 4% (4 μg/mL) and 41 ± 4% (40 μg/mL), while the oil of *E. horridum* was able to inhibit in the order of 31 ± 7% and 79 ± 1%, for 4 and 40 μg/mL. The variability observed for the pharmacological results may be a reflex of the chemical differences.

Considering that the essential oil of *E. horridum* demonstrated a high potency against MAO-B, the IC_{50} value was determined using human recombinant enzyme (BD Gentest). Using concentrations varying from 1 to 200 μg/mL, the IC_{50} value was calculated as 5.65 μg/mL. The maximum inhibition obtained for the tested oil was 94% (at the dose of 200 μg mL^{-1}) and the Hill coefficient in the concentration–response equation was 1.022, indicating an ideal behaviour (Copeland 2005).

The MAO-B inhibitors are mainly related to the potential application as antiparkinson drugs. In fact, people with Parkinson's disease possess higher levels of MAO-B as a consequence of gliosis, promoting a malfunction in the dopaminergic system (Youdim et al. 2006). Moreover, the loss of dopaminergic neurons in

substantia nigra accompanied by the presence of Lewy bodies has also been detected (Jenner 2012). MAO-B inhibitors have been described as a good option for the early treatment of the disease, promoting a mild effect on motor symptoms, also delaying the use of levodopa (Löhle & Reichmann 2011). In addition, MAO-B selective inhibitors are not associated with the 'cheese effect', which is common for non-specific MAO inhibitors (Finberg & Gillman 2011).

It is well known that oxygen heterocyclic compounds are usually able to inhibit MAO-B activity, as coumarins, chromones, and chalcones (Helguera et al. 2012). However, taking into account the GC/MS data obtained for *E. horridum* essential oil, the main compound is pentadecane (53.5%), which is an aliphatic carbon chain. As far as we know, there is no report describing the interaction between a carbon chain and the active site of MAO-B. For this reason, a different mechanism of action has been proposed.

The MAO-B (BD Supersomes^{TM}, BD Biosciences, San Jose, CA) consists of microsomes prepared from insect cells infected with a virus engineered to express the enzyme. Thus, it is not just the enzyme, but membrane constituents are also present during the experiment of MAO inhibition. As highlighted by Novaroli et al. (2005), MAO-B is a membrane-bound enzyme and the mitochondrial microenvironment is important for enzyme activity. In fact, the membrane seems to have a role in increasing the local substrate concentration at the active site of MAO-B (Binda et al. 2004).

There are several reports demonstrating the interaction between *n*-alkanes, like pentadecane, with lipid bilayers membranes. Pope & Dubro (1986) observed that in low concentrations, the alkanes may be dissolved between the lipid chains, without great changes in the bilayer structure. However, longer chains in higher concentrations may align parallel to the lipid acyl chains, increasing the bilayer width and affecting the hydrocarbon chain packing and chain tilt (McIntosh et al. 1980). Considering that pentadecane, the main constituent of the oil of *E. horridum*, is a long-chain hydrocarbon, it is possible that this compound interacts with the bilayer membrane, promoting some conformational changes in it. This interaction may lead to disturbs in some membrane functions, modifying the arrangement around MAO-B, resulting in modified enzyme activity (Szögyi & Cserháti 1993).

In order to evaluate the role of pentadecane in the inhibitory effect of the essential oil of *E. horridum*, the *n*-alkane was evaluated in the enzymatic assay. It was observed that, neither in the higher doses tested (10 μM) the compound was able to inhibit MAO-B activity. Taking this result into account, it is proposed that pendadecane is just responsible for modifying some physicochemical parameters of MAO-B, may be facilitating the entrance of other constituents into the active site, however without the capacity to directly inhibit the enzyme activity. Moreover, as already discussed by Williamson (2001), synergy is very common to occur in essential oils, and other compounds may be responsible for the activity of *E. horridum*.

Conclusions

As far as we know, this is the first time that the chemical constitution of the essential oils from South-Brazilian *Eryngium* species is described. Moreover, through the pharmacological evaluation of the oils, no significant effect was detected over MAO-A. On the contrary, *E. horridum* essential oil was able to inhibit MAO-B activity in the order of 94% (at the dose of 200 μg/mL), demonstrating the promising application of *Eryngium* species as a source of potential CNS bioactive secondary metabolites.

Declaration of interest

The authors report that they have no conflicts of interest. L. C. K. -J., C. S. P., J. S., and A. T. H. acknowledge the fellowship from CNPq/Brazil. T. J. T. S. thanks for the fellowship from CAPES/Brazil and F. G. B. is recipient of a fellowship from FAPERGS/Brazil. The work was supported by CNPq.

References

Adams M, Gmünder F, Hamburger M. 2007. Plants traditionally used in age related brain disorders – a survey of ethnobotanical literature. J Ethnopharmacol. 113:363–381.

Adams RP. 2007. Identification of essential oil components by gas chromatograph/quadrupole mass spectrometry. Carol Stream: Allured Publishing.

Binda C, Hubálek F, Li M, Edmondson DE, Mattevi A. 2004. Crystal structure of human monoamine oxidase B, a drug target enzyme monotopically inserted into the mitochondrial outer membrane. FEBS Lett. 564:225–228.

Calviño CI, Martínez SG, Downie SR. 2008. The evolutionary history of *Eryngium* (Apiaceae, Saniculoideae): rapid radiations, long distance dispersals, and hybridizations. Mol Phylogenet Evol. 46:1129–1150.

Cavaleiro C, Gonçalves MJ, Serra D, Santoro G, Tomi F, Bighelli A, Salgueiro L, Casanova J. 2011. Composition of a volatile extract of *Eryngium duriaei* subsp. juresianum (M. Laínz) M. Laínz, signalised by the antifungal activity. J Pharm Biomed Anal. 54:619–622.

Copeland R. 2005. Evaluation on enzyme inhibitors in drug discovery: a guide for medicinal chemists and pharmacologists. New York: Wiley.

Finberg JPM, Gillman K. 2011. Selective inhibitors of monoamine oxidase type B and the "cheese effect". Int Rev Neurobiol. 100:169–190.

Flamini G, Tebano M, Cioni PL. 2008. Composition of the essential oils from leafy parts of the shoots, flowers and fruits of *Eryngium amethystinum* from Amiata Mount (Tuscany, Italy). Food Chem. 107:671–674.

Helguera MA, Perez-Machado G, Cordeiro NDSM, Borges F. 2012. Discovery of MAO-B inhibitors – present status and future directions. Part I: oxygen heterocycles and analogs. Mini Rev Med Chem. 12:907–919.

Jenner P. 2012. Mitochondria, monoamine oxidase B and Parkinson's disease. Basal Ganglia 2:S3–S7.

Khader M, Bresgen N, Eckl PM. 2010. Antimutagenic effects of ethanolic extracts from selected Palestinian medicinal plants. J Ethnopharmacol. 127:319–324.

Küpeli E, Kartal M, Aslan S, Yesilada E. 2006. Comparative evaluation of the anti-inflammatory and antinociceptive activity of Turkish *Eryngium* species. J Ethnopharmacol. 107:32–37.

Limberger RP, Sobral M, Henriques AT, Menut C, Bessière J-M. 2004. Óleos voláteis de espécies de Myrcia nativas do Rio Grande do Sul. Quim Nova. 27:916–919.

Löhle M, Reichmann H. 2011. Controversies in neurology: why monoamine oxidase B inhibitors could be a good choice for the initial treatment of Parkinson's disease? BMC Neurol. 11:112–118.

Mathias ME, Constance L, Araujo D. 1972. Umbelliferae. In: Reitz R, editor. Flora ilustrada catarinense. Itajaí: Herbário Barbosa Rodrigues. p. 100–197.

McIntosh TJ, Simon SA, MacDonald RC. 1980. The organization of *n*-alkanes in lipid bilayers. Biochim Biophys Acta. 597:445–463.

Novaroli L, Reist M, Favre E, Carotti A, Catto M, Carrupt P-A. 2005. Human recombinant monoamine oxidase B as reliable and efficient enzyme source for inhibitor screening. Bioorg Med Chem. 13: 6212–6217.

Palá-Paúl J, Brophy JJ, Pérez-Alonso MJ, Usano J, Soria SC. 2007. Essential oil composition of the different parts of *Eryngium corniculatum* Lam. (Apiaceae) from Spain. J Chromatogr A. 1175:289–293.

Palá-Paúl J, Copeland LM, Brophy JJ, Goldsack RJ. 2006. Essential oil composition of *E. rosulatum* P.W. Michael ined.: a new undescribed species from eastern Australia. Biochem Syst Ecol. 34:796–801.

Palá-Paúl J, Pérez-Alonso MJ, Velasco-Negueruela A, Vadaré J, Villa AM, Sanz J, Brophy JJ. 2005a. Essential oil composition of the different parts of *Eryngium bourgatii* Gouan from Spain. J Chromatogr A. 1074:235–239.

Palá-Paúl J, Pérez-Alonso MJ, Velasco-Negueruela A, Vadaré J, Villa AM, Sanz J, Brophy JJ. 2005b. Analysis of the essential oil composition from the different parts of *Eryngium glaciale* Boiss. from Spain. J Chromatogr A. 1094:179–182.

Passos CS, Soldi TC, Abib RT, Apel MA, Simões-Pires C, Marcourt L, Gottfried C, Henriques AT. 2013. Monoamine oxidase inhibition by monoterpene indole alkaloids and fractions obtained from *Psychotria suterella* and *Psychotria laciniata*. J Enzyme Inhib Med Chem. 28:611–618.

Pope JM, Dubro DW. 1986. The interaction of n-alkanes and n-alcohol with lipid bilayer membranes: a ^{2}H-NMR study. Biochim Biophys Acta. 858:243–253.

Simões-Pires CA, Debenedetti S, Spegazzini E, Mentz LA, Matzenbacher NI, Limberger RP, Henriques AT. 2005. Investigation of the essential oil from eight species of *Baccharis* belonging to sect. *Caulopterae* (Asteraceae, Astereae): a taxonomic approach. Plant Syst Evol. 253: 23–32.

Szögyi M, Cserháti T. 1993. Interaction of monoamine oxidase inhibitory drugs with some phospholipids. J Pharm Biomed Anal. 11:563–568.

Tao G, Irie Y, Li D, Keung WM. 2005. Eugenol and its structural analogs inhibit monoamine oxidase A and exhibit antidepressant-like activity. Bioorg Med Chem. 13:4777–4788.

Thiem B, Kikowska M, Kurowska A, Kalemba D. 2011. Essential oil composition of the different parts and *in vitro* shoot culture of *Eryngium planum* L. Molecules 16:7115–7124.

Williamson EM. 2001. Synergy and other interactions in phytomedicines. Phytomedicine 8:401–409.

Youdim MBH, Bakhle YS. 2006. Monoamine oxidase: isoforms and inhibitors in Parkinson's disease and depressive illness. Br J Pharmacol. 147:S287–S296.

Youdim MBH, Edmondson D, Tipton KF. 2006. The therapeutic potential of monoamine oxidase inhibitors. Nat Rev Neurosci. 7:295–309.