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Study of Co-Relation between Antidepressant and Anxiolytic Activities Using *Cinnamomum Cassia* Bark in Rodents

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Abstract

The search for psychoactive plants possessing therapeutic potential in the treatment of depression and anxiety has attracted growing interest.

Materials and Methods: The present study is envisaged on studying the antidepressant, anxiolytic activities of methanolic bark extract of Cinnamomum cassia. The In vivo antidepressant and anxiolytic activities was performed by using forced swim test (FST) & tail suspension test (TST), elevated plus maze (EPM) & rotarod test (RRT). Seventy two mice and twenty four rats were divided into four groups of six animals in each group. Group 1 received normal saline; group 2 and 3 received methonolic extract of Cinnamomum cassia, 200 and 400 mg/kg p.o.; group 4 received Imipramine (5mg/kg i.p) Clonazepam (1mg/kg i.p).

Results: In FST & TST rodents were induced the depression in different groups and duration of immobility is recorded as an indicative of its depressant effect. In control group the duration of immobility was found to be 159±0.65 &120.8±0.97. In MECC treated groups II & III at two doses of 200 & 400 mg/kg, bd. wt. the duration of immobility was found to be (125.33±0.99,110±0.69) & (98.3±0.91, 87.3±0.87). From the above results, it is clear that duration of immobility in control group was found to be higher. But in groups treated with the MECC and standard (Imipramine 5 mg/kg, i.p) the duration of immobility was found to be reduced.

In EPM mice treated with clonazepam (1mg/kg) showed significant increase in the percent of open arms entries and time spent, whereas in closed arm the number of entries and time spent were significantly($P<0.05$) decreased. The methanolic extract C. cassia exhibited significant ($P<0.005$) increase in number of open arm entries and time spent with significant ($P<0.05$) reduction in number of entries and time spent in closed arm as compared with control group. Rotarod showed significant ($p<0.01$) reduction in motor activity with clonazepam and C. cassia extract (400mg/kg) as compared with group 2 and 1.

Conclusion: The results of present study indicate that Cinnamomum cassia possess significant antidepressant and anxiolytic activities.

Keywords: *Cinnamomum cassia;* antidepressant; anxiolytic; Imipramine; Clonazepam

Introduction

Depression is a mood disorder characterized by low mood, persistent feeling of sadness, a general loss of interest on things. The mood changes may have a psychotic basis with delusional thinking or occur in isolation and induced anxiety. Depression was previously called as melancholia and now it is called as major depressive disorder or clinical depression (Rang & Dale, 2016). Anxiety is an emotion that predates the evolution of man. Children, adolescents and adults experience anxiety in different forms; while this is visible in some, it can be inferred in others from their physiological and psychological responses. Anxiety also varies in frequency and intensity in different persons, even in response to the same stimulus [1]. Anxiety-depressive diseases are among the main causes of disability in the world and contribute significantly to the global burden of diseases (World Health Organization, 2020). Anxiety is accompanied by a characteristic set of behavioral and physiological responses including avoidance, vigilance and arousal, which evolved to protect the individual from danger [2].

Anxiety and depression are leading psychiatric disorders. The chance of acquiring depression is higher when anxiety disorder exists and also people with depression often feel anxious and worried. Depression and anxiety can occur at the same time. It has been estimated that 45 percent of people with one mental health condition meet the criteria for two or more disorders. Although each condition has its own causes, they may share similar symptoms and treatments.

Materials and Methods

The designing of methodology involves a series of steps taken in a systematic way in order to achieve the goal under prescribed guidelines and recommendation. It includes selection and collection of the medicinal plant, selection of solvents for extraction, selection of dose, standardization of protocol, usage of instruments, preparation of reagents, and formation of protocols and final execution of the standardized protocol. All this requires good build of mind and soft technical hand to handle the materials and procedure in a true scientific manner.

Plant collection and drying

The bark of *Cinnamomum cassia* barks were supplied by a local market and were grounded into fine powder and was authenticated.

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Preparation of plant extract Cinnamon bark was cleaned, then was milled into coarse powder using electrical blender. The powdered material was stored or taken up for extraction process.

Acute toxicity studies

Acute toxicity study was carried out in order to check the toxic effects for methanolic extract of *Cinamommum cassia*. The study was performed as per Organization for Economic Cooperation and Development (OECD). 1175/PO/RcBiBt/S/14/CPCSEA The method is used to evaluate the acute oral toxicity is up and down procedure (OECD guideline-425).

In vivo methods for evaluation of antidepressant activity

In vivo evaluation of antidepressant activity of the methanolic extract of *Cinnamomum cassia* was carried out in following models.

1. Forced swim test
2. Tail suspension test

Forced swim test (FST)

The test is based on the observation that rats when forced to swim in a restricted space from which they cannot escape will eventually cease apparent attempts to escape and become immobile apart from the small movements necessary to keep their heads above water.

This identifiable behavioral of immobility reflects a state of despair in the rat and showed that immobility was reduced by a variety of agents which are therapeutically effective in depression. Swiss albino rats of either sex weighing about 200-250 gm were selected for this study. The FST was performed after 5 days of treatment using a modified form of the traditional method. Swiss albino rats were placed individually in water chamber/tank filled with water (22–25°C) to a depth of 30 cm. The experimental session was of two trials. Conditioning trial on the 4th day and on 5th day of the treatment 2 h from the last dose, the Swiss albino rats were exposed to the cylinders again for 6 min (test session). The frequency and total duration of immobility was determined. Rat was considered immobile when it remained floating in the water, without struggling, making only very slight movements necessary to keep its head above the water. One rat from each group was sacrificed and their brain was isolated and sent for histopathology studies [3].

Tail suspension test (TST)

Swiss Albino mice of either sex weighing about 25-30 gm were selected for this study. The total duration of immobility induced by tail suspension was measured according to the method described by [4]. Depression was produced by suspending the animal from the edge of a table 50 cm above the floor by an adhesive tape placed approx. 1cm. from the tip of the tail. Immobility time was recorded during a 6 min. period. Changes in the immobility duration were studied after administering drugs in separate groups of animals. The antidepressant activity was expressed as reduction in the immobility duration between the control, standard and animals treated with test drug. All treatments were administered once daily for 5 days. On the 5th day, 2 h after the last dose, mice were suspended by tail individually through a paper adhesive tape, above the table top. Animals were allowed to suspend by their tail for 6 min and the duration of immobility was recorded. Mice were considered to be immobile only when suspended passively and completely motionless.

In vivo methods for evaluation of anxiolytic activity

In vivo evaluation of anxiolytic activity of the methanolic extract of leaves of *Cinnamomum cassia* was carried out in following models.

1. Elevated plus maze
2. Rota rod test

Elevated plus maze (EPM)

EPM is extensively used method to examine anxiolytic effect in rodents. The plus maze apparatus is based on the innate aversion of rodents to open and high space. The apparatus has a central platform of 5 cm connected to two open arms (15 cm× 5 cm) and two closed arms (15 cm × 5 cm × 12 cm), bisecting each other. The maze was raised to a height of 25 cm from the ground. Albino Mice of either sex weighing about 150-180 gm were selected for this study. Diazepam and MECC were administered (1 mg/kg, *i.p*) and MECC (200 & 400 mg/kg, *p.o*) mice were placed at the center of the maze facing an open arm. To assess plus maze test, the mouse was individually placed on the central platform facing towards open arm. The percentage of time spent (duration) in open arms and frequency of open arm entries were counted for a period of 5 min. All precaution was taken to ensure that no external stimuli, other than the height of plus maze could invoke anxiety in the animals. Arm entry was defined as all four paws having crossed the dividing line between an arm and the central area. The percentage of time spent in the open arms and number of open arm entries were calculated using the formulas [100 × open/ (open + enclosed)] and (100 × open / total entries), respectively [5].

Rota rod test

The effect on motor coordination was assessed using a Rota-rod apparatus (LE 8500). Rota rod consisted of a base plant form and an iron rod of 3 cm diameter and 30 cm length, with a non- slippery surface. The rod was divided into four equal sections by three disks. The animals were pre-selected in a training session 24 h before the test, based on their ability to remain on the bar (at 12 rpm) for 2 min, and then allowing four mice to walk on the rod at the speed of 12 rpm at the same time observed over a period of 30, 60, and 90 min. Intervals between the mounting of the animal on the rotating bar and falling off of it were registered automatically as the performance time. Time spent in the apparatus was observed for 5 min duration (300 s). Apparatus was cleaned thoroughly between trials with water. All behavioral recordings were carried out with the observer blind to the treatment the mice had received [6].

Results and Discussion

Methanolic extract of leaves of *Cinnamomum cassia* was explored for its *in vivo* antidepressant and anxiolytic activities using suitable rodent models. The percentage yield of methanolic extract was % Yield of extract = 26.5/235 ×100 = 11.2% w/w .

Forced swim test (FST)

Values were expressed as Mean ± SEM (n=6). Statistical analysis was performed by using ANOVA followed by Dunnett's test. Results were compared with control (** $p<0.001$) and standard ($^{ap}<0.05$) (Table 1).

Tail suspension test (TST)

Values were expressed as Mean ± SEM (n=6). Statistical analysis was performed by using ANOVA followed by Dunnett's test. Results were compared with control (**$p<0.001$) and standard (^{aa} $p<0.001$) (Table 2).

Table 1: Effect of MECC on duration of immobility in forced swim test.

Groups	Treatment	Duration of immobility (sec)
I	Saline water	159 ± 0.65
II	MECC (200 mg/kg, p.o)	125.6 ± 0.99**,a
III	MECC (400 mg/kg, p.o)	110 ± 69**,a
IV	Imipramine (5 mg/kg, i.p)	98.5 ± 0.99**,a

Table 2: Effect of MECC on duration of immobility in tail suspension test.

Groups	Treatment	Duration of immobility (sec)
I	Saline water	120.8 ± 0.97
II	MECC (200 mg/kg, p.o)	98.3 ± 0.91**,aa
III	MECC (400 mg/kg, p.o)	87.3 ± 0.87**,aa
IV	Imipramine (5 mg/kg, i.p)	75.66 ± 0.89**

Table 3: Effect of MECC on elevated plus maze.

Groups	Treatment	No of entries into closed arms	Time spent in closed arms(sec)
I	Saline water	15.16 ± 0.66	287 ± 0.92
II	MECC (200 mg/kg, p.o)	12.66 ± 0.60*,a	206.5 ± 0.96**,aa
III	MECC (400 mg/kg, p.o)	8.66 ± 0.45**,a	179.5 ± 0.84**, aa
IV	Clonazepam (1 mg/kg, i.p)	7 ± 0.33**	135 ± 0.76**

Table 4: Effect of MECR on muscle rigidity using rota rod test.

Groups	Treatment	Duration of immobility (sec)
I	Saline water	289±0.091
II	MECC (200 mg/kg, p.o)	179±0.090 **,aa
III	MECC (400 mg/kg, p.o)	194.83±0.380 **,aa
IV	Clonazepam (1 mg/kg, i.p)	63.16±0.72**

Elevated plus maze (EPM)

Elevated plus maze is ubiquitously used model to determine anxiolytic activity and constitutes a simple and routine rodent model for evaluation of behavioral exploratory activity in rodent models.

Values were expressed as mean ± SEM (n=6). Statistical analysis was performed by using ANOVA followed by Dunnett's test. Results were compared with control (** $p<0.001$,* $p<0.005$) and standard (^{aa} $p<0.001$), ^{a} $p<0.005$) (Table 3).

Rota rod test (RRT)

Values were expressed as mean ± SEM (n=6). Statistical analysis was performed by using

ANOVA followed by Dennett's test by comparing with control (**$p<0.001$) and standard (^{aa} $p<0.001$) (Table 4).

Discussion

Antidepressant activity

Depression or major depressive disorder is a mental health condition marked by an overwhelming feeling of sadness, isolation and despair that affects how a person thinks, feels and functions.

Stress induced depression: The FST is based on the assumption that when placing an animal in a container filled with water, it will first make efforts to escape but eventually will exhibit immobility that may be considered to reflect a measure of behavioral despair. This test has been extensively used because it involves the exposure of animals to stress, which was shown to have a role in the tendency for major depression. The decrease in duration of immobility is considered to be a good predictive value in the evaluation of potential antidepressant agents [8]. The TST based on the fact that animals subjected to the short term, inescapable stress of being suspended by their tail, will develop an immobile posture. Various antidepressants reverse the immobility and promote the occurrence of escape related behavior [9].

The preliminary phytochemical investigation of methanolic extract of leaves of *Cinnamomum cassia* revealed the presence of alkaloids, flavonoids, phenolic acids, steroids, tannins were the most prominent. Alkaloids bearing the indole moiety have been described to own affinity toward different serotonin receptors. The structural similarity of indole alkaloids to endogenous neurotransmitters like serotonin has led investigators to predict the potential antidepressant activity of these molecules [10]. Flavonoids were known to act by lowering the corticotrophin releasing hormone as reported by [11] and show antidepressant activity.

Imipramine: was the first tricyclic antidepressant, a class named for its three ring molecular structure. It works by inhibiting the reuptake of certain neurotransmitters in the brain including acetylycholine, dopamine, norepinephrine and serotonin.

Anxiolytic activity

Elevated plus maze test: is based on the natural aversion of rodents to open spaces, and uses conflict between exploration and this aversion. It includes elements of neophobia exploration, avoidance conflict, thus it is often called as an unconditioned spontaneous behavioral conflict model. MECC showed its anxiolytic activity by decreasing the closed arm entries and time spent in closed arms.

Rotarod test: is based on the measuring parameters like endurance, grip strength and motor coordination of subjects and can be used for evaluating the motor coordination in rodent models. MECC did not affect the motor coordination and gripping strength.

Alkaloids: may play an important role in certain neurological diseases. Although many alkaloids are sufficiently lipophilic to enter the cells, they can also interact with proteins or lipids at the cell periphery such as neuroreceptors and ion channels. In the central nervous system (CNS) disorders, anxiety is a universal and generally adaptive response to a threat or danger, but in certain circumstances it can become maladaptive. Its regulation is integrally associated with the function of various neurotransmitter systems, mainly the gamma- aminobutyric acidergic system [12].

Polyphenols flavonoids: specific foods and diets rich in antioxidants have been shown to improve antioxidant status and have anxiolytic effects.

Clonazepam (Benzodiazepines): exert their effects by facilitating the activity of GABA at various sites. Specifically, benzodiazepines bind at an allosteric site at the interface between the alpha and gamma subunits on GABA-A receptor chloride ion channels. The allosteric binding of diazepam at the GABA-A receptor leads to an increase in the frequency at which the chloride channel opens, leading to an increased conductance of chloride ions. This shift in charge leads to a hyperpolarization of the neuronal membrane and reduced excitability of the neuron. Specifically, the allosteric binding within the limbic system leads to the anxiolytic effects seen with diazepam. Allosteric binding within the spinal cord and motor neurons is the primary mediator of the myorelaxant effects seen with diazepam. Mediation of the sedative, amnestic, and anticonvulsant effects of diazepam is through receptor binding within the cortex, thalamus, and cerebellum [13].

Conclusion

The methanolic extract of *Cinnamomum cassia* was screened for its antidepressant by using forced swim test and tail suspension test. Administration of at dose of 200 mg/kg and 400 mg/kg evoked the maximum depressant activity, as indicated by the decrease in the duration of immobility in forced swim test as well as tail suspension test.

The animals have antidepressant activity which might be due to presence of active constituents like alkaloids, aldehydes (cinnamaldehyde) and flavonoids.

The anxiolytic activity was screened by elevated plus maze and Rota rod, the animals have shown anxiolytic response which might be due to presence of active constituents like alkaloids and flavonoids in the extract. The present study revealed that the extract possesses antidepressant and anxiolytic activities

Further studies are needed to be carried out to isolate individual phytochemical constituents of extract and to establishment the exact mechanism.

Conflict of Interest

The authors declare no conflict of interest.

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