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Research Article

A NATURAL WAY TO KEEP DEPRESSION MILES AWAY

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ABSTRACT
'Depression matters because depressive victims matter'. *Tamarindus indica* (Caesalpiniaceae), popularly known as Imli**,** is a perennial evergreen tree with a spreading crown, feathery evergreen foliage and fragrant flowers. Traditionally, Tamarind fruit is used as a digestive, laxative, expectorant, antipyretic and antimalarial agent. In the light of above, the present study was undertaken to test the anti-depressant potential of *Tamarindus indica*. *Tamarindus indica* pulp was administered along with diet at various concentrations ranging from 2%-8% w/w orally to Swiss mice, once daily for 14 successive days. The anti-depressant activity was measured using Forced Swim Test and Tail Suspension Test. *Tamarindus indica* pulp significantly ($p<0.01$) reduced the despair behavior of mice in Forced swim test and immobility duration in Tail suspension test. The anti-depressant efficacy of *Tamarindus indica* pulp was found to be comparable to that of fluoxetine (5-HT reuptake inhibitor) and imipramine (Tricyclic anti-depressant). The combination of *Tamarindus indica* pulp either with sulpiride (50 mg/kg, i.p.) or prazosin (62.5 µg/kg i.p.) or p-CPA (100 mg/kg, i.p.) reversed the enhanced immobility duration in TST model. The reduction in immobility duration produced by Tamarind fruit in the present study reflects its anti-depressant potential. Furthermore, *Tamarindus indica* pulp inhibited the monoamine oxidase (MAO) enzyme, which metabolizes 5-HT and norepinephrine in brain, thereby elevating 5-HT and norepinephrine levels. These findings suggest that *Tamarindus indica pulp* possessed useful anti-depressant activity, which needs to be confirmed clinically.
KEY WORDS: *Tamarindus indica,* Depression, Despair behavior, Immobility, Hypothermia

INTRODUCTION

'Depression matters, because depressive victims matter'. Depression is a serious mental disorder that often manifests with symptoms such as depressed mood, loss of interest in life, feelings of guilt, low self-worth, disturbed sleep, poor appetite, low energy, and poor concentration[1]. Depression affects around, 121 million people worldwide. Depression can lead to suicide, a tragic fatality associated with the loss of about 8, 50,000 lives every year. The World Health Organization (WHO) report has predicted that major depression would become the second cause of illness-induced disability by the year 2020[2]. All clinically effective anti-depressants increase acutely the availability of Norepinephrine and 5-HT at the synapse, which induce long-term adaptive changes and promote neurogenesis[3]. On the other hand, it is found that drugs such as reserpine that cause depletion of brain monoamines induce depression. It is expected, therefore, that serotonergic and noradrenergic systems represent the major targets of current therapeutic treatments and drug development. Tamarind fruit is consumed commonly in India in many food as well as snack preparations. The pulp of Tamarind is an important component in chutneys, pickles, jams, curries, sauces, ice cream, sharbat and in "tamarind fish", a special Indian seafood pickle[4]. It is extensively used in Tamil Nadu, Karnataka and Andhra Pradesh cuisines, where it is used to prepare Rasam, Sambhar, Vatha Kuzhambu and Puliyogare. Traditionally, Tamarind fruit has been used in the management of kidney disorders, fever, malaria and diabetes in human beings and animals[5]. The fruits serve a good source of important minerals such as potassium, phosphorus, calcium and vitamins such as thiamine and niacin[6]. Anti-depressant drugs evoke unpredictable clinical response and show high incidence of adverse effects[7]. Intake of nutraceuticals is an effective substitute to treat depression. Thus, developing an effective and safe medicine originating from traditional remedies may help in minimizing the adverse effects and overall cost of drug discovery process. In the light of above, we were interested to investigate the usefulness of Tamarind fruit in depression.

Indian Imli

MATERIALS AND METHODS

Objectives

The present study was undertaken to explore the anti-depressant potential of *Tamarindus indica* pulp (TIP) using forced swim test, tail suspension test and reserpine induced hypothermia models. An attempt has also been made to determine the underlying mechanism of action of *Tamarindus indica* pulp by co-administration of agents modulating noradrenaline and serotonin levels. In forced swim test, mice were forced to swim individually in a glass chamber containing water, in a restricted, inescapable area, which induced a state of despair behavior. Despair behavior is taken as a typical behavior of animals, wherein the animals surrender to the experimental conditions with minimal limb movements so as to keep the nose just above water, after an initial phase of vigorous activity[8]. Whereas in TST, the immobility of animals is taken as an index of depression[9].

Plant material

The *Tamarindus indica* fruits were 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 **(NISCAIR/RHMD/Consult/-2011-12/1724/264)**

Animals

A total of 30 Wistar rats weighing around 80-100 g divided in 05 groups and 168 Swiss mice (3 months old) weighing around 20-25 g divided in 28 groups were employed in the present study. Each group comprised of a minimum of 6 animals. Mice and rats were procured from disease-free small animal house of Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar (Haryana, India). The experimental protocol was approved by Institutional Animals Ethics Committee (IAEC) and animal care was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India (Registration no. 0436).

Drug protocol

Mice in group I were employed for pilot study carried out to determine the effective concentrations of *Tamarindus indica* pulp (TIP). Mice belonging to groups II to XII were subjected to Tail suspension test (TST). Mice belonging to groups XIII to XVIII were subjected to Forced Swim Test (FST). Mice belonging to groups XIX to XXIV were used for biochemical estimations. Mice belonging to groups XXV to XXVIII were exposed to Photoactometer for assessing the locomotor activity. Rats belonging to groups XXIX to XXXIII were employed in Reserpine induced hypothermia model. *Tamarindus indica* pulp (TIP) was administered in different concentrations (1% to 20% w/w, p.o.) in pilot study to determine optimally effective concentration of TIP. Distilled water (vehicle, p.o.), Fluoxetine (20mg/kg, p.o.), Imipramine (15mg/kg, p.o.) and TIP, were administered orally for 14 successive days. Sulpiride/ Prazosin was administered on 14th day and p-CPA was given once a day from 11th to 14th day in separate groups of mice, 45 min after administration of TIP (8%w/w). At 60 min after administration of the drugs/ distilled water on 14th day, the mice were subjected to TST, FST and biochemical studies. Effect on locomotor activity of mice was studied using a photoactometer. Similarly, distilled water (vehicle), Fluoxetine (20 mg/kg), Imipramine (15 mg/kg) and TIP in different concentrations (2%, 4% and 8%, w/w), were administered orally for 8 successive days to rats for hypothermia studies. The rectal temperature was recorded at 18th, 20th, 22nd and 24th hour. Rectal temperature was measured at zero hour and 18h after administration of reserpine, in reserpine induced hypothermia model.

Statistical analysis

All the results were expressed as mean ± Standard Error (SEM). Data were analyzed using one-way ANOVA followed by Dunnett's test.

RESULTS

Tamarindus indica pulp (2, 4 and 8% w/w, p.o), when administered along with diet reduced both, despair behavior in Forced swim test (FST) as well as immobility duration in Tail suspension test (TST) significantly ($p<0.01$). 8% w/w concentration of TIP showed the most potent effect (**Fig.1 & 2**). The anti-depressant efficacy of TIP was found to be comparable to that of fluoxetine (5-HT reuptake inhibitor) and imipramine (Tricyclic anti-depressant). Hypothermia was induced with the help of reserpine (2 mg/kg, s.c.) in rats. TIP in different concentrations (2, 4 and 8%, w/w, p.o.), when administered for 8 successive days to rats, reversed the hypothermia induced by reserpine. The rectal temperature was determined by insertion of rectal thermometer to a constant depth of 2 cm after 18th, 20th, 22nd and 24th h of reserpine injection (**Fig. 3**). This effect of TIP was found to be similar to that of imipramine (a standard anti-depressant). Sulpiride (50 mg/kg, i.p.), Prazosin (62.5 µg/kg i.p.) and p-CPA (100 mg/kg, i.p.) *per se* increased significantly ($p<0.05$) the immobility duration of mice as compared to the control group. Sulpiride/ Prazosin was administered on 14th day and p-CPA was given once a day from 11th to 14th day in separate groups of mice, 45 min after administration of TIP (8%w/w). The combination of TIP with sulpiride/ prazosin/ p-CPA reversed the enhanced immobility duration in mice (**Fig.4**). The reduction in immobility duration observed in the present study reflects anti-depressant potential of TIP. TIP (2, 4 & 8 % w/w), when administered to mice for 14 successive days, significantly ($p<0.05$) reduced the brain MAO-A (nmol/mg protein) and MAO-B (nmol/mg protein) levels as compared to the control group (**Fig.5**). TIP did not show any significant effect on the locomotor function of the mice as compared to the control group.

DISCUSSION

In forced swim test, mice are forced to swim individually in a glass chamber containing water, in a restricted, inescapable area, which induces a state of despair behavior. Despair behavior is taken as a typical behavior of animals, wherein the animals surrender to the experimental conditions with minimal limb movements so as to keep the nose just above water, after an initial phase of vigorous activity. Whereas in TST, the immobility of animals is taken as the index of depression. Classical anti-depressants, such as imipramine and fluoxetine reduce this immobility duration in TST and diminish the period of despair behavior in FST. If the anti-depressant treatments are given prior to the test, the mice actively persist engaging in escape-directed behavior for longer periods of time[10]. Since, Tamarindus indica did not evoke any change in the locomotor activity of mice, the possible psychostimulant effect of Tamarindus indica pulp is ruled out. In the present study, *Tamarindus indica* pulp (TIP), when administered along with diet, reduced the despair behavior in Forced swim test (FST) as well as duration of immobility in Tail suspension test (TST) significantly. The reduction in despair behavior and immobility duration observed in the present study reflects anti-depressant potential of TIP. The anti-depressant efficacy of TIP was found to be comparable to that of fluoxetine (5-HT reuptake inhibitor) and imipramine (Tricyclic anti-depressant). Reserpine induced hypothermia model is commonly employed to evaluate new anti-depressant moieties[11]. In the present study hypothermia was induced with the help of reserpine in rats. TIP dose dependently reversed the hypothermia induced by reserpine. This effect of TIP was found to be similar to that of imipramine (a standard anti-depressant). Diminution of biogenic amines (noradrenaline and 5-hydroxytryptamine) in the brain causes depression, which is reflected by a state of hypothermia in rodents. Whereas, the increase in body temperature or hyperthermia, indicates a depression-free state of mind[12]. Depression has been associated with diminished serotonergic and noradrenergic neurotransmission. Furthermore, the monoaminergic system is considered to be one of the important targets in the pathophysiology and treatment of depression. In this study, we investigated the possible involvement of monoaminergic system in the anti-depressant effect of Tamarind. In this direction, we investigated the effects of several pharmacological modulators of the

monoaminergic system in combination with Tamarind in mice. In our study, prazosin (α_1-adrenoceptor antagonist) and p-CPA (serotonin synthesis inhibitor) antagonized the effect of Tamarind. These results indicate that Tamarind may be exerting its effect by stimulating α_1-adrenoceptors and 5-HT receptors. Further, prazosin (an α_1- adrenoceptor antagonist) and p-CPA produced increased immobility duration in mice probably through decreased noradrenergic activity due to blockade of α1- adrenergic receptors, and decreased serotonin synthesis, respectively. However, this depressant action of prazosin and p-CPA was attenuated by pre-treatment of animals with TIP. TIP administered to mice for 14 successive days produced a significant inhibition of monoamine-oxidase (MAO) activity. Since noradrenaline and serotonin are metabolized by MAO-A and MAO-B enzymes, inhibition of MAO enzyme (MAO-A as well as MAO-B) would lead to enhanced levels of both noradrenaline and serotonin. This observation further substantiates the suggestion that TIP induced anti-depressant effect is mediated via enhanced levels of nor-adrenaline and 5-HT. TIP is reported to possess powerful anti-oxidant activity as well[13]. Thus, TIP appears to have produced its anti-depressant effect through i) inhibition of MAO-A and MAO-B enzymes, ii) stimulation of α_1-adrenoceptors, and iii) Anti-oxidant activity. However, the involvement of dopamine D_2- receptors, in the anti-depressant effect of TIP cannot be ruled out, since, sulpiride (a selective dopamine D_2-receptor antagonist), reversed the diminished immobility time observed with TIP alone.

CONCLUSION

Tamarind fruit produced an anti-depressant effect in mice, when tested using tail suspension test and forced swim test. This anti-depressant effect appears to be mediated through i) inhibition of MAO-A and MAO-B enzymes, ii) stimulation of α_1- adrenoceptors, and iii) Anti-oxidant activity. Thus, it is worthwhile to investigate clinically the usefulness of Tamarind in managing depression.

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REFERENCES

1. McKenna MT, Michaud CM, Murray CJL, Marks JS. Assessing the burden of disease in the United States using disability-adjusted life years. Am J Prev Med 2005; 28: 415–423.
2. Mao Q, Xian Y, Ip S, Che C. Involvement of serotonergic system in the anti-depressant-like effect of piperine. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35: 1144-1147.
3. Elhwuegi AS. Central monoamines and their role in major depression. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 435–451.
4. Singh D, Wangchu L, Moond SK. Processed products of Tamarind. Nat Prod Rad 2007; 6 (4): 315-321.
5. Havinga RM, Hartl A, Putscher J, Prehsler S, Buchmann C, Vogl CR. Tamarindus indica L. (Fabaceae): patterns of use in traditional African medicine. J Ethnopharmacol 2010; 127 (3): 573-588.
6. Khairunnuur FA, Zulkhairi A, Azrina A, Mohamad Aris MM, Khairullizam S, Zamree MS, *et al*. Nutritional composition, in vitro antioxidant activity and Artemia salina L. lethality of pulp and seed of Tamarindus indica L. extracts. Malays J Nutr 2009; 15: 65–75
7. Kulkarni SK, Dhir A. Current investigational drugs for major depression. Expert Opin Investig Drugs 2009; 18:767–788.
8. Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: a primary screening test for anti-depressants. Arch Int Pharmacodyn Ther 1977; 229: 327–336.
9. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening anti-depressants in mice. Psychopharmacol (Berl) 1985; 85: 367-370.
10. Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing anti-depressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev 2005; 29: 571–625.
11. Makoto S, Keisuke K, Takanori M, Satoshi M, Meiko F. Hypothermia-related testicular toxicity of reserpine in mice. Exp Toxicol Pathol 2007; 59: 187-195.
12. Bill DJ, Hughes IE, Stephens RJ. The thermogenic actions of α_2-adrenoceptor agonists in reserpinized mice are mediated via a central postsynaptic α_2-adrenoceptor mechanism. Br. J. Pharmacol 1989; 96: 133-143.
13. Joyeux M, Mortier F, Flurentin J. Screening of antiradical, antilipoperoxidant and hepatotoprotective effects of nine plant extracts used in Caribbean folk medicine. Phytother Res 1995; 9: 228–230.

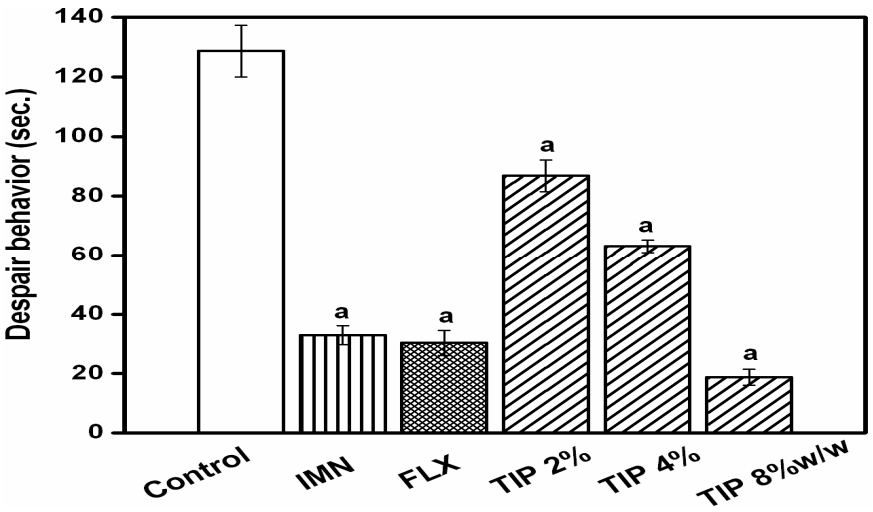

Figure 1: Effect of *Tamarindus indica* pulp on Despair behavior of mice subjected to Forced Swim Test

Values are in Mean ± SEM. (n=6)

TIP= *Tamarindus indica* pulp, FLX= Fluoxetine (20mg/kg, p.o.), IMN= Imipramine (15mg/kg, p.o.) were administered for 14 successive days.

'a' denotes $p<0.01$ when compared to control.

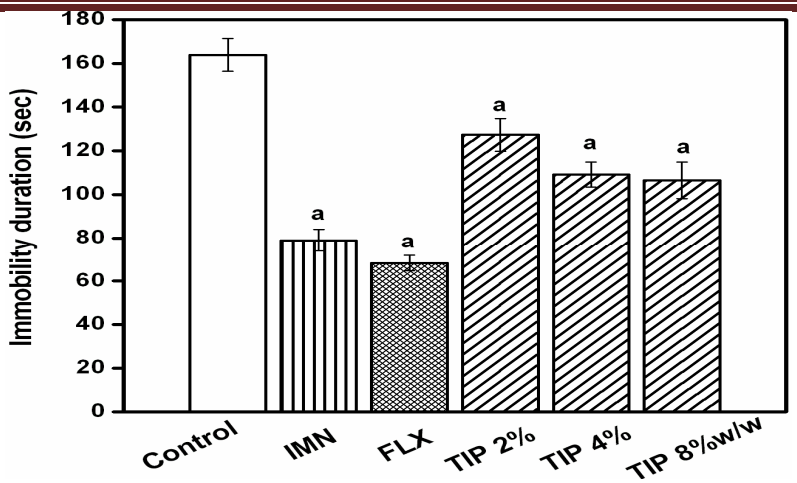

Figure 2: Effect of *Tamarindus indica* pulp on Immobility Duration of mice subjected to Tail Suspension Test
Values are in Mean ± SEM. (n=6)
TIP= *Tamarindus indica* pulp, FLX= Fluoxetine (20mg/kg, p.o.), IMN= Imipramine (15mg/kg, p.o.) were administered for 14 successive days.
'a' denotes $p<0.01$ when compared to control

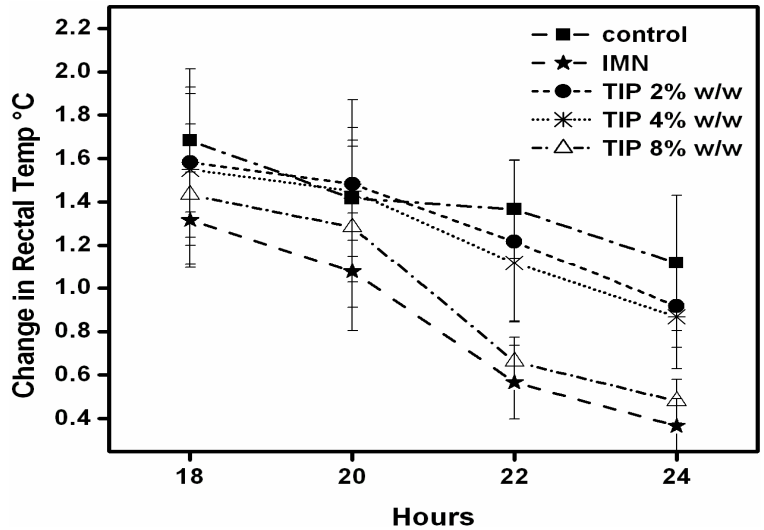

Figure 3: Comparative effect of *Tamarindus indica* pulp and imipramine on Rectal temperature of rats subjected to Reserpine
Values are in Mean ± SEM. (n=6)
TIP= *Tamarindus indica* pulp, IMN= Imipramine (15mg/kg, p.o. for 8 days)

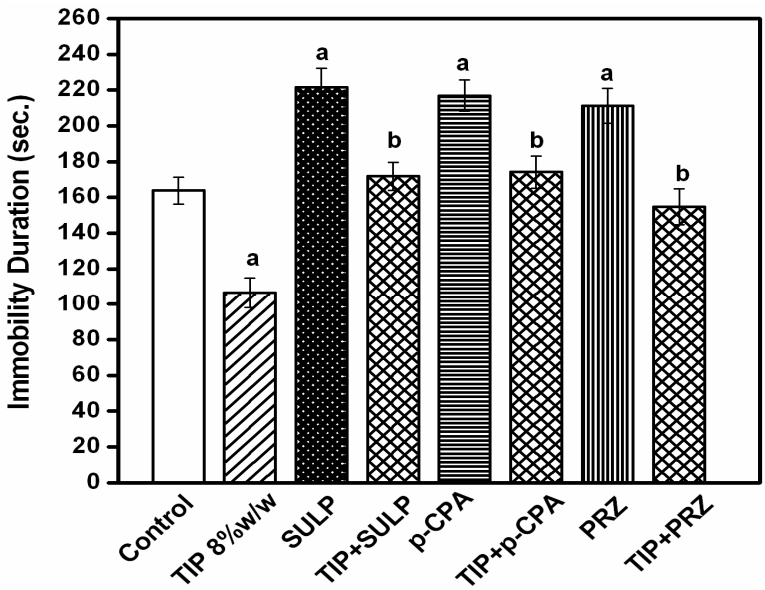

Figure 4: Effect of combination of *Tamarindus indica* pulp (TIP) with prazosin/p- CPA/sulpiride on immobility duration in Tail Suspension Test.
'a' denotes $p<0.05$, when compared to control group,
'b' denotes $p < 0.05$, when compared to SULP/p-CPA/PRZ
PRZ: Prazosin, p-CPA: para chlorophenyl Alanine, SULP= Sulpiride

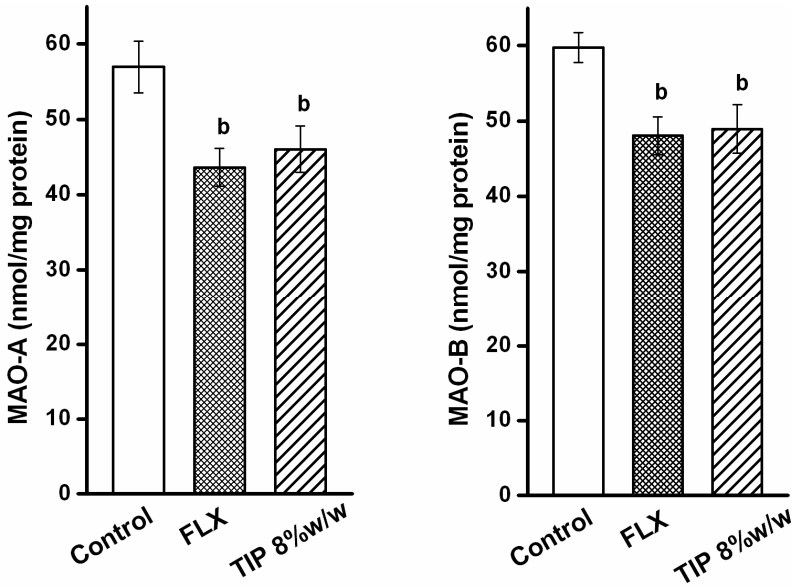

Figure 5: Effect of *Tamarindus indica* pulp (TIP) administered orally for 14 successive days on MAO-A & MAO-B activity in mouse
TIP: *Tamarindus indica* pulp, FLX: Fluoxetine (20 mg/kg, p.o.)
'b' denotes $p<0.05$, as compared to control group.

Tamarind fruit

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