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An investigation on anti-depressant activity of fresh fruit juice of *Malus domestica* in experimental animal models

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Abstract
Introduction: Mental depression is one of the common chronic illnesses that affect the mood, thought, physical health and behaviour of an individual. India is a rich source of medicinal plants used therapeutically to treat various disorders including depression. This study was undertaken to evaluate the anti-depressant effect of acute and chronic administration of fresh fruit juice of *Malus domestica* in experimental animal models.
Methods: We used the fresh fruit juice extract of *Malus domestica* (1 ml/kg and 2 ml/kg), standard drug used was Imipramine (10 mg/kg) and vehicle was 1% tween 80 (1 ml/kg), orally. Four groups of animals were used and each group had six animals. In the acute study drugs/vehicles were administered 60 min prior to the experiments. In the chronic study drugs/vehicles were administered for 10 days and the last dose was given on the 10th day, 60 minutes prior to experiment. Hole Board Test was used for testing antidepressant activity and parameters estimated includes estimation of biochemical parameter (mono amino oxidase). Data was analysed using one-way ANOVA with drug treatment as the independent factor. Post-hoc comparisons were performed using Dunnett's test.
Result: In acute and chronic Hole Board Test, duration, head dipping and counts was significantly increased in the FFJMD treated group but more beneficial effect found in chronic administration in the model and decrease in biochemical parameter such as mono amino oxidase when compared with depressive control. The antidepressant activity of 2 ml/kg was comparable to that of Imipramine 10 mg/kg.
Conclusion: The present study suggests that fresh fruit juice of *Malus domestica* has more beneficial antidepressant activity in chronic administration of 2 ml/kg. It would be advisable to encourage consumption of *Malus domestica* extract in patients with depression because of its nutritional and functional properties. From the present data, it concludes that fresh fruit juice of *Malus domestica* possesses significant anti-depressant activity.

Keywords: anti-depressant activity, imipramine, *Malus domestica*

Introduction

Depression is a chronic illness that affects people of all ages. Although there are many effective antidepressants available today, the current armamentarium of therapy is often inadequate, with unsatisfactory results in about one-third of all subjects treated [1]. This provides impetus to the search of newer and more effective antidepressants. Limitations to the use of available synthetic drugs open a way for alternative treatments for depression.

Plants have always been a source of drugs and herbal medicines are one of the ancient therapies that have stood the test of time. *Malus domestica* is widely consumed as a fresh fruit and juice. It belongs to the family Rosaceae. In India it is commonly seen in Uttaranchal appear during the late summer months, Jammu and Kashmir's apple season may stretch into late November. *Malus domestica* has valuable compounds in different parts of the plant- the fruit, peel, and leaves. Apple contains a large concentration of flavonoids, as well as a variety of other phytochemicals, and the concentration of these phytochemicals may depend on many factors, such as cultivar of the apple, harvest and storage of the apples, and processing of the apples. Concentration of phytochemicals also varies greatly between the apple peels and the apple flesh [2].

The most well studied antioxidant compounds in the apples are quercetin-3 galactoside, quercetin-3-glucoside, quercetin-3-rhamnoside, catechin, epicatechin, procyanidin, cyanidin-3-galactoside, coumaric acid, chlorogenic acid, gallic acid, and phloridzin. Recently researchers have examined the average concentrations of the major phenolic compounds in six cultivars of apples. They found that the average phenolic concentrations among the six cultivars were: quercetin glycosides, 13.2 mg/100 g fruit; vitamin C, 12.8 mg/100 g fruit; procyanidin B, 9.35 mg/100 g fruit; chlorogenic acid, 9.02 mg/100 g fruit; epicatechin, 8.65 mg/100 g fruit; and phloretin glycosides, 5.59 mg/100 g fruit [3]. The compounds most commonly found in apple peels consist of the procyanidins, catechin, epicatechin, chlorogenic acid, phloridzin, and the quercetin conjugates. In the apple flesh, there is some catechin, procyanidin, epicatechin, and phloridzin, but these compounds are found in much lower concentrations than in the peels. Chlorogenic acid tends to be higher in the flesh than in the peel [4]. More recent work has shown that apple peels contain two to six times (depending on the variety) more phenolic compounds than in the flesh, and two to three times more flavonoids in the peels when compared to the flesh [5].

Several lines of evidence suggest that apples and apple products possess a wide range of biological activities which may contribute to health beneficial effects against cardiovascular disease, asthma, obesity, pulmonary dysfunction and cancer [6]. Apple extracts and components,

especially oligomeric procyanidins, have been shown to influence multiple mechanisms relevant for cancer prevention in *in vitro* studies, this includes anti-mutagenic activity, modulation of carcinogen metabolism, modulation of signal transduction pathways. Apple products have been shown to prevent skin, mammary and colon carcinogenesis in animal models [7]. Apart from those mentioned edible properties of apples reportedly used for natural therapies as follows antacid, antidiarrheal, soft laxative, Diuretic and Depurative, Hearing loss [8]. The fruit is antidepressant, astringent and laxative [9].

The apple is also an excellent dentifrice, the mechanical action of eating a fruit serving to clean both the teeth and the gums. It is used in prevention of Cancer, weight loss, cardiovascular disease, diabetes, asthma, alzheimer's and Parkinson, blood sugar regulation, boost immunity, anaemia, Rheumatism [10]. Different authors have studied various parts of *Malus domestica* based products such as juice, wine and jam. However the medicinal properties of *Malus domestica* have been scantily studied. The synergistic action of the constituents of the whole fruit may be superior to that of individual constituents. The CNS activity of *Malus domestica* is a less touched field and there is no report on antidepressant activity of *Malus domestica* as a whole fruit (peel and seed). Hence the present study was planned to explore the antidepressant activity of fresh fruit juice extract of *Malus domestica* on acute and chronic administration in mice.

Materials and Methods

Adult Swiss strain albino mice weighing 25-30 grams, bred in our institutional animal house were used and were housed in clean polypropylene cages in groups of three. A 12:12 hour dark/light cycle at an ambient temperature of 24 ± 2oC were followed. Food and water were available *ad libitum*. Animals were acclimatized for seven days before exposure to the behavioral experiments. Experiments were performed during the light phase of the cycle (10:00-17:00). The study was approved by the Institutional Animal Ethics Committee and was carried out in accordance with the recommendations of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Preparation of the fruit juice

The method of juicing includes, weighing the fresh fruit, (80gm) cut into appropriate sizes and mixed using a blender for two minutes. The pulp obtained was squeezed using muslin cloth and the juice (50ml-60ml/100g) is refrigerated and used for the anti-depressant studies. Each drug solution was freshly prepared just before administration. Drugs and vehicles were administered orally and the doses of each drug were selected on the basis of earlier findings [11].

Animals were grouped into four and each group had six animals. Group 1 received 1% tween 80 in a dose of 1 ml/kg, group 2: imipramine at a dose of 10 mg/kg, group 3 & 4 received FFJMD extract of *Malus domestica* at a dose of 1 ml/kg and 2 ml/kg per day respectively [12]. In the acute study drugs/vehicles were administered 60 min prior to the experiments whereas in the chronic study drugs/vehicles were administered daily for 10 days and the last dose was given on the 10th day, 60 min prior to the experiment. The animal model used for testing antidepressant activity was hole board test [13]. The data on entries into a new area were used to calculate the total amount of locomotion (number of entries into all areas summed together) and the percentage of entries that were in made into the central area. The location of the animal during each of the 10-s time intervals was used to estimate the percentage of time spent in the central area.

In this model the duration, counts and head dipping was measured to evaluate the antidepressant potential of compounds and parameters estimated includes estimation of biochemical parameter (mono amino oxidase) [14].

The data has been analyzed using one-way ANOVA with drug treatment as the independent factor. Post-hoc comparisons were performed by applying Dunnett's test. $p<0.05$ was considered as statistically significant.

Fig 1: Malus domestica

Fig 2: Fresh fruit juice of Malus domestica

Result

In acute and chronic Hole Board Test, duration, head dipping and counts was significantly increased in the FFJMD treated group but more beneficial effect found in chronic administration in the model (Table 1 & 2). On observation of the biochemical parameter, and decreased mono amino oxidase levels were observed (Table 3).

The animal model of depression used in our experiment showed that the antidepressant effect of chronic administration of FFJMD at the dose of 2 mL/kg was comparable to that of imipramine. Thus the present study showed that fruit of *Malus domestica* possesses Anti-depressant activity.

Table 1: Hole board test (Acute)

Groups	Total Locomotion	% Entries Into The Centre	% Time IN The Centre	Frequency OF Head Dipping	Frequency of Rearing
Depressive Control	47.83 ± 0.60	3.83 ± 0.60	2.83 ± 0.60	10.67 ± 0.71	18.83 ± 0.60
Standard Imipramine 10 mg/kg	60.33 ± 0.66***	15.17 ± 0.30***	9.16 ± 0.30***	6.50 ± 0.76***	24.17 ± 0.30***
FFJMD 1 ml/kg	51.00 ± 0.36**	6.33 ± 0.42**	5.50 ± 0.42**	7.50 ± 0.76*	21.50 ± 0.42**
FFJMD 2 ml/kg	61.00 ± 0.44***	14.83 ± 0.47***	8.83 ± 0.47***	5.66 ± 0.80***	23.83 ± 0.47***

All the results are expressed in term of mean±SEM n=6 animals in each group; Statistical significance was determined by ANOVA followed by Tukey's test. *P<0.05, **P< 0.01, ***P< 0.001, statistically significant compared to depressive control group.

Table 2: Hole board test (Chronic)

Groups	Total Locomotion	% Entries Into The Centre	% Time in The Centre	Frequency OF Head Dipping	frequency of Rearing
Depressive Control	56.50 ± 0.76	10.50 ± 0.76	6.50 ± 0.76	11.00 ± 0.63	24.17 ± 0.87
Standard Imipramine 10 mg/kg	60.83 ± 0.60***	18.83 ± 0.60***	13.83 ± 0.60***	18.83 ± 0.60***	29.83 ± 0.60***
FFJMD 1 ml/kg	59.33 ± 0.42*	13.33 ± 0.55**	9.50 ± 0.42**	13.50 ± 0.42*	27.33 ± 0.42**
FFJMD 2 ml/kg	62.50 ± 0.76***	18.00 ± 0.44***	13.00 ± 0.44***	17.67 ± 0.49***	29.00 ± 0.44***

All the results are expressed in term of mean±SEM n=6 animals in each group; Statistical significance was determined by ANOVA followed by Tukey's test. *P<0.05, **P< 0.01, ***P< 0.001, statistically significant compared to depressive control group.

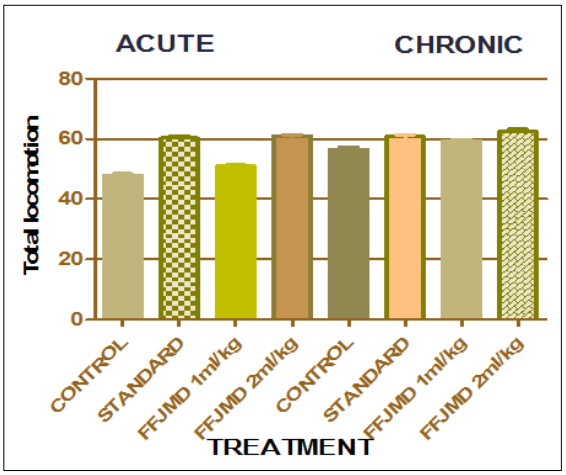

Fig 3: Effect of imipramine and FFJMD on total locomotion period of mice in acute and chronic hole board tests

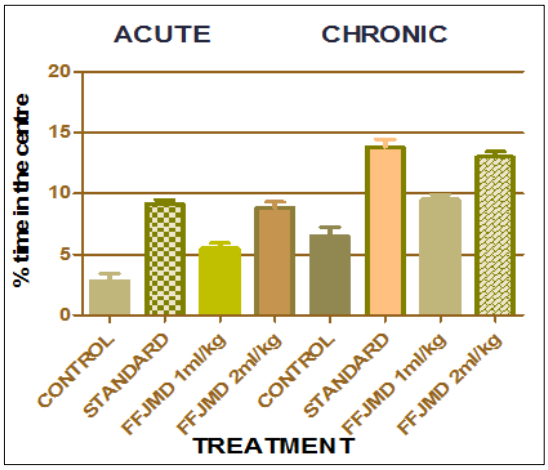

Fig 5: Effect of imipramine and FFJMD on % time in the centre period of mice in acute and chronic whole board tests

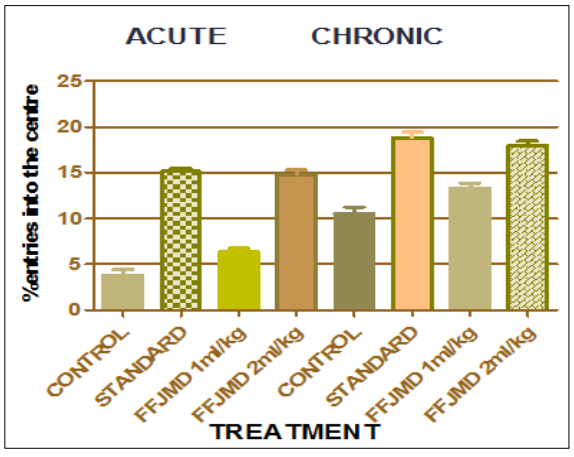

Fig 4: Effect of imipramine and FFJMD on % entries into the centre period of mice in acute and chronic hole board tests

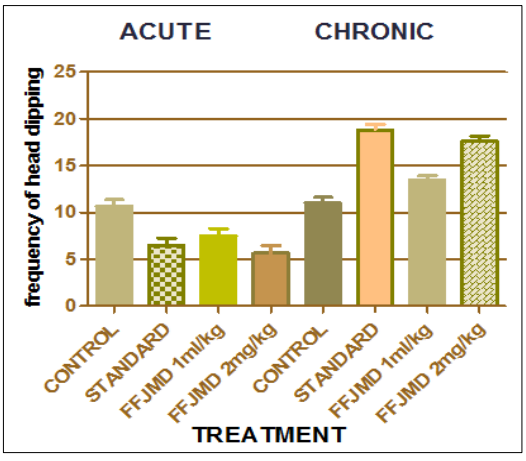

Fig 6: Effect of imipramine and FFJMD on frequency of head dipping period of mice in acute and chronic hole board tests

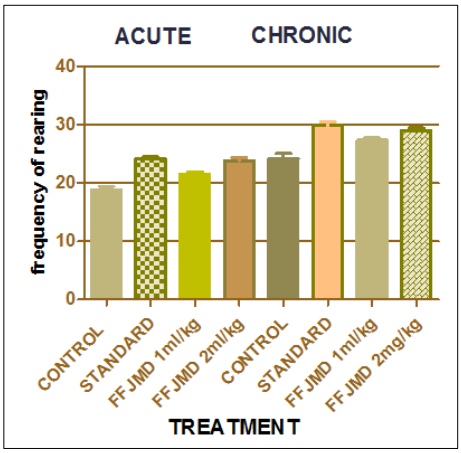

Fig 7: Effect of imipramine and FFJMD on frequency of rearing of mice in acute and chronic hole board tes

Table 3: Monoamino oxidase level in the brain of mice

Dose	MAO (µg/ml)
Depressive Control	28.83±0.60
StandardImipramine 10mg/kg	19.17±0.30***
FFJMD 1ml/kg	25.50±1.17*
FFJMD 2ml/kg	15.83±0.47***

All the results are expressed in term of mean±SEM n=6 animals in each group; Statistical significance was determined by ANOVA followed by Tukey's test. *P<0.05, **P< 0.01, ***P< 0.001, statistically significant compared to depressive control group.

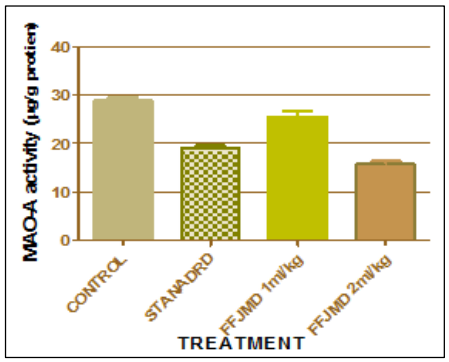

Fig 8: Effect of *Malus domestica* fruit juice in estimation of mono amino oxidase level in the brain of mice

Evaluation of antidepressant activity

A: Oral route administration of drugs in mice

B: Hole Board test in mice

C: The brain extracted for the estimation of biochemical parameters

Fig 9

Discussion

In the present study, the antidepressant activity of fresh fruit juice of *Malus domestica* were studied in classical model for screening animal model for depression, the hole board test and parameters estimated includes estimation of biochemical parameter (mono amino oxidase).

In depression treatment is required for a prolonged period to get an optimal response; hence it is important to perform not only acute but chronic administration of the drugs in animal models. The results of the present study indicate that acute and chronic administration of fresh fruit juice extract of *Malus domestica* at a dose of 1ml/kg and 2 ml/kg has significant antidepressant activity compared to normal control but more beneficial effect was seen in chronic administration on FFJMD extracts. Decrease in biochemical parameter such as mono amino oxidase when compared with depressive control. This antidepressant effect is comparable to that of imipramine. The present study suggests that fresh fruit juice of *Malus domestica* has antidepressant activity.

Phytochemical review showed the presence of flavonoids which have been reported to have multiple biological effects such as Central Nervous System disorders. *Malus domestica* fruit juice also revealed the flavonoids which may attribute the anti-depressant activity.

MAO inhibiting activity by the *Malus domestica* fruit juice and protection of dopamine hydrolysis was comparable to imipramine. Thus antidepressant like activity of the *Malus domestica* fruit juice might also be due to inhibition of MAO, resulting in decreases in the brain levels of monoamines.

Recently, oxidative stress was linked with the pathophysiology of major depression, with significant correlations being found between the severity of depression and erythrocyte super oxide dismutase/lipoperoxidation levels. Meanwhile, treatment with anti- depressant reduces the oxidative stress related to depressive disorder. Additionally, some species has reported to the anti-depressant like properties, also possess antioxidant activity.

Data from earlier study suggest that *Malus domestica* fruit juice has anti-oxidant activity. Therefore, it is possible that the antioxidant activity of the fresh fruit juice from *Malus domestica* fruit juice may contribute to its antidepressant like effects.

However, different kinds of the research study must needed to elucidate the mechanism of action of *Malus domestica* fruit juice in the CNS, the pattern of effects were observed in these experiments suggest the involvement of the norepinephrine neurotransmitters system on its antidepressant like effects. Depression is a neurological disorder that is widely prevalent to modern fast paced life. Stressful lifestyle facilitates the evolution of depressive disorder as the stress can influence the function of central nervous system by altering a number of neurotransmitters, endocrine and neuroendocrine systems [15]. The most lethal complication of depression is the suicidal behavior [16]. Along with the classical theory of decrease in the neurotransmitter levels in the brain leading to the pathogenesis of clinical depression, recent studies have also shown the involvement of oxidative stress in the phenomenon [17]. Depression is usually treated with a combination therapy and medications as well as lifestyle changes. Certain foods and ingredients have been linked to lessening depression including antioxidants. Antioxidants neutralize and reduced mental functioning. The search for a natural product with fast onset of action, wide safety margin and less wide side effects has come to attention. The effective components of herbs that have antidepressant-like effect include flavonoid, oligosaccharide, polysaccharide, alkaloid, organic acid [18].

The present study was designed to elucidate the effect of juice of *Malus domestica* treating depression using Hole board Test in mice. These tests are quite sensitive and relatively specific to all major classes of antidepressant drugs [19]. HBT head dip response and latency until first entry was noted. This induces a state of behavioral despair in animals, which is claimed to reproduce a condition similar to human depression [20]. Hence the present study showed *Malus domestica* might be useful in depression, as it increase decrease in mono amino oxidase in the brain.

Conclusion

The present study was undertaken to assess the antidepressant activity of *Malus domestica* fruit juice. It is thus concluded that, acute and chronic FFJMD (1ml/kg and 2ml/kg) showed antidepressant activity similar to that of imipramine (10 mg/kg) in the hole board in mice but more beneficial effect was found in chronic administration. The mechanism of action of antidepressant activity appears to be primarily due to non-selective inhibition of brain monoamine oxidase enzyme activity. On observation of the biochemical parameter, and decreased mono amino oxidase levels were observed. Thus the present study showed that fruit of *Malus domestica* possesses Anti-depressant activity.

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