

A Review Study on the Traditional Plants has Potential Antidepressant Property

Abstract

Depression refers to a state of low mood and aversion to activity characterized by depressed mood, loss of interest, reduced energy and concentration. The reasons for the disease include stimulation of MAO-A, inhibition of NA and 5-HT. Symptoms include the diminished interest of pleasure, feelings of worthlessness or inappropriate guilt, a decrease in appetite and libido, insomnia, and recurrent thoughts of death or suicide. There are plenty of synthetic drugs used to treat depression but not enough blissful for patients, moreover, these synthetic drugs have potential side effects. After decades of serious obsession with the modern medicinal system, people have started looking at the ancient healing systems like Ayurveda, Siddha, and Unani. Many scientists are researching plant material for treating this disorder and there are lots of publications on it. But this is not sufficient for treating depression; further outcome should come into light that's the purpose of our review.

Keywords: Depression; Antidepressant; Medicinal plant; Force swimming test; Tail suspension test; Open field test

Review Article

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Abbreviations: HBT: Hole Board Test; FST: Force Swimming Test; TST: Tail Suspension Test; OFT: Open Field Test; EPMT: Elevated Plus Maze Test; MACT: Muscle Coordination Activity Test; THB: Triple Horizontal Bars

Introduction

Mental depression that distresses a person's mood, thoughts, physical health and behavior is a chronic illness. Biological and emotional components are associated with symptoms of depression. Retardation of thought, action and appetite are biological symptoms & emotional indicators include mystery, apathy and pessimism, low self-esteem consisting of feeling of guilt, inadequacy and ugliness, indecisiveness and loss of motivation [1]. World health report shows evidence that about 450 million people all over the world suffer from mental or behavioral syndrome [2,3]. This extends to 12.3% of the worldwide affliction of disease, and grounded to rise up to 15% by 2020 [4]. Patients with major depression have symptoms that reflect changes in brain, monoamine neurotransmitters, specifically nor epinephrine, serotonin, dopamine [5]. It is estimated that by the year 2020, depression will result in second greatest increase in morbidity after cardiovascular disease, presenting a significant socioeconomic burden [6]. Mental depressions are mainly two types, specifically unipolar depression and bipolar depression. In unipolar depression, mood swings are constantly in the identical track and is conjoint (about 75% of cases) non familial, evidently accompanying with traumatic life events and complemented by indicators of anxiety and agitation. The following type is bipolar depression (about 25% of cases) occasionally also called as endogenous depression, displays a familiarized pattern, dissimilar to exterior stresses and frequently seems in premature grown-up life, results in vacillating depression and mania over a

period of a few weeks [7]. Although a number of synthetic drugs are being used as the standard treatment for clinically depressed patients, they have adverse effects that can compromise the therapeutic treatment, these common adverse effect include dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety, agitation, drowsiness, and cardiac arrhythmias. Several drug-drug interactions can also occur. These conditions create an opportunity of alternative treatment for depression by the use of medicinal plants. Since all the synthetic drugs available for the treatment of depression have various adverse effects associated with problematic interactions, our aim is to explore the potential of medicinal plants in the management of depression.

Discussion

This review includes detailed description of antidepressant activity of 21 medicinal plants whose roots, leaves, fruits extracts were used to evaluate the activity from various research articles. The tests employed for antidepressant activity includes HBT, FST, TST, OFT, EPMT, and MACT using rotarod and THB. These tests are employed with slight modification from original method, keeping basic concept same.

HBT

Exploratory behaviour of rodents such as mice is evaluated using hole board test. The floor of the apparatus has regularly arranged holes. The animal is placed in the arena. Both frequency and duration of spontaneous elicited hole-poking behavior are then measured during a short period of time. This test also provides a simple method for assessing anxious response of a rodent to an unfamiliar environment. The use of the hole-board in this perspective relies on the hypothesis that the behavior of animals exposed to a novel situation results from competition

between an exploratory tendency and a withdrawal tendency. Thus, anxiety is inversely related to head-dipping behaviour of mice. Other associated behaviors that can be evaluated using the hole board test are grooming, rearing and locomotion [8].

FST

FST is also known as behavioral despair test, is a widely used behavioral test for determining antidepressant activity of a compound. This method is described according to Porsolt [9,10]. In this test, experimental animals are divided randomly into control, standard and extract with five animals in each group. Test preparations are administered once daily over a period of 14 days. Experiment is separated into two sessions with 24 hours interval. In the first session, animals are placed into an acrylic cylinder individually filled with water for 15 minutes. Immobility is not scored in this session. The objective of this session is to adapt the animals to experimental situation as well as to persuade stable and high level of immobility during test session. Twenty-four hours after the pre-test session, the animals were once again exposed to the same conditions for 5 min (test session). Between the pretest session and main session, drug solutions are then administered orally three times as follows: just after the pre-test session, 5 h before the main test, and 1 h before the main test. A mouse is judged immobile if it remained floating in the water, except for small movements to keep its head above the water.

TST

Basic concept of the protocol of TST is similar to FST and differs in that immobility is persuaded by suspending the tail of the experimental animal. Before administering the drug weigh each animal. After administration of the drug, wait for some time to initiate the test, usually 30 min for intraperitoneal and subcutaneous injections, and 60 min for oral administration. Animal's tail is wrapped by adhesive tape to a constant position three quarters of the distance from the base tail. The animal was observed continuously for 6 minutes. To prevent bias in animal behavior test should be performed using blind with coded solutions [11].

OFT

OFT is used to measure anxiety and exploration as well as locomotion in a large field. Mice were placed into the center or one of the four corners of the open field and allowed to explore the apparatus for 5 minutes. To assess the process of habituation to the novelty of the arena, mice were exposed to the apparatus for 5 minutes on 2 consecutive days. The number of line crosses and the frequency of rearing are usually used as measures of locomotor activity, but are also measures of exploration and anxiety. The number of central square entries and the duration of time spent in the central square are measures of exploratory behaviour and anxiety. A high frequency/duration of these behaviors' indicates high exploratory behaviour and low anxiety levels [12].

EPMT

The elevated plus maze test is one of the most widely used tests for measuring anxiety-like behavior. The test is based on

the natural aversion of mice for open and elevated areas, as well as on their natural spontaneous exploratory behavior in novel environments. The apparatus consists of open arms and closed arms, crossed in the middle perpendicularly to each other, and a center area. Mice are given access to all of the arms and are allowed to move freely between them. The number of entries into the open arms and the time spent in the open arms are used as indices of open space-induced anxiety in mice [14].

MCAT

Behavior is made manifest by action, and action requires motor skills, including coordination of the body. MCAT is employed to detect antidepressant activity by evaluating muscle activity. Several apparatus along with distinct procedure are described by Deacon et al. [13].

Rotarod: The Rotarod uses a rod with rotating ability, 3 cm in diameter and supported 30 cm above the base of the apparatus. The surface is knurled in a series of parallel ridges along the longitudinal axis, enabling the mice to grip it effectively. The start speed is adjusted to 4 rpm; the acceleration rate to 20 rpm/min. Maximum speed is 40 rpm. Two flanges prevent the mouse from leaving the rod. They are 30 cm in diameter (this could probably be reduced to 20 cm). Their separation is set at 6 cm (maximum) but may need to be adjusted smaller for sub-adult mice if they tend to turn around on the rod.

THB: The bars are made of brass, 38 cm long, held 49 cm above the bench surface by a wooden support column at each end. The columns are secured to a heavy wooden base. Three bar diameters are available: 2, 4 and 6 mm. The 2 mm bar is the standard, but many mice reach maximum scores on this. Therefore larger diameter bars have been included in an attempt to refine the test, as mice cannot grip these so well.

Traditional plants having potential Antidepressant activity

Centella asiatica Linn

Centella asiatica (CA), a clonal, perennial herbaceous creeper belongs to the family umbellifere (Apiceae). Preliminary phytochemical studies showed the presence of Saponins, Terpenoids, Alkaloids, and Phenols [15]. The plant possess cardiogenic, nerve tonic, sedative to nerves, stomachic, carminative, improves appetite, antileptotic, memory and febrifuge [16]. Several investigations have proposed that this plant possess sedative and anxiolytic [17], antiepileptic [18], memory enhancing [19], cardioprotective [20] and immunomodulation activity. This plant also found to possess antidepressant activity [21].

Momordica charantia

This plant is known as bitter melon, bitter gourd, balsam pear, karela, and pare. It grows in tropical areas of the Amazon, East Africa, Asia, India, South Africa, and the Caribbean and is used traditionally as both food and medicine. Its phytochemicals are alkaloids, flavonoids, glycosides, triterpenoids, steroids, phenols, tannins, oils and fats [22-23]. M. charantia has also been already

documented as antidepressant and anti-anxiety herb. Yet, very less data available on systematic biological investigation about leaves, seeds and root [24-25] of this plant and fruit has never been subjected to systematic biological investigation. The antidepressant activity of unripe fruit along with leaves of *M. charantia* is evaluated using stress induced depression models like FST and TST [26-27].

Tecoma stans

Flowers of *Tecoma Stan* Linn popularly known as “yellow bell flowers” contain flavonoids. Leaves of *Tecoma Stan* contain the alkaloids tecomin and tecostamine are potent hypoglycemic agent when given intravenously. Anthranilic acid is responsible for the antidiabetic activity. Roots are powerful diuretic and vermifuge [28]. *Tecoma* is not a toxic because this plant is used in Latin America as a remedy for diabetes and moreover for feeding cattle and goats in Mexico [29]. Flavonoids have been established to have antidepressant activity [30].

Clitoria ternatea

Clitoria ternatea (CT), a perennial herbaceous plant commonly known as ‘butterfly pea’, has been used for centuries as a traditional Ayurvedic medicine. The roots have laxative, diuretic, anthelmintic and anti-inflammatory properties, and they are useful in severe bronchitis, asthma and hectic fever [31,32]. *Clitoria ternatea* has been reported for nootropic, anxiolytic, anticonvulsant [33], anti-diabetic [34], and antipyretic, anti-inflammatory and analgesic activities [35], among others. It enhances the memory [36] and increases acetylcholine content in rats [37] as well as antidepressant activity [38].

Cucurbita pepo

The species, *Cucurbita pepo* is a cultivated plant of the genus *Cucurbita*. Aqueous and alcoholic extract of *Cucurbita pepo* produced significant antidepressant-like effect in mice in FST and its efficacy was found to be similar to Imipramine. This test is quite sensitive and relatively specific to all major classes of antidepressant drugs. In FST, rats are forced to swim in restricted space from which they cannot escape. This induces a state of behavioral despair in animals, which is claimed to reproduce a condition similar to human depression [39].

Aegle marmelos

Aegle marmelos (AM), a highly reputed Ayurvedic medicinal tree commonly known as the bael fruit tree is found all over India. The tree is endowed with various medicinal properties. Several studies on different parts of AM showed that the plant possess Antidiarrhoeal [40], antidiabetic [41], anticancer [42], radio protective [43], antifungal [44], antimicrobial [45], anti-micro filarial [46], anti-inflammatory, antipyretic and analgesic activities [47]. Methanol leaf extract of *Aegle marmelos* showed significant anxiolytic and antidepressant activities possibly by increasing monoamines level at post synaptic sites. Hence *Aegle marmelos* may be served as a potential resource for natural psychotherapeutic agent against stress related disorders such as anxiety and depression [48].

Rosmarinus officinalis

Rosmarinus officinalis, traditionally known as rosemary, grows wild in most Mediterranean countries [49]. It is often cultivated for its great quantity of essential oils used in the perfume industry and as a flavoring agent. Rosemary has been widely used in traditional medicines and it has been found to have significant antioxidant activity [50]. It has long been known as the herb of remembrance [51], and it has been reported that memory is improved with the use of *R. officinalis* [52,53]. Salvigenin, rosmanol and cirsimaritin compound was isolated from *Rosmarinus officinalis*. It was also found to have antidepressant activity [54].

Melissa officinalis

Melissa officinalis (*Lamiaceae*) or lemon balm is an herbal medicine native to the eastern Mediterranean region and western Asia. Dried or fresh leaves and top aerial section of the plant are the parts which are used as medicine [55]. Lemon balm has been traditionally used for different medical purposes as tonic, antispasmodic, carminative, diaphoretic, surgical dressing for wounds, sedative-hypnotic, strengthening the memory, and relief of stress induced headache [56]. It is currently used for the relief of stress-induced headache, as a mild sedative-hypnotic, and as an antiviral to improve healing of herpes simplex cold sores [57]. All doses of the aqueous extract, used in the study, produced a significant reduction in immobility along with an increase in climbing behavior which is similar to those which have been observed with Imipramine. Essential oil caused a dose-dependent reduction in immobility and an increase in climbing at all studied doses, compared to control group. Only the highest dose (300mg/kg) of essential oil showed a significant increase in swimming behavior. The aqueous extract, but not the essential oil, decreased spontaneous activity in a dose dependent manner [58].

Cassia occidentalis

Cassia Occidentalis is a native plant of southern India, called as Kasmard in Sanskrit, Kasondi in Hindi and Coffee senna in English belongs to family Caesalpiniaceae. Its common name is ponnnavari. The parts used are leaves, seeds and roots. It is used for fever, menstrual problems, tuberculosis and as a tonic for general weakness and illness [59]. *Cassia occidentalis* leaf extracts have antibacterial [60-62], antiplasmodial [63], antimutagenic [64], hepatoprotective [65] and anti-diabetic activity [66]. The plant was also evaluated for the anti-anxiety and antidepressant activity [67].

Basella alba L

Basella alba L. (Synonym: *Basella rubra* Roxb.) is an extremely heat tolerant [68], fast growing perennial vine which belongs to family Basellaceae [69]. It is commonly known as Malabar spinach, Indian spinach, Ceylon spinach, vine spinach [70], climbing spinach [71], East-Indian spinach, Chinese spinach [72] and cyclone spinach [73]. *Basella* is native to tropical Southern Asia, probably originated from India or Indonesia [74]. Numerous bioactive compounds such as flavonoids, Saponins, Phenolic and tannins have been isolated from leaves of *Basella alba*. They are found to possess antidepressant activity [75].

Passiflora foetida

Passiflora foetida (*Passifloraceae*), popularly known as stinking passion flower, is an herbaceous climber that has been widely used in Mexican traditional medicine for the treatment of different central nervous system (CNS) disorders. Chemical constituents in *Passiflora foetida* include hydrocyanic acid, groups of flavonoids and Harman alkaloids [76]. Some reports have pointed out the harman alkaloids as the bioactive constituents of *Passiflora incarnata* Linn, one of the species of *Passiflora* that have been extensively studied chemically and biologically [77,78]. It has found to possess antidepressant activity [79].

Urtica dioica

The present study indicates that *Urtica dioica* produces a specific antidepressant-like effect in animal models predictive of antidepressant properties, FST and TST. Moreover, the effect of the acute or repeated administration of this extract was similar to the action produced by the classical antidepressant fluoxetine and haloperidol [80].

Andrographis paniculata

Andrographis paniculata (*Acanthaceae*) is an Indian herbal medicine used as an anti-inflammatory and antipyretic drug for the treatment of fever, cold, laryngitis, diarrhea, and rheumatoid arthritis [81]. The behavioral despair model was performed in order to investigate the ability of this herbal drug in the elevation of suppressed mood, which is quite common in today's scenario. The results obtained from FST and TST clearly reveals the fact that this drug is potentially quite useful in cases of depression [82].

Hypericum Species (H. perforatum L. and H. maculatum C)

Hypericum perforatum L. (*Hypericaceae*), commonly known as St. John's wort, is one of the best investigated medicinal plants. *Hypericum perforatum* L. (*Hypericaceae*). *H. perforatum* is widely used for the treatment of mild to moderate forms of depression. Some well documented clinical studies [83] had shown that alcoholic extract from these plants have at least the same efficiency as the conventional drugs but with far less side effects. It has been suggested that *H. maculatum* has antipanic and anxiolytic effects on human subjects [84].

Eichhornea crassipes

Eichhornea crassipes commonly known as water hyacinth is a free-floating perennial aquatic plant belongs to the family of Pontederiaceae. The primary chemical constituents are carbohydrates, alkaloids, flavonoids, tannins, saponins, terpenoids, alkaloids, proteins, and phenols they also contain iron, manganese, and zinc [85]. In the traditional medicine, *E. crassipes* used as nervine tonic, stimulant, antispasmodic, antioxidant, antidepressant [86].

Selaginella bryopteris

Selaginella bryopteris is a pteridophytic plant belongs to the family selaginellaceae. Its familiar name is sanjeevani booti. *Selaginella bryopteris* is a lithophytes that grows on the hills of tropical areas, particularly the arawali mountain terrain from

east to west in India and the plants grow luxuriantly during rains exhibiting a lush green velvety landscape. During summer the plants undergo extreme desiccation; fronds curl and become dry virtually dead. In this condition they look like closed fist hence often known in Unani as punjemariam or hathazori. The dry plants when left in water unfold their fronds, turn green and come back to active life. This plant has been found to have antidepressant activity [87].

Artemisia absinthium

Artemisia absinthium (*Asteraceae*) is widely used in Iranian traditional medicine. *Artemisia absinthium* L. (wormwood) (*Asteraceae*) is an aromatic-bitter herb, used as traditionally in Iran. This species known to possess ethno medical and biological properties related to anthelmintic activity [88], antifungal [89], antimicrobial activity [90], choleric, antiseptic, balsamic, depurative, digestive, diuretic, emmenagogue and in treating leukemia and sclerosis [91]. Essential oil composition of this species was reported previously [92]. Its antidepressant activity was also established [93].

Alafia multifora

Alafia multifora (*Apocynaceae*) is a medicinal plant widely distributed in the tropical region of Africa. Phytochemical screening of the stem bark showed the presence of phenols, tannins, flavonoids, anthraquinones, and alkaloids [94]. A wide range of plant-derived flavonoids, terpenes, can cross the blood-brain barrier and are able to influence brain function [95] such as the modulation of the function of inotropic GABA receptors. Due to the presence of flavonoids in the extract of *A. Multifora* and its higher antioxidant activities, it is presumed that this plant might have pharmacological effects at the level of the central nervous system including antidepressant activity [96].

Citrus maxima

Citrus maxima Merr. (*Rutaceae*) is known as pummel. It has been used in indigenous system of medicine as sedative in nervous affections, convulsive cough and in the treatment of hemorrhagic diseases and epilepsy [97] as well as depression [98].

Rosa damascene

R. damascene is a medicinal plant that is mostly known in the world for its perfume effect. However, in traditional medicine, it has been used for treatment of abdominal and chest pain, strengthening the heart, menstrual bleeding, and digestive problems. It also has beneficial effects on depression [99].

Bacopa monniera

Bacopa monniera (Family: Scrophulariaceae), commonly known as Brahmi, is an aquatic herbs distributed throughout the warmer regions of the world including Bangladesh. In Bangladesh, this plant is extensively used in the traditional medicine system as potent therapeutic agent as a neurological tonic to enhance intellectual development [100], to treat epilepsy [101], cardiac [102], respiratory [103] and digestive [104] disorders, toothache and purifies blood. In some parts of this country, Brahmi is used to treat rheumatism and to prevent miscarriage [105]. Its antidepressant activity was also found [106](Table 1).

Table 1: Traditional plants having potential Antidepressant property.

Plant Name	Extract	Animal Model	Method of Testing	Reference Standard Drug	Dose	Reference
Centella asiatica. Linn	Ethanollic Extract of Leaves	Male Wister rats	FST HBT	Imipramine (30 mg/kg)	100 mg/kg 300 mg/kg	21
Momordica charantia	Ethanollic Extract of unripe fruit	Swiss albino female mice	FST TST	Imipramine (15 mg/kg)	100 mg/kg 300 mg/kg 500 mg/kg	27
Tecoma stans	Methanollic and aqueous extract of flowers	male Swiss Albino mice	FST TST	Imipramine (10 mg/kg, i.p.)	30 mg/kg 100 mg/kg	30
Clitoria Ternatea	Ethanollic extract of root	Swiss albino mice and albino rats of either sex	OFT MCAT	Imipramine (15 mg/kg, p.o.)	150 mg/kg 300 mg/kg	38
Cucurbita pepo	Alcoholic and aqueous extract of seeds	Male albino Wistar rats	FST	Imipramine (30mg/ kg)	100 mg/ kg	39
Aegle marmelos	Methanollic Extract of Leaves	Male Swiss Albino mice	EPM TST Digital photoactometer	Imipramine (20 mg/kg) and Fluoxetine (20 mg/ Kg).	75 mg/kg 150 mg/kg 300 mg/kg	48
Rosmarinus officinalis	Isolation of salvigenin, rosmanol and cirsimaritin	Male Swiss Albino mice	FST TST	Imipramine (60 mg/kg)	50-200 mg/kg	54
Melissa officinalis	Aqueous extract of leaves & Essential oil	Male Swiss Albino mice	FST	Fluoxetine (20 mg/kg) and Imipramine (15 mg/kg)	Aqueous extract (25, 75, 150, 300 mg/kg), essential oil (10, 25,75, 150, 300 mg/kg)	58
Cassia occidentalis	Ethanollic and aqueous extract of leaves	Wistar rats (150-200 g) and Swiss albino mice (18-22g) of either sex	FST TST	Fluoxetine (10mg/kg i.p)	500 mg/kg of both aqueous & ethanollic extract	67
Basella alba L	Methanollic extracts of leaves	Swiss albino mice (40-50g) of either sex	FST TST	-	25 mg/kg 50 mg/kg	75
Passiflora foetida	Methanollic extracts of leaves	Male Swiss albino mice	TST FST OFT	Fluoxetine (20 mg/kg) and Imipramine (15 mg/kg)	100 mg/kg 200 mg/kg 300 mg/kg	79
Urtica dioica	Roots and leaves extract	Mice of either sex	FST TST	Fluoxetine (10 mg/kg)	50 mg/kg 100 mg/kg	80
Andrographis paniculata	Ethanollic extract of leaves	Rats of either sex	FST TST	Imipramine (30 mg/kg)	50 mg/kg	82
Hypericum Species (H. perforatum L. and H. maculatum C)	Ethanollic extract of the aerial parts	Female Swiss mice	FST	-	70 mg/kg	84
Eichhornea crassipes	Aqueous and chloroform extract of leaves and shoots	Swiss albino mice of either sex	FST TST	Imipramine (10 mg/kg, p.o)	100 mg/kg 200 mg/kg	86

Selaginella bryopteris	Pet ether, Chloroform Methanol, Ethanol, and aqueous extracts	Swiss albino mice of either sex	HBT Rotarod test	Diazepam (10mg/kg)	250 mg/kg 500 mg/kg	87
Artemisia absinthium	Methanolic extract of aerial parts	Swiss albino mice of either sex	FST TST	Imipramine (5 and 10 mg/kg)	125 mg/kg 250 mg/kg 500 mg/kg 1000 mg/kg	93
Alafia multiflora	Aqueous extract of stem barks	Wistar albino rats and Swiss albino mice of either sex	OFT EPMT	Fluoxetine (10mg/kg, i.p)	150 mg/kg 300 mg/kg	96
Citrus maxima	Aqueous extract of leaves	Swiss albino mice of either sex	FST TST OFT	Fluoxetine (20 mg/kg, i.p.) and Imipramine (30 mg/kg, i.p.)	100 mg/kg 200 mg/kg 300 mg/kg	98
Rosa damascene	Ethanollic extract of flower	Male albino mice	FST	Imipramine (15 mg/kg, i.p)	15 mg/kg 60 mg/kg 90 mg/kg	99
Bacopa monniera	Methanolic extract of leaves	Swiss Albino mice	FST OFT TST	Imipramine hydrochloride (30 mg/kg)	50 mg/kg 100 mg/kg 200 mg/kg	106

HBT: Hole Board Test; FST: Force Swimming Test; TST: Tail Suspension Test; OFT: Open Field Test; EPMT: Elevated Plus Maze Test; MACT: Muscle Coordination Activity Test; THB: Triple Horizontal Bars

Result and Discussion

Since ancient times, people have been using plants in various ways as a source of medicine. We believe that plants having the potential anti-depressant activity can be used as an adjuvant in the treatment of depression and other mood disorders. The collections of herbal plants showing the antidepressant activity were tabulated from the various journals and were reported above. We can conclude that herbal plants are very rich source which is responsible for increasing the antidepressant activity. The plants discussed above having antidepressant property were assessed by different tests. However, further studies are necessary to find the exact mechanism of antidepressant effect and to isolate the active compound (s) responsible for this pharmacological activity.

Conclusion

Marketed antidepressant drugs used for the depression treatment may cause side effects such as vomiting, nausea, irritation, insomnia, tremor, blurred vision, urinary retention etc. To overcome this, natural medicines are used for treatment of depression which will have very less side effects. The aim of our study is to find out new and innovative treatment of depression having fewer side effect (e.g. sedation and anti cholinergic effect), lower toxicity in higher dose, rapid onset of action, greater efficacy, effective in patients non responsive to TCAs and MAOIs.

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Conflict of Interest

No conflict of interest.

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