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PHARMACOLOGICAL SCREENING OF *PRUNUS ARMENIACA* L. KERNEL EXTRACT FOR ANTISTRESS ACTIVITY IN DIFFERENT EXPERIMENTAL ANIMAL MODELS BY *IN VIVO* METHODS: A NATURAL REMEDY TO STRESS

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ABSTRACT

The present study was carried out to evaluate the antistress potential of apricot kernel extract (AKE) in albino mice using different experimental models such as swimming endurance (SET), tail suspension (TST), writhing test (WT) and anoxia stress tolerance (AST). Acute toxicity studies were performed on Wistar rats to select doses of AKE. Diazepam (2 mg/kg i.p.) was taken as a reference drug for comparison. In SET, AKE-treated mice showed a significant ($P<0.01$) decrease in immobility time (46.32 ± 1.086 s and 40.09 ± 1.25 s respectively) at a dose of 100 and 200 mg/kg as compared to the control and standard group. While a significant ($P<0.05$, $P<0.01$ respectively) increase in anoxic tolerance time (32.06 ± 0.42 s and 45.10 ± 1.37 s respectively) was observed in AST at the same doses. In WT, the effect of glacial acetic acid was reduced by AKE at both the doses (100 and 200 mg/kg) as indicated by a decrease ($P<0.01$) in the number of writhes (37.33 ± 0.95, 30.16 ± 1.27 respectively) as compared to control and standard group. In TST, the AKE-treated mice produced a significant ($P<0.01$) decrease in the duration of immobility (34.25 ± 1.10 s and 24.08 ± 1.55 s respectively) in comparison to the control and standard group at both the doses. It was observed that AKE possessed a significant antistress activity at both the doses in all tested models although the results were more prominent at higher dose (200 mg/kg).

Keywords: Immobility, Phytochemical screening, Antistress activity, Acute toxicity studies, *Prunus armeniaca* L. (Apricot)

INTRODUCTION

Stress is a physiologic, behavioral, neuroendocrine and emotional response characterized by psychological and physiological imbalance. This imbalance occurs due to increased demand and a person's ability to meet those needs. Stressful condition is faced by every human in our day-to-day life. Stress affects the body's normal homeostasis and cognitive functions which may lead to the development of major disorders like depression, anxiety, Alzheimer's, Parkinson's disease, hypertension, peptic ulcer, immunosuppression, and reproductive dysfunction **[1, 2]**. According to the World health organization (WHO), a good mental condition is a part of a healthy body and stress is a resistance against once well-being. Stress differs from one individual to another individual. On sensing stress by the hypothalamus, it initiates a chain of reactions that produces a general adaptation syndrome. The stimuli responsible for producing the syndrome are called stressors **[3]**. Stress is a major contributor to psychosocial and physical pathological conditions in humans. There are many medications available in the market for the relief and prevention of stress, although they do not belong to one particular family of medicines. Range of medications like benzodiazepines, CNS stimulants (amphetamines and caffeine) as well as some anabolic steroids may be prescribed to combat stress but due to the incidence of toxicity and dependence, the therapeutic uses of these drugs have limited **[4]**.

As per WHO research, around 80% of the population from developing countries uses traditional medicines for their primary health care needs. Since ancient times India has been practicing the use of herbs as a traditional medicine in their daily life, which is a part of the Ayurveda system of medicine. Nowadays drugs obtained from natural plant sources are emerging as alternative therapies in the treatment of disorders, psychiatric illnesses as they can withstand stress without altering the physiological functions of the body **[5]**.

This study deals with the traditional and pharmacological account of an important medicinal plant apricot **(Figure 1)**. Apricot is a fruit tree mainly cultivated in Jammu & Kashmir, Himachal Pradesh, Uttar Pradesh, Arunachal Pradesh, Nagaland, Meghalaya, Sikkim, Manipur and Uttarakhand. *Prunus armeniaca* L. belonging to family Rosaceae which is commonly known as apricot or khubani. Apricot is a fruit tree widely found in the parts of Central Asia, Mediterranean countries, USA, Russia, Iran, Iraq, Pakistan, Afganistan, Syria, and Turkey.In India it is mainly cultivated in Jammu & Kashmir, Himachal Pradesh and

Uttar Pradesh, Arunachal Pradesh, Nagaland, Meghalaya, Sikkim, Uttarakhand and Manipur.

Figure 1: *Prunus armeniaca* L. (Apricot)

Apricot trees can grow even at a low temperature of -30°C **[6]**. This plant is known as a rich source of carbohydrates, carotenoids (ß-carotene), vitamins like K and C, niacin, thiamine, organic acids, iron, phenols, and volatile compounds viz. benzaldehyde, esters, norisoprenoids, and terpenoids **[7-9]**. In previous research works, it was observed that apricot seeds contain two important substances lecithin and acetylcholine. The anti-stress activity may be the result of these two substances present in apricot seeds. Few research studies have also revealed that apricot seeds contain a variety of B complex vitamins and amygdaline which are strong anti-oxidants and prevent degenerative processes occurring in the brain which also occur in stress **[10]**.

Therefore, the present study has been undertaken to establish the antistress activity of *Prunus armeniaca* L. in mice**.**

MATERIALS AND METHODS

Collection of the plant:

Fresh fruits of *Prunus armeniaca* L. were collected in April 2016 from villages Dugtanidhar and Satbuna (Mukteshwar), district Nainital, Uttarakhand, India and authenticated (voucher specimen no. 118202) by **Dr. Kumar Ambrish**, Scientist, in Botanical Survey of India, Dehradun, Uttarakhand.

Preparation of plant extract:

Apricot kernel extract was prepared by using a Soxhlet apparatus. For this, about 1 kg apricot fruits were taken and seeds were removed. To obtain kernel apricot seeds were hammered. Kernel was completely dried under the shade and powdered. The coarse powder of kernel was extracted with petroleum ether in Soxhlet extractor for 6-8 hours at 70°C. The extract was then filtered by using a Buckner funnel and then Whatman No.1 filter paper. After that, the solvent was removed by the rotary evaporator under reduced pressure and extract was collected. The kernel extract yield was calculated as 28.81% (w/w) and stored at 4°C in a refrigerator until further use.

Chemicals, drugs, and equipments:

Normal saline (0.9%), glacial acetic acid, diazepam, soxhlet apparatus, rotatory evaporator, stopwatch and water bath, etc. were used in this study.

Experimental animals:

All experimental procedures were carried out in strict accordance with the guidelines

of the CPCSEA (The Committee for the Purpose of Control and Supervision of Experiments on Animals) and approved by the Institutional Animal Ethics Committee (IAEC). Healthy albino mice, weighing 25-30 g (6-8 week old) of both sexes were obtained from the institutional animal house of Department of Pharmaceutical Sciences, Bhimtal, Kumaun University Nainital, Uttarakhand, India. They were maintained under good laboratory care (12h light/dark cycle, 22 ± 3˚C, 60±5% humidity), having proper ventilation in the room, provided free access to standard pellets diet and purified drinking water. Animals were fasted for 24 h before experimentation with free access to water. Isolated and noiseless condition was created while conducting the experiment.

Acute toxicity study:

The guidelines stated in OECD (Organization of Economic Cooperation and Development) 423 were followed during the procedures. For this study, healthy female (nulliparous and non-pregnant) albino Wistar rats were taken and apricot kernel extract was administered orally at a dose upto 2000 mg/kg body weight to different groups of mice. Neither food nor water was given to up to four hrs after the treatment and mice were observed for signs of behavioral, neurological toxicity, and mortality for 24 hrs followed by the next 72 hours **[11]**.

Experimental protocols:

The animals were divided into following four groups of six animals each for every model.

In all these groups, treatment was given for seven successive days. After 60 minutes of the last dose, activity like immobility time, anoxic tolerance time etc. was recorded according to each model **[5]**.

Groups	Treatment
Control group (C)	Normal saline (10 ml/kg, p.o.)
Test group 1 (T_1)	Apricot kernels extract (100 mg/kg, p.o.)
Test group 2 (T_2)	Apricot kernels extract (200 mg/kg, p.o.)
Standard group (SD)	Diazepam (2 mg/kg, i.p.)

Swimming endurance test (SET):

The swimming endurance test is the most frequently used behavioral model for screening antistress like activity in rodents. The mice were randomly divided into four groups of six animals each. All treatments were given to mice, once daily for 7 days. The control group was pre-treated with normal saline (10 ml/kg, p.o.) while the test groups (T_1 and T_2) were pretreated with apricot kernel extracts (100 mg/kg and 200 mg/kg, p.o. respectively). The standard group received diazepam (2 mg/kg, i.p.). The swimming test was carried out on the

seventh day, after one hour of oral and 30 minutes of intraperitoneal administration of the standard drug. For this, treated mice were individually forced to swim in open polypropylene vessel (25×15×25cm) containing fresh water to a height of 20 cm. The temperature of the vessel was maintained at 26°±1°C. At this height of water, animals were unable to support themselves by touching the chamber walls or bottom with their paws or tail. Water in the vessel was changed after performing each test because "used water" may alter the behavior of the animal. Each mouse showed vigorous movement during the test. The immobility time was recorded in a total 6 min testing period. Mice were considered immobilized once they stop struggling and remain motionless inside the water with only a few movements enough for keeping their head over water for breathing. Mice were then towel-dried and returned to their cages after performing the test **[5, 12]**.

Anoxic stress tolerance test (AST):

Albino mice were divided into 4 groups of six each. Control group received only normal saline (10 ml/kg, p.o.). Test group T_1 received apricot kernel extract (100 mg/kg, p.o.), test group T_2 apricot kernel extract (200 mg/kg, p.o.) while the standard group was treated with diazepam (2 mg/kg, i.p.). All the treatments were given for seven days. For performing an anoxic tolerance test a confined airtight glass jar of 1 L capacity was taken. After that treated mice were placed in that vessel to induce stress and anoxic tolerance time was noted. Anoxic tolerance time is the time duration of entry of the animal into the vessel and the appearance of the first convulsion. Mice were removed immediately for recovery from the vessel and resuscitated when needed **[5]**.

Writhing test (WT):

The mice were divided into four groups as above. The test groups T_1 and T_2 were pre-treated with AKE at doses 100 mg/kg and 200 mg/kg, p.o. respectively. Pre-treatment of the control group was carried out with normal saline (10 ml/kg, p.o.), whereas the standard group received diazepam (2 mg/kg, i.p.). The groups were given treatment for 7 days. At the end of the seventh day, writhing was induced in mice one hour after oral and 30 minutes after intraperitoneal administration of the standard drug by giving glacial acetic acid (0.4 ml / 20 mg, i.p.). After administration of glacial acetic acid mice showed vigorous movements like writhing, abdominal contractions, trunk twisting and extension of hind limbs. The number of writhing responses produced were observed and recorded in all groups for 20 minutes **[13]**.

Tail suspension test (TST):

In the tail suspension test (TST), mice were divided the same as above. Control group received only normal saline while test

groups (T_1 and T_2) received AKE at doses 100 mg/kg and 200 mg/kg, p.o. respectively for seven days. Diazepam (2 mg/kg, i.p.) was given to the standard group for the same days. On seventh days after treatment, mice were individually suspended by end of tail with adhesive tape (1 cm distant from the end) for a total of 6 minutes from a table having head 5 cm to the bottom. The duration of immobility was recorded during the final 4 minutes interval of the test. Initially, the animals tried to make vigorous movements but after few minutes became immobile. The animal was considered immobile when it hanged passively and became motionless. Each mouse was used only once. The experiment was performed in a darkened room with minimal background noise **[14]**.

Statistical analysis:

All values were shown as mean ± SEM. Comparison between the control and tested groups was made by one way ANOVA followed by the Dunnett test, P values of less than 0.05 and 0.001 were considered to be significant.

RESULTS

Swimming endurance test:

In SET, AKE caused a significant (P<0.01) anti-stress effect after oral administration at 100 mg and 200 mg/kg respectively. The control animals remained immobile for most of the time during the test. Immobility time of the control group was found to be 53.52 ± 0.81 s while treatment groups (T_1 and T_2) showed immobility in 46.32 ± 1.086 and 40.09 ± 1.25 s at the dose of 100 and 200 mg/kg respectively. Immobility time of diazepam treated mice was found to be 34.17 ± 1.02 s at the dose of 2 mg/kg. This test showed that AKE at both the doses significantly (P<0.01) decreased the immobility time when compared to the standard group and control group. A marked increase in swimming time was observed with AKE treated animals at both the doses **(Table 1)**

Anoxic stress tolerance test:

In anoxic tolerance test, the moment when the mouse exhibits the first clonic convulsion was used as the endpoint. Seven days pre-treatment with AKE (100 mg/kg and 200 mg/kg) significantly (P<0.05, P<0.01 respectively) increased the time (32.06 ± 0.42 s and 45.10 ± 1.37 s respectively) taken for clonic convulsions as compared to the control animals (27.02 ± 1.10 s). Similarly, significant (P<0.01) delay (54.64 ± 1.27 s) in clonic convulsionswas also produced in diazepam treatment. (**Table 2)**

Writhing test:

AKE significantly (P<0.01) and dose-dependently (100 mg/kg and 200 mg/kg) decreased glacial acetic acid-induced writhing (37.33 ± 0.95, 30.16 ± 1.27 respectively) as compared to control group (47.5 ± 1.87 s). Similarly, reference drug

diazepam also significantly (P<0.01) decreased the no.of wriths responses (19.83 ± 1.40s) **(Table 3)**.

Tail suspension test:

In TST, animals treated with two doses of AKE (100 and 200 mg/kg, p.o.) showed decreases in their immobility times, which was significant (34.25 ± 1.10 s, P<0.01 and 24.08 ± 1.55 s, P<0.001 respectively) when compared with control group (51.11 ± 1.36 s). Similarly, animals treated with diazepam (2 mg/kg, i.p.) showed a significant decrease in the immobility time (16.84 ± 1.09 s, P<0.01) **(Table 4)**.

Table 1: Effect of AKE and diazepam on swimming endurance test (n=6)

Treatment	Dose	Duration of Immobility (s)
Control	10 ml / kg, p.o.	53.529 ± 0.814
AKE	100 mg/kg, p.o.	46.321±1.086**
AKE	200 mg/kg, p.o.	40.093±1.253**
Diazepam	2 mg / kg, i.p.	46.321±1.024**

AKE=Apricot kernel extract; Values are expressed as mean ± SEM (n=6);
Data were analyzed by using One-way ANOVA followed by Dunnett's test, **P<0.01 vs. control

Table 2: Effect of AKE and diazepam on anoxic stress tolerance test (n=6)

Treatment	Dose	Anoxic stress tolerance time (s)
Control	10 ml/kg, p.o.	27.0245± 1.105
AKE	100 mg/kg, p.o.	32.063±0.4279*
AKE	200 mg/kg, p.o.	45.105±1.372**
Diazepam	2 mg / kg, i.p.	54.647±1.279**

AKE=Apricot kernel extract; Values are expressed as mean ± SEM (n=6);
Data were analyzed by using One-way ANOVA followed by Dunnett's test, *P<0.05, **P<0.01 vs. control

Table 3: Effect of AKE and diazepam on writhing test (n=6)

Treatment	Dose	Number of writhing responses
Control	10 ml / kg, p.o.	47.5± 1.875
AKE	100 mg/kg, p.o.	37.33±0.9545**
AKE	200 mg/kg, p.o.	30.16±1.276**
Diazepam	2 mg / kg, i.p.	19.83±1.4**

AKE=Apricot kernel extract; Values are expressed as mean ± SEM (n=6);
Data were analyzed by using One-way ANOVA followed by Dunnett's test,P<0.01 vs. Control**

Table 4: Effect of AKE and diazepam on tail suspension test (n=6)

Treatment	Dose	Duration of Immobility (s)
Control	10 ml / kg, p.o.	51.113± 1.366
AKE	100 mg/kg, p.o.	34.252±1.104**
AKE	200 mg/kg, p.o.	24.081±1.558**
Diazepam	2 mg / kg, i.p.	16.841±1.094**

AKE=Apricot kernel extract; Values are expressed as mean ± SEM (n=6);
Data were analyzed by using One-way ANOVA followed by Dunnett's test,P<0.01 vs. control**

DISCUSSION

In the present research work, screening of apricot kernel extract (100 mg/kg and 200 mg/kg) was carried out for antistress activity, using different experimental animal models like swimming endurance, anoxic tolerance, writhing and tail suspension test. Diazepam was used as a reference drug for the comparison as it is clinically known for a non-specific anti-stress activity **[13]**. In the case of swimming endurance test, AKE increased the swimming endurance duration, latency of post-anoxic convulsions, mortality protection, and decreased the duration of convulsions in a dose-dependent manner. This exhibit the ability of AKE to improve the physical endurance and overall performance in mice activity. This observation of improvement in physical endurance and overall performance indicates significant anti-stress activity. It was reported that during stress plasma levels of adrenaline and noradrenaline are enhanced while monoamine oxidase (MAO) levels in the brain are decreased **[5]**. Normalizing the plasma level of catecholamine and monoamine oxidase may be the possible mechanism of action of AKE **[15]**. A literature survey reported that flavonoids, triterpenes, and tannins possess a variety of pharmacological activities including antistress activity **[16]**. In the previous studies, phytochemical screening on AKE gave positive tests for flavonoids and tannins **[17, 18]**, thus this might be the reason for the significant antistress activity of AKE. On performing an anoxic stress tolerance test, on depleting oxygen in an airtight vessel resulting in convulsions in animals due to stress. It was observed that pre-treatment with AKE increased stress tolerance duration. This significant increase in anoxia tolerance time is an indication of either resistance to it or a reduction in cerebral oxygen consumption **[16]**. This may also be due to the presence of flavonoids in AKE as flavonoids have the capability to increase the enzyme succinate dehydrogenase in the brain. Succinate dehydrogenase is responsible for the consumption and maintenance of energy in the cellular system of the organism, which assist in adaptive processes during stress **[19]**. In the tail suspension test, AKE significantly reduced the immobility time which was comparable to that of referencedrug diazepam. TST displays a strong sensitivity towards monoamine **[20]**, thus it may be considered that the antistress activity of AKE is due to the inhibition of enzymes Monoamine Oxidase-A and Monoamine Oxidase-B. Therehence result in the escalation of monoamines level **[21, 22]**. In the writhing test, the administration of glacial acetic acid increased the number of writhes due to its hyperalgesic effects on the pain pathway indicating stress

development **[23]**. Acetic acid increases the level of prostaglandins in peritoneal fluids **[24]**. Prostaglandins play an important role in the regulation of HPA axis activity in basal and stress conditions by neurotransmitters and neuropeptides **[25]**. In the present study, AKE-treated mice showed the decrease in the number of writhes which indicates clearly that AKE at both the doses (100 mg/kg and 200 mg/kg) can play a significant role in the inhibition of pain processes, which shows that the extract has anti-stress property. This antistress activity of AKE may be attributed to the inhibition of prostaglandin synthesis **[26]**. Exposure to chronic stress is reported to cause oxidative stress in the brain leading to various adverse physiological consequences. This observation suggests that for stress-induced psychiatric disorders the antioxidant supplement therapy as an adjuvant therapy is very effective [**27]**. In previous studies extract of apricot kernel was found to exhibit an excellent antioxidant potential **[28]**, which may be beneficial in stress conditions. Lecithin administration was found to possess significant antistress activity that correlated with increased serum choline levels **[29]**. Therefore the observed antistress activity of AKE may be due to the presence of lecithin in it **[10]**.

CONCLUSION

The present research was carried out to evaluate the antistress potential of the plant *Prunus armeniaca* L. using *in-vivo* pharmacological screening models. In conclusion, this study provided evidence that the seven-day treatment with the AKE showed antistress (adaptogenic) activity in various acute and sub-acute stress models. AKE increased the duration of anoxic tolerance and swimming endurance by decreasing the immobility time in the stressed mice. Extract also reduced the effect of glacial acetic acid-induced wriths in writhing test and duration of immobility in the TST test. Results of all model revealed that apricot kernel having antistress activity at the dose of 100 and 200 mg/kg. This study provides significant evidence of the medicinal and traditional uses of *Prunus armeniaca* L. in neurobiological disorder (stress). The findings and outcomes of the experiments were encouraging for pursuing further studies on apricot kernel to isolate and characterize bioactive molecule responsible for its antistress activity.

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