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IN VIVO & INVITRO EVALUATION OF ANTIDEPRESSANT ACTIVITY OF SPIRULINA & CLOPIDOGREL IN EXPERIMENTAL ANIMALS

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Abstract:
To date, the search for novel pharmacotherapy from various medicinal plants and their constituents for psychiatric illnesses has significantly progressed. The present study was undertaken to evaluate the antidepressant potential of spirulina & clopidogrel in different animal models like forced swim test (FST).In this study spirulina & clopidogrel, at two dose (150,300 mg/kg & 75,150 mg/kg) respectively, and standard imipramine stock solution prepared with Sodium-CMC (15 mg/kg) were administered on test day to separate groups of Wistar rats and albino mice. From these two animal models it was found that, spirulina & clopidogrel showed significant reduction in the duration of immobility in FST at both dose levels in dose dependent manner and the effect of high dose i.e.300 of spirulina & 150 mg/kg of clopidogrel was compared with imipramine. spirulina & clopidogrel also showed significant antidepressant effect compared to imipramine preparation, study confirmed that spirulina & clopidogrel increase the neurotransmitter levels of NA, DA, 5HT suggesting neurotransmission modulation is a probable mechanism of action. spirulina & clopidogrel possesses significant antidepressant activity.

Keywords: Antidepressant activity, spirulina & clopidogrel, imipramine Forced swim test, Tail suspension test, Serotonin, Noradrenalin, Dopamine.

Introduction:

Depression is one of the most common psychiatric disorders. It is characterized by feelings of intense sadness, helplessness, worthlessness, and impaired functioning (Sally Roach, 2008). The primary clinical manifestations of major depression are significant depression of mood and impairment of function. Some features of depressive disorders overlap those of the anxiety disorders, including *panic-agoraphobia* syndrome, severe phobias, generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. Extremes of mood also may be associated with psychosis, as manifested by disordered or delusional thinking and perceptions that often are congruent with the predominant mood. (Goodman and Gilman's *et al*., 2008). Many neurodegenerative and neuropsychiatric diseases, including depression, have been linked to oxidative stress, a pathological condition arising when physiological oxidative actions by reactive oxygen species are no longer balanced by antioxidative defences. The brain is very vulnerable to oxidative processes both because it consumes about 20% of the oxygen utilized by the body and because it contains great amounts of polyunsaturated fatty acids severely prone to peroxidation, which produces cell degeneration and death. Major depression is accompanied by a decreased antioxidant status and by induction of oxidative and nitrosative (IO&NS) pathways. Antidepressant drugs like Trimipramine, Amoxapine, Fluoxetine having variable side effects such as sleep disturbances, problems with sexual functioning, temporary weight loss, blurred vision, difficulty urinating, weight gain or loss, muscle twitches, increased heart rate, low blood pressure, dizziness and sedation, and insomnia. (Goodman and Gilman's *et al*., 2008) Since on one hand the synthetic drugs having variable side effect as mention above while on the other hand free radical species are responsible for neuropsychiatric disorder such as depression.

Spirulina is a type of cyanobacteria, also known as blue-green algae, and it has a unique structure that sets it apart from other microorganisms. clopidogrel is an antiplatelet medication that is commonly used to reduce the risk of blood clot formation in individuals with certain cardiovascular conditions. The primary mechanism of clopidogrel involves its activation and inhibition of platelet function. Here's a detailed explanation of the mechanism of clopidogrel.

It was hypothesized spirulina & clopidogrel suggest that, spirulina has neuroprotection as well as antioxidant activity. This may be useful in the treatment of depressant. Hence, present study was undertaken to evaluate the antidepressant activity of spirulina & clopidogrel various animal model.

Material and method:

Animals:

- The animals were housed at a temperature of 25 ± 2^{0}C and relative humidity of 45- 55% under 12:12 light: dark cycle. The animals had free access to standard pellet diet All the experiments were approved by the Institutional Animal Ethics Committee (IAEC) of Modern Institutional animal ethical committee, [Approved Protocol No.IAEC/**01/2022/02**].

Drugs and chemicals:

Test drug, spirulina & clopidogrel
Standard drug, Imipramine tablet (Cipla, India)
Vairous Reagents,
Thiobarbituric acid, O-pthalaldehyd, Sodium sulphate, Sodium carbonate, n-butanol (Research Lab Fine chemical Industries, Mumbai, India)
Trichloro acetic acid, DTNB, Phosphoric acid, Phosphate buffer, 0.1N HCL, Heptane, Iodine solution, Ethanol, Acetic acid, Na- CMC (Research Lab Fine chemical Industries, Mumbai, India)

Instruments:

Name of Instruments	Manufacturer
Animal Housing cages (Polypropylene)	B.I.K Industries, Mumbai
Animal weighing electronic balance	-
Chemical weighing balance	-
Professional quartz timer	-
Deep Freezer	BLUESTAR Ltd
Micro centrifuge RM-12C	REMI Instruments
Spectrofluorimeter	ELICO, India
Tissue Homogenizer RQ-127A	REMI Instruments
UV-Visible Spectrophotometer V-530	JASCO Instruments

Preparation and administration of drugs:

Preparation of test drug spirulina & clopidogrel **solution:**

spirulina & clopidogrel to be administered in a two dose (150,300 mg/kg & 75,150 mg/kg) respectively, p.o. body weight of animals. Dose was prepared by dissolving in 1% sodium carboxy - methyl cellulose (Na-CMC) to prepare the stock solution. The different doses were prepared by further diluting the stock solution.

Storage of test drug solution:

Test drug was stored in cool and dry place away from sunlight. Fresh drug solution was prepared for work of each day. The solution were kept in airtight, amber colored bottle and stored at room temperature until ready for use.

Volume and route of test drug administration:

The volume of drug solution to be administered was calculated based upon the body weight of animals by p.o. route.

Selection of dose of spirulina & clopidogrel

The dose for the spirulina & clopidogrel was selected on the basis of the reported LD_{50} values and as the doses used in previous studies.

LD_{50} values

Species	**Route**	**LD_{50}**
Rats	Oral	150 & 300 mg/kg

In the previous study spirulina & clopidogrel administered orally at two dose (150,300 mg/kg & 75,150 mg/kg) respectively a day. Hence, on the basis of this of previous study, the dose for the study of spirulina & clopidogrel was selected as two dose (150,300 mg/kg & 75,150 mg/kg) respectively (Jun-Shik Choi et al.,2005)

Preparation of Impramine solution:

Impramine tablet was purchased from market brand .The concentration of Impramine solution to be administered was 10 mg/kg, p.o. body weight in rat and mice accordingly. Dose was prepared by dissolving in 1% sodium carboxy - methyl cellulose (Na-CMC) to prepare the stock solution. The different doses were prepared by further diluting the stock solution

Storage of Impramine solution:

Impramine was stored in refrigerator (2-8ºC). Fresh Impramine solution was prepared for each day work. The solution was kept in airtight, amber colored bottle and stored until ready for use.

Volume and routes administration of Impramine solution: (Badhe *et al.*, 2010)

The volume of Impramine solution to be administered was calculated based upon the body weight of animals. In case of intraperitoneal administration, the volume administered did not exceed 1 ml/kg body weight. In the screening method for forced swim test and tail suspension test in Rat *Morin Hydrate* and Impramine by oral route for both acute and chronic study.

PHARMACOLOGICAL STUDIES:

ANIMALS:

Species: Male wistar rat (150-200gm)

A .**Despair swim test in Rat. (Acute study)**

Procedure:

The experiment will be performed using Wistar rat.(150-200gm) Animals will be divided into four groups of six animals in each group. (N-6) as follows.

Wistar rats (150-200 gm) will be used for the study. Animals will individually forced to swim inside a vertical water tank (with minor modifications). After 15 min of pretest session in the water the rats will remove and allowed to dry before returned to their home cages. They will again place in the cylinder 24 h later and the total duration of immobility is measured during a 5 min test. Floating behaviour during this 5 min period will found to be reproducible in different groups of rats.An animal will 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 (Guadarrama *et al*., 2008; Vogel *et al*., 2002)

Acute study:

- Group I :- Normal (control)
- Group II: - standard (imipramine-15 mg/kg, p.o.)
- Group III:-receives low dose of spirulina & clopidogrel p.o.(15 mg/kg)
- Group IV:-receives high dose of spirulina & clopidogrel p.o.(30 mg/kg)

Total number of animals required =24.

Test and standard drug will be administered once daily for one day at the end of 1^{st} day animal will be sacrifices and the parameter will be recorded.

2) Chronic study:

Wistar rats weighing (150-200gm) will be divided into four groups containing six animals in each group.
Procedure (Similar procedure for acute and chronic study of FST)

Group I : Normal control (1%Na CMC p.o. for 13 days.)
Group II: standard (imipramine- 15 mg/ kg p.o for 13 days.)
Group III: - receives low dose of spirulina & clopidogrel p.o for 13 days (150, 75 mg/kg)
Group IV:-receives high dose of spirulina & clopidogrel p.o for 13 days (300,150 mg/kg)

Test and standard drug will be administered once daily for 13 days at the end the experiment animal will be sacrifices and the following parameter will be recorded.

Estimation of parameters

Day 1 (for acute study):

1. Behavioral Parameter:

Immobility: The animal will judged to be immobile whenever it remained floating passively in the water and only making those movements necessary to keep its head above the water.

Climbing: Climbing is an active movement with forepaws in and out of the water, usually directed against the walls.

Swimming: Swimming will define as the movements of the four extremities that allow the rat to move around or cross the cylinder.

Biochemical Parameters –Acute Study

- Serotonin level
- Dopamine level
- Noradrenaline level

Estimation of tissue parameters (Latha et al., 2010, Schlumpf et al., 1974).

1. Serotonin estimation

O- Phthaldialdehyde (OPT) method

1. Opt reagent 0.025ml (20 mg in HCL) added to 0.02 ml extract (Upper Phase)
2. Heat it at 100^{o} C for 10 min
3. Cool it and take the reading.

2. Dopamine estimation

Take weighed Brain homogenized in 0.1 N HCl- Butanol (0.85 ml 37 % HCL in 1 liter butanol) then centrifuge at 2000 rpm for 10 min. 0.08 ml supernatant from this solution were removed and add it to 0.2 ml Heptane and 0.025 ml 0.1 m HCL, after addition of this reagent shake that mixture vigorously. This solution was centrifuge at 2000 rpm for 10 min. The upper organic phase was remove, and 0.02 ml of aqueous phase taken for dopamine estimation. To this add 0.01 ml of 0.4 M HCL and 0.01 ml EDTA/sodium acetate buffer (pH 6.9), followed by iodine solution (0.1 M in ethanol), 0.01 ml Na_2SO_3 in 5 M NaOH (0.5 gm Na_2CO_3 in 2 ml H_2O+18 ml 5 M NaOH) and Acetic acid (0.01 ml, 10 M) were added, after 1.5 min then the solution were heated at 100^{o}C for 6 min and then cool to room temperature.

3. Estimation of nor adrenaline:

The assay represents a miniaturization of the trihydroxide method. To 0.02 ml of HCl phase, 0.05 ml 0.4 M EDTA and 0.01 ml Sodium acetate buffer (pH 6.9) were added, Followed by 0.01 ml iodine solution (0.1 M in ethanol) for oxidation. The reaction was stored after two minutes by addition of 0.01 ml Na_2SO_3 in 5 ml NaOH. Acetic acid was added 1.5 minutes later. The solution was then heated to 100^{o} c for 6 minutes. When the sample again reached room temperature, excitation and emission spectra were read in the microcuvette. The intensities of fluorescence in resulting solutions were determined using a spectrofluorometer at wavelengths of 400/500 for dopamine and noradrenaline & 310/365 for serotonin. The concentration of 5 HT in the solution was calculated from the standard curves (Pal, 2009).

Evaluation: The value of each parameter was compared with standard and normal group.

Parameters:

Behavioral Parameter (Vogel *et al*., 2002): Duration of Immobility

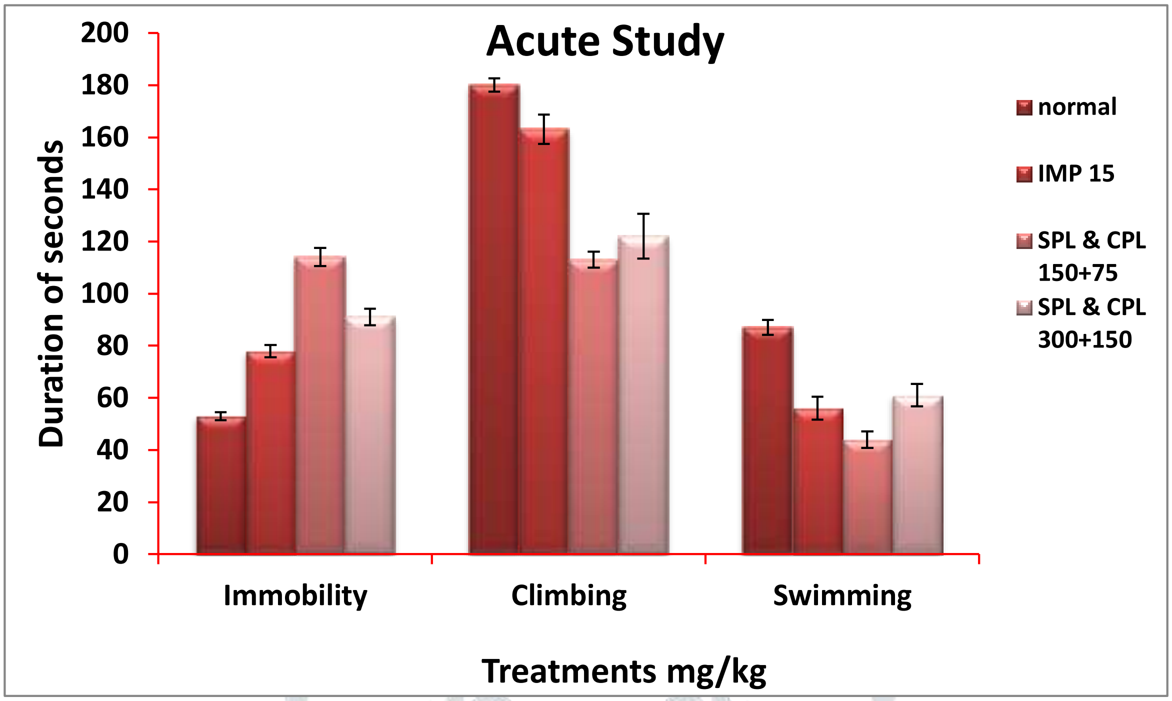
Statistical Analysis:

The Arithmetic mean ± SEM values were calculated for each experiment. The results were analyzed using one-way ANOVA followed by Dunnett's test or Student's 't' test

RESULTS:

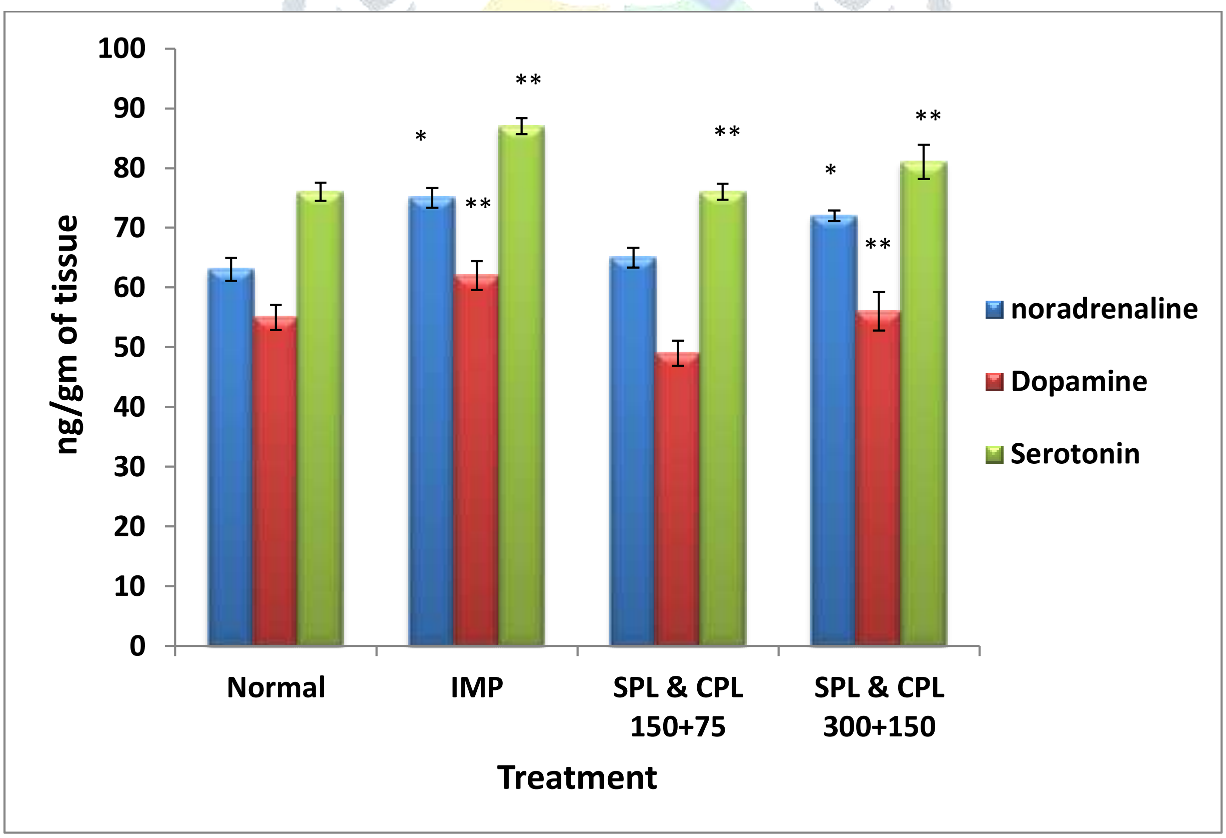
Evaluation of Antidepressant Activity of *spirulina & clopidogrel* in Forced swim test in rats:

Effect of spirulina & clopidogrel in Forced swim test in rats (Acute):



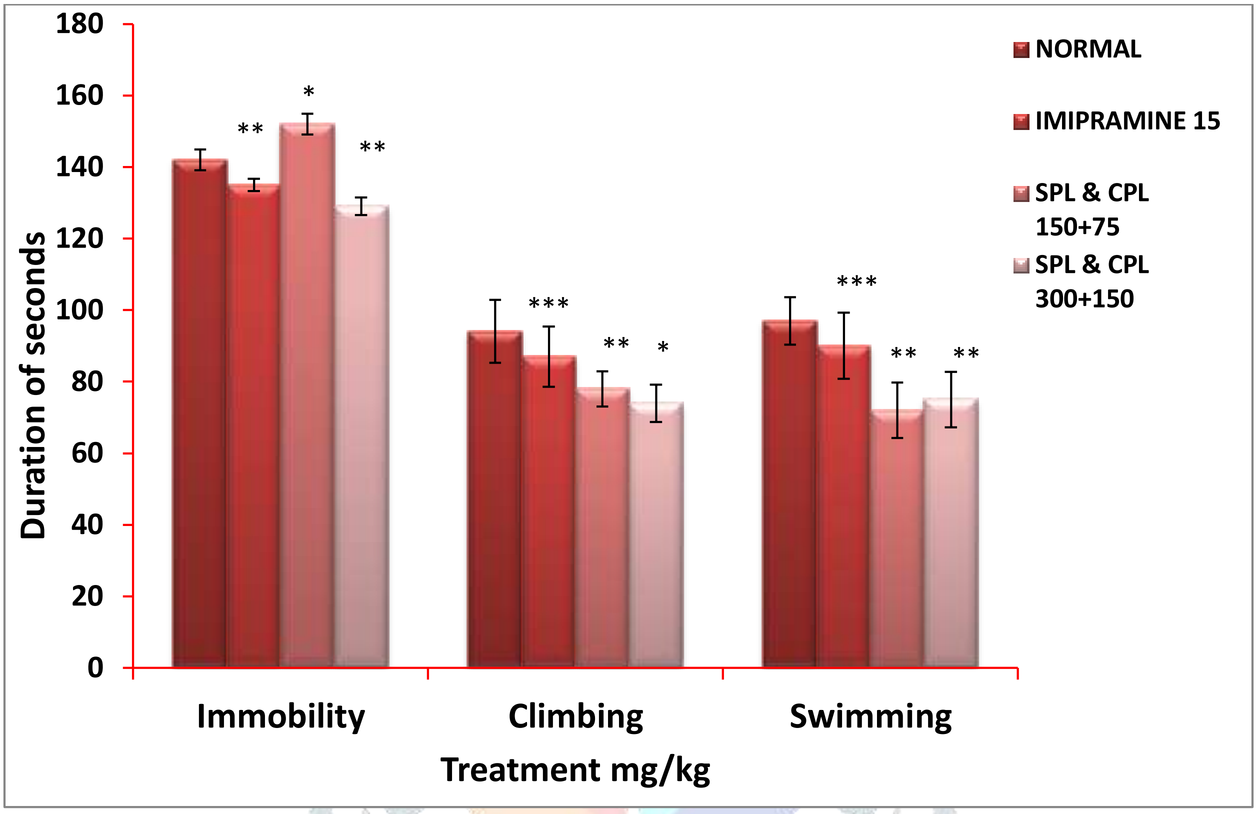
Values are expressed as Mean ± S.E.M, (n=6). **p*<0.05, ***p*<0.01, ****p*<0.001 as compare with normal control group, Using one-way ANOVA followed by Dunnett's test.

Effect of spirulina & clopidogrel on biogenic amines in rat brain (Acute):



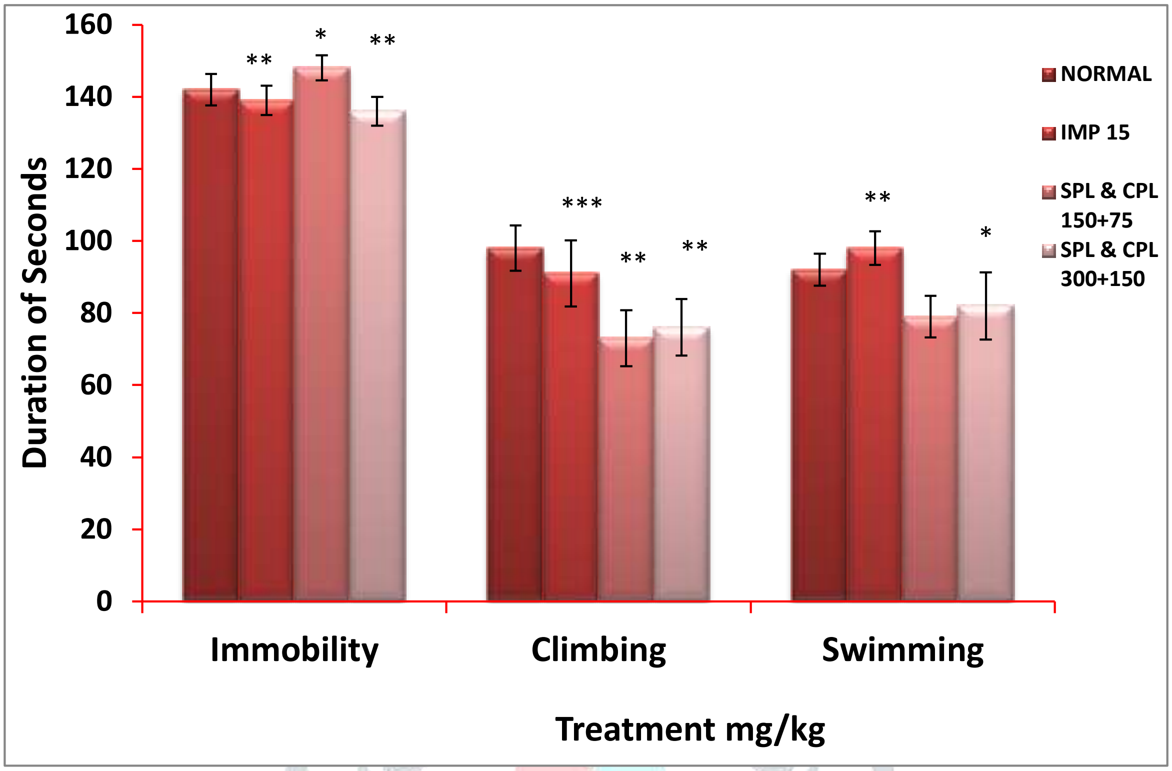
Values are expressed as Mean ± S.E.M, (n=6). **p*<0.05, ***p*<0.01, ****p*<0.001 as compare with normal control group, Using one-way ANOVA followed by Dunnett's test.

Evaluation of Antidepressant Activity of spirulina & clopidogrel in Forced swim test in rats: (7th day Chronic Study)



Values are expressed as Mean ± S.E.M, (n=6). **p*<0.05, ***p*<0.01, ****p*<0.001 as compare with normal control group, Using one-way ANOVA followed by Dunnett's test.

Evaluation of Antidepressant Activity of spirulina & clopidogrel in Forced swim test in rats: (14th day Chronic Study)



Values are expressed as Mean ± S.E.M, (n=6). *p<0.05, **p<0.01, ***p<0.001 as compare with normal control group, Using one-way ANOVA followed by Dunnett's test.

Discussion:

In forced swim test of rat's acute treatments with both Imipramine (15 mg/kg, p.o.) and spirulina & clopidogrel (150,300 mg/kg, p.o) failed to increase the duration of immobility indicating lack of actity on single drug administration.

Imipramine is currently used antidepressant among this group of drugs (Ulak et al., 2010). Tricyclic antidepressants are closely related in structure to the phenothiazines and were initially synthesized (in 1949) as potential antipsychotic drugs. Imipramine was found to be of no use in schizophrenia but effective in depression (Rang et al., 2006). Present study forced swim test for chronic treatment, Administration of Imipramine (15mg/kg, p.o.) showed significant effect on Immobility, climbing and swimming. Our study was finding that drug Imipramine shortened the duration of immobility time in FST because of is block the uptake of amines by nerve terminals, by competition for the binding site of the amine transporter . Synthesis of amines, storage in synaptic vesicles, and release are not directly affected, although Imipramine appears to increase transmitter release indirectly by blocking presynaptic α_2- adrenoceptors. Imipramine inhibit noradrenaline and 5-HT uptake by brain synaptosomes to a similar degree, but have much less effect on dopamine uptake. It has been suggested that improvement of emotional symptoms reflects mainly an enhancement of 5-HT-mediated transmission, whereas relief of biological symptoms results from facilitation of noradrenergic transmission (Ulak et al., 2011).

Administration of Imipramine (15 mg/kg, p.o.) on 7th day and on 14th day showed significantly decreasing duration of Immobility and the duration of climbing, swimming increases significantly as compared to normal control group.

Administration of *spirulina & clopidogrel* (150mg/kg, p.o.) on 7th day showed significantly decreasing duration of Immobility , increases significantly the duration of swimming, climbing on 14th day showed significantly decreasing duration of Immobility and , increases significantly the duration of climbing as compared to normal control group. But in swimming it showed insignificant effect in this regards.

Administration of spirulina & clopidogrel (300mg/kg.,p.o.) on 7th day and on 14th day showed significantly decreasing duration of Immobility and increases significantly the duration of swimming, climbing as compared to normal control group.

The decreases in the immobility time with increasing in the climbing and swimming was observed in case of chronic administration of drug for the period of 14th Days in FST and the animals were then assessed for the antidepressant activity, shows the significant results as compare to acute studies may be due to block the uptake of amines by nerve terminals, by competition for the binding site of the amine transporter. Synthesis of amines, storage in synaptic vesicles, and release are not directly affected, although some spirulina & clopidogrel appear to increase transmitter release indirectly by blocking presynaptic α_2- adrenoeptors. Most TCAs inhibit noradrenaline and 5-HT uptake by brain synaptosomes to a similar degree, but have much less effect on dopamine uptake. It has been suggested that improvement of emotional symptoms reflects mainly an enhancement of 5-HT-mediated transmission, whereas relief of biological symptoms results from facilitation of noradrenergic transmission.

In the case of biochemical parameter estimations in FST acute studies, Imipramine (15mg/kg.p.o.) and spirulina & clopidogrel (150,300mg/kg, p.o.) treated group shown the significant results. In this acute study spirulina & clopidogrel *150 & 75* 300mg/kg, p.o. has shown significant effects on serotonin, but not on nor adrenaline and dopamine level. While spirulina & clopidogrel 300 & 150 mg/kg has showed significant results on serotonin, dopamine and nor adrenaline level.

In the case of biochemical parameter estimations in FST chronic studies Administration of Imipramine (15mg/kg,p.o.) showed significant effect on Dopamine, Serotonin and Nor adrenaline level. Administration of spirulina & clopidogrel (150 & 75mg/kg, p.o.) showed significant effect on Serotonin and Noradrenaline level but on dopamine level it showed insignificant effect in this regards and spirulina & clopidogrel (300 & 150 mg/kg, p.o.) showed significant effect on Serotonin and Noradrenaline and Dopamine level as compare with normal control group.

The biogenic estimation made to find out the possible mechanism of action of spirulina & clopidogrel in experimental animal models as these biogenic amines are importance in study of antidepressant activity, though the level of this monoamine was depleted in depression. Neurobiological basic research as well as clinical studies has revealed that the monoamines (5-HT, noradrenaline and dopamine) have a crucial role in the development of the depression syndrome (Naughton et al., 2000).So our finding suggests that chronic but not the acute administration of spirulina & clopidogrel might be acts as an antidepressant agent by increasing the monoaminergic neurotransmitters.

The present neuro-behavioral studies shown that spirulina & clopidogrel, a polyphenolic antioxidant (Ana Maria Mendoza-Wilson et al., 2011) having antidepressant effects in experimental animal models of depression. However, on the basis of results obtained, decreasing in the duration of immobility with increasing the time of swimming and climbing in FST on chronic treatments produced anti-depressant effect by increasing the concentration of neurotransmitter and serotonin transmission. Some studies have been suggest that modulation in neurotransmitter system might be producing antidepressant effects independent of changes to synaptic transmission (Radhakrishnan et al., 2010).

Since the modernisation of life in developed and developing countries this disorder is increases very highly and by the year 2025 this disorder affects 21-22% people worldwide as per WHO.The current antidepressant therapies having various side effects and limitations to overcome this effect constituent of plants such as flavonoids, glycosides, steroids, alkaloids etc. Our test drug spirulina & clopidogrel having herbal & synthethtic in nature shows the antidepressant activity and the polyphenolic group is enhance the activity by crossing the blood brain barrier (BBB). spirulina & clopidogrel can efficiently cross the blood-brain barrier (Maria Rosario et al., 2009) and may be prevent neuronal death in brain region. Also spirulina & clopidogrel play important role in NMDA receptor overactivation. spirulina & clopidogrel also reduce apoptotic neuronal death induced by glutamate to give its antidepressant action (Maria Rosario et al., 2009).

So from result we can predict that spirulina & clopidogrel may have the significant antidepressant activity by its antioxidant and neuroprotection action also by its radical scavenging activity and its some effects on brain neurotransmitter systems.

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