ANTIDEPRESSANT-LIKE EFFECT OF NATURAL COMPOUNDS OF *MELISSA OFFICINALIS* L

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Abstract. Globally the most common mental disorder is depression. Depression therapy is based on medication supported by psychotherapy or neurofeedback. Drugs that treat or ameliorate the symptoms of depression are called antidepressants. This type of medication presents severe side effects and limitations on risk groups – pregnant women, children, and patients with severe associated pathologies. Therefore, in these therapeutic conditions, it is necessary to use natural compounds with identical primary effects but with much-diminished side effects. This paper presents the recent studies regarding the antidepressant-like effect of compounds extracted from lemon balm, studies that claim the therapeutic effects of these compounds, although their molecular mechanism of action is not fully known. In these circumstances, we hope that this article will be an inspiration for further research.

Key words: depression, *Melissa officinalis* L., natural compounds.

INTRODUCTION

The human brain plays a decisive role in complex processes such as personality formation, development of cognitive processes (memory, attention, thinking etc.) as well as behavioral processes. At the same time, it is an organ that, under the pressure of risk factors, can develop pathologies in the sphere of depression, schizophrenia, bipolar syndrome, etc. [25]. The World Health Organization [81] points that, one in four people in the world will suffer at some point, from neuropsychiatric disorders, because even from 2001, mental disorders represent the main cause of global disability affecting around 450 million people.

Depression is the main mental disorder that affects people from all communities on Earth. The drug therapy of depression is mainly characterized by the class of antidepressant drugs with severe side effects – cardiovascular, digestive etc. Besides, the problem of treatment with synthetic substances is raised in the risk groups – pregnant women, children, patients with severe associated

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pathologies – in which synthetic treatment is severely limited. Recent studies demonstrate that a large number of drugs including antidepressants, cross the placental barrier, or have limitations in children [32, 67].

Since synthetic drugs have limitations in terms of administration to risk groups, natural compounds are of particular interest in the treatment of neuropsychiatric disorders, especially depressive disorders [18, 56].

In the literature, there are data on the neuroprotective effect of different types of phytochemicals extracted from plants such as *Melissa officinalis* L., *Valeriana officinalis* L., *Tilia cordata* Mill., *Matricaria recutita* L., *Passiflora spp*., *Scutellaria lateriflora* L., *Withania somnifera* (L.) Dunal, *Echium amoenum* L., *Lavandula spp*., *Panax ginseng* Baill, *Albizia julibrissin* Durazz, *Rhodiola rosea* L., *Crocus sativus* L., *Hypericum perforatum* L., *Bacopa monniera* Hayata&Matsum, *Eschscholzia californica* Cham., *Ginkgo biloba* L., *Centella asiatica* (L.)Urban, *Piper methysticum* L., etc. [7, 56].

Since ancient times, lemon balm is cultivated for its medicinal purposes for leaves or the aerial part, especially to improve memory, for the treatment of mental illnesses such as depression and anxiety, as well as for the treatment of heart conditions [58]. In addition, the neuroprotective activity of the lemon balm was highlighted [13]. Active compounds from lemon balm leaves show favorable effects on cholinergic function in patients with Alzheimer's disease by binding to muscarinic and nicotinic receptors [26], similar effects to those obtained with the use of the synthetic drugs donepezil and memantine [51].

This paper describes the neuroprotective and antidepressant actions of several natural compounds present in the plant species *Melissa officinalis* L.

MATERIALS AND METHODS

In order to realize this paperwork, articles or scientific materials published in electronic format, in the period 2003–2020 were carefully analyzed, using databases such as Web of Science, PubMed, ScienceDirect, Scopus, Doaj or Google Scholar.

The selection of these articles was made primarily due to the growing interest in the use of pharmaceuticals derived from plant sources, to the detriment of synthetic medication that provides significant benefits in the treatment of neuropsychiatric disorders, especially anxiety or depression, diseases whose incidence is rapidly increasing.

Moreover, to analyze the therapeutic potential of natural compounds, bioinformatics tools such as databases are required. The most commonly used databases are DrugBank, FoodDB, ChEMBL and PDB.

The DrugBank database [77] is a freely accessible online database that contains information on drugs and drug targets, being more a drug encyclopedia

than a drug database. This database is used by the public, but especially by pharmacists, physicians, or chemists. Furthermore, the DrugBank database contains over 13,000 drug entries including small molecule drugs, proteins, peptides, vaccines, allergenic, and discovery-phase drugs, but also over 5,000 non-redundant protein sequences that are linked to these drug entries.

FooDB [78] is the world's largest open-access database that contains information on both macronutrients and micronutrients that give foods their taste, texture, aroma, flavor, and color. Users can browse through this database by food source, name, descriptors, or concentrations.

ChEMBL [76] is a cheminformatics database that contains an impressive number of natural compounds that have drug-like properties including Lipinski parameters, molecular weight, logP or pharmacology, and ADMET data. This database also covers a significant fraction of the SAR and the discovery of modern drugs.

The Protein Data Bank (PDB) [80] is an archive-type database that contains the 3D structures of biological macromolecules, including nucleic acids and proteins. All these three-dimensional structures are found in the form of molecular complexes. Initially, this archive contained only 7 structures, being established at Brookhaven National Laboratory under Walter Hamilton's leadership, in 1971. Currently, PDB is updated weekly and is available worldwide at no costs to users. Currently, this database is widely used by researchers because modeling the molecular structures of proteins is of particular importance for elucidating the mechanisms of action of these proteins with different natural or synthetic compounds.

RESULTS AND DISCUSSIONS

EXPERIMENTAL STUDIES INVOLVED CHEMICAL COMPOUNDS OF *MELISSA OFFICINALIS* L.

Since ancient times, plants have been part of people's lives both as a food source and as curative substances in traditional medicine (or as a raw material for obtaining medicines). Plants have always shown their healing effects in both fresh or dry form, as well as tablets, poultices, tinctures, or in extracts of different types [66].

More than that, recent studies have shown that native plants such *as Melissa officinalis* L. – lemon balm [53], *Tilia cordata* Mill. – lime [4], *Matricaria recutita* L. – chamomile [36], *Hypericum perforatum* L. – St. John's wort (SJW) [75] or *Valeriana officinalis* L. – valerian [29] ameliorate depressive symptoms without knowing exactly which of the chemical compounds in these plants are the active compounds in anxiety or depression.

The classes of compounds that have neuroprotective, antidepressant and/or anxiolytic effects are triterpenes; saponins; alkaloids; polyphenols, of which the most important are flavonoids; essential oils and fatty acids [24, 27].

The primary active constituents of *Melissa officinalis* L. are volatile compounds, terpenes and phenolic compounds [42].

The volatile compounds of lemon balm with a remarkable antidepressant effect, are geranial, neral, citronellal, geraniol, and eugenol [44]. Geranial and neral are the isomeric forms of the citral compound. These volatile compounds have also been found in the species *Cymbopogon citratus*. As Dudhgaonkar *et al.* [23] have shown, these volatile compounds have a strong antidepressant effect, in albino mice. Thus, the administration of *Cymbopogon citratus* powder in the dose of 10 mg/kg showed an efficacy comparable to that of the synthetic antidepressant imipramine.

Geraniol treatment in Chronic Unpredictable Mild Stress (CUMS) mice models led to decrease the interleukin-1β (IL-1β) level by inhibiting the action of nuclear factor kappa B (NF-B), thus providing insight into the use of this compound in the treatment of depression [21].

A derivative of eugenol, namely bis-eugenol, administered at a dose of 10 and 50 mg/kg intraperitoneally (i.p.), induces an increase in the level of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the cerebral striatum area, being correlated with the antidepressant activity observed in the forced swimming test (FST) and the tail suspension test (TST) in mouse models [5].

Terpenes are a group of chemical compounds found in many plant species. The most important triterpenes found in the leaves of *Melissa officinalis* L. are ursolic acid and oleanolic acid. Other terpenes found in this plant species are β-caryophyllene, limonene, ocimene, linalool, and thymol [58].

Ramos-Hryb *et al.* [52] observed that the treatment of mice with 0.1 mg/kg of ursolic acid orally administered, activate protein kinase A (PKA), protein kinase C (PKC), calcium/calmodulin-dependent protein kinase II (CAMK-II) and mitogen-activated protein kinase (MEK1/2), results that suggest the potential antidepressant effect of this compound.

Oleanolic acid exhibits antidepressant-like effects in mice with chronic corticosterone-induced depression (chronic CORT-induced depression) by increasing the preference for sucrose and decreasing immobility time-correlated with decreased serine/threonine-protein kinase (SGK-1) and glucocorticoid receptor (GR) expression, but also with activation of the brain-derived neurotrophic factor-protein kinase B (BDNF-AKT/mTOR) signalling pathway in the hippocampus [22].

A recent study shows that treatment with β-caryophyllene reduces the immobility time in the tail suspension test and forced swim test, as well as a reversal of the anxiogenic effect in streptozotocin (STZ) − induced experimental diabetic BALB/c female mice [3].

D-Limonene has a strong antioxidant activity by removing free radicals, but also antidepressant activity by improving the monoaminergic, neurotrophic, and neuroendocrine systems by restoring the 5-HT, NE and DA levels, results comparable to those recorded with fluoxetine administration [74].

Piccinelli *et al.* [49] demonstrated that by administering 10 mg/kg of (R)-(+)-limonene in a neuropathic pain in rats led to the increase in sensitivity to a cold stimulus and reduces the immobility time in FST.

Ocimene from the essential oil composition of *Ocimum basilicum* L. contributes to decreased serum glucocorticoid levels, increases neurogenesis in the dentate gyrus, reduces neuronal and glial apoptosis, regulates gene and protein expression of GR and BDNF in the hippocampus, indicating an antidepressant effect [12].

Unlike the positive control diazepam, linalool in the active dose of 100 mg/kg does not reduce the performance in case of FST [28]. In addition, this compound does not cause DNA damage, thus nor does it show genetic toxicity, even having an antidepressant-like effect by inhibiting N-methyl-D-aspartate (NMDA) receptors [15].

Treatment with thymol in CUMS mice models restored the level of monoamine neurotransmitters and regulated the dysfunction of the hypothalamic–pituitary–adrenal axis (HPA axis). Furthermore, chronic thymol administration inhibited the activation of pro-inflammatory cytokines, possibly by regulating the NLRP3/caspase-1 pathway [20]. In addition, it has been shown that thymol treatment in the dose of 25 and 50 mg/kg in depressed mice decreases immobility time in the forced swimming test and tail suspension test, as well as the reversal of anhedonia [47].

The approximate amount of volatile compounds and terpenes in *Melissa officinalis* L., expressed as a percentage by mass, is illustrated in Table 1.

The most important phenolic compounds existing in the leaves and flowers of the species *Melissa officinalis* L. are represented by caffeic acid, rosmarinic acid, luteolin, naringin, naringenin, hesperidin, and quercetin [58].

Following experiments on depressive mice, Huang *et al.* [33] observed that caffeic acid inhibits a decrease in norepinephrine levels correlated with an increase in tryptophan and 3-methoxy-4-hydroxyphenylglycol levels in a dose-dependent manner.

Rosmarinic acid exhibits an antidepressant-like effect, inducing increased astrocytic BDNF expression in the hippocampus by modulating extracellular signal-regulated kinase (ERK) phosphorylation [34]. Also, behavioral tests in mice with induced depression indicate that rosmarinic acid causes dopamine modulation and corticosterone synthesis [39].

Table 1

The amount of the most important volatile compounds and terpenes of *Melissa officinalis* L.

Class	Compound	Amount (%)	References
Volatile compounds	Citral	16.10	[29]
		33	[43]
		15.20	[68]
	Geraniol	2.20	[2]
		0.74–0.9	[68]
		3.3–18.0	[59]
	Eugenol	0.12–3.78	[1]
Terpenes	Ursolic acid	0.450	[30]
	Oleanolic acid	0.350	[31]
	β-caryophyllene	12.08–29.14	[57]
		0.01–12.20	[48]
		1.17–18.64	[38]
	D-limonene	0.64	[30]
		0.20–1.23	[1]
	Ocimene	0.5	[46]
	Linalool	4.05	[2]
		0.29–1.37	[1]
	Thymol	0.29	[1]
		0.1	[46]

Luteolin inhibits cytokine expression, nuclear factor kappa B (NFkB) signaling, and Toll-like receptor 4 (TLR4) signaling at micromolar concentrations in immune cells, including mast cells [72]. The mechanism of action of luteolin at the binding site for benzodiazepine at the level of gamma-aminobutyric acid type A GABAA receptors is not yet fully elucidated, although it has a partial affinity for it [16].

In depression screening tests (FST and TST), it was observed that doses of 2.5, 5 and 10 mg/kg of naringin administered i.p. significantly reduced anxiogenic behavior decreasing the duration of immobility [14]. It was highlighted the protective effect of naringin against neurocognitive deficits induced by intracerebral hemorrhage, correlated with the attenuation of oxidative-nitrosative and inflammatory stress [60].

Another natural compound found in *Melissa officinalis* L., with a neuroprotective effect is naringenin. This effect is due to the stimulation of monoamines and the suppression of neuroendocrine signaling leading to the regulation of BDNF in the mice hippocampus [73].

Research realized on mice with mild traumatic brain injury shows that treatment with hesperidin decreased IL-1β, tumor necrosis factor-alpha (TNF-α), and malondialdehyde (MDA) levels and increased BDNF levels in the hippocampus, suggesting the potential antidepressant effect of this compound [40].

The antidepressant activity of hesperidin is also due to the interaction with the presynaptic 5-HT1A receptor, similar effect to that of fluoxetine in TST [65].

Quercetin has antioxidant effects and causes monoamine oxidase A (MAO-A) inhibition, followed by 5-HT growth in the brain [61]. Quercetin is also involved in the regulation of cholinergic and serotonergic functions, thus determining, in addition to improving memory, anxiolytic, and antidepressant effects [54].

The phenolic compounds of *Melissa officinalis* are summarized in Table 2, their approximate quantities being expressed in mg/g.

Table 2

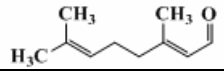
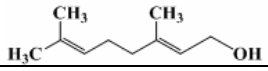
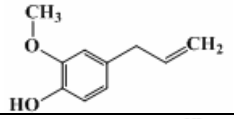
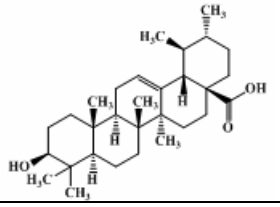
The amount of the most important phenolic compounds of *Melissa officinalis* L.

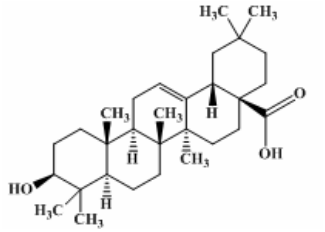
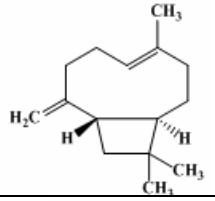
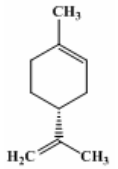
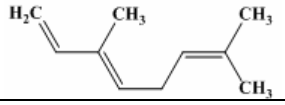
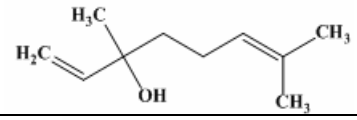
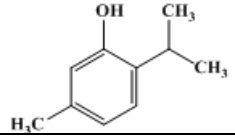
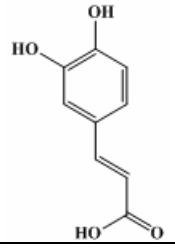
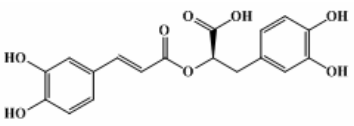
Class	Compound	Amount (mg/g)	References
Phenolic compounds	Caffeic acid	0.0268	[41]
		0.34	[37]
	Rosmarinic acid	45.51	[37]
		6.228	[41]
	Luteolin	0.19	[37]
	Naringin	0.63	[70]
		0.6	[19]
	Naringenin	0.12	[70]
	Hesperidin	9.31	[19]
	Quercetin	1.32	[70]

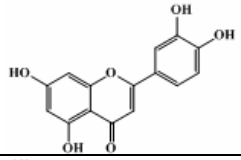
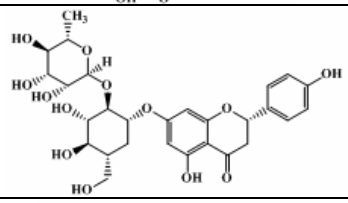
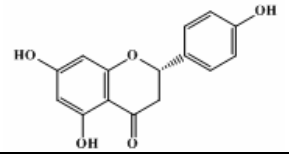
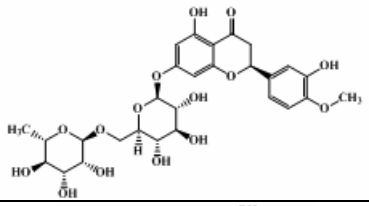
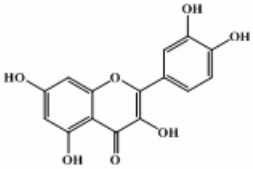
In addition, all chemical structures and canonical SMILES of studied compounds are presented in Table 3.

Table 3

Chemical structures and canonical SMILES of natural compounds of *Melissa officinalis* L.

No	Compounds	Chemical structures	Canonical SMILES
1.	Citral		O=C/C=C(/CC/C=C(/C)C)C
2.	Geraniol		CC(=CCC/C(=C/CO)/C)C
3.	Eugenol		COC1=C(C=CC(=C1)CC=C)O
4.	Ursolic acid		O=C(O)[C@@]54[C@H](/C3=C/C[C@H]1[C@](CC[C@@H]2[C@]1(C)CC[C@H](O)C2(C)C)(C)[C@]3(C)CC4)[C@@H](C)[C@H](C)CC5

No	Compounds	Chemical structures	Canonical SMILES
5.	Oleanolic acid		O=C(O)[C@@]54[C@H](/C3=C/C[C@H]1[C@](CC[C@@H]2[C@]1(C)CC[C@H](O)C2(C)C)(C)[C@]3(C)CC4)CC(C)(C)CC5
6.	β-caryophyllene		CC1=CCCC(=C)C2CC(C2CC1)(C)C
7.	D-limonene		C=C(C)[C@H]1CC=C(C)CC1
8.	Ocimene		C=C/C(C)=C/CC=C(C)C
9.	Linalool		C=CC(C)(O)CCC=C(C)C
10.	Thymol		CC1=CC(=C(C=C1)C(C)C)O
11.	Caffeic acid		C1=CC(=C(C=C1C=CC(=O)O)O)O
12.	Rosmarinic acid		C1=CC(=C(C=C1CC(C(=O)O)OC(=O)C=CC2=CC(=C(C=C2)O)O)O)O

No	Compounds	Chemical structures	Canonical SMILES
13.	Luteolin		C1=CC(=C(C=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O)O
14.	Naringin		CC1C(C(C(C(O1)OC2C(C(C(OC2OC3=CC(=C4C(=O)CC(OC4=C3)C5=CC=C(C=C5)O)O)CO)O)O)O)O)O
15.	Naringenin		C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O
16.	Hesperidin		CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=CC(=C4C(=O)CC(OC4=C3)C5=CC(=C(C=C5)OC)O)O)O)O)O)O)O)O
17.	Quercetin		C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O

IN SILICO STUDIES OF CHEMICAL COMPOUNDS OF *MELISSA OFFICINALIS* L.

Until recently, scientific research was divided into two main types: *in vivo* (within life) and *in vitro* (within the glass). *In vivo* testing must be done taking into account several considerations, namely: the inability to control properly the experimental conditions, resources, and time associated with the experimentation performed on living subjects and, last but not least, the ethical considerations of the experimentation. Although *in vitro* experiments can be performed with fewer resources and faster than *in vivo* experiments, the in vitro model cannot represent the tested entity as part of a whole. Thus, it was necessary to replace these studies with *in silico* (in silicon) studies that combine in vitro and *in vivo* techniques. Complex *in silico* models offers the possibility of elucidating some physiological and especially pathophysiological mechanisms, which cannot be obtained by classical techniques due to ethical or practical considerations [17].

The computational methods used for correlating the chemical structures of the compounds with their properties are quantitative structure-activity relationships (QSAR) and quantitative structure-properties relationships (QSPR). Identifying these relationships helps to discover new compounds with therapeutic potential.

The SAR/QSAR computational methods are based on the idea that the biological activity of any chemical compound is dependent on the position of the atoms that form the molecular structure of that compound. In other words, there is a close dependence between the chemical structure and the functions of that compound. Also, the activities of an entire group of chemicals can be predicted, or even the activities of new chemical compounds, when only the features of a few chemicals in that group are known [71].

Based on the information provided by these mathematical relationships that link the chemical structure and pharmacological activity of a compound in a quantitative manner, we can even predict the interaction of the compound of interest with the body's macromolecular targets [7, 35]. However, the discovery of new binding sites on target proteins is accomplished by molecular modelling and molecular docking [50].

Using the computational method QSAR, Udrea *et al.* [67] analyzed the biological activity of melatonin, resveratrol, linalyl acetate and linalool in the form of inhibition constant (*Ki*) on the SERT receptor, concluding that the biological activity of these compounds (*pKi*) is similar to that of classical antidepressants.

A few researchers studied the effect of luteolin and quercetin on the MAO-A enzyme, using computational biology tools such as docking and they observed that the two natural compounds have high binding efficiency to the amino acid residues present in the target enzyme, thus serve as effective alternatives to the synthetic drugs currently used to treat major depression [63]. In their study, the authors used the structure of the target protein with the code 2Z5X existing in the Protein Data Bank database (Fig. 1) [64].

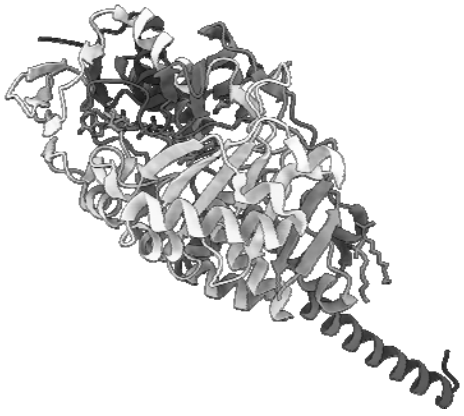


Fig. 1. Crystal structure of human monoamine oxidase A with harmine [64].

More than that, through molecular docking Singla *et al.* [62] used five proteins covering MAO-A, MAO-B, LeuT & Human C-terminal CAP1 receptors along with cocrystallized reference ligands like clomipramine, sertraline, chlorgyline, and deprenyl, and demonstrated the therapeutic potential of ursolic acid as an antidepressant.

Recent molecular docking studies have shown that rosmarinic acid, the most abundant compound of lemon balm acts as a reversible target inhibitor for MAO-A, thus being an antidepressant-like compound [6].

In addition, this compound being so important for the treatment or amelioration of neuropsychiatric or neurodegenerative diseases, it is found in bioinformatics databases in the form of molecular complexes. Thus, by accessing the RCSB PDB database [80] and entering the keywords “rosmarinic acid” we identified four PDB complexes of rosmarinic acid, respectively: “Crystal structure of PrTX-I complexed to Rosmarinic Acid” with the code 3QNL; „Crystal structure of V30M mutant human transthyretin complexed with rosmarinic acid” with PDB code 4PWI; "Myotoxin II from *Bothrops moojeni* complexed with Rosmarinic Acid" with PDB code 6MQD and "Crystal structure of *Coleus blumei* rosmarinic acid synthase (RAS) in complex with 4-coumaroyl-(R)-3-(4-hydroxyphenyl) lactate” with PDB code 6MK2.

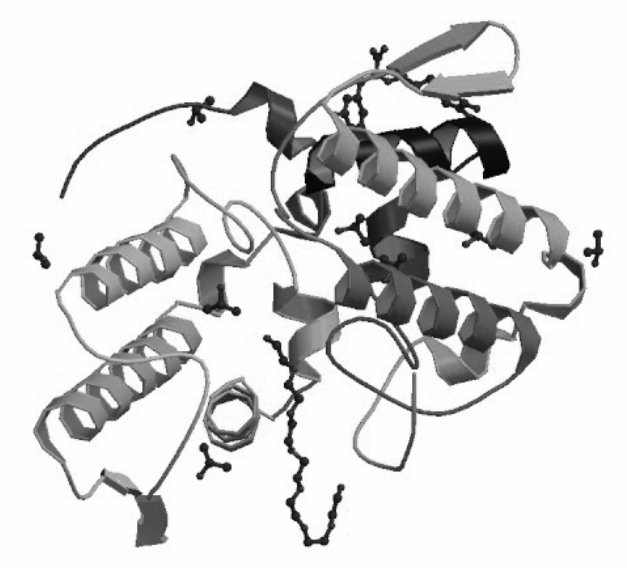


Fig. 2. Crystal structure of PrTX-I complexed to rosmarinic acid [55].

The complex "Crystal structure of PrTX-I complexed to Rosmarinic Acid" with 3QNL PDB code (Fig. 2) was developed by Santos *et al.* [55] who studied the

neutralizing effect of muscle damage and neuromuscular blocking activities of PrTX-I protein found in the venom of the ophidian species *Bothrops pirajai*.

Using MS Word we opened the 3QNL PDB file and we observed that the protein consists of two polypeptide chains A and B with a length of 121 amino acids. The two polypeptide chains show the same composition of amino acid sequences, being homodimers, the first amino acid being serine (SER), and the last amino acid cysteine (CYS).

In the secondary structure of the polypeptide chain A there are four α helices and two 3–10 helices. The first α-helix starts at position 1 with the amino acid serine (SER) and ends at position 15 with the amino acid glycine (GLY). The first helix 3–10 starts at position 110 with the amino acid leucine (LEU) and ends at position 113 with the amino acid tyrosine (TYR).

In the secondary structure of the polypeptide chain B are found four α helices and three 3–10 helices. The first α-helix starts at position 2 with the amino acid leucine (LEU) and ends at position 15 with the amino acid glycine (GLY). The first helix 3–10 starts at position 110 with the amino acid leucine (LEU) and ends at position 113 with the amino acid tyrosine (TYR).

In addition, the polypeptide chain A has one β-helix. The first amino acid of β-helix is in position 75 and is represented by tyrosine (TYR), and the last amino acid is in position 84 and is represented by cysteine (CYS). The second chain of the β-helix on the A chain is antiparallel (–1) to the first which has a zero position (0). The B polypeptide chain has two β-helices. The first begins with the amino acid alanine (ALA) at position 24 and ends with the amino acid glycine (GLY) at position 30, and the second β-helix begins with the amino acid tyrosine (TYR) at position 75 and ends with the amino acid cysteine (CYS) at position 84. The secondary chains of the β-helix on the B chain have antiparallel positions to the first chains.

The PDB complex with the code 3QNL contains as ligands isopropyl alcohol (IPA) and rosmarinic acid (ROA) on the polypeptide chain A and isopropyl alcohol (IPA) and heptaethylene glycol (P33) on the polypeptide chain B. The solvent is water (HOH).

The description of these molecular complexes is essential for computational biology studies that allow the understanding of the proteins interaction with specific targets [8, 9, 10, 11, 43, 68].

For rosmarinic acid we predicted ADME-Tox characteristics (Table 4) by the bioinformatics tool pkCSM [79] which allowed us to observe that this hydroxycinnamic acid shows good blood-brain barrier (BBB) permeability correlated with low toxicity. However, such studies are a current need as the molecular mechanism of action of many natural compounds is not known.

Table 4

The predicted ADME-tox profile of rosmarinic acid

Property	Model name	Predicted value	Unit
Absorption	Water solubility	**– 2.837**	Numeric (log mol/L)
Absorption	Caco2 permeability	**– 1.015**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**44.114**	Numeric (% Absorbed)
Absorption	Skin permeability	**– 2.735**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	**No**	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	**No**	Categorical (Yes/No)
Distribution	VDss (human)	**– 1.019**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.245**	Numeric (Fu)
Distribution	BBB permeability	**– 1.53**	Numeric (log BB)
Distribution	CNS permeability	**– 3.579**	Numeric (log PS)
Metabolism	CYP2D6 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	**No**	Categorical (Yes/No)
Excretion	Total Clearance	**0.308**	Numeric (log mL/min/kg)
Excretion	Renal OCT2 substrate	**No**	Categorical (Yes/No)
Toxicity	AMES toxicity	**No**	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	**0.789**	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	**No**	Categorical (Yes/No)
Toxicity	hERG II inhibitor	**No**	Categorical (Yes/No)
Toxicity	Oral rat acute toxicity (LD50)	**2.675**	Numeric (mol/kg)
Toxicity	Oral rat chronic toxicity (LOAEL)	**3.162**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**No**	Categorical (Yes/No)
Toxicity	Skin sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T. Pyriformis* toxicity	**0.285**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**1.375**	Numeric (log mM)

CONCLUSIONS

The plant species *Melissa officinalis* L. has been used as a medicinal plant since ancient times because it has many biological activities, the most significant of which proved to be those in the neurological spectrum, namely anxiolytic, neuroprotective, and even antidepressant activities.

Through this paper we have tried to highlight that lemon balm preparations can be used successfully as substitutes for synthetic antidepressants which, although effective, have significant side effects and can only be used by a small group of patients. Nevertheless, further studies are necessary because, the mechanism of action of several chemical compounds existing in this plant species is still unknown.

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REFERENCES

1. ABDELLATIF, F., A. HASSANI A, Chemical composition of the essential oils from leaves of *Melissa officinalis* extracted by hydrodistillation, steam distillation, organic solvent and microwave hydrodistillation, *J. Mater. Environ. Sci*., 2015, **6**, 207–213.
2. ADINEE, J., K. PIRI, O. KARAMI, Essential oil component in flower of lemon balm (*Melissa officinalis* L.), *Am. J. Biochem. Biotechnol*., 2008, **4**, 277–278.
3. AGUILAR-ÁVILA, D.S., M.E. FLORES-SOTO, C. TAPIA-VÁZQUEZ, O.A. PASTOR-ZARANDONA, R.I. LÓPEZ-ROA, J.M. VIVEROS-PAREDES, β-caryophyllene, a natural sesquiterpene, attenuates neuropathic pain and depressive-like behavior in experimental diabetic mice, *J. Med. Food*., 2019, **22**, 460–468.
4. ALEX, A., A. SRIVASTAVA, Nutraceuticals for calming and stress. In: *Nutraceuticals in Veterinary Medicine*, R.C. Gupta, A. Srivastava, R. Lall, eds, Springer, 2019, pp. 417–425.
5. AMARAL, J.F., M.I.G. SILVA, M.R.A. DE AQUINO NETO, B.A. MOURA, A.M.R DE CARVALHO, P.F. VASCONCELOS, J.M.B. FILHO, S.J.C. GUTIERREZ, S.M.M. VASCONCELOS, D.S. MACEDO, F.C.F. DE SOUSA, Antidepressant-like effect of bis-eugenol in the mice forced swimming test: evidence for the involvement of the monoaminergic system, *Fundam. Clin. Pharmacol*., 2012, **27**, 471-482.
6. ANDRADE, J.M.D.M., C. DOS SANTOS PASSOS, M.A. KIELING RUBIO, J.N. MENDONÇA, N.P. LOPES, A.T. HENRIQUES, Combining *in vitro* and *in silico* approaches to evaluate the multifunctional profile of rosmarinic acid from *Blechnum brasiliense* on targets related to neurodegeneration, *Chem. Biol. Interact*., 2016, **254**, 135–145.
7. AVRAM, S., A. PUIA, A.M. UDREA, D. MIHĂILESCU, M. MERNEA, F. OANCEA, A. DINISCHOTU, J. STIENS, Natural compounds therapeutic features in brain disorders by experimental, bioinformatics and cheminformatics methods, *Curr. Med. Chem*., 2018, **27**, 78–98.
8. AVRAM, S., A.L. MILAC, D. MIHAILESCU, 3D-QSAR study indicates an enhancing effect of membrane ions on psychiatric drugs targeting serotonin receptor 5-HT1A, *Mol. BioSyst*., 2012, **8**, 1418–1425.
9. AVRAM, S., C. BOLOGA, M. BANDA, M.L. FLONTA, A quantitative structure-activity relationship study used to predict the biological activity of the HIV-1 protease cyclic urea inhibitors, *Romanian. J. Biophys*., 2001, **11**, 11–24.
10. AVRAM, S., C. BUIU, D. DUDA-SEIMAN, C. DUDA-SEIMAN, F. BORCAN, D. MIHAILESCU, Evaluation of the pharmacological descriptors related to the induction of antidepressant activity and its prediction by QSAR/QRAR methods, *Mini. Rev. Med. Chem.*, 2012, **12**(6), 467–476.
11. AVRAM, S., L. MOVILEANU D. MIHAILESCU, M.L. FLONTA, Comparative study of some energetic and steric parameters of the wild type and mutants HIV-1 protease: a way to explain the viral resistance, *J. Cell. Mol. Med*., 2002, **6**, 251–260.

12. AYUOB, N.N., A.E.D.L. FIRGANY, A.A. EL-MANSY, S. ALI, Can *Ocimum basilicum* relieve chronic unpredictable mild stress-induced depression in mice?, *Exp. Mol. Pathol*., 2017, **103**, 153–161.
13. BAYAT, M., A. AZAMI TAMEH, M. GHAHREMANI, M. AKBARI, S. EJTEMAEI MEHR, M. KHANAVI, G. HASSANZADEH, Neuro-protective properties of *Melissa officinalis* after hypoxic-ischemic injury both *in vitro* and *in vivo*, *Daru J. Pharm. Sci*., 2012, **20**, 20–42.
14. BEN-AZU, B., E.E. NWOKE, S. UMUKORO, A.O. ADERIBIGBE, A.M. AJAYI, E.O. IWALEWA, Evaluation of the neurobehavioral properties of naringin in Swiss mice, *Drug Res.* (Stuttg), 2018, **68**, 465–474.
15. COELHO, V., L. MAZZARDO-MARTINS, D.F. MARTINS, A.R.S. SANTOS, L.F. DA SILVA BRUM, J.N. PICADA, P. PEREIRA, Neurobehavioral and genotoxic evaluation of (−)-linalool in mice, *J. Nat. Med*., 2013, **67**, 876–880.
16. COLETA, M., M.G. CAMPOS, M.D. COTRIM, T.C.M DE LIMA, A.P. DA CUNHA, Assessment of luteolin (3',4',5,7-tetrahydroxyflavone) neuropharmacological activity, *Behav. Brain. Res*., 2008, **189**, 75–82.
17. COLQUITT, R.B., D.A. COLQUHOUN, R.H. THIELE, *In silico* modelling of physiologic systems, *Best Pract. Res. Clin. Anaesthesiol.*, 2011, **25**, 499–510.
18. COSTEA, T., C.D. BĂDICEANU, D.C. NUȚĂ, C.E. GÎRD, C. LIMBAN, O. KARAMPELAS, S. AVRAM, Antioxidant activity and drug profile of several thiourea derivatives of 2-thiophene carboxylic acid, *Farmacia*, 2020, **68**, 1047–1054.
19. DASTMALCHI, K., H.J.D. DORMAN, P.P. OINONEN, Y. DARWIS, I. LAAKSO, R. HILTUNEN, Chemical composition and *in vitro* antioxidative activity of a lemon balm (*Melissa officinalis* L.) extract, *LWT*, 2008, **41**, 391–400.
20. DENG, X.Y., H.Y. LI, J.J. CHEN, R.P. LI, R. QU, Q. FU, S.P. MA, Thymol produces an antidepressant-like effect in a chronic unpredictable mild stress model of depression in mice, *Behav. Brain Res*., 2015, **291**, 12–19.
21. DENG, X.Y., J.S. XUE, H.Y. LI, Z.Q. MA, Q. FU, R. QU, S.P. MA, Geraniol produces antidepressant-like effects in a chronic unpredictable mild stress mice model, *Physiol. Behav*., 2015, **152**, 264–271.
22. DONG, S.Q., S.S. WANG, J.X. ZHU, R.H. MU, C.F. LI, D. GENG, Q. LIU, L.T. YI, Oleanolic acid decreases SGK1 in the hippocampus in corticosterone-induced mice, *Steroids*, 2019, **149**, 108419–108419.
23. DUDHGAONKAR, S., M. MAHAJAN, S. DESHMUKH, P. ADMANE, H. KHAN, Evaluation of antidepressant effect of lemon grass (*Cymbopogon citratus*) in albino mice, *Int. J. Basic. Clin. Pharmacol*., 2014, **3**, 656–660.
24. FAJEMIROYE, J.O., D.M. DASILVA, D.R. DEOLIVEIRA, I.A. COSTA, Treatment of anxiety and depression: medicinal plants in retrospect, *Fundam. Clin. Pharmacol*., 2016, **30**, 198-215.
25. FLEMING, T.M., L. BAVIN, K. STASIAK, E. HERMANSSON-WEBB, S.N. MERRY, C. CHEEK, M. LUCASSEN, H.M. LAU, B. POLLMULLER, S. HETRICK, Serious games and gamification for mental health: current status and promising directions, *Front. Psychiatry*., 2017, **7**, 196–215.
26. GOMES, N.G.M., M.G. CAMPOS, J.M.C. ÓRFÃO, C.A.F. RIBEIRO, Plants with neurobiological activity as potential targets for drug discovery, *Prog. Neuropsychopharmacol. Biol. Psychiatry*., 2009, **33**, 1372–1389.
27. GUMA (TANASIEV), N., A.T. BORDEI (TELEHOIU), C. LIMBAN, C. SOGOR, L. MANOLIU, S. AVRAM, Bioinformatics and cheminformatics study of carbazole derivatives – p3c7, p3c7-a20 p3c7-s243, and de novo 2,5-disubstituted 1,3,4-oxadiazole derivatives, *Farmacia*, 2020, **68**, 665–671.
28. GUZMÁN-GUTIÉRREZ, S.L., R. GÓMEZ-CANSINO, J.C. GARCÍA-ZEBADÚA, N.C. JIMÉNEZ-PÉREZ, R. REYES-CHILPA, Antidepressant activity of *Litsea glaucescens* essential oil: Identification of β-pinene and linalool as active principles, *J. Ethnopharmacol*., 2012, **143**, 673–679.

29. HAMID, H.A., A.N.M. RAMLI, M.M. YUSOFF, Indole alkaloids from plants as potential leads for antidepressant drugs: A mini review, *Front. Pharmacol*., 2017, **8**, 81–96.
30. HĂNCIANU, M., A.C. APROTOSOAIE, E. GILLE, A. POIATĂ, C. TUCHILUŞ, A. SPAC, U. STĂNESCU, Chemical composition and *in vitro* antimicrobial activity of essential oil of *Melissa officinalis* L. from Romania, *Rev. Med. Chir. Soc. Med. Nat. Iasi*, 2008, **112**, 843–847.
31. HERODEŽ, Š.S., M. HADOLIN, M. ŠKERGET, Ž KNEZ, Solvent extraction study of antioxidants from Balm (*Melissa officinalis* L.) leaves, *Food Chem.*, 2003, **80**, 275–282.
32. HEWITT, M., J.C. MADDEN, P.H. ROWE, M.T.D. CRONIN, Structure-based modelling in reproductive toxicology: (Q)SARs for the placental barrier, *SAR QSAR Environ. Res*., 2007, **18**, 57–76.
33. HUANG, D., L. ZHANG, J. YANG, Y. LUO, T. CUI, T. DU, X. JIANG, Evaluation on monoamine neurotransmitters changes in depression rats given with sertraline, meloxicam or/and caffeic acid, *Genes. Dis*., 2018, **6**, 167-175.
34. JIN, X., P. LIU, F. YANG, Y.H. ZHANG, D. MIAO, Rosmarinic acid ameliorates depressive-like behaviors in a rat model of CUS and Up-regulates BDNF levels in the hippocampus and hippocampal-derived astrocytes, *Neurochem. Res*., 2013, **38**, 1828–1837.
35. KAR, S., K. ROY, QSAR of phytochemicals for the design of better drugs, *Expert Opin. Drug Dis.,* 2012, **7**, 877–902.
36. KEEFE, J.R., J.J. MAO, I. SOELLER, Q.S. LI, J.D. AMSTERDAM, Short-term open-label chamomile (*Matricaria chamomilla* L.) therapy of moderate to severe generalized anxiety disorder, *Phytomedicine*, 2016, **23**, 1699–1705.
37. KHALLOUKI, F., A. BREUER, M. AKDAD, F.E. LAASSRI, M. ATTALEB, B. ELMOUALIJ, M. MZIBRI, L. BENBACER, R.W. OWEN, Cytotoxic activity of Moroccan *Melissa officinalis* leaf extracts and HPLC-ESI-MS analysis of its phytoconstituents, *Futur. J. Pharm. Sci*., 2020, **6**, 1–12.
38. KITTLER, J., H. KRÜGER, D. ULRICH, B. ZEIGER, W. SCHÜTZE, C.H. BÖTTCHER, A. KRÄHMER, G. GUDI, U. KÄSTNER, H. HEUBERGER, F. MARTHE, Content and composition of essential oil and content of rosmarinic acid in lemon balm and balm genotypes (*Melissa officinalis*), *Genet. Resour. Crop. Evol*., 2018, **65**, 1517–1527.
39. KONDO, S., A. EL OMRI, J. HAN, H. ISODA, Antidepressant-like effects of rosmarinic acid through mitogen-activated protein kinase phosphatase-1 and brain-derived neurotrophic factor modulation, *J. Funct. Food*, 2015, **14**, 758–766.
40. KOSARI-NASAB, M., G. SHOKOUHI, A. GHORBANIHAGHJO, M.M. ABBASI, A.A. SALARI, Hesperidin attenuates depression-related symptoms in mice with mild traumatic brain injury, *Life Sci*., 2018, **213**, 198-205.
41. LEE, J., Caffeic acid derivatives in dried *Lamiaceae* and *Echinacea purpurea* products, *J. Funct. Foods*, 2010, **2**, 158–162.
42. MENCHERINI, T., P. PICERNO, C. SCESA, R. AQUINO, Triterpene, antioxidant, and antimicrobial compounds from *Melissa officinalis*, *J. Nat. Prod*., 2007, **70**, 1889–1894.
43. MILAC, A.L., S. AVRAM, A.J. PETRESCU, Evaluation of a neural networks QSAR method based on ligand representation using substituent descriptors. Application to HIV-1 protease inhibitors, *J. Mol. Graph. Model*., 2006, **25**, 37–45.
44. MIMICA-DUKIC, N., B. BOZIN, M. SOKOVIC, N. SIMIN, Antimicrobial and antioxidant activities of *Melissa officinalis* L. (*Lamiaceae*) essential oil, *J. Agric. Food. Chem*., 2004, **52**, 2485–2489.
45. MORADKHANI, H., E. SARGSYAN, H. BIBAK, B. NASERI, M. SADAT-HOSSEINI, A. FAYAZI-BARJIN, H. MEFTAHIZADE, *Melissa officinalis* L., a valuable medicine plant, *J. Med. Plants Res*., 2010, **4**, 2753–2759.
46. NURZYŃSKA-WIERDAKA, R., A. ANNA BOGUCKA-KOCKAB, G. SZYMCZAKC, Volatile constituents of *Melissa officinalis* leaves determined by plant age, *Nat. Prod. Commun*., 2015, **9**, 703–706.

47. PARENTE, M.S.R., F.R. CUSTÓDIO, N.A. CARDOSO, M.J.A. LIMA, T. SOUSA DE MELO, M.I. LINHARES, R.M. PINHEIRO SIQUEIRA, A. ÁVILO DO NASCIMENTO, CATUNDA FEAJR., C.T. VASCONCELOS DE MELO, Antidepressant-like effect of *Lippia sidoides* Cham (*Verbenaceae*) essential oil and its major compound thymol in mice, *Sci. Pharm*., 2018, **86**, 1–19.
48. PATORA, J., T. MAJDA, J. GÓRA, B. KLIMEK, Variability in the content and composition of essential oil from lemon balm (*Melissa officinalis* L.) cultivated in Poland, *Acta Pol. Pharm*., 2003, **5**, 395–400.
49. PICCINELLI, A.C., J.A. SANTOS, E.C. KONKIEWITZ, S.A. OESTERREICH, A.S.N. FORMAGIO, J. CRODA, E.B. ZIFF, C.A.L. KASSUYA, Antihyperalgesic and antidepressive actions of (R)-(+)-limonene, α-phellandrene, and essential oil from *Schinus terebinthifolius* fruits in a neuropathic pain model, *Nutr. Neurosci*., 2014, **18**, 217–224.
50. PRACHAYASITTIKUL, V., A. WORACHARTCHEEWAN, W. SHOOMBUATONG, N. SONGTAWEE, S. SIMEON, V. PRACHAYASITTIKUL, C. NANTASENAMAT, Computer-aided drug design of bioactive natural products, *Curr. Top. Med. Chem*., 2015, **15**, 1780–1800.
51. PURZA, L., M. ABDEL-DAIM, A. BELBA, C. IOVAN, A. BUMBU, L. LAZĂR, S. BUNGĂU, D.M. ȚIȚ, Monitoring the effects of various combination of specific drug therapies at different stages of Alzheimer′s dementia, *Farmacia*, 2019, **67**, 477–481.
52. RAMOS-HRYB, A.B., M.P. CUNHA, F.L. PAZINI, V. LIEBERKNECHT, R.D.S. PREDIGER, M.P. KASTER, A.L.S. RODRIGUES, Ursolic acid affords antidepressant-like effects in mice through the activation of PKA, PKC, CAMK-II and MEK1/2, *Pharmacol. Rep*., 2017, **69**, 1240–1246.
53. RANJBAR, M., A. FIROOZABADI, A. SALEHI, Z. GHORBANIFAR, M.M. ZARSHENAS, K. SADEGHNIIAT-HAGHIGHI, H. REZAEIZADEH, Effects of herbal combination (*Melissa officinalis* L. and *Nepeta menthoides* Boiss. & Buhse) on insomnia severity, anxiety and depression in insomniacs: Randomized placebo controlled trial, *Integr. Med. Res.,* 2018, **7**, 328–332.
54. SAMAD, N., A. SALEEM, F. YASMIN, M.A. SHEHZAD, Quercetin protects against stress-induced anxiety- and depression-like behavior and improves memory in male mice, *Physiol. Res*., 2018, **67**, 795–808.
55. SANTOS, J.I., F.F. CARDOSO, A.M. SOARES, M. DAL PAI SILVA, M. GALLACCI, M.R.M. FONTES, Structural and functional studies of a bothropic myotoxin complexed to rosmarinic acid: new insights into Lys49-PLA2 inhibition, *PLoS ONE*, 2011, **6**, 28521-28521.
56. SARRIS, J., A. PANOSSIAN, I. SCHWEITZER, C. STOUGH, A. SCHOLEY, Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. *Eur. Neuropsychopharmacol*., 2011, **21**, 841–860.
57. SEIDLER-ŁOŻYKOWSKA, K., R. ZAWIRSKA-WOJTASIAK, E. WOJTOWICZ, J. BOCIANOWSKI, Essential oil content and its composition in herb of lemon balm (*Melissa officinalis* L.) breeding strains, *J. Essent. Oil Res*., 2017, **29**, 351–356.
58. SHAKERI, A., A. SAHEBKAR, B. JAVADI, *Melissa officinalis* L. – A review of its traditional uses, phytochemistry and pharmacology, *J. Ethnopharmacol*., 2016, **188**, 204–228.
59. SILVA, S., A. SATO, C.L.S LAGE, R. SAN GIL, D. AZEVEDO, M.A. ESQUIBEL, Essential oil composition of *Melissa officinalis* L. *in vitro* produced under the influence of growth regulators, *J. Braz. Chem. Soc*., 2005, **16**, 1387–1390.
60. SINGH, N., Y. BANSAL, R. BHANDARI, L. MARWAHA, R. SINGH, K. CHOPRA, A. KUHAD, Naringin reverses neurobehavioral and biochemical alterations in intracerebroventricular collagenase-induced intracerebral hemorrhage in rats, *Pharmacology*, 2017, **100**, 172–187.
61. SINGH, V., G. CHAUHAN, R. SHRI, Anti-depressant like effects of quercetin 4'-O-glucoside from *Allium cepa* via regulation of brain oxidative stress and monoamine levels in mice subjected to unpredictable chronic mild stress, *Nutr. Neurosci*., 2019, 1–10.
62. SINGLA, R.K., L. SCOTTI, A.K. DUBE, *In silico* studies revealed multiple neurological targets for the antidepressant molecule ursolic acid, *Curr. Neuropharmacol*., 2017, **15**, 1100-1106.

63. SIVARAMAN, D., G. VIGNESH, R. SELVARAJ, B.J. DARE, Identification of potential monoamine oxidase inhibitor from herbal source for the treatment of major depressive disorder: An in-silico screening approach, *Der. Pharma. Chem*., 2015, **7**, 224–234.
64. SON, S.Y., J. MA, Y. KONDOU, M. YOSHIMURA, E. YAMASHITA, T. TSUKIHARA, Structure of human monoamine oxidase A at 2.2-A resolution: The control of opening the entry for substrates/inhibitors, *Proc. Natl. Acad. Sci. USA*, 2008, **105**, 5739–5744.
65. SOUZA, L.C., M.G. DE GOMES, A.T.R. GOES, L. DEL FABBRO, C.B. FILHO, S.P. BOEIRA, C.R. JESSE, Evidence for the involvement of the serotonergic 5-HT1A receptors in the antidepressant-like effect caused by hesperidin in mice, *Prog. Neuropsychopharmacol. Biol. Psychiatry*., 2013, **40**, 103–109.
66. ȘUȚAN, N.A., I. FIERĂSCU, R.C. FIERĂSCU, D.Ș. MANOLESCU, L.C. SOARE, Comparative analytical characterization and *in vitro* cytogenotoxic activity evaluation of *Asplenium scolopendrium* L. leaves and rhizome extracts prior to and after Ag nanoparticles phytosynthesis, *Ind. Crop. Prod*., 2016, **83**, 379–386.
67. UDREA, A.M., A. PUIA, S. SHAPOSHNIKOV, S. AVRAM, Computational approaches of new perspectives in the treatment of depression during pregnancy, *Farmacia*, 2018, **66**, 680−687.
68. UDREA, A.M., S. AVRAM, S. NISTORESCU, M.L. PASCU, M.O. ROMANITAN, Laser irradiated phenothiazines: New potential treatment for COVID-19 explored by molecular docking, J. Photochem. Photobiol. B., 2020, 211, 111997−111997.
69. UYANIK, M., B. GURBUZ, Chemical diversity in essential oil composition of leaf, herb and flower in lemon balm (*Melissa officinalis* L.), *Turkjans*, 2014, **2**, 210–214.
70. VASILEVA, I., R. DENKOVA, R. CHOCHKOV, D. TENEVA, Z. DENKOVA, T. DESSEV, P. DENEV, A. SLAVOV, Effect of lavender (*Lavandula angustifolia*) and melissa (*Melissa officinalis*) waste on quality and shelf life of bread, *Food Chem*., 2018, **253**, 13–21.
71. WANG, D.D., L.L. FENG, G.Y. HE, H.Q. CHEN, QSAR studies for the acute toxicity of nitrobenzenes to the *Tetrahymena pyriformis*, *J. Serb. Chem. Soc*., 2014, **79**, 1111–1125.
72. WENG, Z., A.B. PATEL, S. PANAGIOTIDOU, T.C. THEOHARIDES, The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells, *J. Allergy. Clin. Immunol*., 2015, **135**, 1044-1052.
73. YI, L.T., B.B. LIU, J. LI, L. LUO, Q. LIU, D. GENG, Y. TANG, Y. XIA, D. WU, BDNF signaling is necessary for the antidepressant-like effect of naringenin, *Prog. Neuropsychopharmacol. Biol. Psychiatry*., 2014, **48**, 135–141.
74. ZHANG, L.L., Z.Y. YANG, G. FAN, J.N. REN, K.J. YIN, S.Y. PAN, Antidepressant-like effect of *Citrus sinensis* (L.) Osbeck essential oil and its main component limonene on mice, *J. Agric. Food. Chem*., 2019, **67**, 13817-13828.
75. ZIRAK, N., M. SHAFIEE, G. SOLTANI, M. MIRZAEI, A. SAHEBKAR, *Hypericum perforatum* in the treatment of psychiatric and neurodegenerative disorders: Current evidence and potential mechanisms of action, *J. Cell. Physiol*., 2019, **234**, 8496−8508.
76. ***ChEMBL interface documentation, About ChEMBL, https://chembl.gitbook.io/chembl-interface-documentation/about.
77. ***DrugBank, About DrugBank, https://www.drugbank.ca/about.
78. ***FooDB, About FooDB, https://foodb.ca/about.
79. ***pkCSM, http://biosig.unimelb.edu.au/pkcsm/.
80. ***RCSB Protein Data Bank, About the PDB archive and the RCSB PDB, https://www.rcsb.org/pdb/static.do?p=general_information/about_pdb/index.html.
81. ***World Health Organization, World health report: Mental disorders affect one in four people, https://www.who.int/whr/2001/media_centre/press_release/en/.