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TO EVALUATE ANTIDEPRESSANT LIKE ACTIVITY OF COMBINATION OF CILOSTAZOL WITH ZINGIBER OFFICINALE IN MICE."

Medical Science

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ABSTRACT

Objective: To evaluate the antidepressant activity of combination of Cilostazol (20mg/kg) and Hydroalcoholic extract of Zingiber Officinale (175mg/kg).

Methods: In the present study, antidepressant activity of the combination was compared with that offluoxetine in mice by forced swim test.

Results: Cilostazol (20 mg/kg) and Zingiber Officinale (175mg/kg)administered intraperitoneally showedantidepressant activity which wassignificant in decreasing the immobility time when subjected to forced Swim Test. However the activity of Combination was found to be less than that of fluoxetine (20mg/kg).

Conclusion: The combination of cilostazol andZingiber Officinale (175mg/kg)posseses potential antidepressantactivity which could be of clinical importance for the patients suffering from depressivedisorders after evaluating it by further advanced studies.

KEYWORDS

Depression, Antidepressant drugs, Cilostazol, Zingiber Officinale, Forced Swim Test.

INTRODUCTION

Depression is an affective disorder characterized by change in mood, lack of interest in the surroundings, psychomotor retardation and melancholia [1]. In comparison to men, women are twice likely to suffer from depression as the lifetime risk of depression varies from 5 to 12% in men and 10 to 25% in women [2,3]. It is also the leading cause of disability which leads to suicidal tendency among patients of depression. Patients with cardiovascular diseases are at higher risk of developing depression and when it develops, there is two-fold increase in cardiac motility and morbidity for population suffering from various coronary heart diseases.[4-6] Cilostazol(6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone), a 2- oxo-quinoline derivative is mainly used as an antiplatelet agent and in peripheral vascular diseases with intermittent claudication. It also has antithrombotic, vasodilator, antimitogenic and cardiotonic properties which have been observed in various preclinical studies.[7-9] It is a potent inhibitor of the enzyme phosphodiesterase 3A,[10] found in hippocampus, striatum and other sites in brain[11] due to which it has been reported as an antidepressant, antipsychotic, enhancer of memory and also as aid in improving cognitive functions in various preclinical studies.[12-15] The phosphodiesterase inhibitors present a potentially powerful means to manipulate second messengers such as cAMP and cGMP which play an important role in neuronal cell functions.[16]

In Ayurveda, the Indian system of medicine have a number of single and in combination antidepressant drugs which have proved antidepressant effect with least adverse effect, easily availability and cheaper than modern allopathic drugs. Ginger, the rhizome of Zingiber officinale, is one of the most widely used species of the ginger family (Zingiberaceae) and is a common condiment for various foods and beverages. It is used extensively in traditional medicine to treat cold, fever, headache, nausea, and digestive problems and is also used in western herbal medical practices for the treatment of arthritis, rheumatic disorders, and muscular discomfort. [17] The main constituents of ginger are the gingerols, shogaols, paradols, and zingerone.[18]

The major gingerol and shogaol components present in the rhizome of ginger are 6-gingerol and 6-shogaol, respectively. The main aroma defining component is zingiberol, whereas others such as gingediol, monoacyldigalactosyl-glycerol, diarylheptanoids, and phytosterols have also been identified. In some preclinical trials it was found that ginger poses potential antidepressant effect, so it was thought worth to see the potential of combination of ginger with cilostazol in evaluating the antidepressant activity in mice.

MATERIAL AND METHODS

Collection and Preparation of extract

The Zingiber officinale rhizomes (ginger) were cut into smaller pieces, dried under shade for 10 days and pulverized to coarse powder using a manual blender at NIMS Institute of Pharmacy. Powdered rhizomes were then packed into the Soxhlet. solvent used was mixture of ethanol and water in the ratio of 50:50 respectively extraction was continued at the temperature of 50-degree Celsius till clear solvent was observed in the siphon tube. Extraction was concentrated in the water bath at 40 degree Celsius. Concentrated extract was the dried in the hot air oven at 40-degree Celsius dried extract was packet in airtight container19. Cilostazol (Cipla, India) and Fluoxetine (Cadila Pharmaceuticals, India) were used for the experimentation. Cilostazol was given at a dose of 20 mg/kg i.p for 15 days. Fluoxetine given at a dose of 20 mg/kg i.p for 15 days. Cilostazol was dissolved in dimethyl sulphoxide whereas fluoxetine was dissolved in distilled water. [20-22]

ANIMALS

Experiments were performed on Swiss albino mice three / four months of age (25 to 30 g) of either sex. They were procured from the central animal house of NIMS University. The animals were housed in standard polypropylene cages and kept under controlled room temperature (24 ± 2°c) in a 12 hours light dark cycle. They were given standard pellet diet and water ad libitum. They were acclimatized to the laboratory conditions at least one day prior to the behavioral experiments. Food was withdrawn 12 hours before the experiments. The animal handling was performed according to the Good Laboratory Practice (GLP) guidelines,[23] and efforts were made to minimize animal suffering.

Grouping of animals

GROUP	TREATMENTS
CONTROL(n=6)	Treated with distilled water (i.p.,15 days)
STANDARD(n=6)	Treated with Fluoxetine (20 mg/kg i.p., 15 days)
TEST (n=6)	Treated with Cilostazol (20mg/kg i.p., 15 days) and hydroalcoholic extract of zingiber officinale (175mg/kg [24] i.e., 15 days)

Study Design

The antidepressant like activity of Hydroalcoholic extract of Zingiber Officinale in combination with Cilostazol was evaluated with standard drug fluoxetine by forced swim test (FST) in glass jar after drug doses in mice. The drug was administered daily for 14 days and 1 hour before the tests [25]. Routes of administration was Intraperitoneal (i.p) for all

drugs with at least 6 animals in each group.

PARAMETERS ASSESSED

Forced swim test in glass jar was performed as described by Porsolt et al. with few modifications. [23,26,27] This test consists of two parts, an initial training period of 15 min followed 24 h later by actual test for 5 min duration. Mice were individually forced to swim inside a vertical borosilicate glass cylinder of diameter 15 cm and height 40 cm containing fresh water to a height of 15 cm and maintained at 25 ± 1°C. At this level of water, animals were not able to support themselves by touching the bottom or the side walls of the chamber with their hind paws or tail. Water in the chamber was changed after subjecting each animal to FST since used water alters the behavior. Mice placed in the cylinder for the first time were initially highly active, vigorously swimming in circles, trying to climb the wall or diving to the bottom. After 2 to 3 min, activity began to subside and was interspersed with phases of immobility or floating of increasing length. After 5 to 6 min, immobility reached a plateau where the mice remained immobile for approximately 80% of the time. After 15 min in the water, the mice were removed, wiped with dry cloth and allowed to dry before being returned to their home cages. The mice were again placed in the cylinder 24 h later and drugs were administered 1 hr. prior to testing on last day of dosing. The duration of immobility was recorded for a period of 5 min swimming session with the help of video recorder and subsequently analyzed. Mice were considered immobile when they ceased struggling and remained floating motionless in water, making only those movements necessary to keep their head above water.

Statistical Analysis

All the results of tail suspension test forced swim test with activity wheel and forced swim test were expressed as the mean ± standard deviation. Data were analyzed using one-way analysis of variance (ANOVA), followed by Tukey-Kramer multiple comparisons test to determine statistical significance of difference in various groups. Statistical significance was set at $p < 0.05$.[28]

RESULT

In this test(Table 1). Mice treated with Zingiber Officinale (175mg/kg) and Cilostazol 20mg/kg showed decrease in the immobility time, which was significant(70.25± 2.59); P<0.05) when compared with control(121.85± 4.47);. Mice treated with Fluoxetine (20mg/kg), also showed a significant decrease in the immobility time(60.38± 3.16);P<0.05as compared to control(121.85± 4.47). Similarly Mice treated with Zingiber Officinale and Cilostazol showed significant decrease in immobility time(70.25± 2.59); P<0.05) when compared to Fluoxetine(60.38± 3.16).

Table.1 Effect of Cilostazol in combination with Hydroalcoholic extract of Zingiber Officinaleand Fluoxetine on duration of Immobility time(in seconds) in Forced Swim Test.

Treatment	N	Minimum (Immobility time)	Maximum (Immobility time)	Mean (Immobility time)	Standard Deviation
Control	6	115.74	128.12	121.85	4.47
Fluoxetine (20mg/kg)	6	56.22	64.13	60.38	3.16
Cilostazol 20mg/kg and Zingiber Officinale (175 mg/kg)	6	66.88	74.20	70.25	2.59

DISCUSSION

Mood disorders are one of the most common mental illnesses, with a lifetime risk of 10% in general population. Prevalence of depression alone in general population is estimated to be around 5% with suicide being one of the most common outcomes [29-36].Most of the drugs that are currently being used in the treatment of depression have adverse effects that affect the quality of life of the patient. This leads to patient's non- compliance to medication, which further complicates the problem [37,38].Ayurveda mentions a number of single and compound drug formulations of plant origin that are used in the treatment of psychiatric disorders [39] and are claimed to have a better side-effect profile than conventional drugs.

Zingiber Officinale and Cilostazol combination showed significant decreased in immobility time in the dose dependent manner as compared to control mice. The immobility is thought to reflect failure of persistence in escape directed behavior. However, exact mechanism of antidepressant effect of the Ginger rhizome is still unknown but behavioral parameters in forced swimming test confirmed potential antidepressant effect as serotonergic agents. In my previous study[40], only Cilostazol for evaluating antidepressant activity was undertaken and when I see the results I found that the combination of Zingiber officinale and Cilostazol is much more significant.

The drug Cilostazol is thought to be a potent inhibitor of phosphodiesterase III enzyme, which increases cAMP in hippocampus by which the framework of pathophysiology and pharmacotherapy converge on cAMP-mediated signaling rather than on neurotransmitter system[10,11,16]. It has also been seen that cilostazol increases insulin like growth factor-I (IGF-I) in hypothalamus, which is responsible for improving cognitive functions in patients of depression leading to antidepressant like action[41], Moreover, some clinical studies have shown that the drug cilostazol when administered to cardiovascular patients with depression who under-went angioplasty and on adjuvant dual antiplatelet therapy, is effective in treating patients with mild to moderate depression which was seen by a decrease in Montgomery-Asberg Depression Rating Scale (MADRS) scoring compared to baseline ratings[42]Further studies are required to arrive at exact mechanism of action of cilostazol as anti depressant.

CONCLUSION

As medicinal plants have their importance since ancient time, people using it from various ways as a source of medicine. From the above valuable animal study, we conclude that the plant extract *Zingiber officinale in combination with Cilostazol*shows a significant antidepressant activity in FST model of depression with significant decrease in the immobility time.It can be concluded that cilostazol can be a drug of choice specially for cardiovascular patients with mild to moderate depression as it has multiple uses and is devoid of serious adverse effects which occur with the use of various established antidepressant drugs.So, if Combination of Cilostazol is done with an Ayurvedic medicine i.e *Zingiber officinale* which is commonly in use in Indian household and devoid of any side effects can be drugs of choice in patient with Depression in the near future. Further studies on safety and other important parameters are required to confirm and know the exact mechanism of action of cilostazol and *Zingiber officinale*for its antidepressanteffect so that proper clinical trials can be done to give relief for patients suffering from Depression.

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