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Research Article

Inhibition of monoamine oxidase A (Mao-A) enzyme by some medicinal herbs

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Abstract: Monoamine oxidase (MAO) is a flavin-containing enzyme responsible for the metabolism and regulation of neurotransmitter amines and plays a role in neuropsychiatric disorders such as depression and mania. In this study, the inhibitory effects of different concentrations of solutions prepared using distilled water, ethanol, ethyl acetate, petroleum ether, and mixed extracts of *Hypericum perforatum*, *Ginkgo biloba* , *Lavandula angustifolia*, *Zingiber officinale, Tilia tomentosa*., *Cinnamomum aromaticum*, *Menthae piperita*, *Thymus cherlerioides*, *Portulaca oleracea*, *Trachystemon orientalis*, *Allium sativum*, *Petroselinum crispum*, and *Spinacia oleracea* were investigated on monoamine oxidase obtained from rat liver. It was determined that the best inhibitor plant extract for MAO, which has a value of IC_{50}, was 0.071 mg/mL and with a ratio of inhibition of 70.15% ethanol extract of *Hypericum perforatum*. Following *H. perforatum,* the best inhibition effects were observed with the ethanol extract of *Spinacia oleracea* (IC_{50} = 0.074 mg/mL), *Ginkgo biloba* (IC_{50} = 0.075 mg/mL), *Allium sativum* (IC_{50} = 0.080 mg/mL), and the distilled water extract of *H. perforatum* (IC_{50} value of 0.081 mg/mL), respectively. The findings demonstrate that these species can inhibit the enzyme, highlighting their potential as therapeutic agents for neurological disorders.

INTRODUCTION

According to the 2023 World Health Organization (WHO) report, one in every five people reported that they have mental health problems that can have serious consequences, such as depression, sadness, disappointment, guilt, apathy, and loss of interest, which can cause disruptions in social activities (Mirzaei *et al.*, 2019). Depression is a threatening and serious psychiatric disease that can be seen both in childhood and older ages, can affect approximately 17% of the world's population, can destroy the will to live, and potentially affects more than 300 million people worldwide (Altar, 1999; Hindmarch, 2001; Mirzaei *et al.*, 2019; Farahani *et al.*, 2015). The first hypothesis proposed regarding the biological etiology of depression is related to the accidental discovery of mood-elevating effects during tuberculosis treatment in

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the 1950s and the understanding that this was due to the inhibition of the monoamine oxidase enzyme in the central nervous system. In the 1960s, following the discovery of phenothiazine analogs such as imipramine, which was found to have antidepressant properties during efforts to develop new antihistamine drugs, the mechanisms of their action were studied, leading to the formulation of the monoamine hypothesis. The monoamine hypothesis attempts to explain the role of the deficiency of monoamine neurotransmitters in the biological etiology of depression (El-Alfy *et al*., 2012). According to the monoamine hypothesis, monoamines whose concentration decreases in synaptic gaps cause depressive states, and most of the selective serotonin uptake inhibitors (El-Alfy *et al*., 2012), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) have been developed and widely used according to this hypothesis (Boku *et al*., 2018; Hindmarch, 2002). In depression, which occurs as a result of the decrease in some neurotransmitters, the activity of the monoamine oxidase A (MAO-A) enzyme is an indicator of the tendency to depressive disorders (Fathinezhad *et al*., 2019). It has been reported that the monoamine oxidase enzyme is not only an indicator of depressive disorders but also paves the way for cellular apoptosis and various neurodegenerative disorders such as Alzheimer's, Parkinson's, depression, and autism by causing the formation of amine derivatives such as hydrogen peroxide, aldehyde and ammonia, which are formed as a result of the oxidative breakdown of monoamines and most of which are known to have toxic effects at high concentrations(Al-Nuaimi *et al*., 2012; Bhawna *et al*., 2022).

The monoamine oxidase enzyme, located in the outer mitochondrial membranes of neural or non-neural cells involved in catalytic reactions, has basic isomers such as monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). The distribution areas and substrates of these isomers differ from each other. While the substrates of the monoaminoxidase A (MAO-A) enzyme found in the liver and gastrointestinal tract are serotonin and noradrenaline, the main substrates of the monoamine oxidase B (MAO-B) enzyme found in the central nervous system (CNS) and platelets are dopamine and phenylethylamine (Chen & Shih, 1997; Kanazawa, 1994). Hereby, the irreversible inhibition of monoamine oxidase enzymes which started to be used by chance in the early 1950s, is an important discovery in psychiatry, and plays a role in the breakdown of these neurotransmitters, becoming an important step in the treatment of depression and anxiety (Jones & Raghanti, 2021; Shulman *et al*., 2013; Dixon Clarke & Ramsay, 2011). Today, monoamine oxidase inhibitors, which are used as antidepressants, are widely used in psychiatry and in the treatment of neurological disorders due to their neuroprotective properties (Baker *et al*., 2012). However, although existing drugs are effective, it becomes difficult to obtain a therapeutic response due to delays in their mechanism of action (a few weeks), and they can cause side effects such as gastrointestinal problems, weight gain, arrhythmias, and cognitive and sexual disorders (El-Alfy *et al*., 2012). Moreover, the hydrazine-based irreversible monoamine oxidase inhibitors (e.g., phenelzine & tranylcypromine) available and used in the market have been limited to patients, especially due to hepatotoxicity, hypertension, and other side effects after consuming foods containing large amounts of the sympathomimetic amine tyramine (Al-Nuaimi *et al*., 2012). In contrast, reversible MAO inhibitors lack the deleterious effects of older monoamine oxidase inhibitors (Bhawna *et al*., 2022). The consumption of many plants, vegetables, and fruits and/or the different extracts obtained from them are widely used in the treatment of depression and some diseases due to their chemical and diverse profiles (Moragrega & Rios 2021; Payne *et al*., 2012). Hundreds of plants, which have been used in the treatment of diseases since ancient times, have become a potential resource when used at the right time and in the appropriate dosage, as they are harmless, do not cause side effects, and are natural sources (Bayir & Cebe, 2023).

In this study, the inhibitory effects of ethanol, ethyl acetate, petroleum ether, and pure water extracts of thirteen medicinal plants (*H. perforatum*, *G. biloba*, *L. angustifolia*, *Z. officinale*, *T. argentea*, *C. aromaticum*, *M. piperita*, *T. sipyleus*, *P. oleracea*, *T. orientalis*, *P. crispum*, and *S. oleracea*) on the monoamine oxidase (MAO) enzyme isolated from rat liver were investigated *in vitro*. The aim was to explore potential natural sources with fewer side effects that could be used in the treatment of depression.

MATERIAL and METHODS

Materials

Ethanol, ethyl acetate, DMSO, potassium phosphate, and petroleum ether used in the preparation of the plant extract have been provided by Merck (Darmstadt, Germany) as well as Coomassie Brilliant-Blue G-250, sucrose, tyramine, and 4-aminotrypsin, which are necessary both for the performance of inhibition experiments and for the protein content of the rat liver extract, are from Merck. The ethics committee certificate for Wistar rats used to obtain the monoamine oxidase enzyme used in this study was received by the Uludağ University Animal Experiments Local Ethics Committee (2013-05/06).

Hypericum perforatum L., *Ginkgo biloba* L., *Lavandula angustifolia* Miller subsp. *angustifolia* Miller, *Zingiber officinale* Roscoe, *Tilia argentea* DESF. EX DC., *Cinnamomum aromaticum* J. Graham and *Menthae* x *piperita* L. used in the study were identified and purchased from the herbalist plant. *Thymus sipyleus* Boiss. subsp. *sipyleus* var. *Sipyleus* were purchased from Balıkesir Kaz Mountains, and the plants *Portulaca oleracea* L., *Trachystemon orientalis* L. G. Don, *Allium sativum* L., *Petroselinum crispum* (Miller) A.W. Hill, and spinach *Spinacia oleracea* L. were identified and purchased from the market.

Methods

Plant extraction

Plant extracts were prepared using a modified version of the method described by Stafford *et al*. (2007). Plant materials were extracted using solvents (water, 70% ethanol, ethyl acetate, and petroleum ether) at a ratio of 1:10 (w/v) for 5 min in an ultrasonic bath. The solutions were then incubated at 4 °C for 24 h, followed by a second ultrasonic treatment for 5 min. Afterward, the extracts were filtered under vacuum using Whatman No. 1 filter paper. The filtrates were concentrated to dryness under reduced pressure at 40 °C. The dried residues were re-dissolved in DMSO to prepare stock solutions, which were further diluted in 0.2 M potassium phosphate buffer (pH 7.6) as required for the assays (Stafford *et al*., 2007).

Preparation of rat liver homogenate

Wistar rats were acquired from the Uludağ University Faculty of Medicine Experimental Animal Husbandry Application and Research Center and euthanized by the cervical dislocation method. Their livers were removed, and based on the method of Holt and colleagues, the liver tissue was mixed in 0.3 M sucrose at a ratio of 1:40 (w/v). The sample was homogenized using a stainless steel blender homogenizer. The homogenate was centrifuged at 1000 g at 4 ºC for 10 min, and the supernatant was taken and centrifuged again under the same conditions. The pellet remaining at the bottom of the tube was dissolved in 0.3 M sucrose and centrifuged again to obtain the mitochondrial MAO-A enzyme (Holt *et al*., 1997). The pellet was dissolved in potassium phosphate buffer (0.2 M, pH=7.6) for use in experimental procedures.

Inhibition of Monoamine Oxidase-A enzyme

The inhibition of monoamine oxidase A (MAO-A) enzyme activity was evaluated using a modified version of the method described by Stafford *et al.* (2007). The plant extracts at various concentrations (1, 0.5, 0.25, 0.1, 0.01, 0.001, and 0.0001 mg/mL) were added to the test groups to investigate their inhibitory effects on MAO-A. In the experimental procedure, 40 µL of buffer and 120 µL of amino substrate were added to the control well. For the test well, 120 µL of amino substrate (2.5 mM), 40 µL of chromogenic solution (peroxidase (4 U/mL), vanillic acid (1mM), 4-aminoantipyrine (0.5 mM)), 40 µL of enzyme, and 40 µL of plant extract were added. Prior to the measurement, deprenyl (0.5 mM) was added to all wells to selectively inhibit monoamine oxidase-B activity and incubated at 37 °C for 30 min. A Thermo Fisher Multiskan

GO spectrophotometer was used to measure enzyme activity % (Eq. 1) and inhibition % (Eq. 2) at 495 nm to determine the IC_{50} values (Stafford *et al*., 2007).

$$Activity\% = [\left(\frac{Test}{Control}\right) X100] \quad \text{Eq. (1)}$$

$$Inhibition\% = \left[1 - \left(\frac{Test}{Control}\right)\right] X100 \quad \text{Eq. (2)}$$

Statistical Analysis

Statistical analyses in this study were performed using IBM SPSS Statistics software (Version 27). Descriptive statistics, normality tests, and homogeneity of variance tests were conducted on the data. In addition, a one-way analysis of variance (ANOVA) was performed to evaluate differences in the IC_{50} values across various plant species and extraction solvents. Post hoc tests, including Tukey's HSD and LSD, were employed to identify significant differences between groups. Throughout all analyses, a significance value of $p < 0.05$ was taken into account.

RESULTS and DISCUSSION

Mood disorders such as depression are processes that lead to various changes in individuals' internal experiences, behaviors, and perceptions of the world. Depression hinders a person's functionality, creativity, happiness, and satisfaction, resulting in a decreased quality of life and loss of workforce productivity (Mirzaei *et al*., 2019). It has been reported that psychosocial, genetic, and biological factors contribute to the development of depression (Chukwuere, 2021). Research has shown that the levels of biological amines and their metabolites in the blood, urine, and cerebrospinal fluid of individuals diagnosed with depression differ from normal values. In particular, it is believed that disruptions in the metabolism of neurotransmitters such as norepinephrine and serotonin, specifically their production, release, and reuptake, play a role in the emergence of depression and other mood disorders (Bhalchim & Undale, 2021).

Monoamine oxidase (MAO), an enzyme that plays a key role in the metabolism of biological amines, is highly significant in the pathological processes of depression, mania, Alzheimer's disease, Parkinson's disease, and schizophrenia. Interest in MAO activity and MAO inhibitors in the treatment of these diseases has been increasing steadily. MAO inhibitors used in the treatment of these conditions are beneficial by increasing the levels of biological amines (catecholamines and serotonin) (Gülter *et al*., 1999). However, drugs used as MAO inhibitors can cause numerous side effects in patients. The most serious side effects include hepatitis, hypertensive crisis, serotonin toxicity, weight gain, insomnia, sexual dysfunction, dizziness, dry mouth, daytime sedation, and blurred vision (Remick & Froese, 1990; Volz & Gleiter, 1998; Ostadkarampour & Putnins, 2021). Due to the prevalence of these side effects, recent research has focused on plant-based MAO inhibitors, which are thought to have fewer adverse effects.

In this study, the effects of inhibitory solutions at various concentrations prepared using distilled water, ethanol, ethyl acetate, petroleum ether, and mixed extracts of the following plants were investigated on the MAO-A enzyme isolated from Wistar rat liver tissue: St. John's Wort (*H. perforatum*), Ginkgo (*G. biloba*), Lavender (*L. angustifolia*), Ginger (*Z. officinale*), Linden (*T. argentea*), Cinnamon (*C. aromaticum*), Peppermint (*M. piperita*), Thyme (*T. sipyleuss*), Purslane (*P. oleracea*), Eastern Blue Comfrey (*T. orientalis*), Garlic (*A. sativum*), Parsley (*Petroselinum crispum*) and Spinach (*S. oleracea*).

The proportion of bioactive compounds present in the plants can vary significantly depending on several factors, including the extraction method, type of solvent used, plant part utilized (leaf, flower, root, etc.), plant species, temperature, and pressure (Ghenabzia *et al*., 2023). Extraction parameters, particularly temperature, duration, and type of solvent, can significantly affect the yield of bioactive compounds, even when using the same plant species (Monagas *et al*., 2022). Utilizing multiple solvents allows for the extraction of a broader range of compounds present in the plant, as different bioactive compounds have varying solubilities. This approach may enhance the biological activity of the extract. As a result, it becomes possible to obtain specific compounds that may be more effective on the target enzyme being studied. In line with this aim, the effects of water, ethanol, ethyl acetate, petroleum ether, and mixed extracts of the aforementioned plants on MAO-A enzyme were investigated. For each plant species, IC_{50} values were calculated. The IC_{50} value represents the concentration of a substance that inhibits 50% of enzyme activity; a lower IC_{50} indicates a stronger enzyme inhibition capacity (Yildiz *et al*., 2013).

The inhibitory effects of plant materials extracted with different solvents on the MAO-A enzyme were evaluated, and their effects on MAO-A were compared using IC_{50} values, expressed as mean ± standard deviation. Various solvent fractions of thirteen plant species (with some exceptions) inhibited MAO-A enzyme activity to different extents (Table 1). The results demonstrate that the inhibitory potential on MAO-A significantly varies depending on both the plant species and the type of extraction solvent used. The IC_{50} values of the plant extracts ranged from 0.071 ± 0.02 mg/mL to 0.287 ± 0.004 mg/mL (Figure 1).

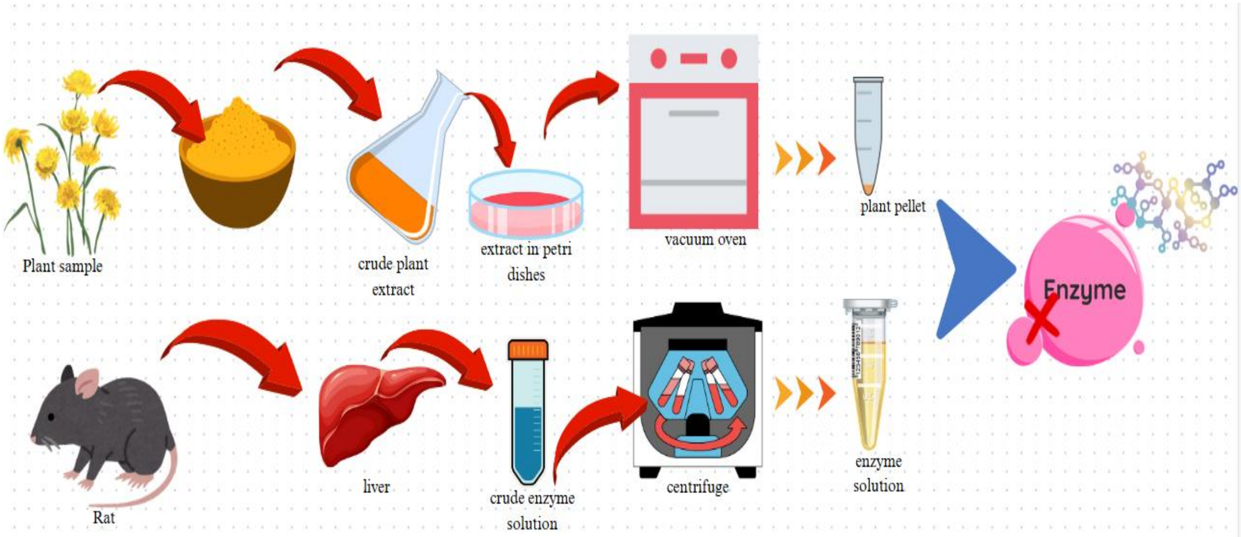

Figure 1. Schematic view of the targeted experimental analysis.

According to the ANOVA descriptive statistics (mean column) presented in Table 1, the IC_{50} values of the plants, ranked from the strongest to the weakest inhibitor, are as follows: *H. perforatum*, *G. biloba*, *S. oleracea*, *A. sativum*, *P. crispum*, *L. angustifolia*, *P. oleracea*, *T. argentea*, *P. oleracea*, *T. sipyleus*, *M. piperita*, *T. orientalis*, *C. aromaticum*, and *Z. officinale*.

The effect on MAO-A inhibition was analyzed using one-way ANOVA, and the results demonstrated that there was no statistically significant difference among the plant species ($f(12, 37) = 1.026$, $p = 0.446$; $p > 0.05$). Therefore, post hoc tests were not conducted. However, the type of solvent was evaluated as a significant determining factor in the bioactive content and biological activity of the extracts. One-way ANOVA results revealed a statistically significant difference among the solvent groups ($f(4, 45) = 3.032$; $p = 0.027$; $p < 0.05$) (Figure 3). Post hoc (Tukey and LSD) analyses revealed that ethanol extracts had significantly lower IC_{50} values compared to those obtained with petroleum ether ($p = 0.012$; $p < 0.05$) and mixed solvents ($p = 0.012$; $p < 0.05$), indicating a stronger inhibitory effect. This finding indicates that ethanol is the most effective solvent for the extraction of MAO-A inhibitors. Additionally, extracts obtained with pure water were found to have significantly lower IC_{50} values compared to those obtained with mixed solvents ($p = 0.045$; $p < 0.05$), suggesting that water may also be considered an effective solvent, second only to ethanol. In contrast, ethyl acetate, petroleum ether, and mixed solvents exhibited higher IC_{50} values, indicating lower inhibitory potential (Figure 2).

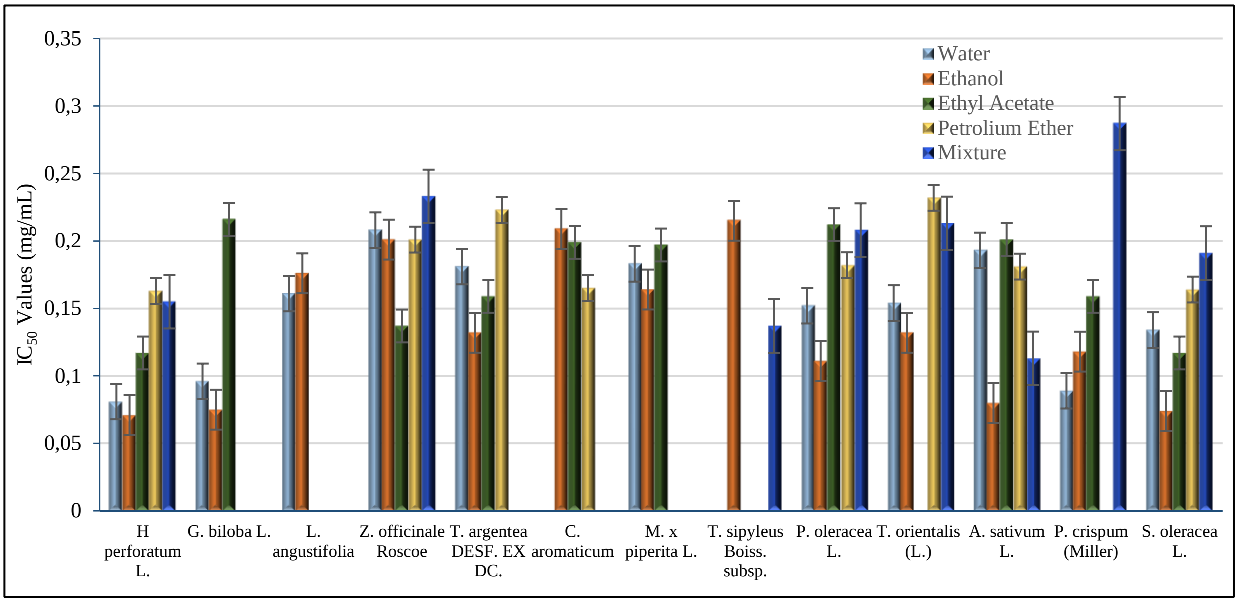

Figure 2. Clustered bar chart showing the distribution of IC_{50} (mg/mL) values for each plant–solvent combination.

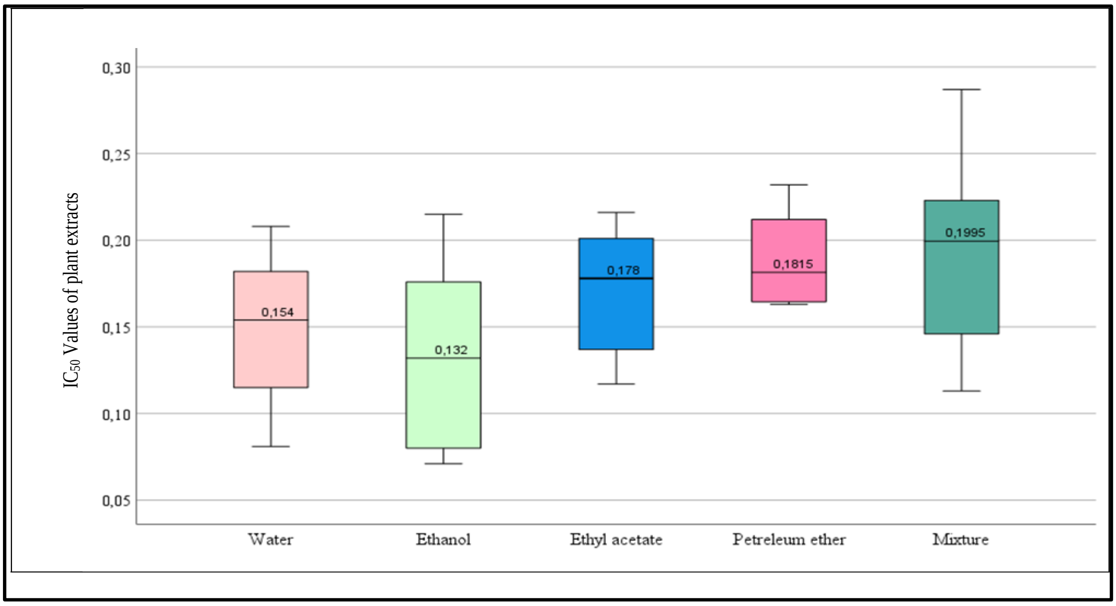

Figure 3. Boxplot showing the IC_{50} values of plant extracts obtained with different solvent types against the MAO-A enzyme (The line and numbers inside the box indicate the median, with the interquartile range represented by the box and outliers by whiskers. In the graph, the median IC50 value of ethanol extracts (0.132) was lower than that of other solvents. Ethanol was followed by water (0.154), ethyl acetate (0.178), petroleum ether (0.1815), and the mixture (0.1995)).

The results highlight that the type of solvent can be at least as influential as the plant species itself. Previously, Markom *et al*. (2007) reported that extraction efficiency may depend on both the polarity of the solvent and that of the compound being extracted (Markom *et al*., 2007). Ethanol, with its moderately polar nature and ability to form hydrogen bonds, is more efficient at dissolving polar biologically active secondary metabolite such as phenolic compounds, flavonoids, and alkaloids. Ethyl acetate, being less polar, shows lower extraction efficiency. Although water, a polar solvent, can dissolve active compounds, it also extracts non-active components like proteins and sugars, which reduces the selectivity of the extraction process (Omara *et al*., 2021).

Table 1. IC_{50} values and statistical analysis of inhibitory effects of various plant extracts on MAO-A enzyme.

Plants	Water (mg/mL)	Ethanol (mg/mL)	Ethyl Acetate (mg/mL)	Petroleum Ether (mg/mL)	Mixture (mg/mL)	One Way Anova		
						**Mean (IC_{50})	*F*	*p*-value
Hypericum perforatum	0.081±0.017	0.071±0.02	0.117±0.005	0.163±0.005	0.155±0.028	0.117		
Ginkgo biloba	0.096 ±0.01	0.075±0.002	0.216±0.013	*	*	0.129	1.026	
Lavandula angustifolia	0.161± 0.019	0.176±0.017	*	*	*	0.168		
Zingiber officinale	0.208 ±0.001	0.201±0.011	0.137±0.009	0.201±0.146	0.233±0.007	0.196	(for plant)	0.446
Tilia argentea	0.181±0.005	0.132±0.006	0.159±0.033	0.223± 0.04	*	0.173		*p* >0.05 (for plant)
Cinnamomum aromaticum	*	0.209±0.029	0.199±0.005	0.165±0.004	*	0.191		
Menthae x *piperita*	0.183±0.014	0.164±0.001	0.197±0.008	*	*	0.181	3.032	
Thymus sipyleus	*	0.215±0.013	*	*	0.137±0.008	0.176	(for solvent)	
Portulaca oleracea	0.152±0.08	0.111±0.001	0.212±0.004	0.182±0.065	0.208±0.03	0.173		0.027 *p* <0.05
Trachystemon orientalis	0.154±0.02	0.132±0.005	*	0.232±0.013	0.213±0.09	0.182		(for solvent)
Allium sativum	0.193±0.007	0.080±0.000	0.201±0.015	0.181±0.009	0.113±0.05	0.153		
Petroselinum crispum	0.089±0.06	0.118±0.01	0.159±0.011	*	0.287±0.004	0.163		
Spinacia oleracea	0.134±0.02	0.074±0.007	0.117±0.013	0.164±0.003	0.191±0.01	0.136		

*It has no inhibition. **Mean IC_{50} values from ANOVA descriptive statistics. According to the LSD results, which is one of the post hoc tests applied for the solvent factor, there is a statistically significant difference between the solvents ethanol and mixed ($p = 0.008$; $p < 0.05$), ethanol and petroleum ether ($p = 0.012$; $p < 0.05$), and water and mixed ($p = 0.045$; $p < 0.05$)

In the study, the lowest IC_{50} values for each solvent were determined as follows: *H. perforatum*'s water (0.081 ± 0.017 mg/mL) and ethanol (0.071 ± 0.02 mg/mL) extracts; the ethyl acetate extracts of *H. perforatum* and *S. oleracea* (0.117 ± 0.005 mg/mL and 0.117 ± 0.013 mg/mL, respectively); the petroleum ether extract of *H. perforatum* (0.163 ± 0.005 mg/mL); and the mixed solvent extract of *A. sativum* (0.113 ± 0.05 mg/mL). When evaluated based on both solvent properties and average IC_{50} values, the plants showing the strongest inhibitory effects on MAO-A were identified as *H. perforatum*, *G. biloba*, *S. oleracea* and *A. sativum* (Table 1).

The well-known antidepressant effects of *H. perforatum* are largely attributed to its MAO inhibitory activity (Dimitrov *et al*., 2011; Das *et al*., 2022). In this study, the IC_{50} values of *H. perforatum*'s ethanol and water extracts were determined to be 0.071 ± 0.02 mg/mL and 0.081 ± 0.017 mg/mL, respectively. These values indicate that *H. perforatum*'s water and ethanol extracts exhibit the strongest MAO-A inhibitory effects among the plant-based inhibitors examined (Table 1 and Figure 1). Herraiz & Guillén (2018) reported that phytochemicals such as pseudohypericin, hypericin, hyperforin, and flavonoids found in *H. perforatum* flower extracts inhibited the human MAO-A enzyme with an IC_{50} of 63.6 µg/mL (0.0636 mg/mL) (Herraiz & Guillén, 2018). These data are consistent with the findings of our study and support the antidepressant potential of *H. perforatum* based on its MAO inhibition activity. *H. perforatum* is widely used for the treatment of mild to moderate forms of depression. Some well-documented clinical studies (Baljak *et al*., 2024) have shown that alcoholic extracts of this plant possess at least the same efficacy as conventional antidepressant drugs, but with significantly fewer side effects (Zirak *et al*., 2019). *St. John's Wort* (*H. perforatum*) has been reported to contain active compounds such as hyperforin, hypericins, and flavonoids, which are believed to be responsible for its antidepressant effects. However, the exact mechanism underlying these effects has not been fully elucidated. The most widely accepted mechanism is the inhibition of monoamine reuptake, which increases the levels of neurotransmitters like serotonin, dopamine, and norepinephrine in the synaptic cleft. Nevertheless, some studies suggest that the antidepressant action may result from a combination of mechanisms and potential synergistic effects among the plant's various bioactive constituents (Herraiz & Guillén, 2018). Suzuki *et al*. (1984) reported that hypericin, isolated from *H. perforatum*, inhibited type A and B monoamine oxidase (MAO) enzymes prepared from rat brain mitochondria treated with selective inhibitors in an *in vitro* environment. Hypericin exhibited a stronger inhibitory effect on MAO-A compared to MAO-B. They also reported that the inhibition of both MAO types was almost irreversible (Suzuki *et al*., 1984). Thiede and Walper (1994) observed approximately 27 % inhibition of MAO activity at high concentrations (10^{-3} M hypericin and 10^{-4} M *H. perforatum* total extract) (Thiede & Walper, 1994). Other researchers have reported that when *H. perforatum* extracts were used in the micromolar range (10^{-6} M), they achieved over 50% inhibition of both MAO types. However, it has been argued that such concentrations are very high and unlikely to be reached *in vivo*. Moreover, at lower nanomolar concentrations (10^{-9} M), the inhibitory effects on MAO enzymes are considered negligible (Zirak *et al*., 2019). Bladt and Wagner (1994) investigated the effects of active compounds isolated from *H. perforatum* extracts on MAO both in vitro, using rat brain homogenates, and *in vivo* on albino rats. They observed approximately 39% inhibition of brain MAO enzyme activity at a flavonoid concentration of 10^{-4} M. However, *in vivo* administration of pure hypericin to albino rats did not result in any observable inhibitory effect (Bladt & Wagner, 1994). Additionally, Sparenberg *et al*. (1993) reported that, alongside *H. perforatum* flavonoids, quercetin and quercitrin molecules also act as MAO-A inhibitors (Sparenberg *et al.*, 1993). Müller *et al*. (1997) reported that *H. perforatum* is not a significant inhibitor of either MAO-A or MAO-B with IC_{50} values exceeding 0.1 mg/mL (Müller *et al*., 1997). However, Linde et al. (1996) reported that *H. perforatum* extracts, at doses ranging from 1.78 to 4.01 g/day, demonstrate superior efficacy in treating depression compared to standard antidepressants, which are effective at doses between 0.78 and 2.94 g/day (Linde *et al*., 1996).

The medicinal use of *G. biloba* L. leaves and fruits is quite widespread. Traditionally, *G. biloba* fruits have been used to treat lung diseases such as asthma, bronchitis, and cough, cardiovascular and cerebrovascular diseases, and urinary tract infections. Additionally, *G. biloba* leaves are used in the treatment of mental disorders, peripheral arterial occlusion, tinnitus, and asthma (Liu *et al*., 2022). Among the bioactive compounds present in the plant, flavonoids such as kaempferol, apigenin, chrysin, and quercetin stand out as key contributors to MAO inhibition (Sloley *et al*., 2000; Mannan *et al*., 2022). Our study confirms the MAO inhibitory effects of these active compounds. The ethanol extracts of *G. biloba* L. exhibited MAO inhibitory activity with an IC_{50} value of 0.075 ± 0.002 mg/mL. Wu and Zhu (1999) reported that *G. biloba* extract inhibited MAO activity with an IC_{50} value of 36.45 µg/mL (0.0364 mg/mL) (Wu & Zhu, 1999). It has been reported that extracts from dried *Ginkgo biloba* leaves inhibit both MAO-A and MAO-B without showing significant selectivity. In contrast, extracts obtained from fresh *Ginkgo* leaves appear to inhibit MAO-A slightly more effectively than MAO-B. This suggests that multiple inhibitory compounds may be present in fresh leaves, with at least one compound exerting a stronger inhibitory effect specifically on MAO-A (White *et al*., 1996). Fehske *et al*. (2009) found that the standardized *G. biloba* extract (EGb761®) preferentially inhibited MAO-A over MAO-B *in vitro*, with an IC_{50} value of approximately 0.2 mg/mL, showing about 10 times greater inhibition of MAO-A compared to MAO-B (Fehske *et al*. 2009).

In the study, the ethanol extract of *S. oleracea* demonstrated strong MAO-A inhibitory activity with an IC_{50} value of 0.074 mg/mL. A review of the literature revealed no previous studies examining the effects of spinach extracts on MAO-A. *S. oleracea* contains various bioactive compounds such as ascorbic acid, apigenin, astragalin, caffeic acid, lutein, β-carotene, ferulic acid, kaempferol, rutin, quercetin, myricetin, luteolin, ortho-coumaric acid, para-coumaric acid, stigmasterol, protocatechuic acids, methylenedioxy flavonol, glycoglycerolipids, 20-hydroxyecdysone, vitamins, spirasaponins, and violaxanthin. These constituents are responsible for the plant's biomedical and pharmacotherapeutic effects (Shah *et al*., 2020). Although data on *S. oleracea*'s role in neurodegenerative diseases is limited, previous studies have reported that flavonoids and glycosides present in spinach possess antidepressant properties (Gudepu *et al*., 2013). Additionally, Son *et al*. (2018) reported that ethanol extracts of *S. oleracea* exhibit anti-stress effects and have therapeutic potential against depressive symptoms (Son *et al*., 2018). The seed extract of *S. oleracea* has also been highlighted for its potential to alleviate psychotic symptoms in mice and its protective role in schizophrenia management (Yadav *et al.*, 2018). These findings are thought to align with the strong inhibitory effect observed in our study.

Garlic is endowed with several medicinal properties (Gebreyohannes & Gebreyohannes, 2013). It has been reported to possess anti-stress properties (Ushijima *et al*., 1997), to improve early cognitive deficits, to have memory-enhancing properties, and to have the potential for preventing the progression of Alzheimer's disease (Chauhan & Sandoval, 2007). A review of the literature reveals that there is only one study on the monoamine oxidase activity of garlic, conducted by Dhingra and Kumar (2008). In this study, Dhingra and Kumar (2008) administered 20 % ethanolic garlic extract orally to mice consecutively for 14 days at doses of 25, 50, and 100 mg/kg. They then evaluated the results using the Forced Swim Test (FST) and Tail Suspension Test (TST). Both FST and TST are widely used behavioral tests modeling depressive-like helplessness. These tests are highly sensitive and are widely used in rodents to predict antidepressant potential by measuring the reduction in immobility time caused by different classes of antidepressant drugs. The researchers found that oral administration of garlic extract (100 mg/kg) to mice for 14 days significantly decreased brain MAO-A and MAO-B activities compared to the control group. The antidepressant-like effect of the extract was reported to be comparable to that of imipramine and fluoxetine. Therefore, they suggested that garlic extract may have potential therapeutic value in the treatment of depressive disorders. Our results demonstrated that the ethanol extract of *A. sativum* exhibited strong MAO-A inhibitory activity, with an IC_{50} value of 0.08 mg/mL (Dhingra & Kumar, 2008).

In conclusion, the data of this study demonstrate that both the plant species and the type of solvent are of the utmost importance in the MAO-A inhibition potential. The results highlight the importance of considering not only the phytochemical components but also the extraction parameters together in the development of plant-based MAO inhibitors.

CONCLUSION

In this study, the inhibitory effects of extracts prepared with different solvents from thirteen plant species on the MAO-A enzyme obtained from Wistar rat liver were evaluated. The findings revealed that the ethanol and water extracts of *H. perforatum*, *G. biloba*, *S. oleracea*, and *A. sativum* exhibited strong MAO-A inhibition with low IC_{50} values. Although no statistically significant difference was found among the plant species, the type of solvent was identified as a determining factor affecting the level of inhibition. The study concluded that solvents have a significant impact on plant extracts, with ethanol and pure water being the most effective solvents overall, followed by ethyl acetate, mixture solvents, and petroleum ether, respectively. In the extraction of plant-based compounds, it has been emphasized that extraction parameters are as important as the plant composition in determining the effectiveness of plant-based inhibitors. Accordingly, certain plant-solvent combinations require additional scrutiny, given that potential therapeutic agents for the treatment of neuropsychiatric disorders such as depression. Additionally, this study provides the first evidence that cinnamon (*C. aromaticum* IC_{50} values of ethanol, ethyl acetate and petroleum ether were 0.209, 0.199 and 0.165 mg/mL, respectively), purslane (*P. oleracea* IC_{50} values of water, ethanol, ethyl acetate, petroleum ether, and mixed were 0.152, 0.111, 0.212, 0.182, 0.208 mg/mL, respectively), ıspıt (*T. orientalis* IC_{50} values of water, ethanol, petroleum ether, and mixed were 0.154, 0.132, 0.232, 0.213 mg/mL, respectively), parsley (*P. crispum*) IC_{50} values of water, ethanol, ethyl acetate, and mixed were 0.089, 0.118, 0.159, 0.287 mg/mL, respectively), and spinach (*S. oleracea* IC_{50} values of water, ethanol, ethyl acetate, petroleum ether, and mixed were 0.134, 0.074, 0.117, 0.164, 0.191 mg/mL, respectively) can be used as MAO-A inhibitors.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors. **Ethics Committee Number**: Uludağ University Local Ethics Committee for Animal Experiments and Uludağ University Faculty of Medicine Laboratory Animal Breeding Application and Research Center, 2013 - 05/06.

Data Availability Statement

Research data is available and can be sent with e-maill upon request.

Authorship Contribution Statement

Nurten Güngör: Investigation, **Serap Doğan**: Project administration, Supervision, Writing-Editing, and Conceptualization. **Ümran Alan:** Writing-original draft, Statistic and Conceptualization **Mehmet Emin Diken**: Investigation, Methodology, Conceptualization. **Hamza Bayhan:** Methodology, Writing-original draft, and Validation.

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