Research Article

Evaluation of *Terminalia bellerica* for its Antipsychotic Potential

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Accepted on: 18-11-2014; **Finalized on:** 31-12-2014.

ABSTRACT

The present study was undertaken to evaluate the antipsychotic potential of *Terminalia bellerica* in experimental animal models. Male Wistar rats (180- 220 g) and Albino mice (25-30 g) were used for the study. The antipsychotic effect of the *Terminalia bellerica* was evaluated on haloperidol induced catalepsy, cooks pole climbing apparatus, locomotor activity on photoactometer and ketamine induced stereotypic behavior. Different groups of rats were fed orally with a specially prepared diet containing various concentrations (4%w/w, 6%w/w and 8% w/w) of *Terminalia bellerica* fruit powder (*TBFP*) for 15 consecutive days. Further, the biochemical estimations were done by estimating brain dopamine levels. The *TBFP* produced significant dose dependent potentiation of haloperidol (1 mg/kg, i.p.) induced catalepsy in rats, significantly increased the time taken by the rats to climb the pole in dose dependent manner, significantly decreased the locomotor activity of rats. The *TBFP* significantly decreased ketamine (50 mg/kg, i.p.) induced stereotyped behavior in a dose dependent manner. *Terminalia bellerica* fruit powder (*TBFP)* significantly decreased the brain dopamine levels. The results suggest that *TBFP* posse's antipsychotic activity. Further neurochemical investigation can explore the mechanism of action of the plant drug with respect to anti-dopaminergic functions and help to establish the plant as an antipsychotic agent.

Keywords: Anti-dopaminergic, catalepsy, stereotypic, ketamine

INTRODUCTION

Traditionally, usage of plants in curing illness has deep roots in man's history and is as ancient as human civilization.[1] In recent years, there has been growing interest in the therapeutic use of plant because of their safety, economical & effective use. *Terminalia bellerica* also referred to as, Beleric Myrobalan belonging to family Combretaceae is a large deciduous tree with a thick brownish gray bark with shallow longitudinal fissures, attaining a height of between 20 to 30 meters. It is found growing wild throughout the Indian subcontinent, Srilanka, and South East Asia, upto 1200 meters in elevation, in a wide variety of ecologies.[2]

Terminalia bellerica is used in traditional medicine due to the wide spectrum of pharmacological activities associated with the biologically active chemicals present in this plant.

The phytoconstituents isolated from various parts of the plant include alkaloid, coumarin, flavones, steroids (β-Sitosterol), lignans (termilignan, thannilignan), tannins (gallic acid, ellagic acid), glycosides (fructose, sucrose, galactose), terpenoid (belleric acid and chebulagic acid), saponin (bellericoside and bellericanin).

Terminalia bellerica is one such plant showing multifarious medicinal properties viz. analgesic activity, antibiofilm activity, anticancer activity, antidepressant activity, antidiabetic activity, antidiarrhoeal activity, anti-ulcer activity, immunomodulatory activity, anti-spasmodic and bronchodialatory activity, antifertility activity, antihypertensive activity, antifungal, antimicrobial activity, anti-inflammatory activity, antioxidant activity.[3] Although several medicinal uses have been reported for *Terminalia bellerica*, no investigative report pertaining to its antipsychotic activity exists. Hence, an attempt has been made to evaluate the antipsychotic activity of the *Terminalia bellerica*.

MATERIALS AND METHODS

The fruits of *Terminalia bellerica* were collected during the months of August, 2014 from local market of Hisar, Haryana and got authenticated from Raw Materials Herbarium & Museum, Delhi (RHMD)-(Ref. NSICAIR/RHDM/2014/2519/98-2). The *Terminalia bellerica* fruits were ground into a fine powder using an electric grinder. Different concentrations of *TBFP* (4, 6, 8% w/w) were fed to separate groups of rats and mice through a specially prepared diet. This special diet comprised of a mixture of *Terminalia bellerica* fruit powder (*TBFP*), wheat flour kneaded with water, a small amount of refined vegetable oil and a pinch of salt (sodium chloride), to impart taste. Each rat consumed around 12 gm/day and mice consumed around 3 gm/day of this specially prepared diet. Control animals received the normal diet consisting of wheat flour, kneaded with water, small amount of refined vegetable oil and a pinch of salt but without *TBFP*.

The concentrations of *TBFP* in diet were determined on the basis of pilot study, acceptability by the animals and literature reports.[4,5]

Animals

Male Wistar rats (180-220 g) and Albino mice (25-30g) were used for the study. The animals were housed in colony cages and maintained under the standard

environmental conditions - temperature 25 ± 2 °C, 12 h light: 12 h dark cycle and 50 ± 5 % relative humidity, with food and water ad libitum. All experiments were carried out during the light period (08.00 -16.00 h). The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and the care of laboratory animals was taken as per the guidelines of CPCSEA, Ministry of Forests and Environment, Government of India (Registration number 0436).

Drugs

All the drug solutions viz. Olanzapine (received as gift samples from Ranbaxy Laboratories), India. Haloperidol (RPG Science Pharmaceutical Pvt. Ltd), Ketamine (Neon Pharmaceutical Pvt. Ltd) in the form of injections, purchased locally from retail chemists, Hisar. Olanzapine was suspended in a vehicle consisting of 5% Tween-80 in 0.9% saline. Haloperidol and Ketamine were diluted in 0.9% saline. Haloperidol (1mg/kg, i.p.), Olanzapine (5mg/kg, i.p.) and Ketamine (50mg/kg, i.p.) were administered daily for a duration of 15 days to the mice and 8 days to the rats.

Haloperidol-induced catalepsy

Haloperidol (1mg/kg, i.p.) was injected on the 16th day to control rats (n = 6) treated with normal diet and to the rat fed with different concentrations of *TBFP* (4, 6, 8 % w/w) through a specially prepared diet. The duration of catalepsy was measured at 0, 60, 90, 120, 150 and 180 min, using Bar test.

Both the forepaws of mouse were placed on a horizontal bar raised 3 cm from the table, and the time required to remove the forepaws from the bar was recorded as the duration of catalepsy. In all the experiments, the observer was blind to the treatment given to the mice. Between experiments, the animals were returned to their home cages.[6]

Cooks Pole Climbing Apparatus

Training and testing of rat was conducted in the pole climbing apparatus, which has a floor that acts as a source of shock. In the centre of the roof there is a wooden pole. The animals were trained as follows. Press the buzzer, Shock of 20v was delivered to the floor grid. The animal was trained to climb the pole to avoid shock. This was repeated until the animals learned to climb the pole soon after hearing the buzzer even without receiving the shock. Such rats, which climb the pole within 3s after pressing the buzzer, were chosen for this study. The conditioning stimulus is presented alone for 4s and then is coincident with the unconditioned stimulus, a scrambled shock delivered to the grid floor, for 26s.

A pole climb response during the conditioned stimulus period terminates the conditioned stimulus and the subsequent unconditioned stimuli. This is considered an avoidance response. A response during the time when both the conditioned and unconditioned stimuli are present terminates both stimuli and is considered an escape response. Test sessions consist of 20 trials or 60 min, whichever comes first. There is a minimum intertribal interval of 90s. Any time remaining in the 30s allotted to make the pole climb is added to the 90s intertribal interval. Responses during this time have no scheduled consequences; however, rats having greater than 10 intertrial interval responses should not be used in the experiment.

Before testing experimental compounds, rats are required to make at least 80% avoidance responses without any escape failures. Data are expressed in terms of the number of avoidance and escape failures relative to the respective vehicle control data.[6]

Ketamine-Induced Stereotypic Behavior in Mice

Animals were divided into six groups and each group consisted of six animals. The control animals received normal diet and treated with Ketamine (50mg/kg, i.p.) for 15 consecutive days. The animals of standard groups received Haloperidol (1mg/kg, i.p.) and Olanzapine (5mg/kg, i.p.), after 30 min Ketamine was given, (50mg/kg, i.p.) for 15 consecutive days.

The animals of test groups received different concentrations of *TBFP* (4, 6, 8%w/w) through a specially prepared diet and after 30 min Ketamine was given (50mg/kg, i.p.) for 15 consecutive days.

Each mouse was individually placed into plastic cages (37 × 24 × 30 cm^3) divided into quadrants by lines on the floor and allowed to acclimatize for at least 30 min before the testing began. Behavioral tests were performed between 10 a.m. and 4 p.m.

The stereotypic behaviour was assessed by counting the number of turning, weaving, head-bobbing and ataxia. Turning was measured by counting turn around every 15 min over 60 min.

Weaving and Head-bobbing were measured by counting its neck wave right and left, and go up and down every 15 min over 60 min. Ataxia was assessed by counting the number of falls of each mouse on the floor of the cage every 15 min over 60 min period.[7,8]

Locomotor Activity

The locomotor activity of rats was measured using Photoactometer (INCO, Ambala, India).[9]

Biochemical Estimation

The animals were sacrificed by cervical dislocation, whole brain was rapidly frozen at -5 °C and brain dopamine levels was spectrofluorimetrically estimated by the methods of Ansell and Beeson[10] as modified by Cox and Perhach.[11]

Statistical Analysis

Results are expressed as Mean ± S.E.M (n = 6). The statistical analysis of data was done using one-way analysis of variance (ANOVA), followed by Dunnett's *t*-

test. Probability level less than 0.05 was considered statistically significant.

RESULTS

Haloperidol-Induced Catalepsy

In control animals, haloperidol (1 mg/kg. i.p.) produced the maximum catalepsy at 120 min (247 ± 5.5s). *TBFP* (4, 6, 8%w/w) through a specially prepared diet, significantly potentiated haloperidol induced catalepsy at each time interval, in a dose dependent manner.

At dose 4, 6 and 8%w/w *TBFP* showed maximum cataleptic score 260.6 ± 6.2s ($p<0.05$), 273.8 ± 9.7s and 275 ± 7.6s ($p<0.01$), respectively at 120 min in haloperidol treated animals (Figure 1).

Cooks Pole Climbing Apparatus

Administration of *TBFP* (4%w/w) through a specially prepared diet for 15 successive days markedly ($p<0.05$) inhibited the conditioned avoidance response in rats as indicated by increased time spent on the grid floor of the chamber. However, the concentrations of 6 and 8% w/w of *TBFP* were remarkably ($p<0.01$) effective in inhibiting the conditioned avoidance response.

The effect of *TBFP* was found to be comparable to that of Olanzapine (5mg/kg, i.p.) (Antipsychotic agent) (Figure 2).

Ketamine-Induced Stereotypic Behavior in Mice

Ketamine (50mg/kg, i.p.) produced stereotypic behavior in mice. Different concentrations of *TBFP* (4, 6 and 8% w/w) through a specially prepared diet for 15 successive days remarkably ($p<0.01$) decreased this stereotypic behavior of mice produced by ketamine.

Animals treated with Haloperidol (1mg/kg, i.p.) and Olanzapine (5mg/kg, i.p.) reversed stereotypic behavior induced by ketamine. The effect of *TBFP* was found to be comparable to that of Haloperidol and Olanzapine (Antipsychotic agents).

Turning Behavior of Mice

Turning behavior was measured by counting the turn-around behavior of each mouse every 15 min over 60 min periods. *TBFP* at the concentration of 6% w/w for 15 successive days showed significant ($p<0.05$) decrease in turning behavior of mice induced by ketamine.

However at the concentration of 8%w/w *TBFP* remarkably ($p<0.01$) decreased the turning pattern of mice induced by ketamine.

At the concentration of 4%w/w showed significant ($p<0.05$) reduction after 15 min. Animals treated with Haloperidol (1mg/kg, i.p.) and Olanzapine (5mg/kg, i.p.) decreased the turning behavior (Figure 3).

Weaving Behavior of Mice

Weaving pattern was measured by counting its paw movements standing on hind legs every 15 min over 60 min period. Concentration 8%w/w *TBFP* remarkably ($p<0.01$) decreased weaving pattern of mice produced by ketamine. During 15 and 30 min *TBFP* 4%w/w showed remarkable ($p<0.05$) decrease in weaving pattern. Concentration 6%w/w *TBFP* remarkably ($p<0.01$) decreased weaving pattern of mice produced by ketamine in first 15 min and reduction in weaving pattern was remarkable ($p<0.05$) after 15 min.

Animals treated with Haloperidol (1mg/kg, i.p.) and Olanzapine (5mg/kg, i.p.) decreased the weaving behavior (Figure 4).

Head-Bobbing Behavior of Mice

Head-bobbing pattern was measured by counting its neck movements towards right and left and up and down every 15 min over 60 min period. Administration of *TBFP* at the concentration of 8%w/w for 15 successive days remarkably ($p<0.01$) reduced head-bobbing pattern of mice produced by ketamine.

Concentration of *TBFP* 6%w/w showed remarkable ($p<0.05$) reduction in head-bobbing pattern in first 15 min, reduced the head-bobbing pattern remarkably ($p<0.01$) at 30 and 45 min. Concentration of *TBFP* 4%w/w showed remarkable ($p<0.05$) reduction in head-bobbing pattern at 30 and 45 min (Figure 5).

Ataxia Behavior of Mice

Ataxia was assessed by counting the number of falls of each mouse on the floor of the cage every 15 min over 60 min period. Administration of *TBFP* 4% w/w although reduced but showed no significant reduction in falling behaviour of mice. *TBFP* at the concentration of 6%w/w for 15 successive days markedly ($p<0.05$) reduced falling behaviour of mice.

Administration of *TBFP* 8% w/w remarkably ($p<0.01$) decreased falling behaviour of mice. There was no falling attempt at 60 min (Figure 6).

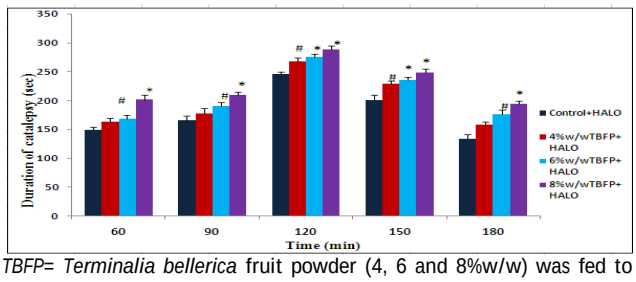
Locomotor Activity

Administration of *TBFP* 4 and 6% w/w, through a specially prepared diet for 15 successive days markedly ($p<0.05$) decreased locomotor activity in rats measured using photoactometer.

However, the concentrations of 8%w/w of *TBFP* was remarkably ($p<0.01$) effective in decreasing locomotor activity. The effect of *TBFP* was found to be comparable to that of Olanzapine (Antipsychotic agent) (Figure 7).

Brain Dopamine Level

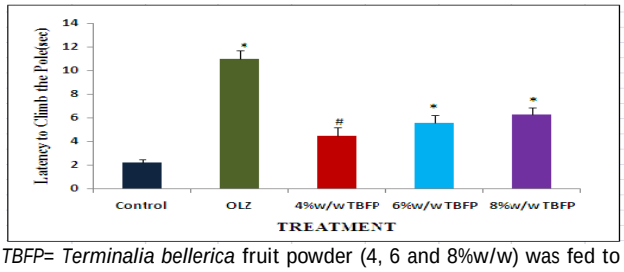
Administration of *TBFP* at the concentration of 4%w/w for 15 consecutive days showed markedly significant ($p<0.05$) effect on brain dopamine level. However, administration of *TBFP* at the concentration of 4 and 8%w/w for 15 consecutive days showed remarkably significant ($p<0.01$) decrease in brain dopamine level in rats compared to control group (Figure 8).



TBFP= Terminalia bellerica fruit powder (4, 6 and 8%w/w) was fed to separate groups of rats through a specially prepared diet. HALO= Haloperidol (1mg/kg, i.p.) was dissolved in normal saline. Values are in Mean ± SEM (n = 6). One way ANOVA followed by Dunnett's t-test.

* denotes p<0.01 and # denotes p<0.05 as compared to control group.

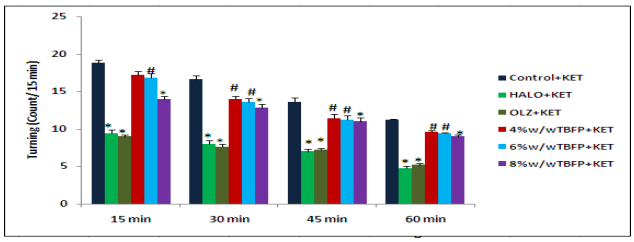
Figure 1: Effect of *TBFP* on Haloperidol Induced Catalepsy in Rats



TBFP= Terminalia bellerica fruit powder (4, 6 and 8%w/w) was fed to separate groups of rats through a specially prepared diet. OLZ= Olanzapine (5mg/kg, i.p.) was dissolved in normal saline. Values are in Mean ± SEM (n = 6). One way ANOVA followed by Dunnett's t-test.

* denotes p<0.01 and # denotes p<0.05 as compared to control group.

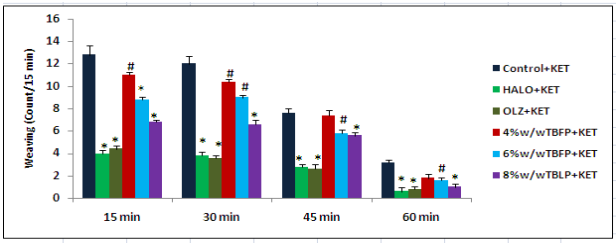
Figure 2: Effects of *TBFP* on Cooks Pole Climbing Avoidance in Rats



TBFP = Terminalia bellerica fruit powder (4, 6 and 8%w/w) was fed to separate groups of rats through a specially prepared diet. KET= Ketamine (50mg/kg, i.p.), HALO= Haloperidol (1mg/kg, i.p.) and OLZ= Olanzapine (5mg/kg, i.p.), were dissolved in normal saline. Values are in Mean ± SEM (n = 6). One way ANOVA followed by Dunnett's t-test.

* denotes p<0.01 and # denotes p<0.05 as compared to control group.

Figure 3: Effect of *TBFP* on Turning Behavior of Mice.



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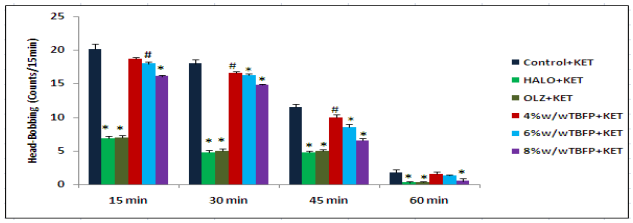
* denotes p<0.01 and # denotes p<0.05 as compared to control group.

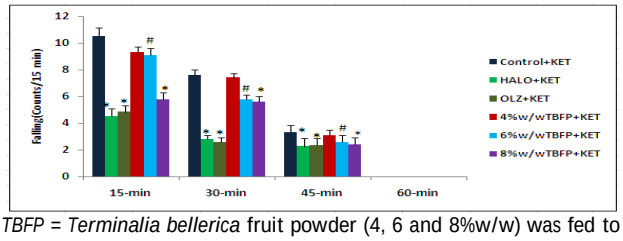
Figure 4: Effect of *TBFP* on Weaving Behavior of Mice



TBFP = Terminalia bellerica fruit powder (4, 6 and 8%w/w) was fed to separate groups of rats through a specially prepared diet. KET= Ketamine (50mg/kg, i.p.), HALO= Haloperidol (1mg/kg, i.p.) and OLZ= Olanzapine (5mg/kg, i.p.), were dissolved in normal saline. Values are in Mean ± SEM (n = 6). One way ANOVA followed by Dunnett's t-test.

* denotes p<0.01 and # denotes p<0.05 as compared to control group.

Figure 5: Effect of *TBFP* on Head-Bobbing Behavior of Mice



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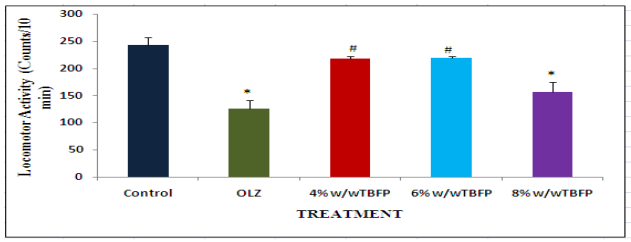
* denotes p<0.01 and # denotes p<0.05 as compared to control group.

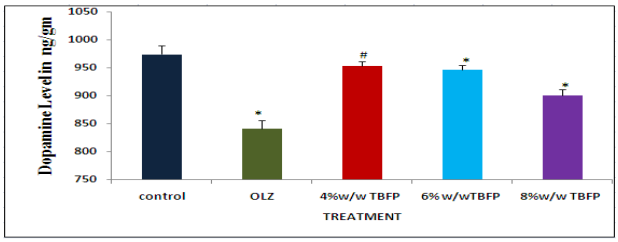
Figure 6: Effect of *TBFP* on Falling Behavior of Mice



TBFP = Terminalia bellerica fruit powder (4, 6 and 8%w/w) was fed to separate groups of rats through a specially prepared diet. OLZ= Olanzapine (5mg/kg, i.p.) was dissolved in normal saline. Values are in Mean ± SEM (n = 6). One way ANOVA followed by Dunnett's t-test.

* denotes p<0.01 and # denotes p<0.05 as compared to control group.

Figure 7: Effect of *TBFP* on Locomotor Activity of Rats



TBFP = Terminalia bellerica fruit powder (4, 6 and 8%w/w) was fed to separate groups of rats through a specially prepared diet. OLZ= Olanzapine (5mg/kg, i.p.) was dissolved in normal saline. Values are in Mean ± SEM (n = 6). One way ANOVA followed by Dunnett's t-test.

* denotes p<0.01 and # denotes p<0.05 as compared to control group.

Figure 8: Effect of *TBFP* on Brain Dopamine Level of Rats

DISCUSSION

Schizophrenia continues to be a mysterious disease fascinating the minds of psychiatrists, pharmacologists and neuroscientists all over the world for more than a century. The crucial welfare of the millions afflicted with schizophrenia is at stake. The cause of schizophrenia is not yet identified. However, it appears from the available reports that schizophrenia results from genetic, occupational and environmental risk factors, which act independently or combine synergistically to develop schizophrenia. In any case, schizophrenia should not be confined to split personality or multiple personality-disorder. Typically, a schizophrenic patient shows both, positive symptoms such as delusions, hallucinations or cognitive dysfunction and negative symptoms such as social withdrawal, inability to articulate or loss of emotional tone positive symptoms refer to a loss of contact with reality and comprise of hallucinations delusions, bizarre behavior and positive formal thought disorders. Negative symptoms refer to a diminution in or absence of normal behaviors and include flat affect, alogia, avolition and anhedonia. Cognitive symptoms manifest as deficits in attention, learning, memory, concentration and executive functions (abstract thinking, problem solving). In the present study, we have focused upon the effects of *Terminalia bellerica* fruit powder on psychosis. Phytochemicals present in *Terminalia bellerica* include alkaloid, coumarin, flavones, steroids (β-sitosterol), lignans (termilignan, thannilignan), tannins (gallic acid, ellagic acid), glycosides (fructose, sucrose, and galactose), terpenoid (belleric acid and chebulagic acid) and saponin (bellericoside and bellericanin). Experimental studies have shown that phenolic compounds particularly flavones, lignans and tannins present in *TBFP* are important antioxidants[12] and superoxide scavengers. The antioxidant activity of *TBFP* may be responsible for its beneficial antipsychotic action. The therapeutic and pharmacological actions of *Terminalia bellerica* (analgesic activity, antibiofilm activity, anticancer activity, antidepressant activity, antidiabetic activity, antidiarrhoeal activity, anti-ulcer activity, immunomodulatory activity, anti-spasmodic and bronchodialatory activity, antifertility activity, antihypertensive activity, antifungal, antimicrobial activity, anti-inflammatory activity, antioxidant activity) are noteworthy.

Haloperidol, a typical neuroleptic produces catalepsy in rodents and extrapyramidal side effects in human.[13] Haloperidol-induced catalepsy is one of the animal models for testing the extrapyramidal side effects of antipsychotic drugs. Haloperidol, (a non-selective D2 dopamine antagonist) induced catalepsy is primarily due to blockade of dopamine receptors in the striatum. The striatum and nucleus accumbens have been implicated as the major brain structures involved in antipsychotic induced catalepsy, which appears due to the blockade of dopamine neurotransmission.[14] In the present study, administration of *TBFP* in a specially prepared diet for 15 successive days in different concentrations (4, 6 and 8%w/w) showed significant ($P<0.05$, $P<0.01$) dose dependent potentiating of haloperidol-induced catalepsy. Thus, the results suggest that *TBFP* shows antidopaminergic activity.

Ketamine Induced stereotypy is a commonly employed interceptive behavioural model to evaluate antipsychotic potential of any drug. Haloperidol and Olanzapine (antipsychotics agents) were used in the present study as standard antipsychotic agents. Administration of *TBFP* in a specially prepared diet for 15 successive days in different concentrations showed significantly ($P<0.05$, $P<0.01$) inhibition of stereotypic behavior in mice as reflected by reduced turning, weaving, head-bobbing and ataxia. Administration of *TBFP* for 15 successive days resulted in significant ($p<0.05$ and $p<0.01$) dose-dependent decrease in locomotor activity which showed the CNS depressant activity of different concentrations of *TBFP*. Administration of *TBFP* for 15 successive days resulted in significant ($p<0.05$ and $p<0.01$) dose-dependent decrease in dopamine levels in brain of rats in the present study. A central role for D2 receptor occupancy in antipsychotic action is now well established, buttressed by neuroimaging studies using positron emission tomography and single photon emission computed tomography.[15] However, the importance of dopamine receptors in the treatment of psychosis does not by itself constitute proof of the involvement of dopamine in psychosis. Administration of *TBFP* may increase the number of dormant receptors, hence resulting in decrease in dopamine turnover in extracellular spaces in the brain.[16] It derives that alkaloids, tannins, flavones and lignans are present in the *TBFP* which may possibly responsible for the psychopharmacological action. Pole-climb avoidance in rats is often used for differentiating neuroleptic activity and sedatives property. Administration of *TBFP* for 15 successive days in different concentrations significantly ($P<0.05$, $p<0.01$) delayed the latency time taken by the animals to climb the pole in Passive Avoidance Paradigm. Since, *TBFP* produced consistent antipsychotic activity in different antipsychotic models; it appears to be a promising antipsychotic agent.

CONCLUSION

The present investigation concludes that the *Terminalia bellerica* fruit powder contains constituents that inhibit dopaminergic neurotransmission and possibly blocks dopamine D2 receptor.

Thus, *TBFP* possesses antidopaminergic activity. The results suggest that the *Terminalia bellerica* may have potential clinical application in the management of psychiatric disorders.

Acknowledgement: I would like to thank all of my colleagues who helped me during this work specially Mr. Kalish Sharma and Miss. Monu Yadav for their unforgettable contribution.

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Source of Support: Nil, **Conflict of Interest:** None.