IJPSR (2022), Volume 13, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 30 June 2021; received in revised form, 03 August 2021; accepted, 05 August 2021; published 01 April 2022

EVALUATION OF ANTI-DEPRESSANT EFFECT OF *ACACIA NILOTICA* LINN LEAVES EXTRACT IN EXPERIMENTAL ANIMALS

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Keywords:

Acacia nilotica Linn., Depression, Imipramine, Tail suspension test, Forced swim test, Spontaneous locomotor activity.

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ABSTRACT: A chronic illness that affects a person's mood, thoughts, physical health, and behavior patterns is considered depression. Currently used anti-depressant drugs such as selective serotonin reuptake inhibitors (SSRI) and tricyclic anti-depressants (TCA) are showing various side effects and thus, the search for a new anti-depressant herb without side effects is important. The intend of the present study was to evaluate the anti-depressant effect of methanol, chloroform and aqueous extract *Acacia nilotica* leaves at doses of 200 mg/kg in experimental animals. *In-vivo* screening models like Forced Swim Test (FST), Tail Suspension Test (TST) and Spontaneous Locomotor activity (SLMA) were used to assess the anti-depressant effects of the methanol, chloroform, and aqueous extracts of *Acacia nilotica* Linn. The dried-up leaves were subjected for shade drying and size reduced to powder and extracted by soxhlet apparatus. The extracts were subjected to phytochemical tests and the carbohydrate, tannins, alkaloids, flavonoids, saponins, glycosides and steroids were found to be present. Imipramine (30 mg/kg, i.p) was used as the reference standard, and it showed significant anti-depressant activity in mice. The significant anti-depressant effects of *Acacia nilotica* could be due to the strong and effective concentration of the active constituent. In the FST model, MEAN (200 mg/kg,po) showed high significant decreases in immobility time (137.3 ± 1.67**). In TST model, MEAN (200 mg/kg, po) showed highly significant decreases in immobility time (147.50 ± 1.19***). In SLMA showed less significant increases in locomotor activity scores (228.2 ± 4.37*). From the literature surveys as well experiments performed, it can be understood that *Acacia nilotica* does pose anti-depressant property.

INTRODUCTION: Depression is a chronic, recurrent psychiatric disorder affecting nearly 21% of the world's population [1, 2]. It is characterized by emotional and physical manifestations, such as feelings of worthlessness, helplessness, guilt or indecision, change in appetite, change in sleep habits, loss of concentration, loss of energy, loss of interest, loss of pleasure, agitation, mental and motor slowing, and social withdrawal [3]. The monoaminergic theory states that depletion of brain neurotransmitters such as 5-hydroxytyrptamine (5-HT), norepinephrine (NE), and dopamine (DA) assumes to play a key role in the pathophysiology of depression [4].

In recent decades, several anti-depressant drugs have been discovered, which include tricyclic anti-depressants, monoamine oxidase inhibitors [5] and

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DOI: 10.13040/IJPSR.0975-8232.13(4).1640-46

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(4).1640-46

selective serotonin reuptake inhibitors (SSRI). Regrettably, all of the medications have serious side effects such as insomnia, anxiety, weight gain, and so on. Nature is widely recognized as the best and most secure source of all medicines. AS a result, it is worthwhile to look for a new anti-depressant drug that is derived from natural sources and has fewer side effects. A drug derived from natural sources is intended to have fewer side effects and complications [6].

Acacia nilotica Linn. wild. ex. Del. is a multipurpose nitrogen-fixing tree legume also known as Gum Arabic tree, Babul, Egyptian thorn, or Pickly Acacia. It is widespread in subtropical and tropical Africa, stretching from Egypt to Mauritania and south to South Africa and in Asia, stretching east to Pakistan and India [7, 8]. Historical evidence suggests that herbal therapies were used to treat convulsive seizures as early as 6000 BC in India, with the origin of Ayurveda [9]. Babul plant has traditionally been used as anti-cancer, anti-tumours, antiscorbutic, astringent, anti-oxidant, natriuretic, colds, congestion, coughs, antispasmodial, diuretic, intestinal pains and diarrhea, nerve stimulant, dysentery, fever, hemorrhages, leucorrhea, ophthalmic, and sclerosis [10].

The plant has been shown to exhibit antibacterial, anti-inflammatory, antiplatelet, aggregatory activity, cestocidal activity, antibacterial effects, spasmogenic, vasoconstrictor actions, antihypertensive, antispasmodic activities, inhibitory effect against hepatitis C virus, cytotoxic activity and antioxidant activity [11]. Earlier studies reveal that no such reports regarding anti-depressant effects of *Acacia nilotica* Linn. leaves extract in experimental animals. Hence the present study has been designed to evaluate the Anti-depressant effects *Acacia nilotica* leaves extract in mice. Therefore this study is designed to investigate the possible effects of an extract of the medicinal plant.

MATERIALS AND METHODS:

Plant Material: *Acacia nilotica* L. fresh leaves were obtained from the Pinder Valley in the Chamoli district of the Himalayan region in Uttarakhand in the month of July-August and shade dried. The leaves of *Acacia nilotica* L. were identified and authenticated by Dr. Sunita Garg, Chief Scientist, Raw Material Herbarium and Museum (RHMD), Delhi CSIR-NISCAIR.

Preparation of Extracts: *Acacia nilotica* L. leaves were shade dried at room temperature and then crushed into a coarse powder with the desired particle size. The powdered material (500 gm) was subjected to successive extraction in a Soxhlet apparatus using increasing polarity solvents-methanol, chloroform, and aqueous. The appearance of colourless solvent in the siphon tube was taken as the endpoint of extraction. The extracts were separately concentrated to dryness using a rotary evaporator. The dried extracts were preserved in vacuum desiccators until further use. The yield was 13.60% w/w, 6.81% w/w, and 16.21% w/w for methanol, chloroform and aqueous extract of *Acacia nilotica* L. respectively [12].

Preliminary Qualitative Phytochemical Screening: The various *Acacia nilotica* Linn. extracts, namely methanol, chloroform, and aqueous was then subjected to qualitative phytochemical screening for the identification of different constituents using standard methods [13, 14].

Drugs and Chemicals: Imipramine Hydrochloride are obtained from S.D. Fine Chemicals, Mumbai, India, were used in the present study. All other chemicals used in the study were obtained commercially and were of analytical grade.

Animal Selection: The National Institute of Biologicals (NIB), Noida, supplied healthy Swiss albino mice of either sex (18-22 gm). The animals were acclimatized for one week in a laboratory environment. They were housed in polypropylene cages and managed to keep at a temperature of 270 °C +/-20 °C with a 12 h dark/light cycle.

They were supplied standard feed and given sufficient water. The experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) constituted under Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA) (Reg. no. 882/Po/Re/S/05/CPCSEA) prior to the beginning of the research work.

Toxicity Studies: The acute toxicity of *Acacia nilotica* leaves extract was determined using albino

mice of either sex with body weights ranging from 18 to 22 g and kept under standard conditions. Prior to the experiments, the animals were fasted for 3 h. Animals were given a single dose of methanol, chloroform and an aqueous leaves extract of *Acacia nilotica* and their mortality was monitored for 48 h (short term toxicity). The next dose was determined using OECD guidelines No 425 based on the short-term toxicity profile. Since no mortality was observed up to a dose of 2000 mg/kg from the LD50 dose, a screening dose of 200 mg/kg of each extract was preferred for further studies.

Anti-depressant Screening Method:

Forced Swimming Test (FST): Behaviour despair was recommended as a model to evaluate anti-depressant activity [15, 16]. All mice of either sex were divided into five groups of six animals each. The control group, group I, was given normal saline (5 ml/kg, p.o.). Imipramine, the standard drug, was given to Group II (15 mg/kg, p.o). Group III –V was given orally at the dose of 200 mg/kg all three extracts of *Acacia nilotica* leaves extract. The treatment was continued for seven days in a row. On the test day, mice were forced to swim alone in an open cylindrical container with having diameter 10 cm and a height 25 cm, filled with fresh water and kept at a temperature of 25 ± 3 °C. After an initial 2 min period of vigorous activity, each animal predicted a typical immobile posture. A mouse was considered immobile when it remained afloat in water without struggling and made only the slightest movements of its limbs to keep its head above water. The total duration of immobility was recorded during the next 4 min of a total 6 min test. The duration of immobility after drugs was administered to various groups of animals was studied. Each animal was used only once. An antidepressant-like effect is indicated by a decrease in the duration of immobility.

Tail Suspension Test (TST): The total length of immobility caused by the tail suspension test was measured. All mice, both sexes, were divided into five groups of six animals each. The control group, group I, was given normal saline (5 ml/kg, p.o.). Imipramine, the standard drug, was given to Group II (15 mg/kg, p.o.), Group III -V was given orally at the dose of 200 mg/kg, p.o all three extracts of *Acacia nilotica* leaves. The treatment was continued for seven days in a row. On the test day, mice were suspended 50 cm above the floor on the edge of the table using adhesive tape placed nearly 1 cm from the tip of the tail. AS an effective method of administering anti-depressants, the total duration of immobility caused by tail suspension was recorded [17]. Immobility time was measured during a 6 min. period [18]. When an animal did not move its body and was hanged passively, it was considered immobile.

Spontaneous Locomotor Activity (SLMA): A digital actophotometer was used to assess spontaneous locomotor activity in naive pre-treated mice. The actophotometer was powered by photoelectric cells that were linked in a circuit with a counter. When the animal cut off the light beam falling on the photocell, a count was picked. These cut-offs were counted for a period of 10 min [19]. All mice of either sex were divided into five groups of six animals each. The control group, group I, was given normal saline (5 ml/kg, p.o.). Imipramine, the standard drug, was given to Group II (15 mg/kg, p.o). Group III -V was given orally at the dose of 200 mg/kg, p.o all three extracts of *Acacia nilotica* leaves. The treatment was continued for seven days in a row. On the test day mice was placed individually in the actophotometer and the difference in locomotor activity scores was noted.

Statistical Analysis: The results are displayed by the mean S.E.M. The current study's findings were analyzed using one-way ANOVA, followed by Dunnett's multiple comparison test. Data were computed for statistical analysis by using Graph Pad PRISM 5 Software.

TABLE 1: PRELIMINARY PHYTOCHEMICAL ANALYSIS IN DIFFERENT EXTRACTS OF *ACACIA NILOTICA L.* LEAVES OBTAINED BY SUCCESSIVE SOXHLET EXTRACTION

Metabolites	Methanolic extract	Chloroform extract	Aqueous extract
Carbohydrates	+	-	+
Tannins	++	+	++
Proteins and amino acids	+	-	+
Flavonoids	++	+	++
Sterols	+	+	-
Triterpenoids	+	+	+
Glycosides	+	-	+
Alkaloids	++	++	+
Saponins	+	-	+

'+'= present '-'= absent

RESULTS:

Preliminary Qualitative Phytochemical Screening: All the extracts of *Acacia nilotica* Linn. leaves had to go through preliminary qualitative phytochemical tests as per the standard guidelines to identify the presence of chemical constituents in the extract for various phytoconstituents were represented in **Table 1.**

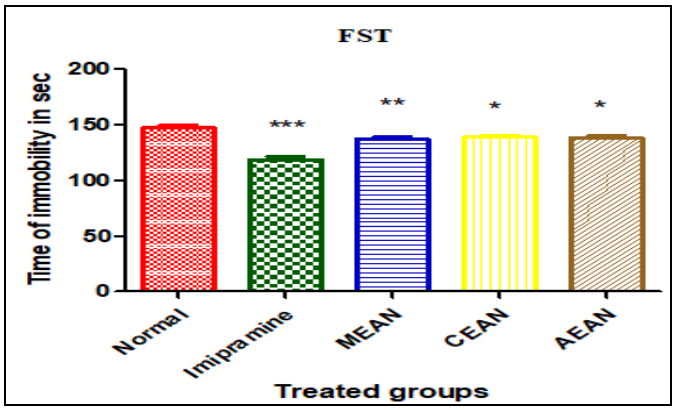
Effect of Extracts on The Immobility Time In Forced Swimming Test (FST) In Mice: The extracts had an anti-depressant effect in the FST because they significantly reduced immobility time compared with the vehicle-treated group 147.3 ± 2.11 sec. The MEAN (200 mg/kg, p.o.) showed good decreases in their immobility times, which was significant 137.3 ± 1.67 sec. ($p<0.01$). CEAN and AEAN, on the other hand, showed a less significant decrease in immobility times, which was 138.5 ± 1.9 sec. ($p<0.05$) and 138.3 ± 2.17 sec. ($p<0.05$) for the doses of 200 mg/kg/ day on 7th day, respectively.

Similarly, animals treated with Imipramine (15 mg/kg, p.o.), showed a high significantly decreased in immobility time (119.00 ± 2.19 sec. ($p<0.001$) on 7th day in FST in mice were represented in **Table 2** and Graph 1.

TABLE 2: EFFECT OF *ACACIA NILOTICA* LINN. EXTRACTS ON FST IN MICE

Experimental groups	Treatment	Dose mg/kg b.w.	Time of immobility in sec
I	Normal (saline)	5 ml/kg	147 ± 2.11
II	Standard (Imipramine)	15 mg/kg	119.0 ± 2.19***
III	MEAN	200 mg/kg	137.3 ± 1.67**
IV	CEAN	200 mg/kg	138.5 ± 1.95*
V	AEAN	200 mg/kg	138.3± 2.17*

All values expressed as Mean ± S.E.M. (n=6 in each group). p values:*<0.05,**<0.01,***<0.001 as compared to vehicle control (saline) (by one-way ANOVA followed by Dunnett multiple comparison test).



GRAPH 1: EFFECT OF *ACACIA NILOTICA* LINN. EXTRACTS ON FST IN MICE

Effect of Extracts on the Immobility Time in Tail Suspension Test (TST) In Mice: The extracts had an anti-depressant effect in the TST because they significantly reduced immobility time compared with the vehicle-treated group 165.5 ± 2.14 sec.

The MEAN (200 mg/kg, p.o.) showed good decreases in their immobility times, which was highly significant 147.50 ± 1.19 sec. ($p<0.001$). AEAN showed significant decreases in immobility times, which was 153.3 ± 2.79 sec.

($p<0.01$) whereas CEAN was not reduced immobility time significantly for the doses of 200 mg/kg/ day on 7th day, respectively. Similarly, animals treated with Imipramine (15 mg/kg, p.o.), showed a high significantly decreased in immobility time (99.17 ± 2.39 sec. ($p<0.001$). on 7th day in FST in mice were represented in **Table 3** and Graph 2.

TABLE 3: EFFECT OF *ACACIA NILOTICA* LINN. EXTRACTS ON TST IN MICE

Experimental groups	Treatment	Dose mg/kg b.w.	Immobility time in seconds
I	Normal (saline)	5ml/kg	165.5 ± 2.14
II	Standard (Imipramine)	15 mg/kg	99.17 ± 2.39***
III	MEAN	200 mg/kg	147.50 ± 1.19***
IV	CEAN	200 mg/kg	163.3 ± 3.07ns
V	AEAN	200 mg/kg	153.3 ± 2.79 **

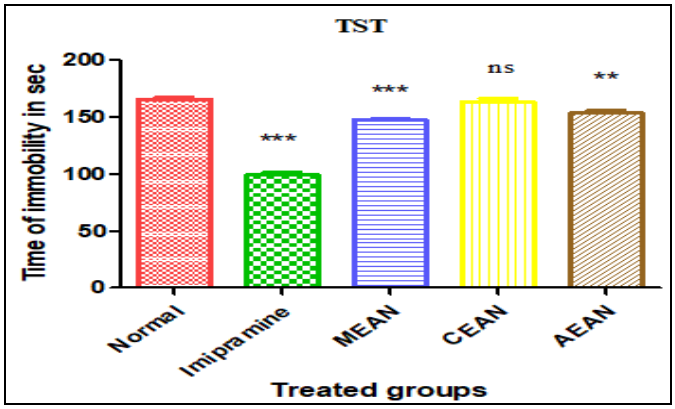
All values expressed as Mean ± S.E.M. (n=6 in each group). p values:*<0.05,**<0.01,***<0.001 as compared to vehicle control (saline) (by one-way ANOVA followed by Dunnett multiple comparison test).

Effect of Extracts on Spontaneous Locomotor Activity in Mice: The extracts showed significantly increased locomotor activity scores when compared with the vehicle-treated group 210.0 ± 2.89. AEAN showed less significant increases in locomotor activity scores, 228.2 ± 4.37 ($p<0.05$) for the doses of 200 mg/kg/ day on the 7th day, respectively. While MEAN and CEAN was not significantly increased locomotor activity scores. Similarly, animals treated with Imipramine (15 mg/kg, p.o.), showed a highly significantly increased in locomotor activity scores 396.7 ± 4.94 ($p<0.001$) on 7th day in mice were represented in **Table 4** and Graph 3.

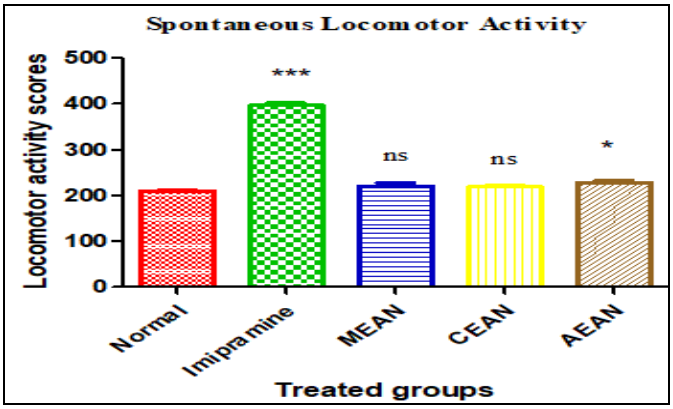
TABLE 4: EFFECT OF *ACACIA NILOTICA* LINN. EXTRACTS ON SPONTANEOUS LOCOMOTOR ACTIVITY IN MICE

Experimental groups	Treatment	Dose mg/kg b.w.	Locomotor activity scores
I	Normal (saline)	5 ml/kg	210.0 ± 2.89
II	Standard (Imipramine)	15 mg/kg	396.7 ± 4.94***
III	MEAN	200 mg/kg	220.5 ± 6.10ns
IV	CEAN	200 mg/kg	218.8 ± 3.56ns
V	AEAN	200 mg/kg	228.2 ± 4.37 *

All values expressed as Mean ± S.E.M. (n=6 in each group). p values:*<0.05,**<0.01,***<0.001 as compared to vehicle control (saline) (by one-way ANOVA followed by Dunnett multiple comparison test).



GRAPH 2: EFFECT OF *ACACIA NILOTICA* LINN EXTRACTS ON TST IN MICE



GRAPH 3: EFFECT OF *ACACIA NILOTICA* LINN. EXTRACTS ON SPONTANEOUS LOCOMOTOR ACTIVITY IN MICE

DISCUSSION: A variety of phytochemicals have been reported to acquire CNS activities. In the present investigation, the anti-depressant activity can be endorsed to the presence of alkaloids, glycosides, flavonoids, tannins, steroids, triterpenoids, and saponin in methanol, chloroform, and aqueous extracts of *Acacia nilotica*, which may be responsible for improving vital neurotransmitters involved in information, memory and processing, which may be beneficial in depression. Triterpenoids and saponins may have improved nerve impulse transmission [20].

The study was undertaken in order to determine the safety and anti-depressant activity of various extracts of *Acacia nilotica*. The findings of the current study indicated that the extracts of *Acacia nilotica* were without any lethal effect in a dose up to 2000 mg/kg and dependent anti-depressant activity through various models. According to our current study, the antidepressant-like activity of various *Acacia nilotica* extracts was found to be comparable to the standard drug Imipramine hydrochloride in all classic depressant models. It blocks norepinephrine (NE) reuptake and has been used as a standard drug in the vast majority of studies. The following reuptake inhibition, imipramine hydrochloride appears to have a beneficial effect in the forced swimming test model due to increased availability of these neurotransmitters, norepinephrine (NE) and serotonin (5HT) at the postsynaptic site [21]. The first depression hypothesis was proposed around 40 years ago, claiming that the primary symptoms of depression were caused by a functional deficiency of cerebral monoaminergic transmitters such as norepinephrine (NE), 5HT, and dopamine (DA) located at synapses [22]. Some research has also found that the plant extract has an adaptogenic effect by normalizing various stress parameters and

monoaminergic levels, implying an antidepressant-like effect by restoring normal monoaminergic neurotransmitters [23]. The increase in locomotor activity indicates a stimulant effect, and various *Acacia nilotica* extracts have shown stimulant effects in actophotometer tests. This prompted us to conduct additional research, this time using depression model paradigms. The prediction of anti-depressant activity is an essential requirement for any anti-depressant screening test, with characteristics such as low cost, robustness, reliability, and ease of use [24]. Based on these criteria, we chose two behavioural despair models in mice: TST and modified FST.

The TST involves suspended mice by their tails for a set period and measuring their immobility. Most anti-depressants reduce immobility time in TST when administered acutely [25]. Test animal's immobility in these models is indicative of behavioural despair, which reflects a depressive state [26]. When mice in modified FST are forced to swim in a confined space, they quickly abandon swimming and come to a halt. Although all anti-depressant drugs reduce immobility in the FST, pharmacologically selective anti-depressant drugs produce two distinct active behavioural patterns [27]. Anti-depressants that selectively inhibit norepinephrine uptake reduce immobility while increasing climbing without impairing swimming. Serotonin reuptake inhibitors, on the other hand, reduce immobility but increase swimming rather than climbing [28].

The recent research showed that a 200 mg/kg dose of *Acacia nilotica* methanolic extract was effective in producing a significant anti-depressant effect in both TST and FST in mice, whereas chloroform and aqueous extracts at the same dose were able to reduce immobility and increase the climbing time without significantly affecting swimming time. The effect of the extract was comparable to standard drug imipramine. The specific mechanism by which *Acacia nilotica* leaves extract produced an antidepressant-like effect is unspecified. However, according to our findings, the pattern of behaviors elicited by the extract in the FST is similar to those elicited by Imipramine, implying that this plant extract acts most likely by increasing norepinephrine neurotransmission is related to climbing behaviour in the modified FST [26]. AS a consequence, we believe that these plant extracts may have anti-depressant properties.

CONCLUSION: In this study, it was revealed that methanolic, chloroform and aqueous extracts of *Acacia nilotica* leaves at a dose of 200 mg/kg in all classic models have an antidepressant-like effect, including the forced swimming test (FST), measurement of locomotor activity test (MLAT), and tail suspension test (TST), comparable to the standard drug Imipramine hydrochloride. *Acacia nilotica* could have anti-depressant properties due to its ability to inhibit MAO enzymes and increase brain serotonin and dopamine neurotransmitter levels. Various types of research studies are required to elucidate the mechanism of action of *Acacia nilotica* in the CNS; the pattern of effects observed in these experiments suggests that the norepinephrine neurotransmitter system is involved in its antidepressant-like effect. The current study also invites more investigation into identifying active compounds in herbal medicines, specifically an antidepressant-like extract of *Acacia nilotica*.

ACKNOWLEDGEMENT: The authors are thankful to Dr. Md Arif Naseer, Professor, Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University, Gangoh, Saharanpur (U.P), India, for providing necessary support to carry out research work.

CONFLICT OF INTEREST: Nil

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How to cite this article:
Shakya MK, Naseer A and Singh R: Evaluation of antidepressant effect of *Acacia nilotica* linn leaves extract in experimental animals. Int J Pharm Sci & Res 2022; 13(4): 1640-46. doi: 10.13040/IJPSR.0975-8232.13(4).1640-46.