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PHARMACOLOGICAL EVALUATION OF ANTIDEPRESSANT AND ANTIANXIETY ACTIVITY OF BUPLEURUM FALCATUM IN ANIMAL MODELS

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Abstract:
Bupleurum falcatum, belongs to the family Apiaceae. Anxiety and Depression are widespread psychiatric disorders affecting around 5% of the population. Furthermore, it is difficult to predict which patient will respond to any given treatment. In the traditional systems of medicine, many plants have been used to treat anxiety and depression for thousands of years. The present study was designed to evaluate the antianxiety and antidepressant activity of the alcoholic and aqueous extracts of Bupleurum falcatum leaves in rodents. Antianxiety activity was tested by exposing rats to unfamiliar aversion in different methods like elevated plus maze model and actophotometer. The results infer that reduced aversion fear elicits antianxiety activity. The antidepressant activity was tested by using forced swim test and tail suspension test. The results infer that reduced immobility time elicits antidepressant activity. It was concluded that alcoholic and aqueous extracts of Bupleurum falcatum leaves having antianxiety and antidepressant activity. Alcoholic extract of Bupleurum falcatum leaves showing more significant activity over the aqueous extract.

Keywords: *Bupleurum falcatum, Antianxiety activity, Antidepressant activity, Elevated plus maze, Actophotometer, Despair swim test, Tail Suspension Test.*

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INTRODUCTION:

Medicinal plants are various plants thought by some to have medicinal properties, but few plants or their phytochemical constituents have been proven by rigorous science or approved by regulatory agencies such as the United States Food and Drug Administration or European Food Safety Authority to have medicinal effects. World Health Organization (WHO) has provided a definition of medicinal plants, that is "A medicinal plant is any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes or which are precursors for synthesis of useful drugs." [1]

World Health Organization (WHO) reported that 80% of the world's population depends on medicinal plants for their primary health care. In the Plant Kingdom, Medicinal plants form the largest single grouping of plants. It is estimated that 30,000 species worldwide fall in this group, of which around 33% are trees [2] Plants are known to be the source of many chemical compounds. Medicinal plants were used by people of ancient cultures without knowledge of their active ingredients. The common practice of taking crude extract orally is laden with hazards as the extracts may contain some toxic constituents. There is an ever increasing need to limit toxic clinical drugs.In modern times, the active ingredients and curative actions of medicinal plants were first investigated through the use of European Scientific methods [3]. The most important ingredients present in plant communities turn out to be alkaloids, terpenoids, steriods, phenols glycosides and tannins [2].

History of plants in medicine [7]:

The earliest known medical document is a 4000-year-old Sumerian clay tablet that recorded plant remedies for various illnesses. The ancient Egyptian Ebers papyrus from 3500 year ago lists hundreds of remedies. The Pun-tsao contains thousands of herbal cures attributed to Shennung, China's legendary emperor who lived 4500 years ago. In India, herbal medicine dates back several thousand years to the Rig-Veda, the collection of Hindu sacred verses. The Badianus Manuscript is an illustrated document that reports the traditional medical knowledge of the Aztecs. Western medicine can be traced back to the Greek physician Hippocrates, who believed that disease had natural causes and used various herbal remedies in his treatments. Early Roman writings also influenced the development of western medicine, especially the works of Dioscorides, who compiled information on more than 600 species of plants with medicinal value in De Materia Medica. Many of the herbal remedies used by the Greeks and Romans were effective treatments that have become incorporated into modern medicine (e.g., willow bark tea, the precursor to aspirin). Dioscorides' work remained the standard medical reference in most of Europe for the next 1500 years.

The beginning of the Renaissance saw a revival of herbalism, the identification of medicinally useful plants. This coupled with the invention of the printing press in 1450 ushered in the Age of Herbals. Many of the herbals were richly illustrated; all of them focused on the medicinal uses of plants, but also included much misinformation and superstition. The Doctrine of Signatures, for example, held that the medicinal use of plants could be ascertained by recognizing features of the plant that corresponded to human anatomy. For example, the red juice of bloodwort suggests that it should be used for blood disorders; the lobed appearance of liverworts suggests that it should be used to treat liver complaints; the "humanoid" form of mandrake root suggests that is should be used to promote male virility and ensure conception.

Many of the remedies employed by the herbalists provided effective treatments. Studies of foxglove for the treatment of dropsy (congestive heart failure) set the standard for pharmaceutical chemistry. In the 19th century, scientists began purifying the active extracts from medicinal plants (e.g. the isolation of morphine from the opium poppy). Advances in the field of pharmacology led to the formulation of the first purely synthetic drugs based on natural products in the middle of the 19th century. In 1839, for example, salicylic acid was identified as the active ingredient in a number of plants known for their pain-relieving qualities; salicylic acid was synthesized in 1853, eventually leading to the development of aspirin. It is estimated that 25% of prescriptions written in the U.S. contain plant derived ingredients (close to 50% if fungal products are included); an even greater percentage are based on semisynthetic or wholly synthetic ingredients originally isolated from plants.

Traditional medicine:

Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous systems of medicine. Traditional preparation comprises medicinal plants, minerals and organic matters etc. Herbal drug constitutes only those traditional medicines that primarily use medicinal plant preparations for therapy. The ancient record is evidencing their use by Indian, Chinese, Egyptian, Greek, Roman and Syrian dates back to about 5000 years.

About 500 plants with medicinal use are mentioned in ancient texts and around 800 plants have been used in indigenous systems of medicine. Indian subcontinent is a vast repository of medicinal plants that are used in traditional medical treatments[8], which also forms a rich source of knowledge. The various indigenous systems such as Siddha, Ayurveda, Unani and Allopathy use several plant species to treat different ailments.

Trends of using traditional medicine:
In some Asian and African countries, 80% of the population depend on traditional medicine for primary health care. In many developed countries, 70% to 80% of the population has used some form of alternative or complementary medicine (e.g. acupuncture). Herbal treatments are the most popular form of traditional medicine, and are highly lucrative in the international marketplace. Annual revenues in Western Europe reached US$ 5 billion in 2003-2004. In China sales of products totaled US$ 14 billion in 2005. Herbal medicine revenue in Brazil was US$ 160 million in 2007 [11].

Modern medicine from medicinal plants:
Medicinal plants play a vital role for the development of new drugs. During 1950-1970 approximately 100 plants based new drugs were introduced in the USA drug market including deserpidine, reseinnamine, reserpine, vinblastine and vincristine which are derived from higher plants. From 1971 to 1990 new drugs such as ectoposide, Eguggulsterone, teniposide, nabilone, plaunotol, Z-guggulsterone, lectinan, artemisinin and ginkgolides appeared all over the world. 2% of drugs were introduced from 1991 to 1995 including paciltaxel, toptecan, gomishin, irinotecan etc.

Plant based drugs provide outstanding contribution to modern therapeutics; for example: serpentine isolated from the root of Indian plant Rauwolfia serpentina in 1953, was a revolutionary event in the treatment of hypertension and lowering of blood pressure. Vinblastine isolated from the Catharanthus rosesus is used for the treatment of Hodgkins, choriocarcinoma, nonhodgkins lymphomas, leukemia in children, testicular and neck cancer. Vincristine is recommended for acute lymphocytic leukemia in childhood advanced stages of hodgkins, lymophosarcoma, small cell lung, cervical and breast cancer[12]. Phophyllotoxin is a constituent of Phodophyllum emodi currently used against testicular, small cell lung cancer and lymphomas. Indian indigenous tree of Nothapodytes nimmoniana (Mappia foetida) are mostly used in Japan for the treatment of cervical cancer. Plant derived drugs are used to cure mental illness, skin diseases, tuberculosis, diabetes, jaundice, hypertension and cancer.

Anti-depressant:
Mental depression as a chronic illness that affects a person's mood, thoughts, physical health and behavior symptoms of depression include biological and emotional components. Biological symptoms include retardation of thought, action and appetite. Emotional symptoms include mystery, apathy and pessimism low self-esteem consisting of feeling of guilt, inadequacy and ugliness, indecisiveness and loss of motivation. Antidepressants drugs such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI) are used to treat depression showing various side effects and thus, the search for new antidepressant herbs without side effects is important. On the basis of phytochemical screening the presence of flavonoids, saponins leaves of *Desmostachya bipinnata* was selected for evaluating its antidepressant activity have been raised. Therefore the present study was aimed to explore this indigenous plant for anti-depressant activity by Forced swim test.

Anti-anxiety:
Anxiety is one of the most common psychiatric disorders which decrease the quality of life worldwide. It is considered among the most prevalent psychiatric syndromes affecting 10 to 30 % of the general population of industrialized societies that affect emotion and cognition and also exhibit >50% co-morbidity with depression. Benzodiazepines are among most frequently prescribed anxiolytics, but now it is widely accepted that several clinical problems are associated with benzodiazepines viz. fairly high risk of dependence, tolerance and addiction in long term use. Abuse liability has also been documented among vulnerable groups and adverse effects on behavior, cognition, immunity, muscle relaxation etc. Anxiolytics or cognitive behavioral therapy has been in practice but many patients remain untreated, experience adverse effects of drugs, or do not get benefited. Till date efficacy of available drugs are limited. In such situation herbal medication may be considered as an alternative to complementary medicine. It has been estimated that 43% of anxiety sufferers use some form of complementary therapy. Use of medicinal plants as a therapeutic approach for psychiatric illness has increased significantly. A number of herbal medicines are being used for the treatment of neurological and psychological disorders. Based on phytochemical screening *Bupleurum falcatum* the presence of saponins and alkaloids has been

conducted to evaluate the anxiolytic effect of both aqueous and alcoholic extracts of *Bupleurum falcatum* leaves in EPM models of anxiety.

MATERIALS AND METHODS:

The designing of methodology involves a series of steps taken in a systematic way in order to achieve the set goal(s) under the prescribed guidelines and recommendations. It includes in it all the steps from field trip to the observation including selection and collection of the medicinal plant, selection of dose value, standardization of protocol, usage of instruments, preparation of reagents, selection of specific solvents for extraction, formation of protocols and final execution of the standardized protocol. All this requires good build of mind and a good and soft technical hand to handle the materials and procedure in a true scientific manner.

Drugs and Chemicals

Drugs and Chemicals used in this study were of analytical grade and of highest purity procured from standard commercial sources in India.

Table No 1: Drugs and Chemicals

S.No	***Materials***	***Company Name***
1.	Diazepam	Nicholos Piramal Ltd
2.	Alcohol	ChangshuYangyuan Chemicals, China.

Instruments:

Following instruments were required for the study:

Table No: 2- List of Instruments used for study

Name of the instrument	***Source***
Centrifuge	Dolphin
Digital weighing balance	Horizon
Glucometer	Horizon
Heating mantle	ASGI®
Refrigerator	Videocon
Actophotometer	Dolphin
Elevated Plus maze apparatus	Dolphin
Glass cylinder	ASGI®
Adhesive tape	YVR medivision Pvt Ltd
Thread	YVR medivision Pvt Ltd
Stop watch	ASGI®
Syringes	YVR medivision Pvt Ltd
Needles	YVR medivision Pvt Ltd

Experimental animals:

Wistar rats (150-200 g) and Swiss albino mice (18-22g) of either sex selected for the study. Animals were housed in appropriate cages in uniform hygienic conditions and fed with standard pellet diet (Amrul Laboratory Animal Diet) and water ad libitum. All the animals were maintained under standard conditions, that is room temperature 26 ± 1°C, relative humidity 45 - 55% and12:12 h light – dark cycle. Animal studies had approval of IAEC.

Plant Material Collection:

The leaves of *Bupleurum falcatum* was collected from the local area in the month of -June.The plant material was cleaned, reduced to small fragments, air dried under shade at room temperature and coarsely powdered in a mixer. The powdered material was stored or taken up for extraction process.

Preparatin of plant extracts:

6.5.1 Preparation of Aqueous Extract:

Fresh leaves of *Bupleurum falcatum* were collected and washed under tap water. The leaves extract used was prepared by taking 20gms of finely cut leaves

into 250ml beaker containing 200ml of water. The contents were mixed well and then the mixture was boiled up to 80-100^{0}C for 4-5hrs. Further the extract was filtered with whatmann filter paper. The filtrate was boiled until the concentrated residue is formed. The concentrated product was sealed in sample covers and stored under room temperature and used for further experiment to check the activities.

Preparation of Alcoholic Extract:
Fresh leaves of *Bupleurum falcatum* were collected and washed under tap water. The leaves extract used was prepared by taking 20gms of finely cut leaves into 250ml beaker containing 200ml of alcohol. The contents were mixed well and then the mixture was boiled up to 50-60^{0}C for 4-5hrs. Further the extract was filtered with whatmann filter paper. The filtrate was boiled until the concentrated residue is formed. The concentrated product was sealed in sample covers and stored under room temperature and used for further experiment to check the activities.

Selection of dose for animal study:
The dose considered for the experiment on rats was obtained from conversion of human dose of *Bupleurum falcatum* (3-5 g/kg). The conversion factor of human dose (per 200 g body weight) is 0.018 for rats and 0.002 for mice (Ghosh 1984). Hence the calculated dose for the rats (considering human dose3 and 5 g/kg) is 200 mg/kg and for mice is 20 mg/kg. Acute toxicity was done at dose of 2000mg/kg body weight.

Pharmacological evaluation:
Preparation of extracts:
The aqueous and alcoholic extracts of *Bupleurum falcatum* suspended in water in presence of 3%v/v Tween-80 solution.

All the drugs were administered orally for experimental purpose. Each time preparations of the extracts were prepared when required. The drugs were administered at a constant volume of 10ml/kg for each animal.

Acute oral toxicity:
The acute oral toxicity of aqueous and alcoholic extracts of *Bupleurum falcatum* was determined by using rats and mice which were maintained under standard conditions. The animals were fasted 12 hour prior to the experiment, up and down procedure OECD guideline no. 425 were adopted for toxicity studies. Animals were administered with single dose of individual extract up to 2000mg/kg and observed for its mortality during 2days and 7days study period (short term) toxicity and observed up to 7days for their mortality, behavioral and neurological profiles.

Screening for antianxiety and antidepressant activity:
The aqueous and alcoholic extracts of *Bupleurum falcatum* leaves were tested for antianxiety activity using elevated plus maze and actophotometer and antidepressant activity using despair swim test and tail suspension test.

Treatment:
Animals were divided into four (I-IV) groups.
Group I - Control group received distilled water (1ml, p.o).
Group II - Standard group received Diazepam (10mg/kg i.p).
Group III - Test group received aqueous extract of *Bupleurum falcatum* (200mg/kg p.o).
Group IV - Test group received alcoholic extract of *Bupleurum falcatum* (200mg/kg p.o).

Procedure for Ant anxiety Activity:
Elevated plus maze (EPM) model:
The apparatus comprises of two open arms (35x5cm) and two closed arms (30x5x15cm) that extend from a common central platform (5x5cm). The floor and walls of the closed arms are made of wood and painted black. The entire maze is elevated to a height of 50 cm above the ground level. Rats weighing (150 – 200gms) were housed in a pair of 10 days prior to the test in the apparatus. During this time the rats were handled by the investigator on alternate days to reduce stress. 30 min and 60min after oral administration of the drug treatment, each rat was placed in the center of the maze facing one of the enclosed arms. During five minutes session, number of entries into open arm and time spent in the open arm were noted14,15. The procedure was conducted preferably in a sound attenuated environment.

Locomotor activity:
The locomotor activity can be easily studied with the help of actophotometer, the rats were grouped and treated with drugs. Turn on the equipment (check & make sure that all the photocells are working for accurate recording) and placed individually each rat in the activity cage for 10 minutes. Note the basal activity score of all the animals. Inject the drug diazepam (Dose: 5 mg/kg, ip; make a stock solution containing 0.5 mg/ml of the drug & inject 1 ml/100 g body wt of mouse), and after 30 mins re-test each mouse for activity scores for 10 mins[16]. Note the difference in the activity, before & after chlorpromazine. Calculate percent decrease in motor activity.

Procedure for Antidepressant Activity:

Despair Swim Test Apparatus:

For the determination of antidepressant activity, forced swim test (FST) protocol was employed. During the test, animals were individually placed in a glass cylinder (20 cm in height, 14 cm in diameter) filled with water up to a height of 10cm, at 25 ± 2°C. All animals were forced to swim for 5 min and the duration of immobility was observed and measured during the 5 min interval of the test. Immobility period was regarded as the time spent by the rats to float in water with no struggle and making only those movements necessary to keep its head above the water. In order to check the fitness level of each test animal, a pre-test was carried out 24 h before the FST by subjecting each test animal to a session of 15 min swimming.

Tail suspension test:

Tail suspension test was performed based on the method prescribed. The mice were suspended 58cm above the floor by means of an adhesive tape, placed approximately 1cm from the tip of the tail. The total duration of immobility was quantified during a test period of 5min. Mice were considered immobile when they were completely remain motionless

Statistical analysis:

The values were expressed as mean ± SEM data was analyzed using one-way ANOVA followed by T-test. Two sets of comparision had made. i.e. Normal control Vs All treated groups. Differences between groups were considered significant at P<0.001 and *P* < 0.05 levels.

RESULTS:

Antianxiety activity of bupleurum falcatum

Elevated plus maze test:

Anxiolytic property of aqueous and alcohol solvent soluble fraction of the leaves of *Bupleurum falcatum* studied at a dose of 200 mg/Kg, using Elevated plus maze experiment.

In elevated plus-maze test (EPM), the ethanolic and aqueous extracts of *Bupleurum falcatum* leaves at a dose of 200 mg/kg p.o. significantly increased the number of entries and time spent into the open arm. The magnitude of the anti anxiety effects 200mg/kg p.o. of alcoholic and aqueous extracts of *Bupleurum falcatum* was comparable to that of diazepam 10 mg/kg i.p. (Figure 1 and 2).

Table: 3 - Data obtained from Elevated Plus Maze experiment

S.No	Groups	Dose	% Preference	Open arm and enclosed arm			
				No.of entries in open arm(M±SEM)		Average time spent (sec±SEM)	
				(O)	(C)	(O)	(C)
1.	Control	-	Open	1	2	34	268
			Closed	1	1	12	282
			Open	2	1	42	258
2.	standard	10	Open	2	1	11	284
			Open	1	1	24	274
			Open	1	1	35	264
3.	AQEBF	200	Open	3	2	42	126
			Open	2	1	32	145
			Open	1	1	28	142
4.	ALEBF	200	Open	3	2	47	130
			Open	1	1	29	151
			Open	2	1	33	147

From the experiment it was observed that mice taken aqueous and alcohol soluble fraction at dose of 200 mg/kg body weight, stayed more time in open arm of Elevated plus Maze apparatus in comparison to standard and negative control group. Moreover they were also stayed less time in closed arm of Elevated plus Maze apparatus in comparison to standard and negative control group. The value obtained from these fraction were statistically significant (p<0.05).

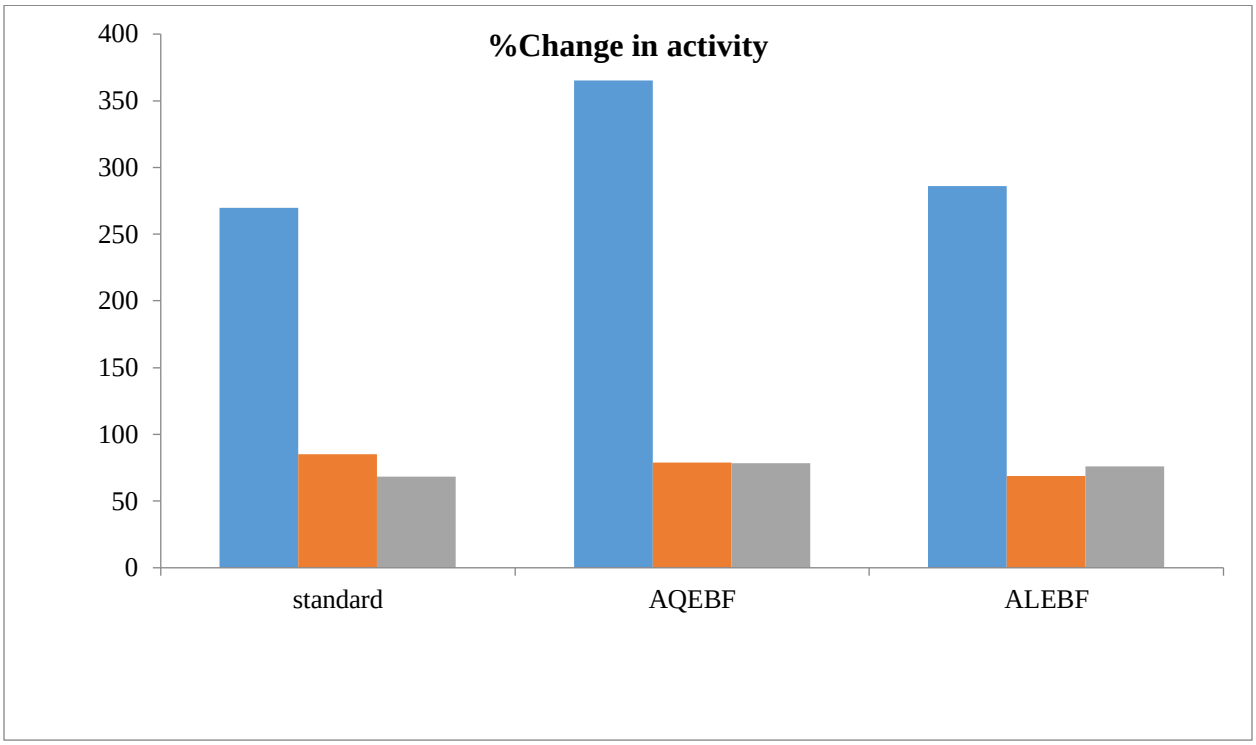
Actophotometer test:

Anxiolytic property of aqueous and alcohol solvent soluble fraction of the leaves of *Bupleurum falcatum* studied at a dose of 200 mg/Kg, using Actophotometer experiment.

The percentage of reduction in locomotor activity with diazepam (10 mg/kg i.p) after 1 hour is 91.0 % i.e. there is highly significant (P<0.000) decrease in locomotor activity compare to control, where as dose of AQEBF and ALEBF (200mg/kg i.p) showed dose dependent decrease in locomotor activity that is 78.3% and75.8% respectively when compared to standard. The values are highly significant (P<0.000) (Table No:----).

Table No: 4. Effect of extracts of *Bupleurum falcatum* on Locomotor activity.

S.No	Groups	Dose (mg/kg)	Locomotor activity (scores) in 10 min		
			Before	After	%change in activity
1.	**control**	**-**	245	--	---
2.	**standard**	**30**	270	85	68.5
3.	**AQEBF**	**200**	365	79	78.3
4.	**ALEBF**	**200**	286	69	75.8



The results are expressed as means ± S.E.M Differences in mean values between groups were analyzed by a one-way analysis of variance (ANOVA). Statistical significance was assessed as $p < 0.05$.

Antidepressant activity of bupleurum falcatum:

Forced swim test:

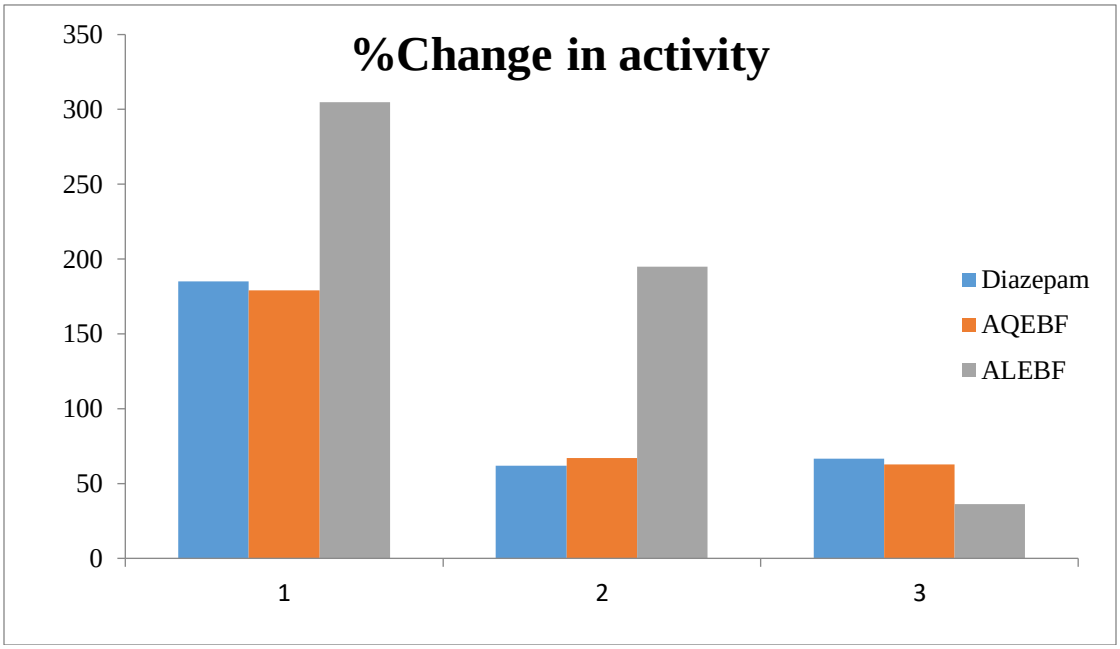
Antidepressant activity of aqueous and alcohol solvent soluble fraction of the leaves of *Bupleurum falcatum* studied at a dose of 200 mg/Kg, using Forced Swim Test experiment.

The anti-depressant activity of AQEBF and ALEBF was assessed using Forced Swimming Test in Swiss albino rats were illustrated in Table No:---. It was observed that AQEBF and ALEDB at a dose of 200mg/kg exhibited significant reduction in immobility time when compared to control in dose dependent manner. Similarly the animals treated with diazepam (10mg/kg) as expected showed significant decrease in immobility time.

Table No 5:. Effect of extracts of *Bupleurum falcatum* on Anti-depressant activity.

S. No	Group	Dose(i.p; mg/kg)	Immobility period		% change in activity
			Before	After	
1	Control	5ml/kg	134	--	---
2	Diazepam	10mg/kg	185	62	66.48%
3	AQEBF	200mg/kg	179	67	62.6%
4	ALEBF	200mg/kg	305	195	36.06%

The results are expressed as means ± S.E.M Differences in mean values between groups were analyzed by a one-way analysis of variance (ANOVA). Statistical significance was assessed as $p < 0.05$.



Graph-1: Effect of extracts of *Bupleurum falcatum* on Anti-depressant activity

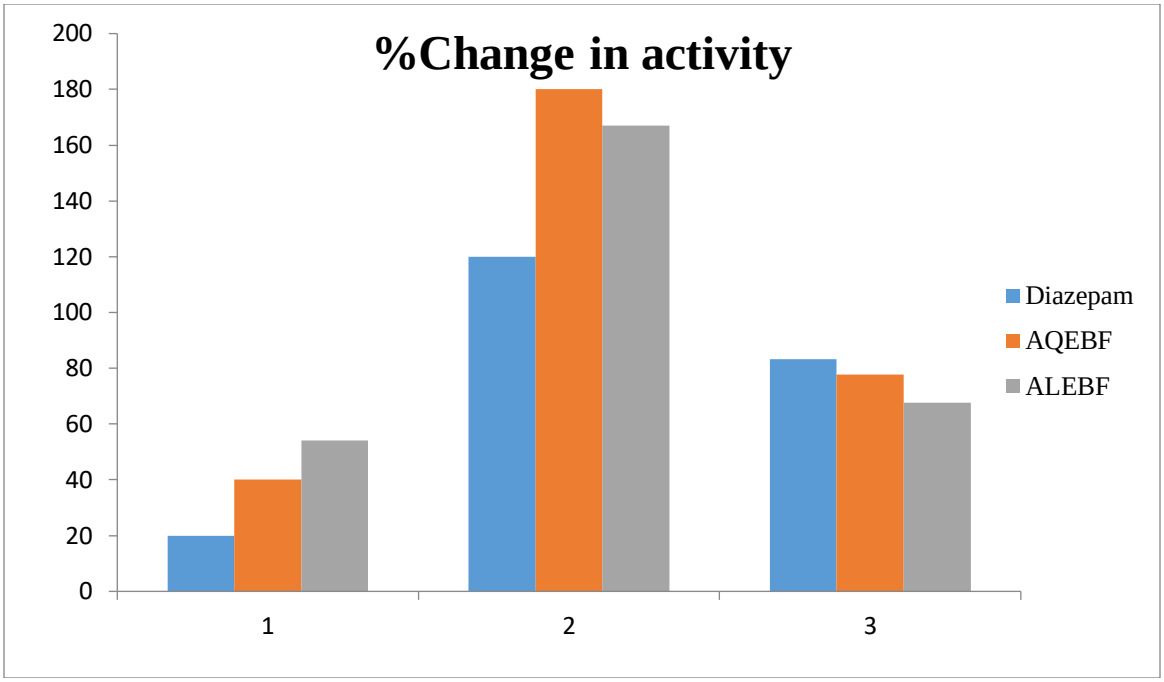
Tail suspension test:

Antidepressant activity of aqueous and alcohol solvent soluble fraction of the leaves of *Bupleurum falcatum* studied at a dose of 200 mg/Kg, using Forced Swim Test experiment.

In tail suspension test, the alcoholic and aqueous extracts of leaves of *Bupleurum falcatum* at a dose of 200 mg/kg i.p. significantly decreased the immobility time. The magnitude of the antidepressant effects of 200 mg/kg i.p. of alcoholic and aqueous leaves of *Bupleurum falcatum* was comparable to that of Diazepam 10 mg/kg i.p. (Table ---).

Effect of Ethanolic and Aqueous Extracts of *Bupleurum falcatum* Leaves on Tail Suspension Test in Mice at Different Time Intervals:

S.No	Treatment	Dose (mg/kg)	Duration of immobility		%change in activity
			Before	After	
1.	Control	---	40	-----	------
2.	Standard	10	20	120	83.33%
3.	AQEDB	200	40	180	77.8%
4.	ALEDB	200	54	167	67.7%



DISCUSSION:

Phytochemical analysis:

The phytoconstituents are known to play an important role in bioactivity of medicinal plants. In qualitative phytochemical analysis reveals the presence of alkaloids, flavonoids, tannins, terpenoids and saponins have associated with various degree of anti-microbial, anti-bacterial, anti-fungal, anti-oxidant and anti-termites. Therefore, the anti-diabetic, hypoglycemic, anti-depressant, anti-anxiety, skeletal muscle relaxant property, locomatar activity, anti-inflammatory, analgesic and diuretic activities were observed in this study may be due to the presence of chemical constituents in both aqueous and alcoholic extracts of *Bupleurum falcatum.*

Behavioural activities:

Anti-depressant activity:

Open field test:

Open field behavioral model was used to study exploratory and locomotor activity in this investigation. Reported studies have shown that stress factors account for the decreases in mobility and functional responses against novel environment. The purpose of including this test was to assess the general activity of the animals after performing FST. The results observed in the open field test showed that i.p administration of aqueous and alcoholic extracts of *Bupleurum falcatum* (200 mg/kg) did not significantly increase the locomotor activity in unstressed groups of rats as compared with their control groups. However, aqueous and alcoholic *Bupleurum falcatum* administered rats following the exposure to repeated restraint stress showed significant ($p<0.01$) increases in locomotor / exploratory activity on an open field arena. It is therefore, suggested that the extract has the ability to reverse or normalize the locomotor suppressant behavior in laboratory animals and hence may help to cope with immobility factor associated with depression in humans. In the present study that administration of aqueous and alcoholic *Bupleurum falcatum* at the dose of 200 mg/kg significantly altered the behavioral deficits induced by injections of atypical neuroleptic, haloperidol and increased brain serotonin metabolism in mice. The results are in general agreement with our previous studies in continuation to this plant and indicating its antidepressant-like activity in behavioral models of depression.

Forced swim test:

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. Commonly used Antidepressants often cause adverse effects, and difficulty in tolerating these drugs is the most common reason for discontinuing an effective medication, for example the side -effects of Selective Serotonin Reuptake Inhibitor (SSRIs) include: nausea, diarrhea, agitation, headaches. Sexual side-effects are also common with SSRI's. The Food and Drug Administration requires Black Box warnings on all SSRIs, which state that they double suicidal rates

(from 2 in 1,000 to 4 in 1,000) in children and adolescents. Side effects of Tricyclic Antidepressants (TCA's) include drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, akathisia, hypersensitivity, changes in appetite and weight, sweating, sexual dysfunction, muscle twitches, weakness, nausea and vomiting, hypotension, tachycardia, and rarely, irregular heart rhythms.

In the present study we have evaluated the antidepressant activity of *Bupleurum falcatum* of both aqueous and alcoholic extracts in FST. The development of immobility when rodents are placed in an inescapable cylinder of water during FST reflects the cessation of their persistent escape-directed behavior. Conventional drugs reliably decrease the duration of immobility in animals during this test. This decrease in duration of immobility is considered to have a good predictive value in the evaluation of potential antidepressant agents. Exact mechanisms underlying the antidepressant action cannot be concluded at the moment due to the presence of large number of Phytochemical in the *Bupleurum falcatum.* However, the antidepressant activity may be attributed to the presence of saponins, flavonoids and tannins in the extract. It is possible that the mechanism of anxiolytic action of AQEEU and ALEEU could be due to the binding of any of these phytochemical to the $GABA_A$ -BZD_S complex.

Anti-anxiety activity

Elevated plus maze method:

Anti-anxiety activity of *Bupleurum falcatum* was evaluated by employing a widely used model, i.e. elevated plus-maze. The mean number of entries and time spent by mice in open arms Amongst aqueous and alcoholic extracts of *Bupleurum falcatum* significantly increased mean number of entries and mean time spent by mice in open arms of elevated plus maze apparatus at the dose of 200 mg/kg with respect to control, thereby producing anti-anxiety activity. Phytochemical screening of aqueous and alcoholic extracts showed presence of flavonoids and tannins. Flavonoids have shown anti-anxiety activity in various studies. Further, the anxiolytic effect of flavonoids has been attributed to its effect on central nervous system and benzodiazepine receptors. Therefore, flavonoids of aqueous and alcoholic extracts of *Bupleurum falcatum* may be responsible for the anti-anxiety activity. It may possible that the mechanism of anxiolytic action of AQEBF and ALEBF could be due to the binding of any of these phytochemicals to the GABAA-BZD complex. In support of this, it has been found that flavones bind with high affinity BZD site of the $GABA_A$ receptor. The plant *Bupleurum falcatum* also contains flavones which may responsible for its anxiolytic activity. So the anxiolytic activity of AQEBF and ALEBF might involve an action on GABAergic transmission or effects on serotonergic transmission or due to its mixed aminergic potentiating effect.

CONCLUSION:

The results obtained in this study indicate that the n-hexane, ethyl acetate and methanol fractions of the leaves of *Bupleurum falcatum* have significant CNS Depressant and Anxiolytic activities in animal model systems. The medicinal values of the plant leaves may be related to their constituent phytochemicals. So, further detailed investigations are needed to isolate and identify the active compounds present in the plant extract and its various fractions and their efficacy need to be done. It will help in the development of novel and safe drugs for the treatment of different types of CNS disorders.

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