Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i18.3098

ANXIOLYTIC AND ANTIDEPRESSANT ACTIVITY OF *CARICA PAPAYA* SEEDS AND LEAVES EXTRACTS IN MICE

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Abstract

Context: *Carica papaya* (Caricaceae) originally belongs to tropical region of America. It is an edible and juicy fruit. Seeds are present inside the fruit. All the parts of the tree especially fruits, seeds and leaves have many medicinal properties. *C. Papaya* fruit acts as anti-diabetic, for liver disease, its seeds act as hypoglycemic, hypolipidimic, cardioprotective, contraceptive etc. In Ethiopian traditional medicine, *C. papaya* has been used to treat a variety of ailments, including stress.

Objective: The purpose of the present study was to investigate the anxiolytic effects of various extracts of the seeds and leaves of *C. papaya*.

Materials and methods: Fresh ethanolic and methanolic extract of seeds and leaves of *C. papaya*were prepared and administered to mice and rats for anxiolytic activity such as Cage crossing, Head dip, Stationary rod, Open field and Light and Dark on mice and Forced swimming test on rats.

Results: Both the extracts of *C.papaya* decreased anxiety, fear related behavior in mice and rats. We observe that the number of cage crossed decrease which indicates decrease in anxiety, also the number of head dips gradually decrease which shows anxiolytic effect. The investigation within the peripheral square crosses was diminished showing the antidepressant action. For both the extracts, two-way ANOVA data analysis produces pretty significant outcomes, i.e. ($P < 0.00$).

Conclusion: The current investigation adequately established that the extracts of *C. papaya* has an anxiety-reducing impact on mice, suggesting that it may represent a novel strategy for the treatment of anxiety.

Keywords: Anti-anxiety, anti-depressant, *C. papaya*, Light and Dark model and Stationary rod

INTRODUCTION

A subjective feeling of unease, sadness, or scary is referred to as anxiety. It is the most common psychiatric disease in the general population. An uncomfortable feeling of inner conflict called anxiety is frequently accompanied by restless behavior, physical problems, and thinking. Anxiety disorders

are characterized by excessive anxiety, which can significantly reduce life quality and lead to a number of psychological illnesses (Doukkali et al. 2015).

Herbs that play a vital role in the global health care system and are a well-established source of medicine (Hussein et al. 2000). In order to treat CNS diseases like anxiety, numerous traditionally used plants have pharmacological activity with potential therapeutic benefits (Ahsan et al. 1990; Gilani et al. 2005). In this study, we attempt to assess the anxiolytic activity of *Carica papaya* due to the growing demand for herbal remedies.

Carica papaya **(papaw** or **pawpaw)** belongs to family Caricaceae. It is an edible fruit which cultivated throughout the tropical and sub-tropical region of America especially Southern Mexico to Central America. Its various parts are employed in traditional medicine to cure a variety of ailments (Ming et al. 2008; Yogiraj et al. 2014). It has a wide range of biological potential, including antibacterial, anthelmintic, hypoglycemic and hypolipidemic, antiprotozoan, antifertility, antitumor, diuretic, wound healing, abortifacient, free-radical scavenging, antifungal, neuroprotective, antihypertensive, antiinflammatory and antiviral activities (Jaiswal et al. 2010; Parle and Gurditta 2011; Thanaraj and Terry 2011; Lim 2012).

The chemical components found in the various papaya parts in dry pulp of papaya fruits, there are many nutrients are present, mainly carbohydrates. In 100g of dry pulp 11.9 – 21.5g of dietary fibers are present. 3.79 – 8.26g of crude protein in 100gm of dry matter are present (Nwofia et al. 2012). In fruit pulp of papaya there are two types of carbohydrates is present i.e. cell wall polysaccharides and sugar soluble. In development process of fruit's ripening, the types of sugar vary from glucose to sucrose up to 80% of total sugar (Selvaraj et al. 1982). In papaya fruits N, K, Ca, Mg, P, Fe, Cu, Zn, Mn, micro and macro minerals are also present. Along with all these carotenoids, vitamin C, B-6, K, riboflavin, niacin, thiamin is also found. Papaya fruits also contain beta-carotene-5-6-epoxide, beta-crytoxanthin, lycopene, and zeta-carotene. The fruit of papaya also contain moisture content up to 87.47 - 91.32% (Oloyede 2005). The leaves of *Carica papaya* contain saponins, cardiac glycosides, alkaloids. It also contains many minerals for example Ca, Mg, Na, K, Fe and Mn. Vitamins, ascorbic acid, thiamine, riboflavin are the constituents that are also found in the leaves of papaya (Ayoola and Adeyeye 2010). The papaya leaves also contain 5.84 – 10.80% of crude protein, 81.27 – 85.17% moisture content, 11.41 – 13.15 % crude fiber, 43.61 – 48.42 % carbohydrates. It also contains fats and ash (Ngozi et al. 2010). The leaves also contain carpaine and pseudocarpaine (Ikeyi et al. 2013). The seeds of *Carica papaya* contain carotene, fatty acids, carbohydrate (Jaiswal et al. 2010). Ca, P is also present. 72.2% protein, 28.3% lipids, 54.4% crude fiber is also present. It also contains sugar (Passera and Spettoli 1981).

MATERIALS AND METHODS

Plant material

The seeds were collected under the supervision of a pharmacognostic person from papaya fruits while the leaves were collected from the nursery of Karachi, Pakistan.

Preparation of extract

Air dried and powdered leaves and seeds of *C. papaya* (300 gm) were successively extracted separately with methanol and ethanol in a Soxhlet apparatus and then filtered. After filtration kept the filtrate for one week for further evaporation.

Animals

For study, Swiss Albino mice and Wister rats were taken. We took animal from the animal house of Jinnah University for Women, Karachi. Mostly 4 - 5 mice and 3 – 4 rats kept in a cage separately because they are very social, but in some conditions single mouse and rat is kept in single house, such as violent stains, if they have head mounts or if there was any surgical involvement in experiment (Carobrez and Bertoglio 2005). In the animal place they were held under standard condition for a total 12 h day and 12 h night cycle. The room temperature of the animal house ought to be 22 ± ºC. The ordinary behavior of animals should have checked several time which incorporate eating, drinking,

peeing, pooing, searching, investigating, biting, covering up, climbing, playing, settling, burrowing, and including with other cage mates. Other than normal food libitum was also provided to them. The animal house environment should be quite. During each experiments try to kept them as relaxed as possible to get the appropriate result because the stress affects the result (Elliott and Grunberg 2005). Before the activity keep them in laboratory 1 hour before so they familiarize with the lab environment (Wronski et al. 1985; Van Loo et al. 2004).

Grouping

We divided mice into five groups which are: Group 1: The control mice of weight 27.06gm receive normal food, water and libitum. Group 2: 10 mice of weight 31.29gm along with normal food, water and libitum receive ethanolic extract of leaf. Group 3: 10 mice of weight 25.44gm along with normal food, water and libitum receive methanolic extract of leaf. Group 4: 10 mice of weight 29.45gm long with normal food, water and libitum receive ethanolic extract of seed. Group 5: 10 mice of weight 28.33gm along with normal food, water and libitum receive methanolic extract of seed.

Similarly rats also divided into five groups which are: Group 1: the control rats of weight 250gm receive normal food and water. Group 2: 10 rats of average weight 262gm receive ethanolic extract of leaf. Group 3: 10 rats of average weight 203gm receive methanolic extract of leaf. Group 4: 10 rats of average weight 197gm receive ethanolic extract of seed. Group 5: 10 rats of average weight 160gm receive methanolic extract of seed.

All the drugs were freshly prepared before each experiment. The dose was given to mice and rats at 11:00 am daily for 30 days.

Treatment Schedule:

For Mice Group 2 received 0.0078mg/ml of ethanolic extract of leaf. Group 3 received 0.0063mg/ml of methanolic extract of leaf. Group 4 received 0.0073mg/ml of ethanolic extract of seed. Group 5 received 0.0070mg/ml of methanolic extract of seed. For Rats Group 2 received 0.78gm/3ml of ethanolic extract of leaf. Group 3 received 0.60gm/3ml of methanolic extract of leaf. Group 4 received 0.57gm/3ml of ethanolic extract of seed. Group 5 received 0.48gm/3ml of methanolic extract o seed. The doses of extracts were calculated to administer approx. 1 mg/ 5 ml of the extract solution. The dose was given once daily.

Activities:

Mice: The anxiolytic activity, memory, locomotion and explorations by the animals were examined using cage crossing, head dip, stationary rod, open field and light and dark box on day 0, 1, 7, 20 and 30. In all activities the duration of activity was 10 min except stationary rod. In stationary rod the time taken to cross the rod was observed.

Rats: The antidepressant activity was examined using FST on day 0, 1, 7, 20 and 30. The time duration of activity was 10 min.

Apparatus and test procedure:

Cage crossing: A translucent home cage made up of polymethyl methacrylate of size 26x26x26 was used for the observation of loco motor activity in a familiarize environment. The cage surface was covered with sawdust.

Procedure: Each mouse was separately placed in the cage to familiarize the environment for 5 minutes. After 5 minutes, the no. of cage crossed and no. of jumps were observed for 10 minutes (Najam and Riaz 2016).

Head dip: For the observation of emotional state of rodents head dip apparatus was used by observing exploration activity. The apparatus was comprised of a box made by wood (35cm x 45cm x 45cm) containing four holes of size 2.5 cm in diameter at equal distance on each sides (Kliethermes and Crabbe 2006).

Procedure: The mouse was placed in the centre of head dip apparatus and the no. of head dip were evaluated for 10 minutes (Hart et al. 2010).

Stationary rod: To observe the memory, balance and learning a linear rod of 5/8" in diameter was used. The length of rod was 2" and is 18" above from the surface (Najam 2003).
Procedure: Mouse was forced to walk on the rod and the time taken to cross the rod was observed (Najam and Riaz 2016).

Open field:
An open topped wooden box having square area of 76cm x 76cm having 42cm high walls. The ground was partitioned into 25 squares of 10cm each. The floor and walls was white on color (Bronikowski et al. 2001).
Procedure: The mouse was placed in the central square of the open field and the movement of mice in central squares and especially in peripheral squares were observed (Mandillo et al. 2008).

Light and dark box:
For the observation of anxiety-like behavior a square box (26cm x 26cm x 26cm) was used having two chambers transparent in color which was referred as light compartment and black in color which was referred as dark compartment joint with a door of (12cm x 12cm) (Samad et al. 2017).
Procedure: The mouse was placed in dark area of the chamber and the time spent in light area and no. of transitions were observed (Crawley and Goodwin 1980).

Force swimming test: To judge the depression like symptoms in rats a glass box of height 56cm and width 30cm was used (Detke et al. 1995). The level of water was neither too low so rat touches the bottom nor too high so escaping was easy. The level should be around 21cm to 23cm (Borsini and Meli 1988).
Procedure: The rat was put into water and forced to swim and their immobility time and rescue behavior was observed (Cryan et al. 2005).

RESULTS:

1. CAGE CROSSING EFFECT:

The effect of ethanolic extract of leaf: At day 0 the significant value was 21.80 ($p<0.000$), after 1 day of administration the mean of cage crossing was 33.10 with standard deviation ± 2.283 ($P<0.000$), after 7 day of administration the mean of cage crossing was 22.30 with standard deviation ± 1.252($P<0.000$), after 20 day of administration the mean of cage crossing was 21.38 with standard deviation ± 1.179($P<0.000$) and after 30 day of administration of ELE mean of cage crossing was 21.43 with standard deviation ± 2.395($P<0.000$).

The effect of methanolic extract of leaf: At day 0 the significant value was 23 ($p<0.000$), after 1 day of administration the mean of cage crossing was 22.80 with standard deviation ±1.333 ($P<0.000$), after 7 day of administration the mean of cage crossing was 22.60 with standard deviation ±1.275 ($P<0.000$), after 20 day of administration the mean of cage crossing was 17.50 with standard deviation ±1.179 ($P<0.000$) and after 30 day of administration the mean of cage crossing was 16.70 with standard deviation ±0.823 ($P<0.000$).

The effect of ethanolic extract of seed: At day 0 the significant value was 21 ($p<0.000$), after 1 day of administration the mean of cage crossing was 23.80 with standard deviation ±1.789 ($P<0.000$), after 7 day of administration the mean of cage crossing was 17.40 with standard deviation ±1.578 ($P<0.000$), after 20 day of administration the mean of cage crossing was 16.90 with standard deviation ±1.101 ($P<0.000$) and after 30 day of administration the mean of cage crossing was 0.00 because the all the mice died before day 30.

The effect of methanolic extract of seed: At day 0 the significant value was 21.80 (p<0.000), after 1 day of administration the mean of cage crossing was 27.00 with std. dev. ± 5.704 (P<0.000), after 7 day of administration the mean of cage crossing was 26.58 with std. dev. ± 2.425 (P<0.000), after 20 day of administration the mean of cage crossing was 14.08 with std. dev. ± 1.475 (P<0.000) and after 30 day of administration the mean of cage crossing was 12.00 with std. dev. ± 1.516 (P<0.000).
Effect of ELE, MLE, ESE and MSE in comparison with the controlled group on cage crossing has been shown in Table 1, the highly significant result has been obtained, i.e. P<0.000.

2. HEAD DIPS

The effect of ethanolic extract of leaf: At day 0 the significant value was 6.10 (p<0.000), after 1 day of administration the mean of head dips was 21.40 with standard deviation ± 1.075 (P<0.000), after 7 day of administration the mean of head dips was 17.90 with standard deviation ± 1.06(P<0.000), after 20 day of administration the mean of head dips was 13.80 with standard deviation ± 1.033(P<0.000) and after 30 day of administration the mean of head dips was 3.70 with standard deviation ± 0.675(P<0.000).

The effect of methanolic extract of leaf: At day 0 the significant value was 6.19 (p<0.000), after 1 day of administration the mean of head dips was 10.30 with standard deviation ±1.76 (P<0.000), after 7 day of administration the mean of head dips is 9.90 with standard deviation ±1.247 (P<0.000), after 20 day of administration the mean of head dips is 9.10 with standard deviation ±1.370 (P<0.000) and after 30 day of administration the mean of head dips is 8.80 with standard deviation ±1.317 (P<0.000).

The effect of ethanolic extract of seed: At day 0 the significant value was 6.89 (p<0.000), after 1 day of administration the mean of head dips was 6.00 with standard deviation ±0.943 (P<0.000), after 7 day of administration the mean of head dips was 5.70 with standard deviation ±1.418 (P<0.000), after 20 day of administration the mean of head dips was 3.30 with standard deviation ±0.823 (P<0.000) and after 30 day of administration the mean of head dips was 0.00 because the all the mice died before day 30.

The effect of methanolic extract of seed: At day 0 the significant value was 6.96 (p<0.000), after 1 day of administration the mean of head dips was 19.40 with std. dev. ± 1.516 (P<0.000), after 7 day of administration the mean of head dips was 13.40 with std. dev. ± 1.265 (P<0.000), after 20 day of administration the mean of head dips was 12.80 with std. dev. ± 1.059 (P<0.000) and after 30 day of administration the mean of head dip was 12.40 with std. dev. ± 1.265 (P<0.000).

3. STATIONARY ROD (time taken by mice to cross the rod)

The effect of ethanolic extract of leaf: At day 0 the significant value was 93.71 (p<0.000), after 1 day of administration the mean of time taken to cross the rod was 78.10 with standard deviation ± 1.287 (P<0.000), after 7 day of administration the mean of time taken to cross the rod was 74.10 with standard deviation ± 3.326 (P<0.000), after 20 day of administration the mean of time taken to cross the rod was 43.80 with standard deviation ± 3.743 (P<0.000) and after 30 day of administration the mean of time taken to cross the rod was 31.60 with standard deviation ± 0.823 (P<0.000).

The effect of methanolic extract of leaf: At day 0 the significant value was 94.00 (p<0.000), after 1 day of administration the mean of time taken to cross the rod was 116.70 with standard deviation ±3.529 (P<0.000), after 7 day of administration the mean of time taken to cross the rod was 114.30 with standard deviation ±2.452 (P<0.000), after 20 day of administration the mean of time taken to cross the rod was 90.30 with standard deviation ±1.889 (P<0.000) and after 30 day of administration the mean of time taken to cross the rod was 51.70 with standard deviation ±1.337 (P<0.000).

The effect of ethanolic extract of seed: At day 0 the significant value was 98.00 (p<0.000), after 1 day of administration the mean of time taken to cross the rod was 192.70 with standard deviation

±2.111 (P<0.000),after 7 day of administration the mean of time taken to cross the rod was 190.00 with standard deviation ±1.886 (P<0.000),after 20 day of administration the mean of time taken to cross the rod was 80.80 with standard deviation ±1.398 (P<0.000) and after 30 day of administration the mean of time taken to cross the rod was 0.00 because all the mice died before day 30 (P<0.000).

The effect of methanolic extract of seed: At day 0 the significant value was 97.16 (p<0.000), after 1 day of administration the mean of stationary rod was 165.80 with std. dev. ± 1.751 (P<0.000), after 7 day of administration the mean of stationary rod was 152.20 with std. dev. ± 3.490 (P<0.000), after 20 day of administration the mean of stationary rod was 142.30 with std. dev. ± 2.058 (P<0.000) and after 30 day of administration the mean of stationary rod was 119.40 with std. dev. ± 1.776 (P<0.000).

4. OPEN FIELD (no. of central square cross)

The effect of ethanolic extract of leaf: At day 0 the significant value was 18.91 (p<0.000), after 1 day of administration the mean of number of central square crosses was 15.50 with standard deviation ± 1.080 (P<0.000), after 7 day of administration the mean of number of central square crosses was 13.80 with standard deviation ± 0.789 (P<0.000), after 20 day of administration the mean of number of central square crosses was 8.80 with standard deviation ± 0.919 (P<0.000) and after 30 day of administration the mean of number of central square crosses was 8.50 with standard deviation ±0.850 (P<0.000).

The effect of methanolic extract of leaf: At day 0 the significant value was 18.73 (p<0.000), after 1 day of administration the mean of number of central square crosses was 21.90 with standard deviation ±1.663 (P<0.000), after 7 day of administration the mean of number of central square crosses was 13.80 with standard deviation ± 0.789 (P<0.000), after 20 day of administration the mean of number of central square crosses was 5.40 with standard deviation ±1.506 (P<0.000), after 30 day of administration the mean of number of central square crosses was 3.30 with standard deviation ±1.567 (P<0.000).

The effect of ethanolic extract of seed: At day 0 the significant value was 18.63 (p<0.000), after 1 day of administration the mean of number of central square crosses was 18.80 with standard deviation ±1.059 (P<0.000), after 7 day of administration the mean of number of central square crosses was 18.70 with standard deviation ±1.636 (P<0.000),after 20 day of administration the mean of number of central square crosses was 17.50 with standard deviation ±3.567 (P<0.000),after 30 day of administration the mean of number of central square crosses was 0.00 because the all the mice died before day 30.

The effect of methanolic extract of seed: At day 0 the significant value was 18.93 (p<0.000), after 1 day of administration the mean of number of central square crosses was 24.40 with std. dev. ± 1.265 (P<0.000),after 7 day of administration the mean of number of central square crosses was 8.90 with std. dev. ± 1.197 (P<0.000), after 20 day of administration the mean of number of central square crosses was 8.70 with std. dev. ± 1.337 (P<0.000) and after 30 day of administration the mean of number of central square crosses was 5.70 with std. dev. ± 0.949 (P<0.000).

***5.* OPEN FIELD (no. of peripheral square cross)**

The effect of ethanolic extract of leaf: At day 0 the significant value was 87.91 (p<0.000), after 1 day of administration the mean of number of peripheral square crosses was 105.40 with standard deviation ± 3.204 (P<0.000), after 7 day of administration the mean of number of peripheral square crosses was 89.80 with standard deviation ± 1.033 (P<0.000), after 20 day of administration the mean of number of peripheral square crosses was 85.70 with standard deviation ± 1.636 (P<0.000) and after 30 day of administration the mean of number of peripheral square crosses was 67.10 with standard deviation ±1.524 (P<0.000).

The effect of methanolic extract of leaf: At day 0 the significant value was 87.43 (p<0.000), after 1 day of administration the mean of number of peripheral square crosses was 121.70 with standard deviation ±2.497 (P<0.000), after 7 day of administration the mean of number of peripheral square crosses was 107.70 with standard deviation ±1.567 (P<0.000), after 20 day of administration the mean of number of peripheral square crosses was 67.20 with standard deviation ±2.150 (P<0.000) and after 30 day of administration the mean of number of peripheral square crosses was 58.00 with standard deviation ±1.032 (P<0.000).

The effect of ethanolic extract of seed: At day 0 the significant value was 88.43 (p<0.000), after 1 day of administration the mean of number of peripheral square crosses was 98.90 with standard deviation ±2.283 (P<0.000),after 7 day of administration the mean of number of peripheral square crosses was 95.20 with standard deviation ±1.751 (P<0.000),after 20 day of administration the mean of number of peripheral square crosses was 95.00 with standard deviation ±1.944 (P<0.000) and after 30 day of administration the mean of number of peripheral square crosses was 0.00 because the all the mice died before day 30.

The effect of methanolic extract of seed: At day 0 the significant value was 88.14 (p<0.000), after 1 day of administration the mean of number of peripheral square crosses was 98.10 with std. dev. ± 0.994 (P<0.000), after 7 day of administration the mean of number of peripheral square crosses was 80.90 with std. dev. ± 1.370 (P<0.000), after 20 day of administration the mean of number of peripheral square crosses was 80.40 with std. dev. ± 2.459 (P<0.000) and after 30 day of administration the mean of number of peripheral square crosses was 42.30 with std. dev. ± 2.214 (P<0.000).

6. LIGHT AND DARK BOX [time spent in illuminated box (sec)

The effect of ethanolic extract of leaf: At day 0 the significant value was 205.20 (p<0.000), after 1 day of administration the mean of time spent in illuminated area was 183.00 with standard deviation ± 2.108 (P<0.000), after 7 day of administration the mean of time spent in illuminated area was 195.60 with standard deviation ± 1.776 (P<0.000), after 20 day of administration the mean of time spent in illuminated area was 204.90 with standard deviation ± 3.929 (P<0.000) and after 30 day of administration the mean of time spent in illuminated area was 214.00 with standard deviation ± 1.700 (P<0.000).

The effect of methanolic extract of leaf: At day 0 the significant value was 203.98 (p<0.000), after 1 day of administration the mean of time spent in illuminated area was 242.60 with standard deviation ±2.716 (P<0.000), after 7 day of administration the mean of time spent in illuminated area was 268.10 with standard deviation ±2.424 (P<0.000), after 20 day of administration the mean of time spent in illuminated area was 304.90 with standard deviation ±5.131 (P<0.000) and after 30 day of administration the mean of time spent in illuminated area was 310.70 with standard deviation ±2.983 (P

The effect of ethanolic extract of seed: At day 0 the significant value was 210.38 (p<0.000), after 1 day of administration the mean of time spent in illuminated area was 116.00 with standard deviation ±3.055 (P<0.000),after 7 day of administration the mean of time spent in illuminated area was 125.30 with standard deviation ±4.668 (P<0.000),after 20 day of administration the mean of time spent in illuminated area was 327.80 with standard deviation ±3.734 (P<0.000) and after 30 day of administration the mean of time spent in illuminated area was 0.00 because all the mice died before day 30 (P<0.000).

The effect of methanolic extract of seed: At day 0 the significant value was 212.95 (p<0.000), after 1 day of administration the mean of time spent in illuminated area was 144.30 with std. dev. ± 3.529 (P<0.000), after 7 day of administration the mean of time spent in illuminated area was 153.10 with std. dev. ± 1.969 (P<0.000), after 20 day of administration the mean of time spent in illuminated area

was 219.10 with std. dev. ± 4.606 (P<0.000) and after 30 day of administration the mean of time spent in illuminated area was 240.80 with std. dev. ± 2.251 (P<0.000).

7. IMMOBILITY TIME

The effect of ethanolic extract of leaf: At day 0 the significant value was 56.14 (p<0.000), after 1 day of administration the mean of immobility time was 33.60 with standard deviation ± 1.174 (P<0.000), after 7 day of administration the mean of immobility time was 10.00 with standard deviation ± 0.667 (P<0.000), after 20 day of administration the mean of immobility time was 5.60 with standard deviation ± 0.843 (P<0.000) and after 30 day of administration the mean of immobility time was 2.40 with standard deviation ± 0.516 (P<0.000).

The effect of methanolic extract of leaf: At day 0 the significant value was 46.06(p<0.000), after 1 day of administration the mean of immobility time was 16.50 with standard deviation ±1.080 (P<0.000), after 7 day of administration the mean of immobility time was 6.11 with standard deviation ±0.889 (P<0.000), after 20 day of administration the mean of immobility time was 2.40 with standard deviation ±0.543 (P<0.000) and after 30 day of administration the mean of immobility time was 1.00 with standard deviation ±0.643 (P<0.000).

The effect of ethanolic extract of seed: At day 0 the significant value was 36.89 (p<0.000), after 1 day of administration the mean of immobility time was 24.70 with standard deviation ±1.337 (P<0.000), after 7 day of administration the mean of immobility time was 16.11 with standard deviation ±0.889 (P<0.000),after 20 day of administration the mean of immobility time was 9.30 with standard deviation ±2.791 (P<0.000) and after 30 day of administration the mean of immobility time was 5.11 with standard deviation ±0.593 (P<0.000).

The effect of methanolic extract of seed: At day 0 the significant value was 17.81 (p<0.000), after 1 day of administration the mean of immobility time was 114.60 with std. dev. ±1.430 (P<0.000), after 7 day of administration the mean of immobility time was 20.40 with std. dev. ±2.485 (P<0.000), after 20 day of administration the mean of immobility time was 17.76 with std. dev. ±2.808 (P<0.000) and after 30 day of administration the mean of immobility time was 15.16 with std. dev. ±0.519 (P<0.000).

DISCUSSION

When compare with other psychiatric conditions such as depression or schizophrenia, anxiety is categorized as normal condition as well as psychiatric condition. It appears mostly with other diseases. Its diagnosis is difficult but when the symptoms disturb the normal regular activity its termed as psychiatric condition and at that time treatment is needed (Walia et al. 2018; Steimer 2022).

For new anxiolytics medicine which must be safe and effective, researcher looking for remedies from plants. It's easy to investigate other than psychiatric condition to test on animals but quite difficult to test psychiatric condition on animals (Cryan and Sweeney 2011).

Cage crossing

In home cage activity the number of cage crosses was decreased more significantly as compared to control. Decrease in number of cage crosses depicts decrease anxiety in the animal from *Carica papay* (Mill et al. 2002). Combination of calcium and magnesium is very effective against panic disorder, anxiety, fear etc. which is present in leaves that's why ethanolic and methanolic leaf extract show activity (Carroll et al. 2000). In seeds calcium and phosphorous is present, their combination is very effective for anxiety and fear that's why ethanolic and methanolic seed extract gives anxiolytic activity (DiMeglio and Imel 2019). Before day 30 all the mice died who receive ethanolic seed extract indicating that ethanolic seed extract contain some constituents which may react with ethanol and produce toxic effect which is not suitable for mice for more than 21 days (Ayotunde and Ofem 2008).

Head dip

In head dip action the qua receptor ntity of head dip was diminished all the more essentially as contrast with control. Abatement the quantity of head dip show decline in uneasiness in the mice from *Carica papaya* (File and Wardill 1975). When calcium and magnesium combine together they show very good effect on panic anxiety fear etc. Exactly from pharmacological point of view, administration of Mg^{2+} instantly prior to the acquiring of a learning effort should have a detrimental effect on that task given the non-competitive antagonist properties of Mg^{2+} at the NMDA receptor. However, in some cases a facilitative effect can be shown. In seeds calcium and phosphorous is available, their mix is exceptionally viable for tension and dread that is the reason ethanolic and methanolic seed extract gives anxiolytic action (DiMeglio and Imel 2019). Before day 30 all the mice died who get ethanolic seed extract which shows that a few constituents may respond with ethanol and produce lethal impact which isn't reasonable for mice for over 21 days (Ayotunde and Ofem 2008).

Stationary rod

In stationary rod activity it was observed that after the administration of ethanolic and methanolic extract of *Carica papaya* the mice crossed the rod in minor time when contrasted with control (Najam 2003). The effect suggest that the *Carica papaya* enhance learning, memory and gripping power because of calcium and magnesium in leaves and calcium and phosphorous in seeds (Linder et al. 1989; Komatsu et al. 2008). Increase in the level of magnesium causes the antagonistic action at NMDA receptors thus increasing cognition, memory and learning but before day 30 all the mice passed away who get ethanolic seed extract which show that a few constituents may respond with ethanol and produce lethal effect which isn't appropriate for mice for over 21 days (Ayotunde and Ofem 2008).

Open field (Central square crosses)

In open field modular our study shows that the number of central square crosses was decreased gradually, practically identical to control, offer ascent to the reason that *Carica papaya* shows antidepressant effect (Carola et al. 2002). The animal at acute dosing feels fearless but after continuous dosing of methanolic and ethanolic extracts of *Carica Papaya* seeds and leaves, the explorations decreases gradually which can be related to increase in learning of the animals after repeated exposures. Combination of calcium and magnesium is viable against alarm issue, uneasiness, dread and so on which is available in leaves that are the reason ethanolic and methanolic leaf extract show anxiolytic effect (Carroll et al. 2000). In seeds calcium and phosphorous is available, their combination is powerful for nervousness and dread that is the reason ethanolic and methanolic seed extract gives antidepressant activity (DiMeglio and Imel 2019). Before day 30 all the mice died who receive ethanolic seed extract which indicates that ethanolic seed extract which indicate that some constituents may react with ethanol and produce toxic effect which is not suitable for mice for more than 21 days (Ayotunde and Ofem 2008).

Open field (peripheral square crosses)

In the open field activity, the peripheral square crosses were diminished all the more altogether. Peripheral square crosses we can say that *Carica papaya* possess antidepressant profile which made the mice agreeable enough to decrease the open field exploration (Nogueira Neto et al. 2013). Combination of calcium and magnesium is very effective against panic disorder, anxiety, fear etc. which is present in leaves that's why ethanolic and methanolic leaf extract show antidepressant activity (Carroll et al. 2000). In seeds calcium and phosphorous is present, their combination is very effective for anxiety and fear that's why ethanolic and methanolic seed extract gives antidepressant activity (DiMeglio and Imel 2019). Before day 30 all the mice died who receive ethanolic seed extract which indicates that ethanolic seed extract which indicate that some constituents may react with ethanol and produce toxic effect which is not suitable for mice for more than 21 days (Ayotunde and Ofem 2008).

Light and dark

Light and dark box test depends on natural attribute of mice to hate splendidly lit up territories and on the unpremeditated exploratory behavior of mice in light of mellow stressors, for example novel condition and light (Bourin and Hascoët 2003). As indicated by our investigation the time spent in light box is expanded. This result also witness the CNS anxiolytic effect of plant (Walia et al. 2018). Combination of calcium and magnesium is very effective against panic disorder, anxiety, fear etc. which is present in leaves that's why ethanolic and methanolic leaf extract show anxiolytic activity (Carroll et al. 2000). In seeds calcium and phosphorous is present, their combination is very effective for anxiety and fear that's why ethanolic and methanolic seed extract gives anxiolytic activity (DiMeglio and Imel 2019). Before day 30 all the mice died who receive ethanolic seed extract which indicates that ethanolic seed extract which indicate that some constituents may react with ethanol and produce toxic effect which is not suitable for mice for more than 21 days (Ayotunde and Ofem 2008).

Forced swimming test

From our observation we conclude that the immobility time was decreased as compare to control which indicates antidepressant activity (Armario et al. 1988). Combination of calcium and magnesium is very effective against panic disorder, anxiety, fear etc. which is present in leaves that's why ethanolic and methanolic leaf methanolic show antidepressant activity (Carroll et al. 2000). In seeds calcium and phosphorous is present, their combination is very effective for anxiety and fear that's why ethanolic and methanolic seed extract gives antidepressant activity (DiMeglio and Imel 2019).
As compared to seed, leaves have more quantity of calcium, phosphorous and magnesium, which indicate that leaves have strong anxiolytic activity rather than seeds. Also in leaves the level of iron is more, which increase the level of hemoglobin causing improving of blood circulation, which also increase anxiolytic effect.

CONCLUSION:

We conclude that the ethanolic and methanolic extract of seed and leaves of *Carica papaya* have antidepressant activity. However, chronic toxicity profile of *C. papaya* should be explored.

DISCLOSURE STATEMENT

The authors report no conflict of interest

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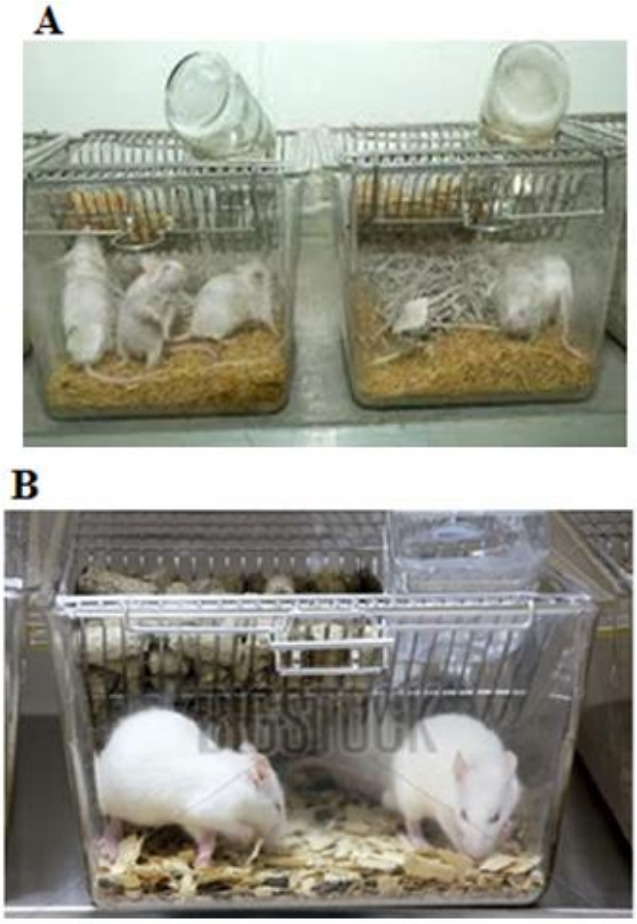

Figure 1: (A) Mice and (B) Rats

Table 1: Effect of extracts on cage crossing

Number of cage crossing / 10 minutes					
	Day 0	**Day 1**	**Day 7**	**Day 20**	**Day 30**
Groups	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Control	21.00 ± 2.357	23.00± 2.741	21.27 ± 2.357	21.38 ± 2.386	21.43 ± 2.395
ELE	21.80± 3.084	33.10 ± 2.283	22.30 ± 1.252	16.50 ± 1.179	14.80 ± 0.850
MLE	23 ± 2.741	22 ± 1.333	22.60 ± 1.275	17.5 ± 1.179	16.70 ± 0.823
ESE	21 ± 2.357	23.80 ± 1.789	17.40 ± 1.578	16.90 ± 1.101	0.00 ± 0.00
MSE	21.80 ± 2.752	27.00 ± 5.704	26.58 ± 2.425	14.08 ± 1.475	12.00 ±12.516
		***+++	***+++	***+++	***+++

***+++($p<0.000$) is highly significant.

Table 2: Effect of Extracts on head dips (no. of head dips)

Number of head dips / 10 minutes					
	Day 0	**Day 1**	**Day 7**	**Day 20**	**Day 30**
Groups	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Control	6.10 ± 1.370	6.23 ± 1.385	7.13 ± 1.484	7.95 ± 1.549	8.00 ± 1.780
ELE	6.10 ± 1.370	21. 40 ± 1.075	17.90.±1.06	13.80±1.033	3.70 ± 0.675
MLE	6.19 ± 1.389	10.30 ± 1.767	9.90 ± 1.247	9.10 ± 1.370	8.80 ± 1.317
ESE	6.89 ± 1.894	6.00± 0.943	5.70 ± 1.418	3.30 ± 0.823	0.00 ± 0.00
MSE	6.96 ± 1.794	19.40 ± 1.516	13.40 ± 1.265	12.80 ± 1.059	12.40 ± 1.265
		***+++	***+++	***+++	***+++

***+++($p<0.000$) is highly significant.

Table3: Effect of Extracts on stationary rod (time taken by mice to cross the rod)

Time taken by mice to cross the rod					
	Day 0	**Day 1**	**Day 7**	**Day 20**	**Day 30**
Groups	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Control	93.70 ±3.057	93.89 ± 3.143	94.85 ± 3.326	95.00 ± 3.743	96.96 ± 3.798
ELE	93.71 ±3.157	78.10 ± 1.287	74.10 ± 1.969	43.80 ± 2.251	31.60 ± 0.823
MLE	94.00 ± 3.013	116.70 ± 3.529	114.30 ± 2.452	90.30 ± 1.889	51.70 ± 1.337
ESE	98.00 ± 3.019	192.70 ± 2.111	190.00 ± 1.886	80.80 ± 1.398	0.00 ± 0.00
MSE	97.16 ± 3.194	165.80 ± 1.751	152.20 ± 3.490	142.30 ±2.058	119.40 ± 1.776
		***+++	***+++	***+++	***+++

***+++(p<0.000) is highly significant.

Table 4: Effect of Extracts on central square crosses

Number of central square crosses / 10 minutes					
	Day 0	**Day 1**	**Day 7**	**Day 20**	**Day 30**
Groups	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Control	18.90 ± 1.792	18.89 ± 1.771	19.80 ± 1.791	19.42 ± 1.743	17.33 ± 1.732
ELE	18.91 ± 1.732	15.50 ± 1.080	13.80 ± 0.789	8.80 ±0.919	8.50 ± 0.850
MLE	18.73 ± 1.754	21.90 ± 1.663	17.10 ± 1.449	5.40 ± 1.50	3.30 ± 1.567
ESE	18.63 ± 1.639	18.80 ± 1.059	18.70 ± 1.636	17.50 ± 3.567	0.00 ± 0.00
MSE	18.93 ± 1.642	24.40 ± 1.265	8.90 ± 1.197	8.70 ± 1.33	5.70 ± 0.949
		***+++	***+++	***+++	***+++

***+++(p<0.000) is highly significant.

Table 5: Effect of Extracts on peripheral square crosses

Number of peripheral square crosses / 10 minutes					
	Day 0	**Day 1**	**Day 7**	**Day 20**	**Day 30**
Groups	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Control	87.70 ± 2.751	88.19 ± 2.431	89.63 ± 2.423	89.39 ± 2.463	88.43 ± 2.496
ELE	87.91 ± 2.543	105.40 ± 3.204	89.80 ± 1.033	85.70 ± 1.636	67.10 ± 1.524
MLE	87.43 ± 2.439	121.70 ± 2.497	107.70 ± 1.567	67.20 ± 2.150	58.00 ± 1.032
ESE	88.43 ± 2.649	98.90 ± 2.283	95.20 ± 1.751	95.00 ± 1.949	0.00 ± 0.00
MSE	88.14 ± 2.444	98.10 ± 0.994	80.90 ± 1.370	80.40 ± 2.459	42.30 ± 2.214
		***+++	***+++	***+++	***+++

***+++(p<0.000) is highly significant.

Table 6: Effect of Extracts on light and dark box [time spent in illuminated box (sec)

Time spent in illuminated box (sec)					
	Day 0	**Day 1**	**Day 7**	**Day 20**	**Day 30**
Groups	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Control	202.50 ± 9.336	205.51 ± 9.454	202.98 ± 9.673	203.00 ± 9.349	203.43 ± 9.876
ELE	205.20 ± 9.876	183.00 ± 2.108	195.60 ± 1.776	204.90 ± 3.929	214.00 ± 1.700
MLE	203.98 ± 9.432	242.60 ± 2.716	268.10 ± 2.424	304.90 ± 5.131	310.70 ± 2.983
ESE	210.38 ± 10.90	116.00 ± 3.055	125.30 ± 4.668	327.80 ± 13.734	0.00 ± 0.00
MSE	212.95 ± 9.90	144.30 ± 3.529	153.10 ± 1.969	219.10 ± 4.606	240.80 ± 2.251
		***+++	***+++	***+++	***+++

***+++(p<0.000) is highly significant.

Table 7: Effect of Extracts on immobility time

Immobility time / 10 minutes					
	Day 0	**Day 1**	**Day 7**	**Day 20**	**Day 30**
Groups	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Control	64.70 ± 3.802	56.81 ± 3.916	50.89 ± 3.991	60.89 ± 4.011	45.07 ± 4.119
ELE	56.14 ± 3.428	33.60 ± 1.174	10.00 ± 0.667	5.60 ± 0.843	2.4o ± 0.516
MLE	46.06 ± 3.996	16.50 ± 1.080	6.11 ± 0.889	2.40 ± 0.543	1.00 ± 0.643
ESE	36.89 ± 3.142	24.7 ± 1.337	16.11 ± 0.799	9.3 ± 2.791	5.11 ± 0.593
MSE	17.81± 3.119	114.60± 1.430	20.40 ± 2.485	17.76 ±2.808	15.16 ± 0.519
		***+++	***+++	***+++	***+++

***+++(p<0.000) is highly significant.