

PAPITA FRUIT: A DELICIOUS REMEDY FOR DEPRESSION

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ABSTRACT

Papita, a fibrous, juicy and tasty fruit, belonging to family Caricaceae is scientifically known as *Carica papaya* L. Traditionally, Papaya is used as an abortifacient and as a wound-healer. Furthermore, Papaya possesses several medicinal properties such as anti-hypertensive, anti-oxidant, anti-tumor, anti-fertility, hypo-lipidaemic, anthelmintic, nephro-protective, anti-inflammatory, anti-amoebic, anti-bacterial and anti-sickling property. There are no reports in literature pertaining to CNS actions of *Carica papaya*. In the light of above, the present study was undertaken to test the antidepressant potential of *Carica papaya* fruit. *Carica papaya* pulp (CPP) was administered at various concentrations ranging from 4% to 16% w/v, p.o. to Swiss mice for 15 days and Wistar rats for 6 successive days. The antidepressant activity was measured using forced swim test (FST), tail suspension test (TST) and reserpine induced hypothermia model. The efficacy of Papaya was compared with standard antidepressant drugs such as fluoxetine (20mg/kg, p.o.), imipramine (15mg/kg, p.o.) and phenelzine (20 mg/kg, p.o.). The results of the present study showed that Papaya pulp significantly decreased immobility time in both FST and TST models. It also reversed the hypothermia induced by reserpine. The efficacy of Papaya was found to be comparable to fluoxetine, imipramine and phenelzine. Furthermore, *Carica papaya* juice inhibited the monoamine oxidase MAO-A and MAO-B activity and reduced significantly malondialdehyde (MDA) levels. These findings reveal the antidepressant potential of Papaya. The probable mechanism of action for the beneficial effect of Papita in depression appears to be related to its i) MAO inhibitory activity ii) tyrosine, phenylalanine (NE precursors) and tryptophan (5-HT precursor) content and iii) antioxidant property.

KEY WORDS: Hypothermia, Despair, Papaya, Immobility.***Author for Correspondence**Dr. Milind Parle, Pharmacology Division, Dept. Pharm. Sciences (Accredited by NBA), Guru Jambheshwar University of Science & Technology, HISAR-125001 Haryana, India E-mail: mparle@rediffmail.com**INTRODUCTION**

According to the World Health report, approximately 121 million people are suffering from depression worldwide, yet only a small section of them receives the most basic treatment. Depression is considered as an affective disorder characterized by low mood, lack of interest in the surroundings, psychomotor retardation, anhedonia, low energy levels, suicidal tendencies and melancholia. It is a major disease affecting nearly 15-20% of the population in the world^{1,2}. At present, there are several types of antidepressants used in clinical practice, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs)^{3,4}. The efficacy of medicines for the management of depression

is limited. Therefore, herbal therapies should be considered as alternative/complementary medicines.

Carica papaya L, commonly known as Papaya/Papita, is well known for its excellent nutritional and medicinal values throughout the world. The prominent medicinal properties of Papaya include anti-fertility^{5,6}, anti-hypertensive⁷, hypo-glycemic⁸, hypo-lipidaemic⁸, anti-helmintic⁹, anti-amoebic¹⁰, wound-healing¹¹, anti-bacterial¹², anti-tumor¹³, anti-sickling¹⁴ and free radical scavenging activities^{15,16}. Phytochemically, the whole plant contains enzymes (papain), carotenoids, alkaloids, monoterpenoids, flavonoids, minerals and vitamins. However, there is no scientific evidence for the therapeutic potential of Papaya in neuropsychiatric disorders. Literature reports reveal that Papaya contains good amount of tyrosine, phenylalanine (precursors of NE) as well as tryptophan (a precursor of 5-HT)¹⁷. Since

5-HT and NE levels fall considerably in depression, we were interested to investigate the usefulness of papaya in depression.

MATERIALS AND METHODS

Objectives

The present study was undertaken to explore the antidepressant potential of *Carica papaya* pulp (CPP) using forced swim test, tail suspension test and reserpine induced hypothermia models. Noradrenaline (NE) and serotonin modulating agents were co-administered to determine the underlying mechanism of action.

Plant material

The fresh Papaya (*Carica papaya*) fruit was purchased from local market of Hisar and got authenticated from Raw Materials Herbarium and Museum, National Institute of Science Communication and Information Resources (NISCAIR), New Delhi. *Carica papaya* pulp was administered in different concentrations (4, 8, 16%, w/v, p.o.) daily for a duration of 6 days to rats and 15 days to mice.

Animals

A total of 120 Swiss mice divided into 24 groups & 30 Wistar rats divided in 05 groups were used in the present study. The animals were used once only for a specific animal model. Each group comprised of a minimum of 5 animals. Adult (3-4 months old) female mice weighing around 20-25 g and aged (9-11 months old) male rats weighing around 220-230 g were procured from the Disease Free Small Animal House, Lala Lajpat Rai University of Veterinary Sciences, Hisar. The experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) and the care of animals was taken as per the guidelines of CPCSEA, Ministry of Forests and Environment, Government of India (Registration number 0436).

Drug protocol

Mice belonging to group I were subjected to pilot study carried out to determine the effective concentrations of *Carica papaya* pulp (CPP). Mice belonging to groups II to VIII were subjected to tail suspension test (TST). Mice belonging to groups IX to XV were subjected to forced swim test (FST). Mice belonging to groups XVI to XX were used for biochemical estimations. Mice belonging to groups XXI to XXIV were exposed to Photoactometer for assessing the locomotor activity. Rats belonging to groups XXV to XXIX were employed in Reserpine induced hypothermia model.

Distilled water (vehicle, p.o.), Fluoxetine (20 mg/kg, p.o.), Imipramine (15 mg/kg, p.o.), Phenelzine (20 mg/kg, p.o.), and CPP in different concentrations (4%, 8% and 16%, w/v, p.o.) were administered for 15 days to

mice. At 60 min after administration of drugs/vehicle/CPP on 15th day, duration of immobility was recorded in mice in TST, FST and biochemical studies were carried out. Effect on locomotor activity of mice was studied using a photoactometer. Similarly vehicle, Fluoxetine (20 mg/kg), Imipramine (15 mg/kg) and CPP in different concentrations (4% w/v) were administered orally for 6 successive days to rats for hypothermia studies. The rectal temperature was recorded on days 0, 6, 7 and 8. Rectal temperature was measured immediately before and 18 hr after administration of reserpine in reserpine induced hypothermia model.

EXPERIMENTAL DESIGN

Tail Suspension Test

Tail suspension test (TST) is a commonly employed behavioral model for screening of antidepressant like activity in mice^{18,19}. Animals were moved from their housing colony to laboratory in their own cages and allowed to adapt to the laboratory conditions for 1-2 hr. Briefly, each mouse was individually suspended to the edge of a table, 50 cm above the floor, by adhesive tape placed approximately 1 cm from the tip of the tail. The total period of immobility was recorded manually for 6 min. Animal was considered to be immobile when it didn't show any body movement, hung passively and was completely motionless.

Forced Swim Test

Forced swim test (FST) was employed as another model to test anti-depressant activity²⁰⁻²⁴. In this model, mice are forced to swim in a restricted space from which they cannot escape²⁵. "Despair behaviour" was defined as a behaviour in which animals surrender to the swimming pool conditions and make minimal movements of the limbs so as to keep the nose above the water surface²⁶. Mice were forced to swim individually in glass jar (25 cm x 12 cm x 25 cm) containing 15 cm deep fresh water and maintained at 25°C ±3°C. After an initial 2 min period of vigorous activity, each animal showed typical despair behaviour or assumed an immobile posture. The total duration of immobility was recorded during the next 4 min of total 6 min test. The changes in immobility duration were studied after administering various drugs in separate groups of animals.

Reserpine induced hypothermia model

Reserpine induced hypothermia model is commonly employed to evaluate new antidepressant drugs. Depletion of biogenic amines (noradrenaline, 5-hydroxytryptamine and dopamine) in the brain induces hypothermia in rodents, a state of depression²⁵. Chronic administration of reserpine produced the state of major

depression in rats. Reserpine induced behavioral depression was correlated to the depletion of brain monoamines²⁷. CPP/vehicle/imipramine/fluoxetine was administered for 6 days to rats of different groups. On 6th day, animals were injected with reserpine (2 mg/kg, s.c.), 60 minutes after feeding the CPP/vehicle/imipramine/fluoxetine. The rectal temperature was measured before and after eighteen hours of reserpine by inserting the rectal thermometer to a constant depth of 2 cm.

STATISTICAL ANALYSIS

All the results were expressed as mean \pm Standard Error (SEM). Data were analyzed by one-way ANOVA followed by Dunnett's t-test.

RESULTS AND DISCUSSION

Fresh *Carica papaya* pulp (CPP) in different concentrations (4, 8 and 16%, w/v, p.o.) diminished the duration of immobility significantly ($p < 0.01$), when administered for 15 days to mice in tail suspension test. The effect of CPP was found to be comparable to that of fluoxetine (5-HT reuptake inhibitor), imipramine (Tricyclic antidepressant) and phenelzine (Monoamine oxidase inhibitor) (**Fig. 1**). CPP in different concentrations (4, 8 and 16%, w/v, p.o.) diminished despair behavior significantly ($p < 0.01$), when administered for 15 days to mice. The effect of CPP was found to be comparable to that of fluoxetine (5-HT reuptake inhibitor), imipramine (Tricyclic antidepressant) and phenelzine (Monoamine oxidase inhibitor) (**Fig. 2**). Hypothermia was induced with the help of reserpine (2 mg/kg, s.c.) in rats. CPP 4%, w/v, p.o., when administered for 6 days to rats, reversed the hypothermia induced by reserpine. (**Fig. 3**). *Carica papaya* pulp when administered to mice for 15 successive days in different concentrations (4, 8 and 16%, w/v, p.o.), significantly ($p < 0.01$) reduced the brain MAO-A (nmol/mg protein) and MAO-B (nmol/mg protein) activity as compared to the control group (**Figs. 4, 5**). Furthermore, CPP produced a significant ($p < 0.01$) decrease in brain MDA levels (nmol/mg tissue) as well (**Fig. 6**).

Despite the wide use of *Carica papaya* in daily life, there are no scientific reports on the CNS effects of Papaya fruit. Antidepressant potential of *Carica papaya* pulp (CPP) was tested in mice by employing two standard experimental models viz: Forced Swim Test and Tail Suspension Test^{18, 21}. In tail suspension test (TST) the duration of immobility reflects the helplessness of animals¹⁹, which is similar to depression seen in human patients. Forced swim test (FST) is another experimental model popularly employed for testing the antidepressant activity in laboratory animals. In this model, animals are

forced to swim in a restricted space from which there is no escape²⁵. Despair behavior is defined as behavior in which animals surrender to the swimming pool conditions and make minimal movements of the limbs so as to keep the nose above the water surface²⁶. The duration of despair is correlated with depression observed in human patients. Both the above models are sensitive, stress-free and give reproducible results. In the present study, Papaya fruit consistently reduced the duration of immobility in TST and the period of despair behaviour in FST, thereby revealing the antidepressant potential of Papaya fruit. This antidepressant activity of Papaya fruit was comparable to antidepressant effect of imipramine, a tricyclic antidepressant (TCA) medicine commonly prescribed in human patients.

The results obtained with mice were confirmed in rats as well, using reserpine induced hypothermia model. Hypothermia or decreased body temperature is associated with the state of depression. Whereas, the increase in body temperature or hyperthermia, is linked with a depression-free state²⁷. In the present study, Papaya fruit reversed reserpine induced hypothermia in rats, thereby indicating its usefulness in depression. The pathophysiology of depression reveals that serotonin and noradrenaline (NE) levels are significantly reduced in the brains of depressed patients²⁸. Reserpine induced depression is mediated via depletion of brain monoamines²⁹. Monoamine oxidase enzymes (MAO-A and MAO-B) metabolize noradrenaline and serotonin to their inactive forms. Therefore, if MAO activity could be inhibited, there would be enhancement in the effects of NE and serotonin. In the present study, Papaya fruit concomitantly inhibited both MAO-A and MAO-B enzymes, when administered for 15 days. This effect of Papaya was comparable to the action of phenelzine, a standard MAO inhibitor. Thus, the underlying mechanism of Papaya fruit appears to be related to its MAO inhibitory activity by virtue of which there was increase in the concentrations of NE and serotonin. Furthermore, literature reports reveal that Papaya contains good amount of tyrosine, phenylalanine (precursors of NE) as well as tryptophan (a precursor of 5-HT)¹⁷. This fact suggests that tryptophan and phenylalanine occurring naturally in Papaya might be contributing favorably respectively enhanced synthesis of 5-HT and NE. Papaya fruit when administered for 15 days also reduced MDA levels in mice, thereby indicating that there was less generation of free radicals in brain.

CONCLUSION

This is the first study revealing the anti-depressant potential of *Carica papaya* fruit in rodents. In the present

study, fresh *Carica papaya* pulp (CPP) reduced the immobility duration of mice significantly in tail suspension test (TST) and diminished the despair behavior induced by forced swimming in mice. Furthermore, reserpine induced hypothermia was also reversed by CPP in rats. All these findings when taken together reflect the anti-depressant potential of Papaya/Papaya fruit. The probable mechanism of action for the beneficial effect of Papaya in depression appears to be related to its i) MAO inhibitory activity ii) tyrosine, phenylalanine (NE precursors) and tryptophan (5-HT precursor) content and iii) antioxidant property.

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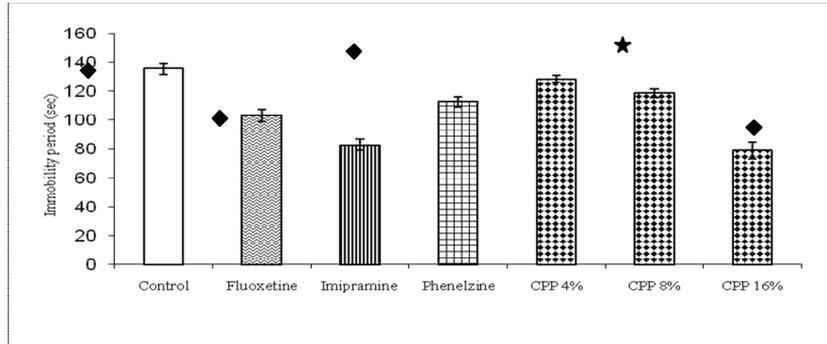


Fig.1: Effect of *Carica papaya* pulp on Immobility duration of mice subjected to Tail Suspension Test
Values are in Mean ± SEM. (n=5)

Fluoxetine (20 mg/kg, p.o.), Phenelzine (20 mg/kg, p.o.) and Imipramine (15 mg/kg, p.o.) were administered for 15 successive days.

◆ denotes $p < 0.01$, ★ denotes $p < 0.05$ as compared to control group. CPP = *Carica papaya* pulp (4%, 8% & 16% w/v, p.o.) was administered for 15 successive days. One way ANOVA followed by Dunnett's t-test.

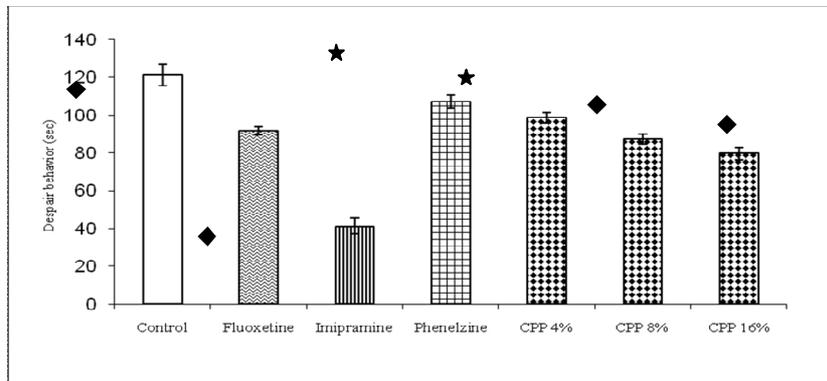


Fig.2: Effect of *Carica papaya* pulp on despair behavior of mice subjected to Forced Swim Test
Values are in Mean ± SEM. (n=5)

Fluoxetine (20 mg/kg, p.o.), phenelzine (20 mg/kg, p.o.) and Imipramine (15 mg/kg, p.o.) were administered for 15 consecutive days.

◆ denotes $p < 0.01$ & ★ denotes $p < 0.05$ as compared to control group. CPP = *Carica papaya* pulp (4%, 8% & 16% w/v, p.o.) was administered for 15 successive days. One way ANOVA followed by Dunnett's t-test.

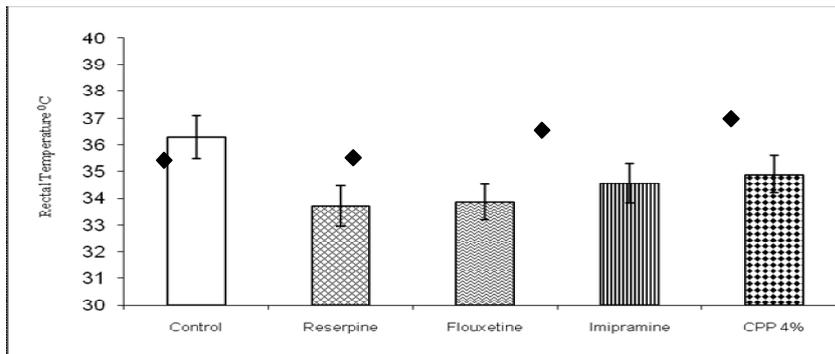


Fig.3: Reversal of Reserpine induced hypothermia by *Carica papaya* pulp
Values are in Mean ± SEM. (n=5)

Fluoxetine (20 mg/kg, p.o.) and Imipramine (15 mg/kg, p.o.) were administered for 6 consecutive days.

CPP = *Carica papaya* pulp 4% w/v, p.o. administered for 6 consecutive days.

◆ denotes $p < 0.01$ when compared to control group.

One way ANOVA followed by Dunnett's t-test.

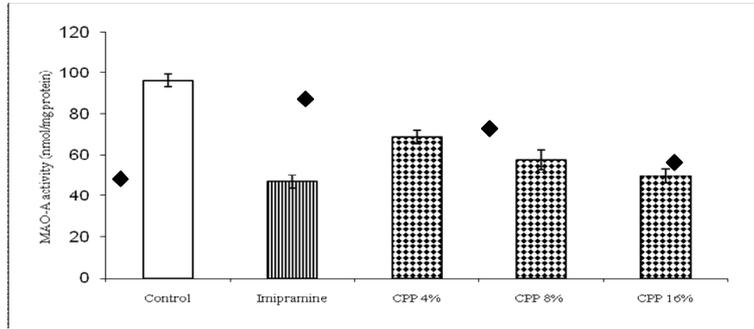


Fig.4: Effect of *Carica papaya* pulp on MAO-A activity in mice
Values are in Mean ± SEM. (n=5)

Imipramine (15 mg/kg, p.o.) was used as a standard anti-depressant drug.

◆ denotes $p < 0.01$, when compared to control group.

CPP = *Carica papaya* pulp (4%, 8% & 16% w/v, p.o.) was administered for 15 successive days.

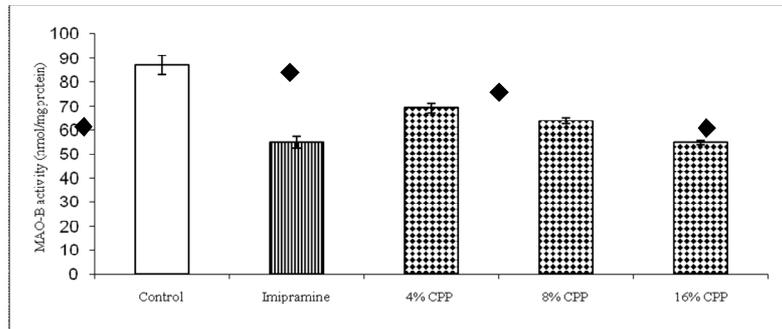


Fig.5: Effect of *Carica papaya* pulp on MAO-B activity in mice
Values are in Mean ± SEM. (n=5)

Imipramine (15 mg/kg, p.o.) was used as a standard anti-depressant drug.

◆ denotes $p < 0.01$, when compared to control group.

CPP = *Carica papaya* pulp (4%, 8% & 16% w/v, p.o.) was administered for 15 successive days.

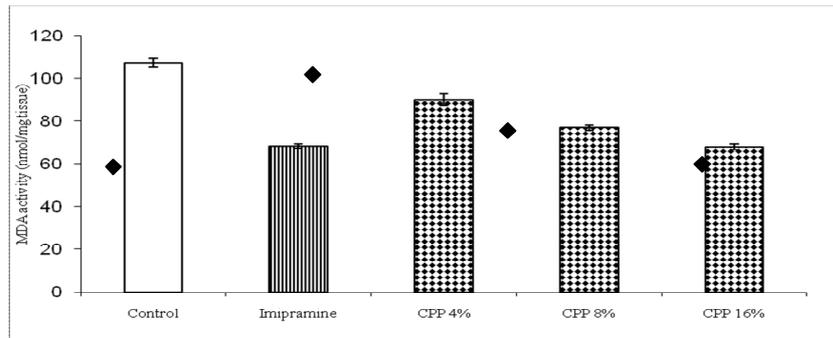


Fig.6: Effect of *Carica papaya* on MDA levels in mice
Values are in Mean ± SEM. (n=5)

Imipramine (15 mg/kg, p.o.) was used as a standard anti-depressant drug.

◆ denotes $p < 0.01$, when compared to control group.

CPP = *Carica papaya* pulp (4%, 8% & 16% w/v, p.o.) was administered for 15 successive days.



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