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Research Article

ANTIDEPRESSANT ACTIVITY OF SPIRULINA PLATENSIS IN EXPERIMENTALLY INDUCED DIPRESSION IN MICE

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ABSTRACT

The spray dried powder of Spirulina platensis was used to treatment of depression in different doses (100mg/kg, 200 mg/kg and 400 mg/kg) and Impramine (15mg/kg) as standard drug in experimental animal models like Forced swim test in mice, Tail suspension test in mice, Clonidine induced aggression behaviour in mice test, L-dopa induced hyper activity and aggressive behavior in mice, 5-HT induced head twitches in mice, From all the experimental model results were observed that the Spirulina platensis was possess the dose dependent anti depressant activity.

Keywords: Spirulina platensis , Depression, Imipramine, 5-HT, L-dopa, Clonidine.

INTRODUCTION

The monoamine biochemical theory of depression is the monoamine hypothesis, proposed by Schildkraut in 1965, which states that depression caused by a functional deficit of monoamine transmitters at certain sites in the brain, while mania results from functional excess. (Baker and Dewhurst, 1985; Maes and Meltzer, 1995; Manji et al., 2001) Mood disorders are among the most prevalent forms of mental illness. Severe forms of depression affect 2%–5% of the U.S. population, and up to 20% of the populations suffer from milder forms of the illness. Depression is almost twice as common in females as males. Another roughly 1%–2% are afflicted by bipolar disorder (also known as manic-depressive illness), which affects females and males equally. Mood disorders are recurrent, life threatening (due to the risk for suicide), and a major cause of morbidity worldwide (Nestler et al., 2002).

Human studies have reported a number of oxidative disturbances in patients with major depression, including oxidative damage in erythrocytic membranes as suggested by the depletion of omega-3 fatty acids (Peet et al., 1998); elevated lipid peroxidation products; oxidative DNA damage; increased concentrations of the endogenous inhibitor of endothelial Nitric oxide (NO) synthase asymmetric dimethyl arginine and decreased NO.

Human studiesas well as animal studies have suggested that major depression produced by CMS is associated with elevated lipid peroxidation levels (Bilici et al., 2001). On the other hand, it has been reported that increased ROS production may cause the destruction of phospholipids and altered viscosity of neuron membranes, and consequently the changes in membrane viscosity may affect serotonergic and catecholaminergic receptor functions.

In addition, MDA directly exerts inhibitory effect on serotonin binding areas on the recptor. An intricate relationship exists between serotonin metabolism and oxidative stress (Bilici et al., 2001).

The effect of increasing monoamine levels (dopamine, 5-HT and NE) on BDNF and growth factors may be one mechanism that produces the antidepressant response.

The antidepressant effects such as the naphthodianthrone hypericin, the phloroglucinol derivative hyperforin (Chatterjee et al., 1998), and the flavonoids hyperoside, miquelianin, and isoquercitrin. Furthermore, flavonoids as well as hypericin had an effect on HPA axis function and related gene expression in both stressed and unstressed animals after repeated administration.

The barks of Magnolia officinalis have been used in traditional Chinese medicine to treat a variety of mental disorders including depression (Wang et al., 2005). These results suggested that the mixture of honokiol and magnolol possessed potent antidepressant-like properties in behaviors involving the normalization of biochemical abnormalities in the serotonergic system in rats (Xu et al., 2008). In animal models of depression rely on one of two principles: actions of known antidepressants or responses to stress (Porsolt, 2000; Lucki, 2001). These behavioral tests have not normally been utilized in depression research and may offer new insights into the neurobiological mechanisms involved (Nestler et al., 2002).

Consequently, CRH hyper function, as well as monoamine hypo function, may be associated with depression (Holsboer, 1999).

MATERIALS AND METHODS

Plant materials

The spray dried powder of Spirulina platensis is employed in this experiment was obtained from Nihal traders Pvt. Ltd, Hyderabad.

Experimental animals

Wistar strain albino rats (150-200 g) and albino mice (20-30 g) of either sex were obtained from Sainath Agencies, Hyderabad. The animals were housed in polypropylene cages at an ambient temperature of 25 °C± 1°C and 45–55% RH, with a 12:12 h light/dark cycle. The animals had free access to commercial food pellets and water ad libitum unless stated otherwise. Animals were acclimatized for at least one week before using them for experiments and exposed only once to every experiment. The care and maintenance of the animals were carried out as per the approved guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The research protocols were approved by the Institutional Animal Ethical Committee (IAEC).

DRUGS AND CHEMICALS

Thiobarbituric acid and DTNB reagent (HiMedia Laboratories Ltd., Mumbai), Trichloroacetic acid (Qualigens Fine Chemicals, Mumbai), Riboflavin (Astra IDL, Bangalore), Sodium dihydrogen phosphate and Disodium hydrogen phosphate (S.D. Fine Chemicals, Mumbai), Lorazepam (Ranbaxy, India), 1,1,3,3,-Tetraethoxy propane, O-Dianisidine, Imipramine hydrochloride, 5-Hydroxy Tryptophan (5-HTP), Clonidine and L-DOPA (Sigma, St. Louis, USA) were used in the study. The other chemicals and solvents used were of analytical grade and purchased from commercial suppliers. Imipramine (IMP), 5-HTP, clonidine, L-DOPA, Lorazepam was administered intraperitoneally by dissolving in normal saline.

ACUTE TOXICITY STUDY

Acute toxicity study – up and down procedure – was carried out as per the guidelines set by Organization for Economic Co-operation and Development (OECD). If animal dies at particular dose, lower dose was given to next animal and if animal survives at a particular dose next higher dose was given for remaining animals. The maximum upper limit dose 2000 mg/kg of SP was administered orally to mice. Animals were observed individually after dosing. Observation included mortality and clinical signs, such as changes in skin fur, eyes and mucous membranes.

GROSS BEHAVIOUR IN RATS

The gross behaviors, e.g. body positions, locomotion, rearing, tremors, gait was observed. The effect of SP on passivity, grip strength, pain response, stereotypy, vocalization, righting reflex, body weight and water intake was assessed (Lipnic et al., 1995). Pilot study was carried out with various doses (50, 100, 200 and 400 mg/kg, per oral route to rats) of SP. At doses of 100, 200 and 400 mg/kg, it was active and at 50 mg/kg it was inactive. Based on this observations three different doses (100, 200 and 400 mg/kg) of SP were selected in the present studies.

DRUG TREATMENT SCHEDULE

Animals were divided into five groups of six animals each except in antioxidant studies, where six groups of animals (n= 6) were taken. The animals were pretreated orally with 0.3% Carboxymethylcellulose (CMC) suspension of SP for 7 days daily at the doses of 100, 200 or 400 mg/kg/day. All the experimental procedures were started on day 7, 1 h after the drug administration. In case of FST (8 days) the drug administration was continued till the end of the experimental schedule. Control (I group) rats received the vehicle (0.3% CMC suspension), Group II, III and IV rats received the SP at the doses of 100, 200 and 400 mg/kg/day, p.o. respectively and group V rats received either IMP (15mg/kg, i.p.) or Lorazepam (2.5 mg/kg, i.p.).

IN VIVO MODELS OF DEPRESSION EMPLOYED IN THE STUDY

Forced swimming test (FST)

Principle: Behavioral despair was proposed as a model to test for antidepressant activity. It was suggested that mice or rats forced to swim in a restricted space from which they cannot escape are induced to a characteristic behavior of immobility. This behavior reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression.

Advantages of the method are the relative simplicity and the fact that no interaction with other drugs is necessary. Like in other behavioral tests, e.g. the catalepsy test in chicken, not only antidepressants and monoamine oxidase inhibitors but also central stimulants give positive results.

Procedure: The procedure was described by Porsolt et al. (1978) was used. Swimming sessions were conducted by placing rats in individual glass cylinders (45 cm high×20 cm in diameter) containing (25±2 °C) water 38 cm deep, so rats could not support themselves by touching the bottom with their feet. Two swimming sessions were performed between 12:00 h and 19:00 h, an initial 15 min pretest followed 24 h later by a 6 min test.

Rats were divided into 5 groups (n=6)

Group-1 vehicle (0.3% CMC)
Group-2 Spirulina (100 mg/kg, p.o.)
Group-3 Spirulina (200 mg/kg, p.o.)
Group-4 Spirulina (400 mg/kg, p.o.)
Group-5 Imipramine (15 mg/kg, i.p.)

Doses were given once daily for 7 days. On the 7th day rats were subjected to 15 min pretest. After 15 min, in the water the rats were removed and allowed to dry in a heated enclosure (32 °C) before being returned to their home cages. They were again placed in the cylinder 24 h later and the total duration of immobility was measured during a 6 min test. Floating behavior during this 6 min period had been found to be reproducible in different groups of rats. An animal was judged to be immobile whenever it remains floating passively in the water in a slightly hunched but upright position, its nose just above the surface. The total immobility time for the period of 6 min was recorded with the help of stopwatch.

Tail suspension test (TST)

Principle: The "tail suspension test" has been described by Steru et al. (1985) as a facile means of evaluating potential antidepressants. The immobility displayed by rodents when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in humans. Clinically effective antidepressants reduce the immobility that mice display after active and unsuccessful attempts to escape when suspended by the tail.

Procedure: Mice were divided into 5 groups (n=6)

Group-1 vehicle (0.3% CMC)
Group-2 Spirulina (100 mg/kg, p.o.)
Group-3 Spirulina (200 mg/kg, p.o.)
Group-4 Spirulina (400 mg/kg ,p.o.)
Group-5 Imipramine (15 mg/kg, i.p.)

Doses are given once daily for 7 days. On the 7th day, 1hr after the administration of the test and standard drugs, mice were suspended on the edge of a table 50 cm above the floor by the adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6 min period (Rodrigues et al., 2002). Animal was considered to be immobile when it did not show any movement of body and hanged passively.

5-HTP induced head twitches in mice

Principle: According to the monoamine hypothesis of depression compounds exert antidepressant activity because they are capable of enhancing central noradrenergic and/or serotoninergic functions. Several antidepressant agents potentiate serotonin effects by a block of the re-uptake of

serotonin. DL-5-Hydroxytryptophan is used as the precursor of serotonin. Enzymatic breakdown is inhibited by the MAO-inhibitor pargyline. In mice the characteristic symptom of head twitches is observed.

Procedure: Mice were divided into 5 groups (n=6)

Group-1 vehicle (0.3% CMC)
Group-2 Spirulina (100 mg/kg, p.o.)
Group-3 Spirulina (200 mg/kg, p.o.)
Group-4 Spirulina (400 mg/kg, p.o.)
Group-5 Imipramine (15 mg/kg, i.p.)

Doses were given once daily for 7 days. On the 7th day, 1hr after the administration of the test and standard drugs, mice were treated with 5-HTP (100 mg/kg i.p.) and the numbers of head twitches performed by each mice was counted by staggering method using three 2 min periods (19–21 min), (23–25 min), (27– 29 min) after 5-HTP administration and number of head twitches were scored live by a blind observer (Schreiber et al., 1995).

Clonidine-induced aggression in mice

The method of Morpurgo (1968) was used. Mice were divided into 5 groups of 8 each (n=8), each group contain 4 pairs of mice, two pairs from each sex (each pair contained same sex of mice).

Group-1 vehicle (0.3% CMC)
Group-2 Spirulina (100 mg/kg, p.o.)
Group-3 Spirulina (200 mg/kg, p.o.)
Group-4 Spirulina (400 mg/kg, p.o.)
Group-5 Lorazepam (2 mg/kg, i.p.)

Doses were given once daily for 7 days. On the 7th day, Clonidine was given 1 h after the administration of the test and standard drugs. The animals were then caged in bell shaped glass jar with a floor area of approximate 16 cm2. The biting/fighting episodes were recorded live by a blind observer over a period of 30 min, in each pair.

L-DOPA induced hyper activity and aggressive behavior in mice (LHA)

Mice were treated with L-DOPA (100 mg/kg i.p.) and the experiment was performed according to the method of Serra et al., 1990. Mice were divided into 5 groups of 8 each (n=8), each group contain 4 pairs of mice, two pairs from each sex (each pair contained same sex of mice).

Group-1 vehicle (0.3% CMC)
Group-2 Spirulina (100 mg/kg, p.o.)
Group-3 Spirulina (200 mg/kg, p.o.)
Group-4 Spirulina (400 mg/kg, p.o.)
Group-5 Lorazepam (2 mg/kg, i.p.)

Doses were given once daily for 7 days. On the 7th day, L-DOPA was given 1 h after the administration of the test and standard drugs, Stages of activity and aggressive behavior were recorded live every 10 min for 30 min after L-DOPA administration by the blind observer. The different parameters of observation were piloerection, salivation, increase in motor activity, irritability, reactivity, jumping squeaking, and aggressive fighting. The scores were graded in the following manner:

0-No effect; **1**-Piloerection, slight salivation, slight increase in motor activity; **2**-Piloerection, salivation, marked increase in motor activity and irritability; **3**-Piloerection, profuse salivation, marked increase in motor activity, reactivity, jumping, squeaking and aggressive fighting.

STATISTICAL ANALYSIS

Results were expressed as mean ± S.E.M. Statistical analysis was performed using one-way analysis of variance (ANOVA). If the overall P-value was found statistically significant ($P < 0.05$), further comparisons among groups were made according to Newman Keuls test. All statistical analyses and the diagrammatic representation of the data were performed by using Graph pad Prism, Version 5 software.

RESULTS

Forced Swim Test (FST) results showed that both SP (100, 200 and 400 mg/kg, p.o.) and imipramine (15 mg/kg, i.p.) significantly decreased the duration of immobility time in a dose dependent manner in FST model. Post-hoc analysis showed that the SP (100, 200 and 400 mg/kg) and Imipramine (IMP) treated groups were significantly different ($p<0.001$) from the vehicle treated group (Fig. 1).

Tail Suspension Test (TST) results showed that both SP (100,200,400 mg/kg, p.o.) and imipramine (15 mg/kg, i.p.) significantly decreased the duration of immobility time in a dose dependent manner in TST model. Post-hoc analysis showed that the SP (100, 200 and 400 mg/kg) and IMP treated groups were significantly different ($p<0.001$) from the vehicle treated group (Fig. 2).

5-HTP induced head twitches in mice were represented the effect of SP and IMP on 5-HTP-induced head twitches in

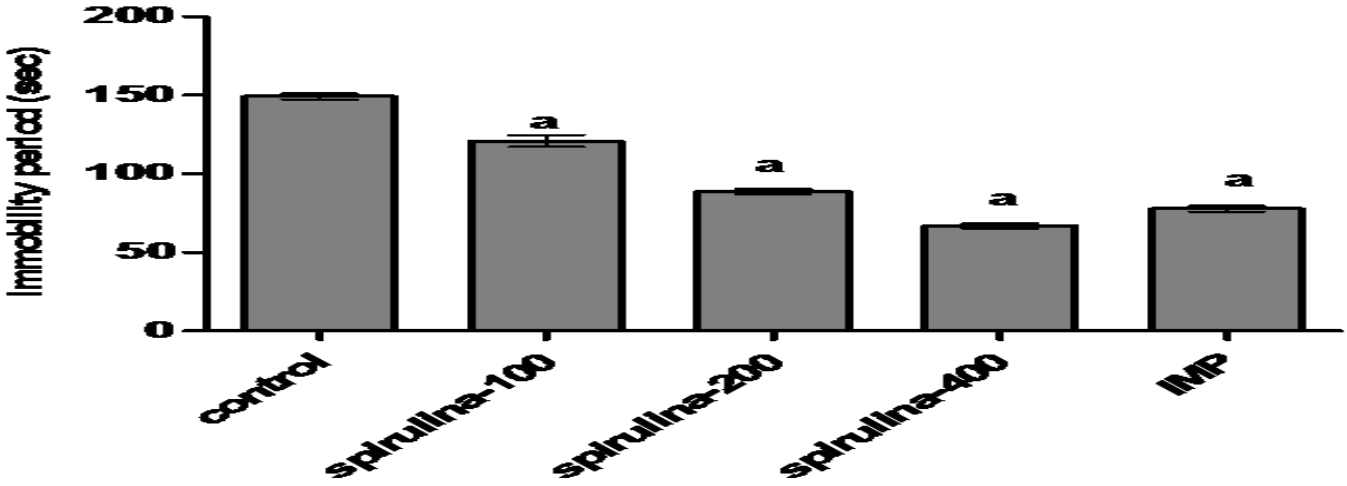

Figure1. Effect of *SP* on forced swim test (FST) , the values were Mean ± S.E.M. (n = 6). a = p<0.001 compared to control.

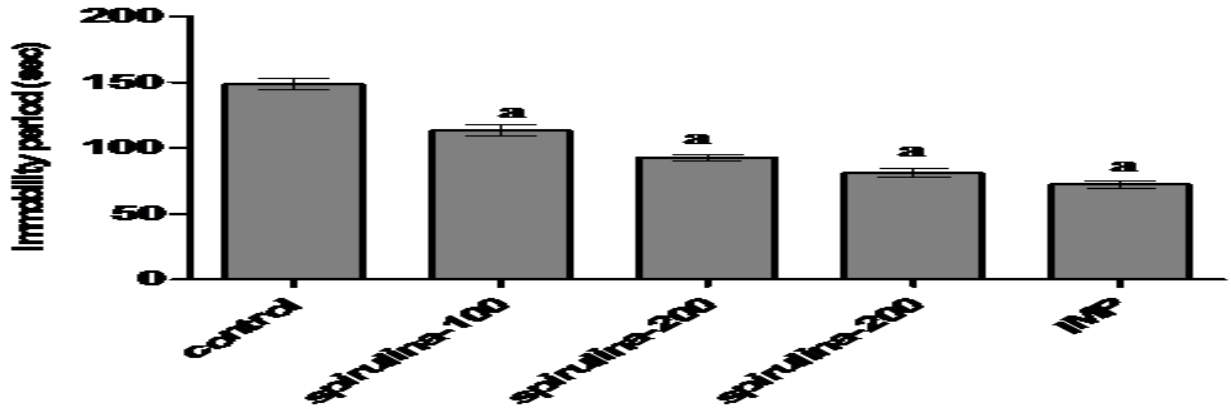

Figure 2. Effect of SP on tail suspension test (TST) in mice, the values were Mean ± S.E.M. (n = 6). a = p<0.001 compared to control.

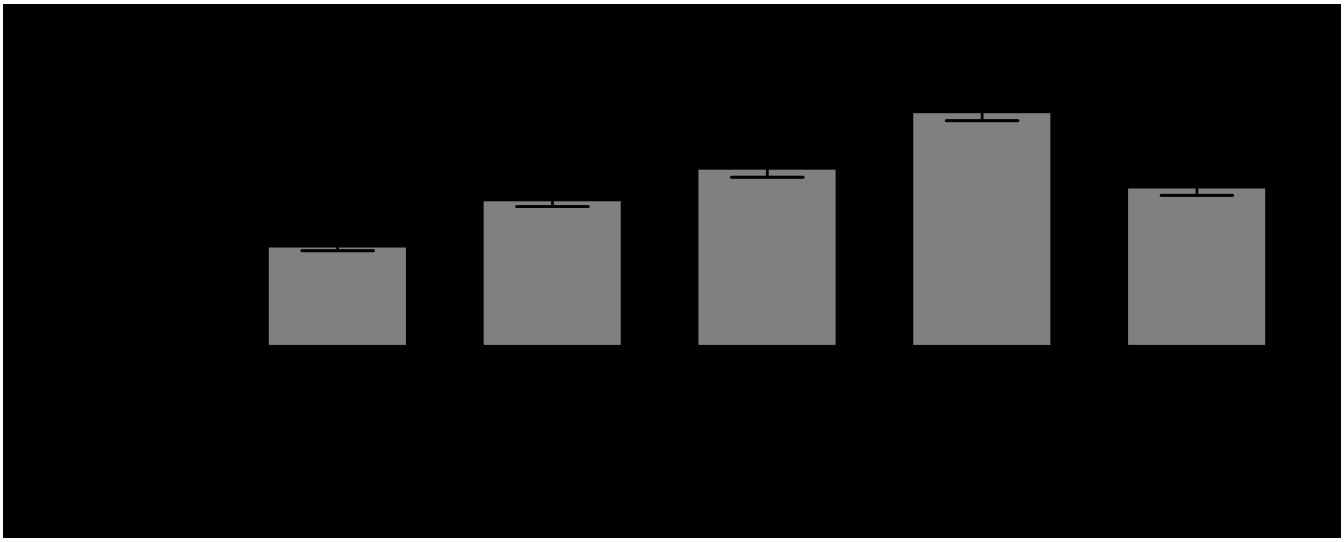

Figure. 3. Effect of *SP* on 5-HTP-induced head twitches in mice, the values were Mean ± S.E.M. (n = 6). a = p<0.001 compared to control.

Table 1. Effect of *SP* and lorazepam on L-DOPA-induced hyperactivity and aggressive behavior in mice.

Group no.	Treatment (dose in mg/kg)	Behavioral score(MEAN ± SEM)
I	Control (0.3% CMC)	1
II	Spirulina (100 mg/kg, p.o.)	2.25 ± 0.1443[a]
III	Spirulina (200 mg/kg, p.o.)	2.375 ± 0.125 [a]
IV	Spirulina (400 mg/kg, p.o.)	2.75 ± 0.1443 [a]
V	Lorazepam (2.5 mg/kg, i.p.)	2.25 ± .1443 [a]

The values were expressed Mean ± S.E.M. (n = 6). a = p<0.001 compared to induced group.

Table 2. Effect of *SP* and lorazepam on clonidine induced aggression in mice.

Group no.	Treatment (dose in mg/kg)	MEAN ± SEM	
		Latency to 1st attack	No. of bouts
I	Control (0.3% CMC)	341.3 ± 12.7	21.5 ± 1.19
II	Spirulina (100 mg/kg, p.o.)	372.3 ± 4.498[a]	17.5 ± .6455 [a]
III	Spirulina (200 mg/kg, p.o.)	394.3 ± 1.109[b]	15.5 ± .6455 [b]
IV	Spirulina (400 mg/kg, p.o.)	475.3 ± 8.23 [b]	12.25 ± 1.109 [b]
V	Lorazepam (2.5 mg/kg, i.p.)	498.5 ± 3.969 [b]	11.5 ± .6455 [b]

The values were expressed Mean ± S.E.M. (n = 6). a = p<0.001 compared to induced group.

Table 3. Effect of *SP* and lorazepam on clonidine induced fighting response in mice.

Group no.	Treatment (dose mg/kg)	% Response(MEAN ± SEM)	
		Latency to 1st attack	Fighting response
I	Control (0.3% CMC)	100 ± 12.7	100 ± 1.19
II	Spirulina (100 mg/kg, p.o.)	109.8 ± 4.498 [a]	81.395 ± .6455 [a]
III	Spirulina (200 mg/kg, p.o.)	115.53 ± 1.109 [b]	72.09± .6455 [b]
IV	Spirulina (400 mg/kg, p.o.)	139.26 ± 8.23 [b]	56.976 ± 1.109 [b]
V	Lorazepam (2.5 mg/kg, i.p.)	146.06 ± 3.969 [b]	53.48± .6455 [b]

The values were expressed Mean ± S.E.M. (n = 6). a = p<0.001 compared to induced group.

mice. Post-hoc analysis revealed that three doses of SP (100, 200 and 400 mg/kg, $p<0.01$, $p<0.001$) significantly increased the 5-HTP-induced head twitches in comparison to control group. Further, the dose of 400 mg/kg was more effective than 100, 200 mg/kg. Similarly, IMP treated group showed significant increase ($p<0.001$) in the 5-HTP-induced head twitches compared to control. However, the effect of 400 mg/kg of SP was significantly higher than IMP ($p<0.001$) (Fig. 3).

L-DOPA induced hyperactivity and aggressive behavior in mice reslts were reveals the effect of SP and lorazepam on L-DOPA-induced hyperactivity and aggressive behavior is shown in Table 1. Post-hoc analysis revealed that three doses of SP (100,200 and 400 mg/kg, $p<0.001$) significantly increased the L-DOPA-induced hyperactivity and aggressive behavior (LHA) in comparison to control group.

Results obtained as per table 2 indicates the effect of SP (100, 200 and 400 mg/kg, p.o.) and lorazepam (LA; 2.5 mg/kg) on the latency to first attack and the number of bouts in the clonidine induced aggressive behavior in mice. Post-hoc analysis showed that SP ($p<0.001$) significantly increased the latency to first attack and decrease the no. of bouts compared to control.

Table 6 Indicates the effect of SP (100, 200 and 400 mg/kg, p.o.) and lorazepam (LA; 2.5 mg/kg) on the latency to first attack and the number of bouts in the clonidine induced fighting behavior in mice. Post-hoc analysis showed that SP ($p<0.001$) significantly increased the latency to first attack and decrease the fighting responses compared to control.

DISCSSION

Thus, a growing number of herbal medicines have been introduced to psychiatric practice and they have been chosen as alternative therapies to alleviate severe symptoms of depression (Kessler et al., 2001). The antidepressant effect of traditional herbs in therapy. The effective components of herbs that have antidepressant- like effect include flavonoid, oligosaccharide, polysaccharide, alkaloid and organic acid, etc. Herbal drug used in depression are Centella asiatica, Hypericum perforatum, Rhodiola rosea, Pfaffia paniculata, Rauwolfia serpentine, Rhododendron molle, Shizandra chinesis, Thea sinensis, Uncaria tomentosa, Valeriana officinalis and Withania somnifera (Mamedov, 2005).

Spirulina Platensis (SP) is a type of fresh-water blue-green algae which grows naturally in warm climate countries and has been considered as supplement in human and animal food (Ruiz Flores et al., 2003). The numerous toxicological studies have established its safety for human consumption (Hirahashi et al., 2002). They have been found to be rich source of minerals, essential fatty and amino acids, vitamins - especially vitamin B12 and antioxidant pigments such as carotenoids (Belay, 2002). SP has anti-oxidant property as it contains carotenoids and also rich in amino acids like Tryptophan, Phenylalanine, Tyrosine (Jassby, 1983). These amino acids essential for the synthesis of Serotonin, Noradrenaline, Dopamine in the body. Normally depletion of neurotransmitters like Serotonin, Noradrenaline leads to depression. Since Spirulina is a rich source of antioxidant principles and the precursors of the above biological amines, it is expected to have antidepressant activity.

In addition, several studies showed that Spirulina species exhibit various biological activites such as anti-inflammatory (Reddy et al., 2000), antitumor (Mittal et al., 1999), hepatoprotective (Sharma et al., 2007), radio protective (Verma, 2000), antimicrobial (Sharma et al., 2007), strengthening immune system (Qureshi et al.,1995, Qureshi et al., 1996), metalloprotective (Shastri, 1999) and antioxidant effects (Upasani and Balaraman, 2003). But, still today no scientific study was carried out to find antidepressant activity of SP. Hence, it was felt worthwhile to investigate the antidepressant activity of SP.

Animal models are widely used in pre-clinical antidepressant evaluation and to provide insights into the neuropathology of depression (Garcia, 2002). The forced swim and tail suspension tests are the most widely used tools for inducing behavioral deficits which can subsequently be reversed by antidepressant treatments. There is a significant correlation between clinical potency and effectiveness of antidepressants in both models (Machado et al., 2009).

In the present study, 7 days pre-treatment with SP at the doses of 100, 200 and 400 mg/kg showed antidepressant activity in the forced swim test and tail suspension tests. The FST is the tool most widely used for assessing antidepressant activity preclinically. The widespread use of this model is largely a result of its ease of use, reliability across laboratories, and ability to detect a broad spectrum of

antidepressant agents (Borsini and Meli, 1988). Most clinically active antidepressants are effective in the FST, while neuroleptics and anxiolytics produce different effects (Porsolt et al., 1979).

In the forced swim test, SP significantly reduced immobility period suggesting anti-depressant activity and the activity was comparable to the reference drug IMP. Immobility is a state of lowered mood or hopelessness, which the rats experience when they are allowed to swim in a restricted space from which they cannot escape. This is thought to reflect either a failure to persist in escape directed behavior after persistent stress or the development of passive behavior that disengages the animal from active forms of coping with stressful stimuli (Lucki, 1997). The tail suspension test (TST) is widely used as a dependable animal model of depression to screen new antidepressants, as well as to investigate the mechanism of action of new antidepressants (Cryan et al., 2005). In the TST, mice are forced to hang in a confined space from which they cannot escape, and exhibit a characteristic behavior of immobility. This immobility, referred to as behavioral despair in animals, is believed to reproduce a condition similar to human depression. Thus, a reduction in the total duration of immobility indicates an antidepressant effect (Cryan et al., 2005; Steru et al., 1985; Willner, 1984). Additionally, many studies have shown that the test is highly sensitive to the major classes of the clinical antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), the tricyclic antidepressants (TCAs), and the monoamine oxidase inhibitors (MAOIs) (Cryan et al., 2005; Detke et al., 1995).

SP significantly reduced immobility period in the forced swimming test and tail suspension tests indicating antidepressant activity. Both these models of depression are widely used to screen new antidepressant drugs. These tests are quite sensitive and relatively specific to all major classes of antidepressant drugs including tricyclics, serotonin-specific reuptake inhibitors, and monoamine oxidase (MAO) inhibitors. In FST, rats are forced to swim in a restricted space from which they cannot escape, and are induced to a characteristic behavior of immobility. It has been argued that the TST is less stressful than FST and has greater pharmacological sensitivity (Thierry et al., 1986). Thus, the combined observations from both FST and TST indicate the antidepressant activity of SP. Depression has been linked to perturbations in the neurotransmission involving brain 5-HT, norepinephrine (NE) and dopamine activity (Maes and Meltzer, 1995; Posener et al., 1994). Clinical studies show that combined 5-HT and NE reuptake inhibitor is more effective than used alone (Anderson, 1998; Nelson et al., 2004). Based on these observations, we evaluated the role of NE in the antidepressant effect of SP. SP significantly increased the clonidine-induced aggressive behavior indicating increased activity of noradrenergic system (Ozawa et al., 1975). Hence, the antidepressant activity of SP may involve both serotonergic and noradrenergic systems. Several studies have shown that the antidepressant effect involves augmentation of dopaminergic neurotransmission (Serra et al., 1990). Such interference with the dopaminergic system could explain at least in part the acute effects of some of the antidepressants. However, SP also alter L-DOPA induced aggressive behavior indicating effect on the dopaminergic system. Hence, it is possible that this may be the reason for significant effect of SP on L-DOPA-induced aggression.

The above results indicate that SP has antidepressant activity by virtue of its action on serotonergic, noradrenergic and dopaminergic systems based on behavioral experimental evidence. Generally, repeated treatment with antidepressants has been reported to facilitate both serotonergic and/or noradrenergic transmission (Blier and De Montigny, 1994). The dual action of SP may have several advantages over SSRIs. Further, clinical studies have shown that mixed 5-HT and NE reuptake inhibitors (SNRIs) are effective and well-tolerated antidepressants (Tran et al., 2003; Zajecka and Albano, 2004).

The present study establishes the antidepressant activity of SP in rodent models of depression. Further, results from behavioral experiments indicate that this activity may be due to the facilitatory effect on serotonergic, noradrenergic and dopaminergic system .

CONCLSION

The results from the present study confirm the antidepressant activity of Spirulina platensis, since it reduced the immobility in both FST and TST. In the present study, SP significantly increased the frequency of 5-HTP induced head twitches, Clonidine induced aggression and L-DOPA induced

hyperactivity and aggressive behavior indicating its enhanced activity on serotonergic, noradrenergic and dopaminergic pathways respectively. Our results also confirm the involvement of serotonergic, noradrenergic and dopaminergic pathways in depression. Pretreatment with SP also significantly increased the levels of SOD and Catalase with simultaneous decrease in LPO levels in rat brain, suggesting its strong antioxidant activity. Since oxidative stress is reported to play an important role in depression, the antioxidant activity of SP might be a part of the mechanism for its antidepressant activity.

Results from behavioral experiments indicate that the antidepressant activity of Spirulina platensis might be due to the facilitatory effect on serotonergic, noradrenergic and dopaminergic systems apart from the antioxidant activity.

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