COMPARATIVE PHARMACOLOGICAL SCREENING OF ANTI-DEPRESSANT ACTIVITY OF DIFFERENT PARTS OF *NYCTANTHES ARBOR-TRISTIS* PLANT IN MICE

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Abstract

There is a wide spectrum of severity in the mood disorder depression. Depression is caused by a disruption in the equilibrium of neurotransmitters. The present study was based in the comparative pharmacological screening of anti-depressant activity of different parts of *Nyctanthes arbor-tristis* plant in mice. Chemicals and drugs were obtained from the local market in Bareilly. The leaves and flower of the plant *Nyctanthes arbor-tristis* was collected in the month of April 2022 from Botanical Garden, MJPRU Bareilly and nearby area. Fresh plant materials were collected and authenticated by a Resident Botanist and Alok Srivastava, Professor (Department of Plant science), MJP Rohilkhand University, Bareilly. It was extracted using Soxhlet apparatus. Extract was characterized by phytochemical screening, TLC and UV analysis. From the IVRI in Bareilly, Uttar Pradesh, we choose Swiss albino mice weighing 30-40g. The protocol of the depressant activity investigation was approved by the Institutional Animal Ethical Committee. Seven days before the start of the trial, the animals were acclimated to the laboratory environment. Mice were divided into 6 groups (Group I- VI). Forced swimming test was performed in evaluation of anti-depressant activity. In results, test groups at both the dose levels showed anti-depressant potential however, leaves showed much potential than flower when observed in FST. In conclusion, the antidepressant efficacy of all available controls, gold standards, and experimental medicines were investigated during the current 14-day trial. Phytochemical research using TLC and UV spectroscopy revealed the presence of flavonoid in N. Arbor tristis leaf and flower extract, which was responsible for shortening mice's periods of inactivity.

Keywords: *Nyctanthes arbor-tristis*, phytoconstituents, hydroalcoholic, flavonoids, FST.

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INTRODUCTION

There is a wide spectrum of severity in the mood disorder depression. Depression is caused by a disruption in the equilibrium of neurotransmitters [1]. Gamma-aminobutyric acid (GABA), adrenaline, serotonin, and dopamine are all examples of well-known neurotransmitters. Serotonin is a neurotransmitter associated with depression [2]. Depression is a mental and physical disorder that has devastating effects on a person's life, including poor self-esteem, feelings of worthlessness and guilt, inability to concentrate, lower productivity, and increased suicide rates [3]. The research indicated that lifetime depression rates averaged 14.6% in high-income nations and 11.1% in low- and middle-income countries. However, 35.9 percent of Indians and 12.3 percent of Chinese reported ever having a Major Depressive Episode (MDE) throughout their lifetimes [4,5].

Nyctanthes arbor-tristis belongs to Oleaceae family. The *N. arbor* prefers a somewhat shaded setting. It is grown all throughout the tropics and subtropics of the planet. N. arbor is a species that originated in dry deciduous forests on rocky hilltops [6]. The northern regions of Pakistan and Nepal, together with northern India and southeast Thailand, are all within its native range. The eastern border of Nepal with Assam, eastern Assam, Bengal, and Tripura, the middle area of the nation up to the Godavari River in the south, and the outer Himalayas are all places where you may find this species in India [7,8].

NA has some biological activities like antioxidant [9], anti-inflammatory [10], antileishmanial [11]. Seed extract of NA contains various glycosides which have anti-inflammatory and immunomodulatory activities [12]. "Earlier researchers have reported the isolation of polysaccharides, phenylpropanoid ß-sitosterol, iridoid glycosides, glycoside, ß-amyrin, glycosides, hentriacontane, nyctanthoside, benzoic acid, iridoid glucoside, nyctanthic acid, friedelin, lupeol, oleanolic acid, 6ß-hydroxylonganin, alkaloids, tannins, terpenoids, glycosides, and arbortristoside A, B, C from this plant" [13].

Fig 1. *Nyctanthes arbor-tristis* plant

Taxonomy

Kingdom: Plantae
Division: Angiosperms
Class: Dicotyledonae
Sub class: Gamopetalae
Series: Bicarpellatae
Order: Gentiales
Family: Oleaceae
Genus: *Nyctanthes*
Species: *arbor-tristis*

MATERIAL AND METHOD

Drugs, Chemicals and materials: The following drugs, chemicals and materials were used in the present research work.

- Fluoxetine as a standard drug
- Reserpine (For induction)
- Carboxy methyl cellulose (2% w/v)
- Nyctanthes arbor-tristis Extract
- Distilled water
- 70% Ethanol
- Whatmann filter Paper
- Cloth towel
- Standard mice group housing cage
- Forced swimming apparatus

Collection of Plant Material

The leaves and flower of the plant *Nyctanthes arbor-tristis* was collected in the month of April 2022 from Botanical Garden, MJPRU Bareilly and nearby area.

Identification and Authentication

It is a woody shrub that may grow up to 10 meters tall and can live anywhere from 5 to 20 years. It has white blooms that emit a strong, pleasant aroma all night long. Bareilly is home to the medicinal plant *Nyctanthes arbor-tristis*, which has been examined and identified after being gathered there. Fresh plant materials were collected and authenticated by a Resident Botanist and Alok Srivastava, Professor (Department of Plant science), M.J.P Rohilkhand University, Bareilly.

Extraction of the plant

Leaves: Debris will be removed from the new plant material by washing it with distilled water, and then it will be dried at 35-40oC for 10 days. After being ground to a powder in an electric grinder, the substance was sieved using a No. 60 mesh screen. The powdered dried leaves will be extracted using hydro-alcohol (80:20 v/v) in a Soxhlet device for 72 hours. Drying is used to eliminate any remaining solvent. The yield of the hydro-alcoholic extract is around 4.6% w/w.

Flower: NAT flowers were picked first thing in the morning, when their scent is at its most, and then given a thorough cleaning before being air dried in the shade. The dry ingredients are milled into a fine powder and macerated in 80% v/v ethanol for 7 days at room temperature.

1. Preparation of extract of leaves was performed by using following steps-

Leaves of plant *Nyctanthes arbor-tristis* was collected
↓
Leaves was shade dried for 10 days
↓
After that, it was pulverized in electric grinder and powdered
↓
The powdered material extracted through Soxhlet apparatus for 72 hours each
↓
The extract was obtained

2. Preparation of extract of flowers was performed by using following steps-

Flowers of plant N. Arbor tristis was collected early in the morning
↓
Flowers was shade dried for 8 days
↓
Dried material finely powdered and macerated thrice with 80% v/v ethanol for 7 days
↓
The extract was obtained

Fig 2. Extraction of flower

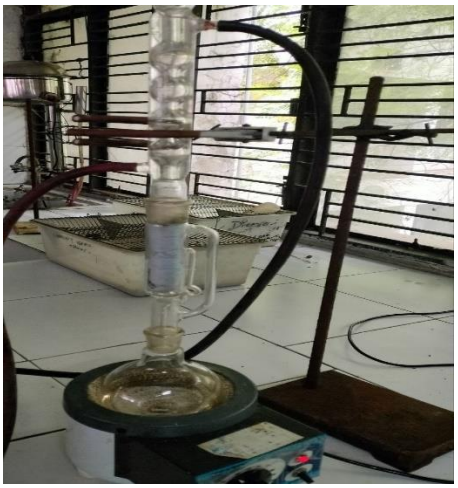


Fig 3. Extraction of leaves by Soxhlet apparatus

Phytochemical screening of extract: Hydroethanolic extract of leaves was subjected to conventional phytochemical tests to determine the presence of bioactive chemicals [14].

Test for Tannin
There were 5 drops of 10% lead acetate added to 5 millilitres of plant extract. Tannin is present when a pale-yellow precipitate forms.

Test for Saponin
The extract was diluted by boiling 1 millilitre in 10 millilitres of water before being filtered using Whatman filter paper. There was a vigorous shaking of 5 ml of filtrate and 2 ml of regular distilled water. The presence of saponins is indicated by the appearance of steady, persistent foam.

Test for Flavonoids
To only one milliliter of the extract, some diluted sodium hydroxide was added. The plant extract became a vivid yellow, but when a few drops of diluted acid were added, the color quickly faded. (50 percent concentration).

Test for Terpenoid
Two millilitres of chloroform were added to half a gram of plant extract, and the same amount of strong sulphuric acid was added. The presence of terpenoids is indicated by an interface coloration of reddish brown.

Test for Phenolic compounds
Two milliliters of plant extract, five drops of 1% ferric chloride, and one milliliter of potassium ferro cyanide were mixed to produce a bluish-green solution, demonstrating the presence of a phenolic component.

Test for Reducing sugar
Filtered distilled water was used to dissolve 0.5 g of plant extract. For 5 minutes, the filtrate was boiled with 2 drops each of Fehling's solutions A and B. When reducing sugar is present, a bright orange precipitate form.

Test for Steroid
To a solution of two milliliters of plant extract in five milliliters of chloroform, strong sulphuric acid was added. A two-stage change in density is diagnostic of steroid use.

Test for Alkaloids:
Some diluted hydrochloric acid was added to the extract, and then it was filtered. The filtrate obtained when treated with

- Dragendorff's reagent- brown precipitate,
- Mayer reagent - cream color precipitate and
- Hager reagent - yellow precipitate, indicated the presence of alkaloids.

Fig. 4 Froth appears

Fig. 5 Yellow precipitate

Fig. 6 Brown precipitate

TLC analysis
TLC was used to evaluate extracts for their constituents. A non-polar basic solvent, an intermediate-polar basic solvent, and a polar basic solvent were used in the TLC analysis. A clear graph of all the potential chemicals in the extract was obtained by progressively increasing the polarity of the solvent systems. Benzene, being a nonpolar basic solvent, was utilized to separate out the extract's non-polar components. Ammonium base is employed as a solvent to speed up the separation of alkaloids and terpenoids on a TLC plate because of their basic nature. Nonpolar mobile phase was formed by mixing 9 parts benzene to 1 part ethanol to 1 part ammonium hydroxide. Chloroform, ethyl acetate, and formic acid (5:4:1) made up the intermediate polar basic solvent. Ethyl acetate, ethanol, and water made up the polar basic solvent in a ratio of 8:1.2:0.8. After TLC, the plates were examined under ultraviolet light to identify the compounds present. The plates were soaked in a 10% sulfuric acid solution, let to dry, and then heated to 80-90 °C to get the desired char. This aided in the spot's fixation and made it more apparent. The plates were then dried in the dark after being dipped into a 0.04% DPPH solution for flavonoid detection. The plates were washed with Folin & ciocalteu reagent and dried for polyphenol detection [15].

UV ANALYSIS
Preparation of sample
The samples were prepared by dissolving 10 milligrams (mg) into 100 milliliters (ml) of distilled water (w/v concentration of 10%).
Double beam UV-Visible Spectrophotometer Model Shimadzu-1800 was used to acquire the UV absorption spectra for extract between 200 and 400 nm.

Determination of λmax
Pure medications have been shown to have better results. The purity of pharmaceuticals may be

determined using a variety of techniques. When compared to other techniques, UV spectroscopy stands out as the most advantageous due to its low cost and high reliability and reproducibility of findings. One way to find out how potent a medicine is to analyze its UV spectrum. The drug's maximum allowed dose is fixed and cannot be altered under any circumstances. When a compound's max value shifts, it's no longer as pure as it once was. Using UV spectroscopy, we calculated the maximum wavelength (max) of leaf extracts from the plant *N. arbor-tristis*. Using a UV spectrophotometer, a UV-visible spectrum was obtained from a solution of leaf extract in distilled water at a concentration of 10 g/ml. From 200 to 400 centimeters, the sample was scanned [16].

Preparation of calibration curve

The extract was diluted to the appropriate volume in a series of 10ml volumetric flasks using aliquots ranging in concentration from 1 to 10 g/ml. The absorbance of each solution was measured at 386 nm and compared to the blank diluents using the equipment in photometric mode. Using absorbance on the ordinates and extract concentration on the abscissa, a calibration curve was developed.

Phytochemical analysis of plant extracts

Phytoconstituents	**Name of Test**	**Result**
Alkaloids	Hager's test Dragendroff's reagent Mayer reagent	+++
Anthraquinones	Chloroform layer test	-
Cardiac glycosides	Killer-Killani's test	+
Flavonoids	Ammonia test (modified	+
Reducing sugars	Fehling's test	-
Saponins	Frothing test	+++
Steroids	Salkowski's test	++
Tannins	FeCl3 test	-
Terpenoids	Salkowski test (modified)	-

Preparation of animals

From the IVRI in Bareilly, Uttar Pradesh, we choosen Swiss albino mice weighing 30-40g. Mice are kept in normal housing with a 12:12 light-dark cycle and temperatures between 24 and 28% and 60% and 70% relative humidity. The animals are given a pellet meal and free access to water. All tests are performed between the hours of 8 am and 16 pm local daylight time. The protocol of the depressant activity investigation was approved by the Institutional Animal Ethical Committee. Seven days before the start of the trial, the animals were acclimated to the laboratory environment.

Group design

Six Swiss albino mice were randomly assigned to one of 6 groups based on their gender. All the test solution was freshly prepared daily.

Table 1. Group design

GROUP	**TREATMENT**
Group I	Vehicle-treated control (2% carboxymethyl cellulose).
Group II	Fluoxetine hydrochloride (20mg/kg).
Group III	100 mg/kg hydroethanolic extract of leaves
Group IV	400mg/kg hydroethanolic extract of leaves
Group V	100 mg/kg hydroethanolic extract of flowers
Group VI	400 mg/kg hydroethanolic extract of flowers

EVALUATION PARAMETER

Induction of Depression

In order to evaluate antidepressant activity of test drug, first requirement is the induction of depression in animals. To induce depression in animals, Reserpine in a dose 0.5 mg/kg is administered intra-peritoneally to animals for 14 days prior to acquisition trial. Then, evaluation of antidepressant activity is performed using Forced Swim Test.

Forced Swim test

The device was a cylinder made of opaque Plexiglas (50 cm in height, 20 cm in width) that was 30 cm deep in room temperature water. For the duration of the 6-minute swim test, we will be looking for signs of immobility, which we will define as the absence of any escape efforts beyond those required to maintain the animal's head above water. One of the behavioral profiles indicative of an antidepressant's effectiveness is a decrease in sedentary behavior.

In the current research, mice with a natural affinity for swimming were placed in a tank from which they could not escape, inducing a behavior of immobility that was interpreted as a symptom of behavioral despair. The antidepressant effect has been linked to a decrease in bed rest. The research used Swiss Albino mice. The day before the experiment, the mice are brought to the lab and housed in individual cages where they have unrestricted access to food and drink. The antidepressant effect was measured in a cylindrical Perspex tank (40 cm high, 18 cm in diameter) filled with water at 22 5 °C up to the 15th centimeter. There will be an induction period of 15 minutes followed by a testing period of 6 minutes during FST [17].

Mice are induced for 24 hours before being tested in tanks. In the trial phase, the amount of time spent sitting still was timed in seconds. After 24 hours, they are given either the test extracts (given one hour before to the test) or the standard medication (given thirty minutes prior to the test), and the total time of immobility is assessed over the course of a 6-minute test.

RESULTS AND DISCUSSION

Percentage yield

The percentage yield was calculated as 64.56% when weight of practical yield was compared with theoretical yield.

Phytochemical constituents

The following table shows the list of chemical constituents that were observed in the extract of leaves of plant *Nyctanthes arbor-tristis*-

Table 2. Phytochemicals in ethanolic extract of *N. arbor tristis*

Chemical Constituents	Types of tests	Ethanolic extract of *N. arbor tristis*
Saponins		
	Foam test	+
Alkaloids		
	Dragendroff's test	+
	Mayer's test	+
	Wagner's test	+
	Hager's test	+
Carbohydrates		
	Fehling's test	+
	Benedict's test	+
Tannins		
	Shinoda test	+
Proteins		
	Biuret test	+
	Million's test	+
	Xanthoprotein test	+
	Ninhydrine test	+
Glycosides		
	Keller-killiani test	+
	Bromine water test	+
	Legal's test	+
Amino acids		
	Ninhydrine test	+
	Test for tyrosine	+
Terpenes		+
Flavonoid	Lead acetate	+

(+) = present,(-) = absent

Whole plant exhibited a rich source of above-mentioned chemical constituents.

UV Spectrophotometer

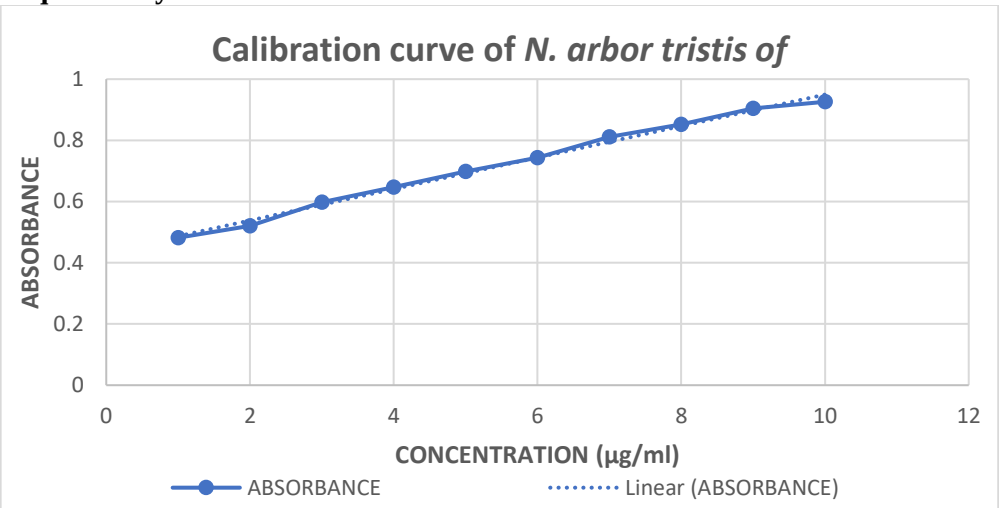
Calibration Curve of leaves extract of *N. arbortristis* in distilled water

For the preparation of calibration curve, the calibration samples were prepared from stock solution (1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 µg/ml). The "Shimadzu 1800 UV Spectrophotometer" was used to measure the sample's absorbance at 386 nm. The following table shows the absorbance at various concentrations:

CONCENTRATION (µg/ml)	ABSORBANCE
1	0.482
2	0.521
3	0.578
4	0.61
5	0.633
6	0.692
7	0.713
8	0.852
9	0.9
10	0.926

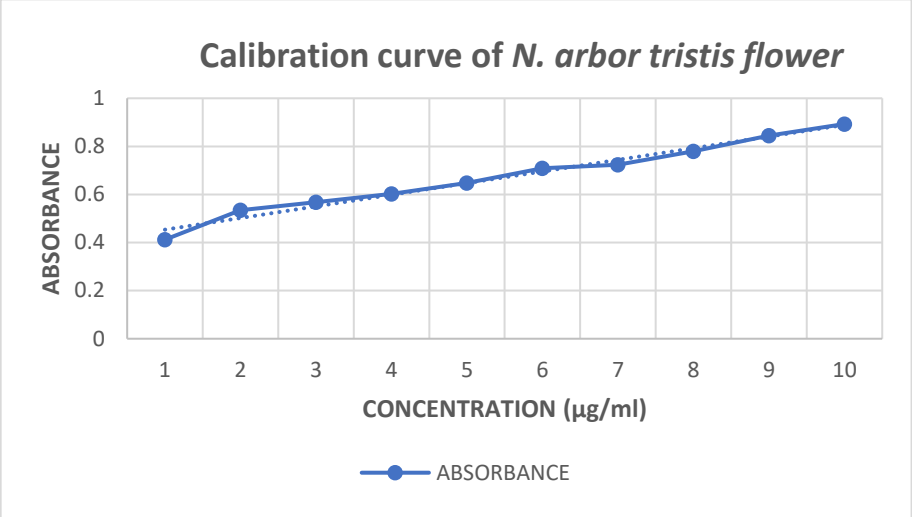
The standard graph plotted between absorbance and concentration, on “X” and “Y” axis respectively was to be linear.

Straight line equation:- y = mx + c



UV analysis of Flower extract:

CONCENTRATION (µg/ml)	ABSORBANCE
1	0.412
2	0.534
3	0.568
4	0.602
5	0.648
6	0.709
7	0.724
8	0.779
9	0.845
10	0.893



Statistical Analysis: By averaging and standardizing the outcome indicators, we were able to quantify the relative effectiveness of the several medications under investigation. Analysis of variance (ANOVA) was used to look at how various medications performed. ANOVA and Bonferroni's post hoc test were used to examine the results. The 5% significance threshold (*p value 0.05) was used to identify differences.

Forced Swim Test Method: In this study, the immobility duration of animals given test drug 2 (a combination of 400 mg/kf of fresh NAT leaves and NAT flower extract) was significantly shorter than that of animals given NAT flower extract. Test medication 2 decreased immobility time by 38.68% compared to the control, while both 400 mg/kg of fresh leaves NAT and the control reduced immobility time by 39.63% and 30.59%, respectively.

Table 3. Depicts immobility period FST in all groups

Group	Treatment for 14 days	Dose	Immobility Period (sec)
1	Control	Vehicle treated 2% CMC	157± 5.2
2	Standard	Fluoxetine (20mg/kg)	108.5± 8.3
3	Test 1	100 mg/kg fresh leaves extract of NAT	132.6± 7.9
4	Test 2	400 mg/kg fresh leaves extract of NAT	120.5± 7.3

There were six participants in each group, and results are shown as the mean + standard deviation.

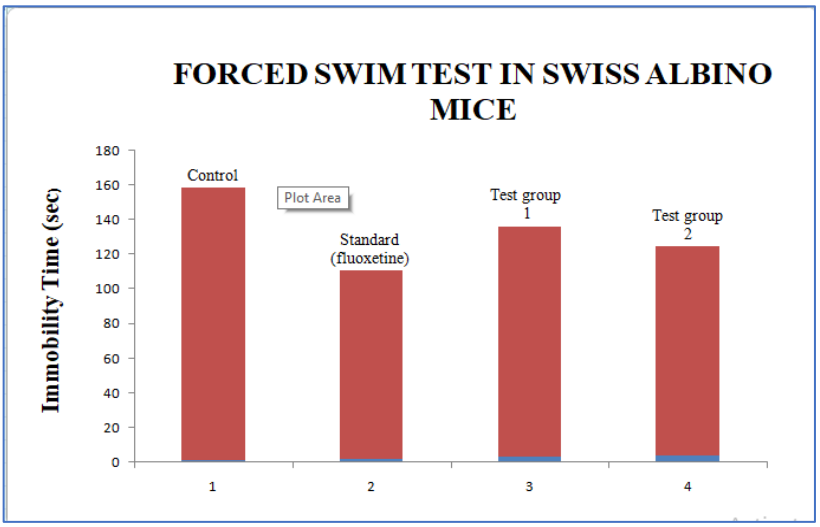
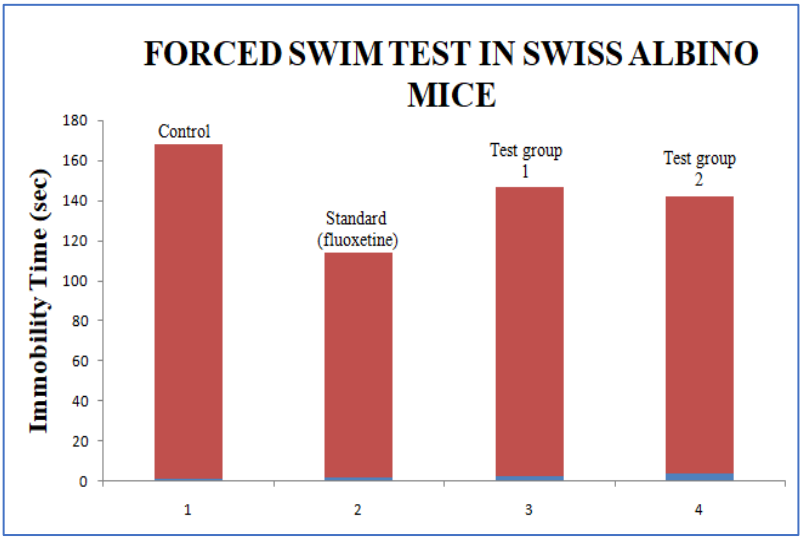


Table 4: Immobility period Forced swimming test in all groups

Group	Treatment for 14 days	Dose	Immobility Period (sec)
1	Control	Vehicle treated 2% CMC	166.7± 3.1
2	Standard	Fluoxetine (20mg/kg)	111.7± 8.0
3	Test 1	100 mg/kg fresh flowers extract of NAT	143.5± 7.1
4	Test 2	400 mg/kg fresh flowers extract of NAT	138.2± 6.2

There were six participants in each group, and results are shown as the mean + standard deviation.



Biochemical assay of animals *(Mus musculus):*

Estimation of blood glucose level in fasting mice-

The ethanolic extract of leaves of *N. Arbor tristis at* the dose of 100 mg/kg and 400 mg/kg showed the blood glucose level of 102±0.29*** mg/dl and 128±0.20** mg/dl respectively. In addition, blood glucose was observed as 133±0.25*** mg/dl in control group. Fluoxetine treated group also showed the normal blood glucose level as 108.32±0.31***mg/dl.

Both glucose level were estimated in fasting mice and glucose levels were observed as normal when compared among all groups.

Table 5. Blood glucose level (mg/dl) in fasting mice

Treatment	**Body weight (g)**	**Blood glucose level (mg/dl)**
Distilled water	35	133±0.25***
Fluoxetine (20mg/kg)	25	108.32±0.31**
Ethanolic extract leaves of *Nyctanthes arbor tristis cordifolia* (100 mg/kg)	50	102±0.29***
Ethanolic extract of *Nyctanthes arbor tristis* (400mg/kg)	40	128±0.20***

Level of significance denoted by *; n= 6

Values were exhibited in Mean ± SEM

2 Estimation of blood glucose level in non-fasting mice-

Rodents were also evaluated for blood glucose level in non-fasting state. All the test groups showed a normal blood glucose level when tested. At 60 minutes, blood glucose level was observed as 128±0.21***mg/dl and 135±0.41***mg/dl in the ethanolic extract of leaves of *N. Arbor tristis* treated mice at the dose of 100 mg/kg and 400 mg/kg respectively. Whereas, control group treated with distilled water also showed normal blood glucose as 101±0.48***mg/dl and standard group as 110.82±0.23***mg/dl at 60 min.

The blood glucose level were estimated as 135±0.25***mg/dl, 126±0.28***mg/dl and 123±0.20***mg/dl in ethanolic extract of *N. Abor tristis* 100 mg/kg and 400 mg/kg at time interval of 15min, 45min and 60 min, respectively. Whereas, control group showed blood group level as 105±0.30**mg/kg, 118±0.29***mg/dl and 132±0,42**mg/dl at the time intervals of 15min, 30min and 45min, respectively.

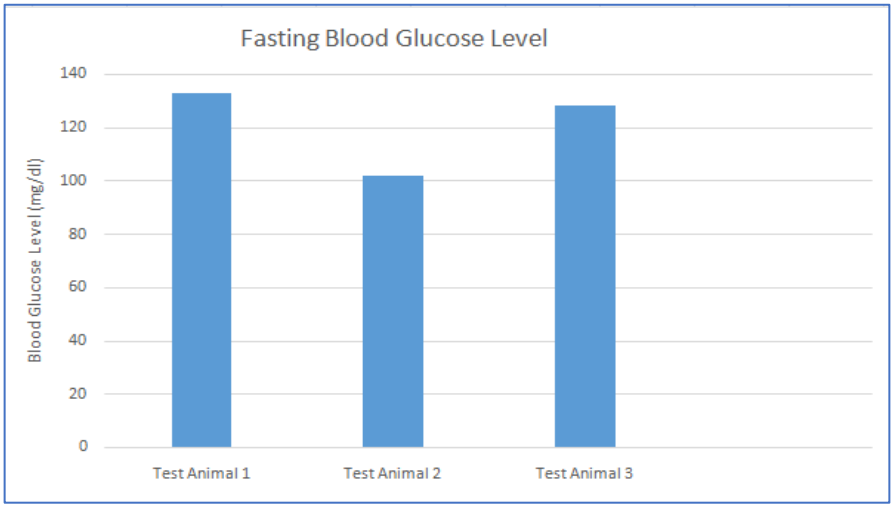
Also, in non-fasting mice the effect of *N. arbortristis* was not influential. They exhibited for normal blood glucose level.

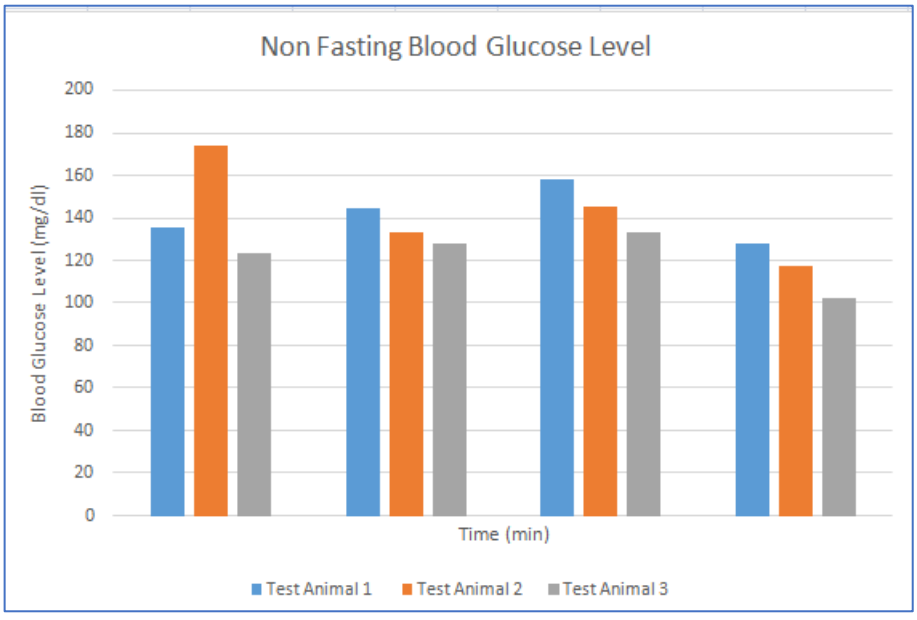
Table 6. Blood glucose level (mg/dl) in non-fasting mice

Treatment	**Body weight (g)**	**Blood glucose level (mg/dl)**			
		15min	**30min**	**45min**	**60min**
Distilled water	35	109.62±0.17**	114.15±0.20***	125.53±0.41**	98.12±0.46***
Fluoxetine (20 mg/kg)	25	114.15±0.20***	119.17±0.53**	127.36±0.14	109.62±0.17**
Ethanolic extract of leaves of *N.arbor tristis* (100 mg/kg)	50	119.17±0.53**	130.64±0.18***	122.34±0.62	114.15±0.20***
Ethanolic extract of leaves of *N.arbor tristis* (400mg/kg)	40	130.64±0.18***	98.12±0.46***	119.17±0.53**	119.17±0.53**

Level of significance denoted by *; n= 6
Values were exhibited in Mean ± SEM

As already indicated, several phytoconstituents such flavonoids, saponins, and tannins were found in the *N.arbor tristis* phytochemical testing. It is well known that the flavonoid component has antioxidant and anti-depressant properties. This outlines the extract's method of action in some detail. It is necessary to conduct additional research to identify the anti-depressant substance. Despite clinical research, the neurochemical underpinnings of anti-depressant activity remain poorly understood.





The extract's antidepressant action might be attributed to one or more Phytochemical. However, the Phytochemical responsible for this action must be identified. Based on the pattern of reduced immobility time, the leaves, flowers of NAT indicated adequate antidepressant effect in the current investigation, but the main objective of this work is to identify that which part of plant NAT showed more significant activity on depression. So, here we have found that both leaves and flower extract of *Nyctanthes arbor tristis* showed antidepressant activity. Hence, extract of leaves of NAT reported more significant activity as compare to the extract of flower.

The increased prevalence of depression in the United States is linked to substantial increases in both morbidity and mortality, making it all the more urgent to address these issues and find workable solutions. Existing treatments for these illnesses all have significant limitations, therefore novel methods are constantly appreciated. As it is well-known that natural materials with therapeutic

potential have fewer adverse effects than pharmaceuticals, they are gaining importance in clinical research [18]. Several animal models are used to study stress-induced behaviour and the effects of antidepressants. [19]. These models are based on the clinical co occurrence of depression episodes and stressful life events. Reducing the period of inactivity during forced swimming has been shown to rely heavily on an increase in central 5-hydroxytryptamine (5-HT) and catecholamine neurotransmission.

CONCLUSION

Nyctanthes arbortristis extract showed antidepressant efficacy in a dose-dependent manner by reducing the time duration of immobility of mice in the Forced swimming test compared to the control group. By studying how antidepressants work, we know that they boost monoaminergic synaptic neurotransmission by inhibiting the reuptake of 5-hydroxytryptamine and non-adrenaline. The neurological consequences of depression models vary. Treatment with antidepressants was successful in reversing these consequences. Based on the findings of the research, it is obvious that the synapse-localized antagonists of 5-hydroxytryptamine and nor-adrenaline are the primary instigators of depression. Dopaminergic action of antidepressant medicines was the first setting in which this effect was applied to the model.

The antidepressant efficacy of all available controls, gold standards, and experimental medicines were investigated during the current 14-day trial. Phytochemical research using TLC and UV spectroscopy revealed the presence of flavonoid in N. Arbor tristis leaf and flower extract, which was responsible for shortening mice's periods of inactivity.

FUNDING

Nil.

CONFLICT OF INTEREST

None.

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