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ORIGINAL ARTICLE

THE EFFECTS OF AEGLEMARMELOSON DEPRESSION IN WISTAR RATS AND IT'S COMPARISON WITH IMIPRAMINE.

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Abstract:

Present study was done to see the antidepressant effect of Aeglemarmelosand its comparison with the standard treatment with imipramine in wistar rats. The study was done using Forced swim test (FST). From the results of present study it is concluded that Aeglemarmelos has antidepressant activity as shown by the results of force swim test. Aeglemarmelos extract at both the doses (100 mg/Kg, 200 mg/Kg, p.o) significantly decreased the duration of immobility, indicating an antidepressant activity. Comparatively, higher dose has been found to be more effective than lower dose.

KEYWORDS

Aeglemarmelos, antidepressant, imipramine.

INTRODUCTION

Advances in science and technology have contributed to an enormous improvement in the life span and quality of life of humankind. However, modern life stress, associated competition and tribulation are responsible for the surge in incidence of variety of psychiatric disorders. Depression is one of the types of mood disorders. Depression, in general, is classified as major depression (i.e., unipolar depression) or bipolar depression (i.e., manic depressive illness). Major depression is defined as depressed mood on a daily basis for a minimum duration of 2 weeks, characterized by sadness, indifference, apathy, or irritability and is usually associated with: changes in sleep patterns, appetite, and weight; motor agitation or retardation; fatigue; impaired concentration and decision-making; and thoughts of suicide. Approximately 15% of the population experiences a major depressive episode at some point in life, and 6–8% of all outpatients in primary care settings satisfy diagnostic criteria for the disorder. The term minor depression is used for individuals who experience at least two depressive symptoms for 2 weeks but who do not meet the full criteria for major depression. Despite its name, minor depression is associated with significant morbidity and disability and also responds to pharmacologic treatment (Reus, 2012). Depression is approximately twice as common in women as in men (Kessler et al., 1994) and the incidence increases with age in both sexes.

Depressive symptoms also can occur secondary to other illnesses such as hypothyroidism, Parkinson's disease, and inflammatory conditions. Further, depression often complicates the management of other medical conditions (e.g., severe trauma, cancer, diabetes, and cardiovascular diseases (Andrews and Nemeroff, 1994). Traditional system of medicine consists large number medicinal plants, which showing their potential therapeutic utilities. Aeglemarmelos, commonly known as a bael, belongs to Rutaceae Family, widely grown in India (Patel et al. 2012), is one of the gifts of nature to mankind.

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Numerous pharmacological studies have been conducted on different parts of Aeglemarmelos. This plant is having great potential to cure the diseases like diabetes, hyperlipidemia, peptic ulcer, diarrhoea, dysentery, cancers etc. It has also shown its effect as cardio protective, anti bacterial, anti fungal, radio protective, anti pyretic, analgesic, antioxidant, hepatoprotective, and many more.

However, there are only few studies of Aeglemarmelos pertaining to central nervous system activities. Hence in the present study, Neuropsychopharmacological effects of Aeglemarmelos (Bael) were studied in wistar rats.

MATERIALS AND METHODS

The study was conducted in the Department of Pharmacology and Therapeutics, King George's Medical University, Lucknow (Erstwhile ChhatrapatiShahujiMaharaj Medical University). Ethical clearance was obtained from the Institutional Animal Ethics Committee before conducting the study.

EXPERIMENTAL ANIMALS & REARING CONDITIONS –

Adult healthy Male Wistar rats weighing 160-200 gm had been used in study. Animals had been obtained from CPCSEA-certified animal house [Indian Institute of Toxicology Research, Lucknow (IITR)]. They were allowed to access normal rat pellet diet and water ad libitum and were kept in Institutional animal house under temperature controlled environment [25 ± 2°C] with 12 hours' light and dark cycle. The animals were housed for two weeksprior to the experiments to acclimatize to new environment. The maintenance of the animals and the experimental procedures were in accordance with the guiding principles of Institutional Animal Ethics committee and the 'Guide for the Care and Use of Laboratory Animals', National Research Council, 1996 (Latest revision in 2011). The guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India were followed.

DOSAGE FORMS, DOSES AND SOURCES OF THE DRUGS

Following drugs were used in this study.

A)Test Drugs - Bael (Aeglemarmelos)- Drug (extract form) was dissolved in normal saline and administered orally with the help of feeding cannula in a doses of 100 mg/ kgbw and 200 mg/ kgbw (Shankharananth, 2007). It was purchased from market (Aeglemarmelos extract, Himalaya Drug Company).
B)Standard drugs - Imipramine: Dose 20 mg/kgbw. i.p (Kitamura et al., 2004) Tablets were purchased from government authorized medical store.

EXPERIMENTAL PROTOCOL –

The present study had been designed to evaluate Neuropsychopharmacological effects of Aeglemarmelos(Bael) that includes antidepressant in male wistar rats.

ANIMAL GROUPS

A total number of 24 Male Wistar rats were included in the study. They were kept in Institutional Animal House under standard conditions. All the animals received normal rat pellet diet and water ad libitum. All the animals were allowed to get acclimatised to the new environment for period of 2 weeks.Rats were randomly divided into 4 groups, each group containing 6 rats to see the effect of Aeglemarmeloson depression and its comparison with imipramine, were studied.

Neuropsychopharmacological Evaluation

Following validated behavioural models of rodents were used to assess the neuropsychopharmacological effects of Aeglemarmelous extract.

Assessment of Antidepressant Activity in rats using Forced swim test:

Grouping:

Albino Wistar rats weighing between 160- 200 gms were randomly divided into 4 experimental groups, each group containing 6 rats.

Group 1: Rats were administered Normal saline p.o (1 ml)
Group 2: Rats were administered aeglemarmelous extract (100 mg/kg) p.o.
Group 3: Rats were administered aeglemarmelous extract (200 mg/kg) p.o.
Group 4: Rats were administered standard drug Imipramine (20 mg/kg) i.p.

PROCEDURE:

Forced swim test (FST) is the most widely used pharmacological model for assessing antidepressant activity. The apparatus consisted of transparent cylinder (20 cm diameter and 40 cm height) filled to 30 cm depth with water at room temperature (Charles et al., 2009). In this test, eachrat was placed in a cylinder with enough water (filled to 30 cm depth) so that it could not touch the bottom with its hind paws (Porsolt et al., 1977a; Porsolt et al., 1977b; Porsolt et al., 1978). The animal showed an immediate burst of activity, try to escape, and then eventually adopted an "immobile" posture, where it will make only those movements necessary to keep its head above water.

The first 15-min session was conducted prior to drug administration and without behavioural recording. This prior habituation session ensures a stable and high duration of immobility during the 5-min test session, usually performed 24 hr later (Porsolt et al., 1978).

Rats were administered the normal saline (control group), standard treatment and extracts doses at 24 hr (i.e., immediately after the first habituation session), 4 hr, and 60 min (for oral administration of drugs) or 30 min (for i.p. administration of drugs) before the test.

Thirty minutes after i.p. and 1 hr after oral administration of drugs, rats were gently dropped individually into transparent cylinder for the 5 min. Duration of immobility was recorded during this 5min swimming test. Rat was judged to be immobile when it floated in a upright position motionlessly or making small movements of its limbs necessary to keep its head above water. These four groups received the respective treatment for consecutive 30 days and duration of immobility was noted again at 10th, 20th and 30th day. The water was changed after each animal testing. After each test trial the rats were dried before returning to their respective home cages.

ASSESSMENT:

The changes in immobility duration were studied after administering drugs in separate group of animals. The mean immobility time of control and drug treated groups was compared.

STATISTICALANALYSIS

A one-sample Kolmogorov-Smirnov test was used to investigate whether the variables were normally distributed. The one way analysis of variance (ANOVA) was used to assess the comparability of the groups assigned to the treatment groups. Independent t test/Tuke's pairwise comparison was used to compare the different parameters like immobility time, transfer latency, open arm activity, number of visits, reaction time and duration of stay on rotarod between respective treatment groups. Differences in treatment effects within groups and between the treatment and control groups were tested by a multivariate analysis of variance repeated-measures design with treatment type as a between-subject factor (2 groups) and treatment effect (baseline compared with follow-ups) as a within-subject factor. A significant P value for the treatment effect indicated a change over time in the combined values of the groups and was further investigated by using a paired t test for each individual group. Between group differences in treatment effect were indicated by significant interactions between treatment effect and treatment type. The percent change from baseline to follow-ups was also calculated for each group. Statistical significance was based on a two-tailed P value < 0.05.

RESULTS

Assessment of Antidepressant Activity

The antidepressant effect on different treatment group (Group 1: Control, Group 2: Aeglemarmelous extract 100 mg/kg, Group 3: Aeglemarmelous extract 200 mg/kg, Group 4: Imipramine 20 mg/kg) have been summarized in Table 1.The immobility time was 61.17±2.85 seconds at day 1 which

decreased to 60.33±2.25 at day10, 59.83±2.31 at day 20 and 57.67±1.75 at day 30 in Group 1. Similar observation was found for Group 2, 3 and 4.

Table 1: Effect of Aeglemarmelous extract on immobility time at Day 1 to Day 10, 20 and 30 day (FORCED SWIM TEST)

Groups	Immobility time (in seconds) (Mean±SD)			
	DAY 1	DAY 10	DAY 20	30 DAY
Group 1	61.17±2.85	60.33±2.25	59.83±2.31	57.67±1.75
Group 2	46.00±2.60	42.50±1.87	39.00±1.41	37.67±1.75
Group 3	41.00±1.78	38.00±1.41	35.67±2.25	34.83±1.16
Group 4	36.33±2.16	33.00±2.19	30.17±1.60	30.31±1.72

The immobility time was significantly different at day1 between Group 1 and Group 2 ($p<0.01$), 3 ($p<0.01$) &4 ($p<0.01$). Similar observation was found at Day10, Day20 and Day30 in Group 1. Group 2 was also significantly different between Group 3 ($p<0.01$) and 4 ($p<0.01$) at day1. Almost similar observation was found at day 10, day 20 and day 30. The Group 3 was significantly different from Group 4 at day1 and same was at day 10, 20 and 30 (Table-2).

Table 2: Comparison of Antidepressant Activity between Groups

Groups		Immobility time (in seconds)							
		DAY 1		DAY 10		DAY 20		30 DAY	
		Mean d/f	p-value	Mean d/f	p-value	Mean d/f	p-value	Mean d/f	p-value
Grp1 Vs	Group 2	15.16	<0.01*	17.83	<0.01*	20.83	<0.01*	20.00	<0.01*
	Group 3	20.16	<0.01*	22.33	<0.01*	24.16	<0.01*	22.42	<0.01*
	Group 4	24.83	0.01*	27.33	<0.01*	29.66	<0.01*	27.36	<0.01*
Grp 2 Vs	Group 3	5.00	<0.01*	5.00	<0.01*	3.33	< 0.05*	2.84	<0.05*
	Group 4	9.66	<0.01*	9.66	<0.01*	8.83	<0.01*	7.36	<0.01*
Grp 3vs	Group 4	4.66	<0.05*	5.00	<0.01*	5.00	<0.01*	4.52	<0.01*

* Statistically significant **Mean difference -Mean d/f**

The immobility time was 24.8% lower in Group 2, 33% in Group 3 and 40.6% in Group 4 as compared to Group 1 at day1. However, this was 25.7% lower in Group 2, 37% lower in Group 3 and 45.3% in Group 4 than Group 1 at day10. Almost similar observation was found at day 20 and day 30 in all the groups (Table-3).

Table 3: Assessment of antidepressant activity: Mean percentage change as compared to control group (Group 1)

Groups	Immobility time (Mean percentage change)			
	Day 1	Day 10	Day 20	Day 30
Group 1	-	-	-	-
Group 2	24.8	25.7	34.8	34.7
Group 3	33.0	37.0	40.4	39.6
Group 4	40.6	45.3	49.6	47.4

DISCUSSION

Any mental illness significantly affects feeling, thinking and behaviour of a person. Stresses of life can precipitate number of mental illnesses. Modern day life style leads to numerous stressful conditions. Anxiety and depression are widely prevalent psychiatric disorders. Moreover their prevalence is increasing day by day. Stress might influence learning-and-memory processes by suppression of adult neurogenesis or by affecting neurochemical systems (for example, catecholamines, opiates, glucocorticoids).

Due to the various side effects of allopathic drugs used for treatment of these diseases, there is continuous search for alternative treatment. So it is prudent to look for options which are efficacious & safer. Indigenous system of medicine including natural herbs are time tested way of treatment. Herbal medicines emphasize the prevention of diseases, rejuvenation of our body systems, maintain balance and harmony and extend the life span (Mahe et al., 1978). Medicinal herbs are indispensible part of traditional medicine practiced all over the world due to easy access, low cost and ancestral experience. Number of plants have been being used for management of mental illness. Some of them are as follows:

For treatment of anxiety- Bacopamonniera(kumar, 2006), Citrus paradise (Gupta et al., 2010), Azadirachtaindica, Centellaasiatica;

For treatment of depression- Allium cepa (Sakakibara et al., 2008), Bacopamonniera(Sairam et al., 2002), Centellaasiatica(Rajput et al., 2011), Curcuma longa (Yu et al., 2002);

For improving learning and memory-Ginkgo biloba, Glycyrrhizaglabra, Piper longum, Bramhi, Shatavari, Shankhapushpi.

Several activeconstituents, which can be of immense importance as drugs, are the precursors for synthesis of many drugs (Dhankhar and Ruhil, 2011). Their effectiveness, low cost and comparative freedom from serious toxic effects make these medicines not only popular but also an acceptable mode of treating diseases even in modern times. Due to the various unavoidable adverse effects of available allopathic medicines, management of various diseases without any untoward side effects is still a challenge for modern medical science. So several herbal plants having various bioactive phytochemicals, possessing several activities and no or very less adverse effects have been explored.

Number of studies have shown beneficial effects of Aeglemarmelos as antiviral, antibacterial, antifungal, anticancer, antihyperlipidemic, antidiabetic and antioxidant agents. However, there are only few studies pertaining to neuropsychopharmacological actions of Aeglemarmelos. Many phytoconstituents like flavonoids, saponins, quercetin, phenols, skimmianine and ascorbic acid have shown very important role in management of psychiatric illnesses. The herbal plants which are used for treatment of various psychiatric illnesses in traditional medicines contains these phytoconstituents. Phytochemical screening of Aeglemarmeloshaveshown the presence of many phytoconstituents including flavonoids, saponins, quercetin, phenols, skimmianine and ascorbic acid (Patel and Sahu, 2012). Hence, we hypothesised that, due to the presence of these important phytoconstituents similar to the other herbal plants being used for many psychiatric illnesses,Aeglemarmeloscould have the potential place in treatment of such type of illnesses.

The present study was undertaken to explore the Neuropsychopharmacological effects of Aeglemarmelos(Bael) as antidepressantin wistar rats.The dose of Aeglemarmelos was based on previous studies (Shankharananth, 2007). Extract form needs less amount to be administered, previous trials and experimental studies have been mostly performed using extract (ethanolic or aqueous) forms and also they are soluble in normal saline. Therefore we have chosen the extract-form in our study.

We have chosen the oral route for administering the herbs as a drug, as this route is natural & usual route of taking herbal drugs if prescribed by a physician. This route doesn't need assistance of others and is quite easy in terms of intake.

A total number of 24 male Wistar rats were included in the study. Rats were randomly divided into 4 groups, each group containing 6 rats. All the animals were allowed to get acclimatised to the new environment for period of 2 weeks. Group 1 to 4 were used to assess the effect of Aeglemarmelos on depression were studied.

Forced swim test is the most widely used pharmacological model for assessing antidepressant activity. The FST involves placing the animal in a cylinder with sufficinent water so that it cannot touch the bottom with its hind paws (Porsolt et al.,1977a; Porsolt et al.,1977 b; Porsolt et al.,1978). A normal animal shows an immediate burst of activity, tries to escape, and then eventually adopts an "immobile" posture, where it makes only those movements necessary to keep its head above water. This behaviour reflects a state of despair. Rats were administered the respective doses at 24 hr (i.e., immediately after the first habituation session), 4 hr, and 60 min (for oral administration of drugs) or 30 min (for i.p. administration of drugs) before the test. Two or three test substance administrations before the test provide more stable

pharmacological results than a single administration. Classical antidepressants such as the monoamine oxidase inhibitors, tricyclics, and atypical antidepressants all decrease the duration of immobility in animals in a dose-dependent manner (Borsini and Meli, 1988; Porsolt et al.,1977a; Porsolt et al.,1977 b).

This decrease in duration of immobility is considered to have a good predictive value in the evaluation of potential antidepressant agents. In the present study, A. marmelosextract at both doses i.e. 100 mg/kg, p.o. daily and 200 mg/Kg, p.o. daily, showed significant decrease in immobility time on 1st, 10th, 20th and 30th day when compared to control ($p<0.01$), indicating an antidepressant activity (Table 1,2). But A. marmelosextract at higher dose (200 mg/Kg, p.o.) showed more percentage reduction in the duration of immobility on 1st, 10th, 20th and 30th day when compared with lower dose (Table 3). These results shown by A. marmelos were consistent with previous study (Kothari et al., 2010).

Numerous neural pathways are involved in the pathophysiology of depression and anxiety states. Therefore, a great number of neurotransmitters are thought to be involved in underlying mechanisms of these diseases (Palucha and Pilc, 2002). Imipramine prevents reuptake of noradrenaline and serotonin resulting in their increased availability in the synapse and therefore an increase in adrenergic and serotonergic neurotransmission (Tatsumi et al., 1997). Since catecholamine and 5-hydroxytryptamine is implicated in etiology of depression, the positive effect of these drugs in FST seems to be due to increased availability of these neurotransmitters at the postsynaptic receptor sites.

Exact mechanisms underlying the antidepressant action cannot be concluded due to the presence of large number of phytochemicals in the Aeglemarmelos. However, the antidepressant activity may be attributed to the presence of phenols, quercetin, flavanoids and ascorbic acid in the extract (Pemminati et al., 2010). It has been shown that quercetin is a selective MAO-A (monoamine oxidase A) inhibitor, thereby increases the levels of monoaminergic neurotransmitters in the brain (Chimenti et al., 2006; Saaby et al., 2009).

Another possible mechanism of action is the attenuation of oxidative stress produced during depression. Aeglemarmeloshas antioxidant properties and effectively reduces the oxidative stress (Sabu and Kuttan, 2004; Upadhya et al., 2004) possibly due to the presence of phenols, flavonoids and tannic acid in the plant.

Hence, due to the presence of a number of phytoconstituents including flavonoids, quercetin, tannic acid, phenols, eugenol, marmesinin, ascorbic acid, skimmianine and saponinetc or any other mechanisms, Aeglemarmelos possesses antidepressant, nootropic, analgesic and anxiolytic properties. In addition, it also improves motor co-ordination. Aeglemarmeloscan be a safe and effective indigenous drug for the treatment of number of psychiatric disorders including anxiety and depression. However, a more extensive study is necessary to determine the exact mechanism of action of the extracts and its active compound(s).

Conclusion

The present study was designed to evaluate the neuropsychopharmacological effects (antidepressant) of Aeglemarmelos extract. These effects were compared with standard drugs of their class Imipramine. From the results of present study following conclusion may be drawn -Aeglemarmelos has antidepressant activity as shown by the results of force swim test.Aeglemarmelos extract at both the doses (100 mg/Kg, 200 mg/Kg, p.o) significantly decreased the duration of immobility, indicating an antidepressant activity. Comparatively, higher dose has been found to be more effective than lower dose.

Present study [an experimental study to evaluate the neuropsychopharmacological effects (antidepressant) of Aeglemarmelos. Extract shows that Aeglemarmelospossesses antidepressant properties. All these effects could be attributed a number of phytoconstituents including flavonoids, quercetin, tannic acid, phenols, eugenol, marmesinin, ascorbic acid, skimmianine and saponin. These phytoconstituents are also present in other herbal extracts which are in use since ages. These phytoconstituents are supposed to be safe without any major adverse effects. These findings are in favour of using A. marmelos as antidepressant drug. However the results from present study have limitations in the form of short duration of study, only one or two selected models and less number of animals. The other limitation of this study is lack of measurement of various biochemical parameters at various time intervals. Large scale animal study with inclusion of more animal models and biochemical parameters will strengthen the findings of present study. If A. marmelos passes through the positive results in animal study, clinical studies may be planned in future. No wonder that A. marmelos will become a safe and effective indigenous drug for the treatment of number of psychiatric disorders including anxiety and depression.

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