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Original article

In-vitro antidepressant property of methanol extract of *Bacopa monnieri*

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ABSTRACT

Objectives: The present investigation was aimed to analyze the antidepressant activity of methanol extract of *Bacopa monnieri* using albino rats.
Methods: Three doses of methanol extract (25, 50 and 100 mg/kg), and standard (imipramine hydrochloride, 25 mg/kg) were administered to albino rats. Methanol extract was subjected to use forced swimming test, tail suspension test and locomotor activities.
Results: At 25 mg/kg, 50 mg/kg and 100 mg/kg doses, immobility time decreased at 49.6%, 59.5% and 69.9%, respectively than control (p value < 0.0001). Tail suspension test increased immobility time at higher doses of methanol extract. Locomotor activities were statistically significant at 25 mg/kg and 50 mg/kg (p value = 0.005), and non significant at 100 mg/kg (p value = 0.781) in experimental animal. The experimental animals treated with plant extract showed varying levels of monoamine oxidase - A (MAO-A) activity. MAO - A level of the control animal was 2.87 ± 0.021 ng/mL and it reduced in the experimental albino rats treated with imipramine hydrochloride (2.73 ± 0.09 ng/mL). The amount of MAO-A in the experimental animals treated with methanol extract at 25 mg/kg (p = 0.01), and 50 mg/kg (p value = 0.0001) showed significant decrease in MAO-A activity in rats brain than control.
Conclusions: The present finding revealed antidepressant effect of methanol extract of *B. monnieri* in Albino rats.

1. Introduction

Plants are the major sources of various medicines and are used for treating various illnesses and diseases. Natural products form plant sources have been widely used since ancient times and the application of herbal medicines for the treatment and prevention of various disorders and diseases remains highly popular. Recently, the search for novel drugs from medicinal plants has attracted much more attention. Natural products have been considered as an alternative to costly synthetic medicine to treat and prevent diseases. The increasing side effects of costly synthetic medicines have led to the application of therapeutic molecules form the plant sources. There exists potential interest in the investigation of novel medicine from plant sources that may be a useful alternative, in either the treatment or the prevention of various diseases and disorders. Although various medicinal plants have immense therapeutic value, however many medicinal plants from the natural sources remains unexplored or not described in the medical dictionary. Hence, it is important to analyze and validate the traditional medicinal plants to validate scientifically using animal models.

Depression is a chronic psychiatric problem which affects work performance and social life of organisms. Millions of people of almost all age groups are affected by this disease. According to WHO, depression is the second most disease which causes severe disability. Depression is a kind of mental disease mainly associated with the interactions of biological, social and psychological factors. Biochemical, genetic parameters, environmental and personal conditions triggered this mood disorder (Eliwa et al., 2021).

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Depression is characterized by various symptoms, including increased agitation, fatigue, decreased interest in pleasurable stimuli, changes in appetite, worthlessness or feeling of hopelessness and suicidal thoughts in some of the cases (Cash et al., 2021). Depression causes ill health and induces various illnesses such as, lung diseases, cancer, stroke, and cardiovascular diseases (Goodwin, 2006), obesity and diabetes, loss of vision and hearing (Huang et al., 2010). The amounts of monoamine neurotransmitters such as noradrenaline, serotonin, and adrenocorticotropic hormone, cortisol, corticotrophin-releasing hormone, corticotrophin-releasing factor, dopamine, monoamine oxidase, adenylyl cyclase, hypothalamic–pituitary–adrenal (HPA) axis are important biomarkers for the diagnosis of depression. Depression is significantly associated with biological, social and psychological factors. A higher vitamin C intake decreased the risk of osteoporosis. Differences in biochemicals in the brain, stressful life, less self-confidence also contribute significantly to depression (Rabiei and Rabiei, 2017).

Medicinal plants consist of psychotropic property and showed lower risk than common synthetic drugs. Generally, neuroprotective molecules are associated with psychotropic properties and polyphenols, such as, flavonoids have lot of potential to treat depression. Plant phytochemicals prevent mitochondrial toxicity and has been reported previously. Phytochemicals improve mitochondrial biogenesis and balance microchondrial membrane functions and this is considered as the first step of apoptosis (Matraszek-Gawron et al., 2019). Medications are widely used for the treatment of depression such as, selective serotonin reuptake inhibitors, monoamineoxidase inhibitors, and tricyclic antidepressants (Kim et al., 2017; Park et al., 2016a, Park et al., 2016b; Ilavenil et al., 2016a; Ilavenil et al., 2016b; Barathikannan et al., 2016; Surendra et al., 2016). However, the side effects such as increased body weight, sleep, cardiovascular problem have been reported (Hieronymus et al., 2021). The search for novel alternatives to handle depression is initiating pharmacologists into various natural sources mainly phytochemicals. Traditionally, various plants are used to treat neurological health problems and *Bacopa monnieri* is one of the important plants. *B. monniera*(L.) (Shen et al., 2009). Wettst is used to treat as a mild sedative, insomnia, epilepsy and memory enhancing. Roodenrys et al. (2002) revealed that this medicinal plant is able to minimize the memory dysfunction in animal model and detected that saponins are the major active phytochemicals. *B. monnieri* (L.) is widely used to treat various nervous disorders, skin disorders, provide relief to patients with anxiety, improve learning, digestive aid, epilepsy, insanity and asthma (Cuong et al., 2017; Ilavenil et al., 2017). It contains bacosides A and B, herpestine, nicotine, alkaloid brahmine, stigmastanol, triterpenoid saponins, D-mannitol, betulinic acid, β-sitosterol and glutamic acid (Devishree et al., 2017). The aim of this work was to analyze antidepressant property of methanol extract of *B. monnieri* (L.) after two weeks of treatment in experimental animal model.

2. Materials and methods

2.1. Experimental animal

Healthy albino rats (125 – 130 g) were used for this study and maintained at 12 h dark/light cycle in animal house. The relative humidity and temperature of the animal house were 60 – 70% and 28.0 ± 2.0 °C, respectively. Pellet feed was provided to the animals and freshwater was supplied throughout acclimatization period. The selected experimental animals were acclimatized in the animal house for two weeks prior to conducting the tests into various groups such as, experimental groups (25 mg/kg, 50 mg/kg and 100 mg/kg), standard group and control group. The experimental, standard and control groups were fasted for 12 h before to perform the experiments. All experimental protocols were approved by Institutional Animal Ethical Committee (ALB/121/2020).

2.2. Acute toxicity analysis

Toxicity of methanol extract was performed in albino rats weighing from 125 to 130 g. All experiments were performed according to Institutional Animal Ethical Committee guidelines. The experimental animals were divided into three groups (n = 6) and methanol extract was supplemented at three different doses (25 mg/kg, 50 mg/kg and 100 mg/kg) to the experimental animal. Then the behavioural changes and mortality were continuously monitored for every 24 h up to 96 h. No behavioural changes and mortality was observed during this period and the selected doses were safe to the experimental animal.

2.3. B. monnieri (L.) and sample preparation for treatment

The whole plant was collected in the month of July 2020 and was identified by standard method. The voucher specimen was stored and the voucher number was assigned (BN06-2020). The collected plant powder was ground mechanically and extracted with methanol for 96 h in an orbital shaker at 150 rpm. The extract was carefully filtered using a vacuum filtration unit. Initially the extract was dried at room temperature and further dried using sodium sulphate. The dried sample was suspended appropriately in Millipore water and used for assay.

2.4. Phytochemical screening

The methanol extract was screened for the presence of phytochemicals by standard method. The extract was diluted appropriately for screening experiments (Malar et al., 2020; Atif et al., 2020).

2.4.1. Determination of phenol content

Total phenol content of the methanol extract was determined as suggested previously using Folin Ciocalteau's reagent. The methanol extract or gallic acid (0.5 mL) was diluted appropriately and mixed with 1 M sodium carbonate (4 mL) and FolinCiocalteau's reagent (5 mL). The reaction mixture was incubated for 30 min and the colour intensity was read at 765 nm against reagent blank. Gallic acid was used as the standard and the total phenol content of the methanol extract was expressed as gallic acid equivalent/g (mg/g of dry extract) (Al-Dhabi et al., 2020).

2.4.2. Determination of flavonoid content

Total flavonoid content of the methanol extract was determined by aluminium chloride assay method. The methanol extract (1.5 mL), was mixed with 10% aluminium chloride (0.1 mL), 0.1 mL potassium acetate (1 M), and double distilled water (2.5 mL). It was incubated for 30 min at room temperature and the absorbance was read at 415 nm against reagent blank.

2.5. Experiment setup

Methanol extract of *B. monnieri* was used as the sample for all experiment until otherwise stated. Dried methanol extract was suspended in double distilled water and used for analysis. Imipramine hydrochloride (Sigma, USA) was prepared in Millipore water and administered at 25 mg/kg concentration and *B. monnieri* was prepared at various concentrations and administered at 25 mg/kg, 50 mg/kg and 100 mg/kg. The standard and methanol extract were given orally to the experimental animal for two weeks at

24 h interval. To the control rat, 200 µL physiological saline was administered orally.

2.6. Antidepressant activity

2.6.1. Forced swimming test (FST)

Behavioural despair or forced swimming test has been generally proposed to investigate the antidepressant properties of rats. This method was based on the analysis of experimental albino rats exposed to induce forced swimming, and this required minimum risk to the experimental animal just to keep their heads above the water level. The experimental albino rat was divided into standard, experiment and control. In each experiment five animals were maintained (n = 6). Methanol extract was administered to the experimental animals at three different doses. It was administered daily basis between 9.00 and 10 am for two weeks. Experimental animals were maintained in an acrylic cylinder (25 cm diameter × 50 cm height) filled with tap water to a depth of 20 cm for 20 min at 28 ± 2 °C after two weeks of treatment. After 24 h, the animals were exposed to the same experimental conditions for 10 min. FST was carried out between 10 and 11 am as described previously (Moreno-Santos et al., 2021).

2.6.2. Locomotor activity analysis

Locomotor activity was performed to analyze the mobility of albino rat. A total of 30 albino rat was divided into five different groups (n = 6). To the experimental animal, methanol extract (25 mg/kg, 50 mg/kg and 100 mg/kg) was supplemented, imipramine hydrochloride was used as the standard, and physiological saline was administered to the control rats. Plant extract and standard were administered to the experimental and positive control animals before 30 min of the experimental trials. The experimental Albino rats were maintained in an open field apparatus composed of 45 cm arena (diameter) divided into 16 equal areas. After 15 h of final treatment, the experimental rat was placed in the centre of the arena. The behavioural parameters such as, rearing frequencies, locomotion and defecations were observed within 5 min (Zhang et al., 2021).

2.6.3. Tail suspension test

Tail suspension test is one of the useful tests to determine antidepressant activity of the experimental animal. This assay is mainly used to test mood levels which generally indicate variation in mood level. In this method a total of 26 Albino rats were incubated with plant extract and standard. All experimental rats were kept at the center of the stand. A total of six stands were prepared and each stand comprising a clamp which is located about 20 cm from the floor. The experimental Albino rats were monitored for 7 min and result was observed (Zhang et al., 2021).

2.6.4. Monoamine oxidase- a (MAO-A) analysis

The experimental rats from all five groups were sacrificed on 15th day of final treatment. The brain was dissected out from the skull and homogenized the brain using phosphate buffered saline (0.1 M, pH 7.4) for the analysis of MAO-A content. Determination of MAO-A was performed using enzyme-linked immunosorbent assay method as described previously (Baluchnejadmojarad et al., 2017). For the determination of MAO-A the pre-coated 96-well strip plate was used for analysis. To the 96 well plates, 100 µL samples was introduced and incubated for 1 h at 37 °C. Then, 100 µL detection solution A was applied and incubated at 37 °C for 60 min. The plates were washed three times and added 100 µL working detection solution B and incubated at 37 °C for 30 min. Then, 50 µL stop solution was added and the microplate was read at 450 nm using an ELISA plate reader.

2.6.5. Statistical analysis

The experimental results were described as mean ± SD. One way analysis of variance (ANOVA) was performed followed by Dunnett's *t*-test. The variation between experimental and control groups were analyzed and the p - value < 0.05 was considered as significant.

3. Results

3.1. Phytochemicals from the methanol extract of B. monnieri (L.)

The preliminary screening analysis revealed the presence of various phytochemicals from the methanol extract and the result was depicted in Table 1. Total phenolic content of methanol extract of *B. monnieri* was 33.93 ± 4.7 mg/g GAE and the flavonoid content was 30.07 ± 2.9 mg/g quercetin equivalent.

3.2. Forced swimming test (FST)

Three different doses of methanol extract of *B. monnieri* were applied to analyze the antidepressant property of plant revealed in Fig. 1. The methanol extract at 25 mg/kg reduced immobility duration and the variation was significant (F value = 88.4; P < 0.001). At 50 mg/kg and 100 mg/kg doses of methanol extract, immobility period reduced significantly (<0.0001). Imipramine hydrochloride administered at 25 mg/kg was used as a positive control, which decreased immobility time (30.63 ± 2.9 s).

3.3. Tail suspension test

Methanol extract and imipramine hydrochloride (25 mg/kg) induced immobility time in tail suspension test. In the control the immobilizing time was 194 ± 4.4 s and it reduced significantly

Table 1
Phytochemicals of methanol extract of *B. monnieri* (L.).

Phytochemicals	Result
Saponin	+
Terpenoid	–
Phlobetannin	+
Tannin	+
Flavonoid	+
Phenol	+
Cardiac glycoside	+
Anthraquinone	–
Steriod	+
Alkaloid	+

+ present; – absent.

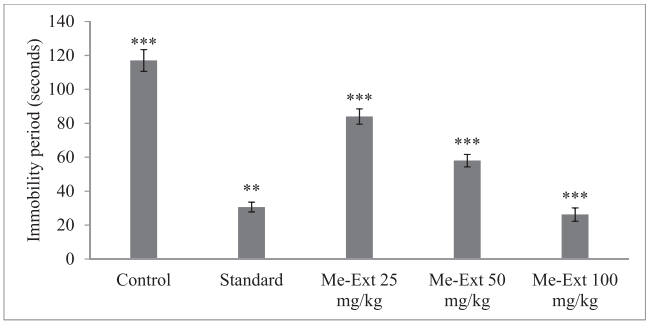

Fig. 1. Effect of *B. monnieri* (25, 50 and 100 mg/kg) and imipramine hydrochloride (25 mg/kg) on duration of immobility time in FST. Results are presented as mean ± standard deviation (SD) (n = 6). *** p < 0.0001 when compared with control experiments, ** p < 0.001 when compared with control experiments.

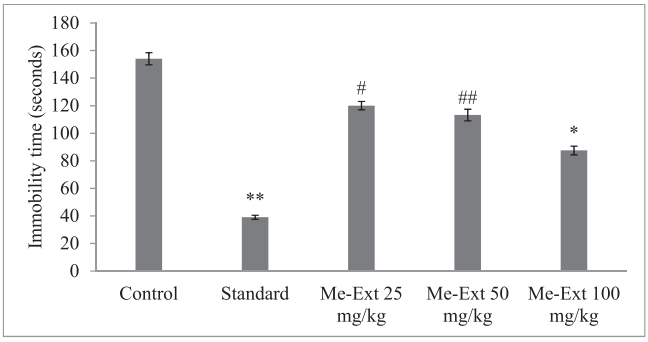

Fig. 2. Effect of *B. monnieri* (25, 50 and 100 mg/kg) and imipramine hydrochloride (25 mg/kg) on duration of immobility time in TST. Results are presented as mean ± standard deviation (SD) (n = 6). **p < 0.001 analyzed with control, # p = 0.005 compared with control experiment; ## p = 0.0005 analyzed with control; and * p < 0.01 level in plant extract treated with 100 mg/kg concentration.

in standard group (39 ± 1.5 s). As described in Fig. 2, the administered three doses of methanol extract reduced the immobility time than control experimental trials. At 25 mg/kg, 50 mg/kg and 100 mg/kg doses, immobility time decreased at 49.6%, 59.5% and 69.9%, respectively than control. The p value was < 0.001 for standard and was insignificant at 25 mg/kg dose (p greater than 0.05).

3.4. Locomotor activity of the experimental animal

Locomotor activities were statistically significant at 25 mg/kg (F–value: 102.4; p value: 0.001), 50 mg/kg (F–value; p value: 0.005), and non significant at 100 mg/kg (F – value: 0.0883; p value: 0.781) (Fig. 3).

3.5. Influence of methanol extract on monoamine oxidase- a (MAO-A) levels in the whole brain of experimental animals

The experimental animals treated with methanol extract and standard showed varying levels of MAO-A activity was described in Fig. 4. Monoamine oxidase- A level of the control animal was 2.87 ± 0.021 ng/mL and it reduced in experimental Albino rats treated with imipramine hydrochloride (2.73 ± 0.09 ng/mL). The amount of MAO-A in the standard group of animal showed significant reduction of enzyme activity than control experiment (F = 8.24; p = 0.05). The experimental animals treated with methanol extract of the plant extract at 25 mg/kg (F value: 18.6; p = 0.01), 50 mg/kg (F value: 172.05; p = 0.0001) and 100 mg/kg (F value: 620; p < 0.0001) showed significant decreased level of MAO-A activity than control.

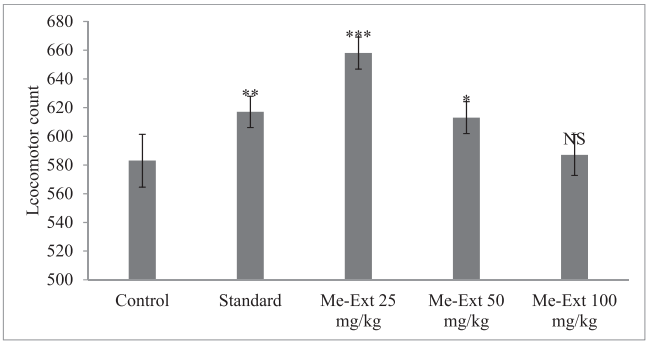

Fig. 3. Effect of *B. monnieri* (25, 50 and 100 mg/kg) and imipramine hydrochloride (25 mg/kg) on locomotor activity. Results are presented as mean ± standard deviation (SD) (n = 6). *p value = 0.001, ***p value = 0.001, * p value = 0.01 and NS = non signfificant.

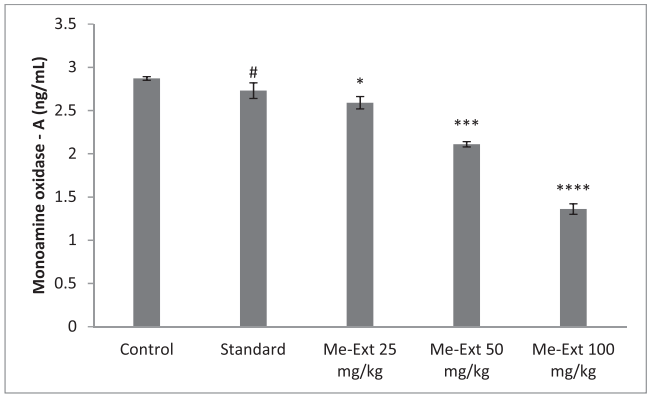

Fig. 4. Methanol extract on monoamine oxidase- A (MAO-A) levels in the whole brain of experimental animals. Analysis of variance was used and the significant level (p value) was < 0.05 (#), 0.01 (*), 0.0001 (***), and <0.0001 (****).

4. Discussion

Medicinal plants contain various phytochemicals and the co-occurrence of phytochemicals improved therapeutic property than single compounds. In medicinal plants, phytochemicals exert a positive influence on antioxidant, neuroprotective, and anti-inflammatory property. These molecules can treat depression, inflammation and oxidative stress is commonly recognized as important factors associated with depressive disorder and other nervous disorders. Generally, mentally depressed patients have an increased number of various inflammatory markers and molecules associated with oxidative stress such as, DNA, proteins and lipids. The decreased level of polyunsaturated fatty acids, vitamin E, ascorbic acid, glutathione and coenzyme Q-10 also reported (Matraszek-Gawron et al., 2019). Depression is one of the life-threatening, debilitating, and common illnesses and has been reported previously (Park et al., 2016a, Park et al., 2016b; Antonisamy et al., 2016). Many antidepressant molecules act via various mechanisms involving the dopaminergic, noradrenergic and serotonergic systems. Most of the antidepressant drugs and mood-stabilizing drugs cause various clinical complications (Wang et al., 2018). Hence, novel molecules are still required for the treatment of depression-like diseases. In the present study, an indigenous *B. monniera* (L.) produced potential antidepressant activities when analyzed in FST, TST and locomotor activity. Tail suspension tests and Forced swimming test are the two important methods used for the screening antidepressant drugs (Cryan et al., 2005).

Antidepressant substances are widely used to reduce the inactivity time in the experimental animal models. Antidepressant property of various secondary metabolites from plant sources has been reported. These phytochemicals are phenolic compounds, include, sub-groups of flavonoids, lignans, stilbenes, anthraquinones, coumarins and chromones (Garcia-Salas et al., 2010). Ghosh et al. (2007) reported that the solvent extract of *Bacopa monnieri* contained more than 45 mg/g pyrocatechol equivalent. The present finding showed that various doses of methanol extract of *B. monniera* (L.) showed potent antidepressant-like property and was dose dependent. Serotonin reuptake inhibitors and tricyclic antidepressants such as, amoxapine, desipramine, and imipramine are used for treatmenting depression. These drugs have a lot of side effects such as, visual impairments, sexual disorders, weight gain, digestive disorders, tachycardia, and orthostatic hypotension. Long term application of benzodiazepines leads to memory loss. Herbal medicines have fewer side effects, safe and used to treat various diseases including, cardiovascular diseases, memory loss, cancer, diabetes and depression. Recently, Shahamat et al. (2016) used *P.*

anisum plant for the determination of anti-depressive molecules. The seeds of these medicinal plants showed a number of biological activities, including, anti-stress effects, anti-inflammatory, analgesic, antioxidant, antimicrobial, immunomodulating, anticancer, antidiabetic, antihypertensive, and diuretic properties. Safflower is traditionally used to treat various diseases and has antidiabetic, anti-inflammatory, analgesic, and antioxidant properties. It also shows biological properties such as, immunosuppressive, neuroprotective, antihypertensive, vasodilating and anticoagulant properties (Delshad et al., 2018).

Micromeria is one of the important medicinal plants applied widely in various countries. It can cure or treat asthma, fever, inflammation, cardiac problems, skin diseases and digestive disorders. The species *Micromeria* have cytotoxic, hepatoprotective, gastroprotective, anti-inflammatory, anticholinesterase, antioxidative, antimicrobial and antifungal properties. *Micromeria* species such as, *M. myrtifolia* is used to treat gastrointestinal disorders and gallstone problems. However, the areal part of the plant is used as a sedative or relaxant. The phytochemical components of *M. myrtifolia* revealed oxygenated monoterpene derivatives, monoterpene hydrocarbons, phenolic compounds, oxygenated sesquiterpenes, carboxylic compounds and hydrocarbons (Küpeli-Akkol et al., 2019). Many studies showed that the *B. monniera* (L.) consists of various phytochemicals, including, alkaloid, carbohydrate, phenol, cardiac glycoside, flavonoids, steroid, saponin, tannin and phlobatannin (Saha et al., 2020). Shen et al. (2009) administered 50 mg/kg, 100 mg/kg and 200 mg/kg extract and reduced immobility times (49.7%, 67.2%, and 71.3%) in mice was observed. In this study, immobility times reduced in Albino rat considerably in FST when the methanol extract was administered at various doses. The high antidepressant property may due to the presence of polyphenolic content of methanol extract, increase in active behaviours and decrease in immobility time in swimming. The amount of phenolic and flavonoid content was similar with previous study (Ilavenil et al., 2017).

The antidepressant molecules from the plant extract produce a noradrenergic or dopaminergic elevation considerably reduced immobility by enhancing swimming character. The increased activity of central serotonin by antidepressant molecules reduced immobility time in experimental animals. FST has been used to analyze antidepressant activity of various solvent extracts. For instance, the methanol extract of *Foeniculum vulgare* showed antidepressant property at 250 and 500 mg/kg (Jamwal et al., 2013). In another study, ethanol and aqueous extract of *Pimpinella anisum* showed antidepressant activity at 100 and 200 mg/kg concentration in FST in experimental animal (Shahamat et al., 2016).

One way ANOVA revealed significant variation of MAO-A levels in the animals treated with plant extract and standard than control. MAOs play significant roles in the regulation of many monoamine amine neurotransmitters such as dopamine, 5-hydroxytryptamine and noradrenaline. MAOs consists of MAO-A and MAO-B, these two play potent role in various neurological disorders and physiological functions. The elevated level of MAO-A and B were found with neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Yeung et al., 2019). MAO-A inhibitors has been recommended to treat various mood disorders including depression, however, some of the inhibitors has been used to treat Parkinson's disease (Tzvetkov et al., 2017).

5. Conclusions

The present finding revealed the antidepressant property of *B. monnieri* in methanol extract on Albino rats. The experimental Albino rats were treated with various doses of methanol extracts (50, 100, and 200 mg/kg) and showed improved immobility time in depressions models such as, TST and FST. The experimental animals treated with plant extract showed varying levels of MAO-A activity. MAO - A level of the control animal was 2.87 ± 0.021 ng/mL and it reduced in the experimental albino rats treated with imipramine hydrochloride (2.73 ± 0.09 ng/mL). The impact of methanol extract was dose dependent. *B. monnieri* inhibited MAO-A activity in the brain at higher concentrations. These findings revealed that *B. monnieri* would be an alternative for the treatment of antidepressant disorder.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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