Int J Pharm Bio Sci 2016 Oct ; 7(4): (P) 74 - 82

Original Research Article **Pharmacology**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

ANTI-PSYCHOTIC POTENTIAL OF *FOENICULUM VULGARE* IN RODENTS

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ABSTRACT

Foeniculum vulgare (Fennel), generally known as Saunf belonging to Apiacae family is one of the most popular and widely used medicinal plants in traditional medicine. Fennel contains volatile compounds, flavonoids, phenolic compounds, fatty acids, and amino acids. There is no documented report on utility of Fennel in psychiatric disorders in literature. Therefore, this study was undertaken to explore anti-psychotic potential of Fennel using Ketamine- induced stereotypic behaviour in mice, pole climbing avoidance in rats and swim induced grooming in mice. Fennel, when administered orally to rodents in two different concentrations of 500mg/kg and 1000mg/kg for 21 days, inhibited Ketamine -induced stereotypic behaviour, reduced swim -induced grooming behaviour and decreased pole - climb avoidance behaviour. In our biochemical estimations both, brain dopamine level and acetyl cholinesterase activity were significantly reduced by Fennel whereas, brain glutathione levels were remarkably increased by Fennel. These findings taken together reveal anti-psychotic potential of Fennel.

KEY WORDS: **Fennel, antioxidant, psychosis, dopamine**

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INTRODUCTION

Nature provides us with numerous wonderful fragrances, which have their own medicinal value. Fennel, commonly known as Saunf *Foeniculum vulgare* and belonging to Apiacae family is one of them.[1] India is the greatest manufacturer of fennel in the world. Fennel is cultivated in many states of India including Gujarat, Rajasthan and Uttar Pradesh.[2] Fennel contains volatile compounds, flavonoids, phenolic compounds, fatty acids, and amino acids[1]. It shows several pharmacological properties like anti-microbial, anti-pyretic, anti-spasmodic, anti-thrombotic, apoptotic, anti-viral, anti-inflammatory, anti-mutagenic, anti-nociceptive, chemomodulatory, anti-tumour, hepatoprotective, hypoglycaemic, hypolipidemic and memory enhancing property.[3] In daily life, people chew Fennel seeds after meals to refresh mouth and prevent bad odour. Taking fennel juice regularly, helps to streamline the digestive tract and promotes a healthy bowel movement. Fennel helps in curing digestive, endocrine, reproductive, and respiratory system related disorders. It also acts as a galactagogue stimulating milk production in lactating mothers.[4] A decoction of the leaves and roots of fennel is useful for snake-bites. Fennel is often used to restore psychological and physical well being of patients. However, there are no concrete reports on utility of Fennel in psychiatric disorders in literature. Schizophrenia continues to be a mysterious disease, fascinating the minds of psychiatrists, pharmacologists and neuroscientists all over the world for more than a century. Schizophrenia occurs in all known human societies at a prevalence rate of around 1%, though there is variation according to degree of illness and geographical setting. Thecrucial welfare of the millions afflicted with schizophrenia is at stake.[5] Therefore, this project was undertaken to explore anti-psychotic potential of Fennel using various experimental models of psychosis.

MATERIALS AND METHODS

Plant material

The seeds of Fennel (*Foeniculum vulgare*) were purchased from local market of Hisar and got authenticated from NATIONAL HERBARIUM OF CULTIVATED PLANTS (NHCP), New Delhi- (Ref. NHCP/NBPGR/2016-12). Fennel seeds were powdered and aqueous suspension was prepared using Ca-rboxy methyl cellulose as a suspending agent

Experimental animals

A total of 66 adult Swiss mice weighing around 20-25g and 30 Wistar male rats weighing around 180-200g were procured from Disease Free Small Animal House of Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar. All the animals were housed in Psychopharmacology laboratory under controlled conditions of temperature in a natural 12 h each light - dark cycle. Water boiled wheat porridge (dalia) was given to the animals as food. The animals were acclimatized for at least 5 days to the laboratory conditions before behavioural experiments. Experiments were carried out between 09:00 am to 5:00 pm. The experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) and the care of animals was taken as per guidelines of CPCSEA, Ministry of Forests and Environment, Government of India (Registration number 0436). Each observation was recorded in a separate group of mice/rats. Each group consisted of six animals, and each animal was used only once in the study.

Drug protocol

Haloperidol, 1 mg/kg, i.p. (RPG Science Pharmaceutical Pvt. Ltd), Olanzapine, 5 mg/kg, i.p. (Intas Pharmaceuticals Ltd) and Ketamine, 50 mg/kg, i.p. (Troikaa Pharmaceuticals Ltd) were administered daily for duration of 21 days to the separate groups of animals. Vehicle was administered to control group for 21 consecutive days.

LABORATORY MODELS EMPLOYED FOR TESTING PSYCHOSIS

Ketamine- induced stereotypic behaviour in mice[6]

In this model, animals were divided into seven groups and each group consisted of six animals. The control group I received only saline (1ml/kg, i.p) and negative control group II received Ketamine (50mg/kg, i.p). The animals of groups III, IV received Haloperidol (1mg/kg, i.p) and Olanzapine (5mg/kg, i.p) respectively and after 30 min Ketamine (50mg/kg, i.p) was given, for 21 consecutive days. Group V received Fennel only (1000 mg/kg, p.o.) for 21 days. The animals of test groups VI and VII received different concentrations of Fennel (1000 mg/kg, 500 mg/kg, p.o) respectively and after 30 min Ketamine was given (50mg/kg, i.p) for 21 consecutive days. Each mouse was individually placed into a separate plastic cage ($37 \times 24 \times 30$ $cm^{3)}$, which was divided into quadrants by lines on the floor and was allowed to acclimatize for at least 30 min before the experiments. Behavioural tests were performed between 9 am to 4 pm. The stereotypic behaviour was assessed by counting the number of turning, weaving, and head bobbing counts. Turning was measured by counting turn around attempt of each mouse every 10 min over 60 min period. Weaving and Head-bobbing counts were measured by counting its neck movements towards right/left, and up/down every 10 min over 60 min. Ataxia was assessed by counting the number of falls every 10 min over 60 min. [7]

Pole climb - avoidance in rats[8]

In this model, animals were divided into five groups and each group consisted of six animals. The control group VIII received only the vehicle. The animals of groups IX and X received Haloperidol (1mg/kg, i.p) and Olanzapine (5mg/kg, i.p) respectively for 21 consecutive days. The animals of test groups XI and XII received different concentrations of Fennel (1000 mg/kg, 500 mg/kg, p.o) respectively, for 21 consecutive days. The pole-climb avoidance paradigm is an avoidance escape procedure used to separate neuroleptics from sedatives and anxiolytics. Whereas, sedative compounds suppress both avoidance and escape behaviour at approximately the same doses, neuroleptic drugs

reduce avoidance at lower doses than those affecting escape behaviour. The procedure and end-point observed in the present study was as described earlier [8]. Data were expressed in terms of the number of avoidance attempts and escape failures relative to the respective vehicle control group.

Swim induced grooming in mice [9]

In this model, the control group XIII received only the vehicle. The animals of group IXV received Haloperidol (1mg/kg, i.p), for 21 consecutive days. The animals of test groups XV and XVI received different concentrations of Fennel (1000 mg/kg, 500 mg/kg, p.o) respectively, for 21 consecutive days. Sixty minutes after treatments, mice were placed individually in swimming cylinders (8x8x18cm high) filled with water (32°C) for three min. They were then removed and dried with towel for 30 seconds and placed immediately into perspex boxes individually. The number of grooming attempts was recorded over 15 min. period as described in literature [9].

BIOCHEMICAL ESTIMATIONS

Estimation of brain neurotransmitters and glutathione levels

The animals were sacrificed by cervical decapitation under light anaesthesia on 22nd day 90 min after drugs administration. Immediately after decapitation, the whole brain was dissected out. Brain dopamine levels [10], brain AChE activity [11], and brain glutathione [12] levels were estimated as per procedure described earlier in literature.

STATISTICAL ANALYSIS

All values were expressed as mean ± S.E.M. The data were analyzed using one way ANOVA followed by Dunnett's t-test. $p<0.05$ was considered to be statistically significant.

RESULTS

Preliminary studies

Foeniculum vulgare was administered orally to mice in different concentrations in preliminary studies to delineate optimally effective concentrations for further studies.

Effect of Fennel on Ketamine induced stereotypic behaviour of mice

The stereotypic behaviour was quantified by measuring the number of turning, weaving, falling and head-bobbing counts produced by mice upon Ketamine administration. Turning behaviour was measured by counting the turn-around of each mouse every 10 min over 60 min period. Weaving behaviour was measured by counting its paw movements and standing on hind legs attempts every 10 min over 60 min period. Head-bobbing behaviour was measured by counting its neck movements towards right/left and up/down every 10 min over 60 min period. Falling was assessed by counting the number of falls of each mouse on the floor of the cage every 10 min over 60 min period. Administration of Fennel *per se* didn't evoke any significant behavioural changes in mice. But, Fennel, when administered at 1000 mg/kg and 500 mg/kg concentrations orally for 21 successive days remarkably ($p<0.01$) decreased the stereotypic behaviour of mice produced by Ketamine. Animals pre-treated with Haloperidol (1mg/kg, i.p) and Olanzapine (5mg/kg, i.p) reduced the stereotypic behaviour induced by Ketamine. The effect of Fennel was found to be comparable to that of Haloperidol and Olanzapine (Marketed anti-psychotic agents).

Effect of Fennel on turning behaviour of mice

Administration of Fennel *per se* didn't evoke any significant behavioural changes in mice. But, administration of Fennel (p.o for 21 days) at the concentration of 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) dose dependently decreased the turning behaviour of mice induced by Ketamine. Animals pre-treated with Haloperidol (1mg/kg, i.p) and Olanzapine (5mg/kg, i.p) also decreased the turning behaviour of mice as expected (See Fig 1).

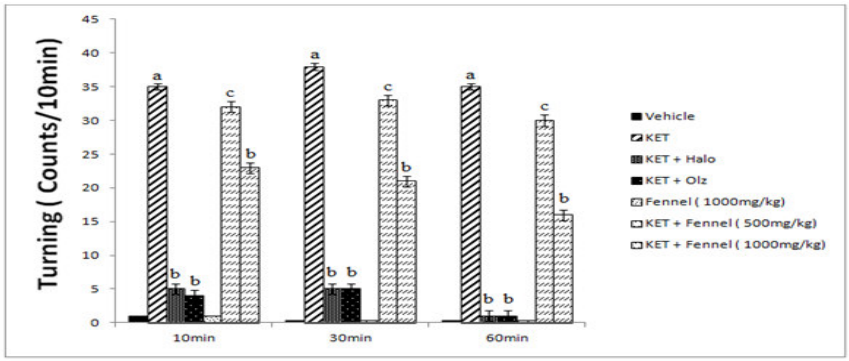

Figure 1

Effect of Fennel on Ketamine induced turning behaviour of mice,when observed every 10 min. over 60 min. period.

Values are in mean ± SEM (n = 6).
a denotes p<0.01 as compared to control group.
b denotes p<0.01 as compared to Ketamine group.
c denotes p<0.05 as compared to Ketamine group.

KET = Ketamine, Halo = Haloperidol, Olz = Olanzapine
Fennel was administered at 500 mg/kg and 1000 mg/kg per orally for 21 days.
Statistical analysis was carried out by one way ANOVA followed by Dunnett's t-test.

Effect of Fennel on weaving behaviour of mice

Administration of Fennel *per se* didn't evoke any significant behavioural changes in mice. But, administration of Fennel (p.o for 21 days) at the concentration of 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) dose dependently decreased the weaving behaviour of mice induced by Ketamine. Animals pre-treated with Haloperidol (1mg/kg, i.p) and Olanzapine (5mg/kg, i.p) also decreased the weaving pattern exhibited by mice (See Fig 2).

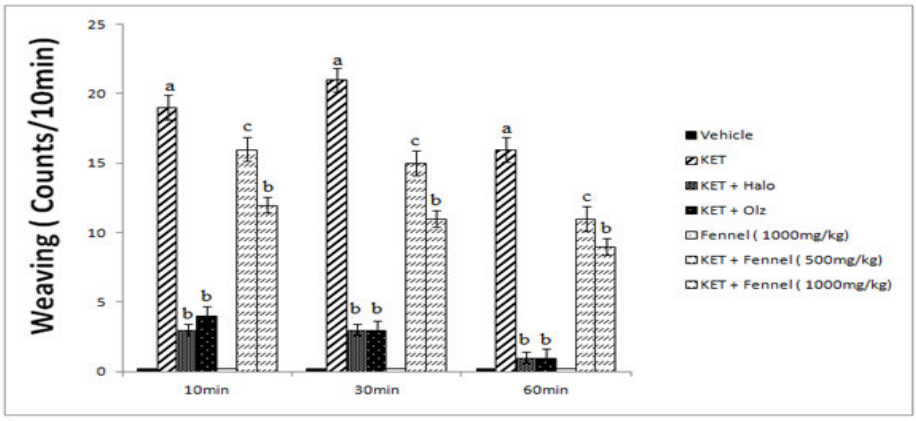

Figure 2
Effect of Fennel on Ketamine induced weaving behaviour of mice, when observed every 10 min. over 60 min. period

Values are in mean ± SEM (n = 6).
a denotes $p<0.01$ as compared to control group.
b denotes $p<0.01$ as compared to Ketamine group.
c denotes $p<0.05$ as compared to Ketamine group.
KET = Ketamine, Halo = Haloperidol, Olz = Olanzapine
Fennel was administered at 500 mg/kg and 1000 mg/kg per orally for 21 days.

Effect of Fennel on head-bobbing behaviour of mice

Administration of Fennel *per se* didn't evoke any significant behavioural changes in mice. But, administration of Fennel (p.o for 21 days) at the concentration of 500 mg/kg ($p>0.05$) and 1000 mg/kg ($p<0.01$) significantly decreased the head-bobbing behaviour of mice induced by Ketamine. Animals pre-treated with Haloperidol (1mg/kg, i.p) and Olanzapine (5mg/kg, i.p) also decreased the head-bobbing counts in mice (See Fig 3).

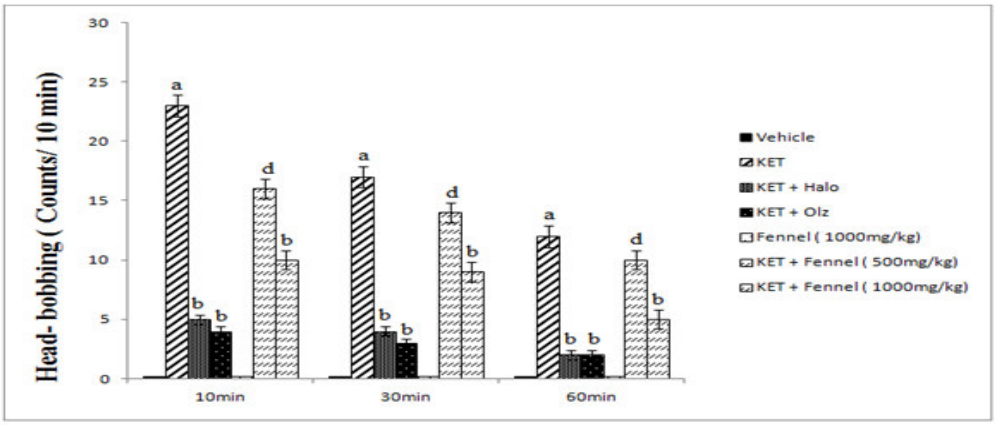

Figure 3
Effect of Fennel on Ketamine induced head-bobbing behaviour of mice, when observed every 10 min. over 60 min. period.

Values are in mean ± SEM (n = 6).
a denotes $p<0.01$ as compared to control group.
b denotes $p<0.01$ as compared to Ketamine group.
d denotes $p>0.05$ as compared to Ketamine group.
KET = Ketamine, Halo = Haloperidol, Olz = Olanzapine
Fennel was administered at 500 mg/kg and 1000 mg/kg per orally for 21 days.
Statistical analysis was carried out by one way ANOVA followed by Dunnett's t-test.

Effect of Fennel on falling behaviour of mice

Administration of Fennel *per se* didn't evoke any falling behaviour in mice. Administration of Fennel (p.o for 21 days) at the concentration of 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) dose dependently decreased the falling behaviour of mice induced by Ketamine. Animals pre-treated with Haloperidol (1mg/kg, i.p) and Olanzapine (5mg/kg, i.p) also decreased the falling behaviour (See Fig 4).

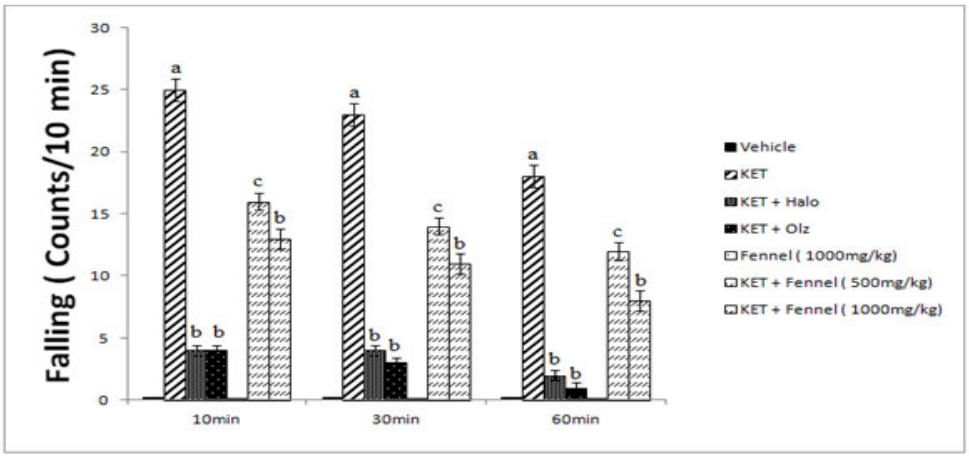

Figure 4

Effect of Fennel on Ketamine induced falling behaviour of mice, when observed every 10 min. over 60 min. period.

Values are in mean ± SEM (n = 6).
a denotes p<0.01 as compared to control group.
b denotes p<0.01 as compared to Ketamine group.
c denotes p<0.05 as compared to Ketamine group.
KET = Ketamine, Halo = Haloperidol, Olz = Olanzapine
Fennel was administered at 500 mg/kg and 1000 mg/kg per orally for 21 days.
Statistical analysis was carried out by one way ANOVA followed by Dunnett's t-test.

Effect of Fennel on pole climb avoidance in rats

Administration of Fennel (p.o) at the concentration of 500 mg/kg ($p<0.05$) and 1000 mg/kg remarkably ($p<0.01$) inhibited the conditioned avoidance response in rats as indicated by increased time spent on the grid floor of the chamber (See Fig 5). The effect of Fennel was found to be comparable to that of established anti-psychotic agents Haloperidol (1 mg/kg, i.p.) and Olanzapine (5 mg/kg, i.p.).

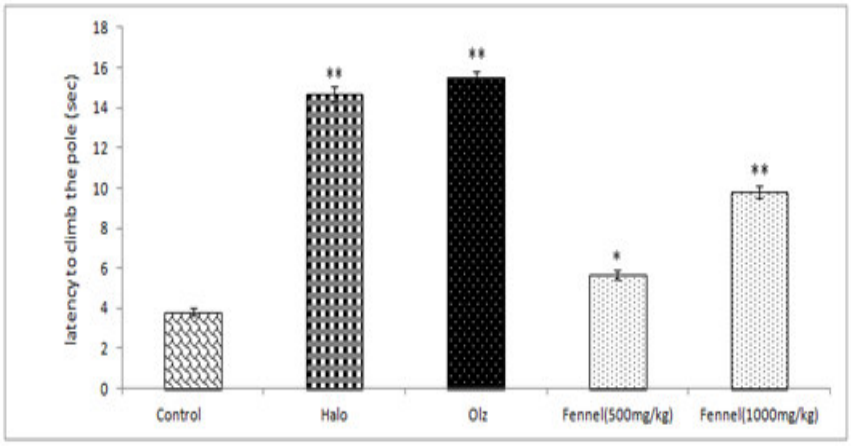

Figure 5

Effect of Fennel on pole climb avoidance in rats

Values are in mean ± SEM (n = 6).
**** denotes p<0.05 as compared to control group.***
***** denotes p<0.01 as compared to control group.***
Halo = Haloperidol, Olz = Olanzapine
Fennel was administered at 500 mg/kg and 1000 mg/kg concentration per orally for 21 days.
Statistical analysis was carried out by one way ANOVA followed by Dunnett's t-test.

Effect of Fennel on swim induced grooming attempts of mice

Fennel, at both the concentrations (p.o for 21 days) of 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) decreased the number of grooming attempts in swim-induced grooming model of mice as compared to the controlgroup.(See Fig6).

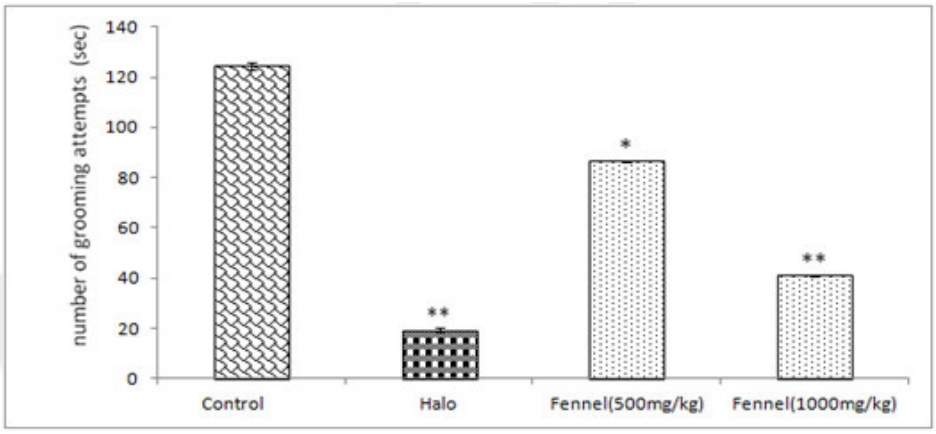

Figure 6
Effect of Fennel on number of grooming attempts of mice in swim induced grooming model.

Values are in mean ± SEM (n = 6).
**** denotes p<0.05 as compared to control group.***
***** denotes p<0.01 as compared to control group.***
Halo = Haloperidol
Fennel was administered at 500 mg/kg and 1000 mg/kg per orally for 21 days.
Statistical analysis was carried out by one way ANOVA followed by Dunnett's t-test.

Effect of Fennel on brain dopamine level

Administration of Fennel (p.o) at the concentration of 1000 mg/kg for 21 consecutive days showed remarkable ($p<0.01$) decrease in brain dopamine levels of rodents as compared to the control group (See Fig 7)

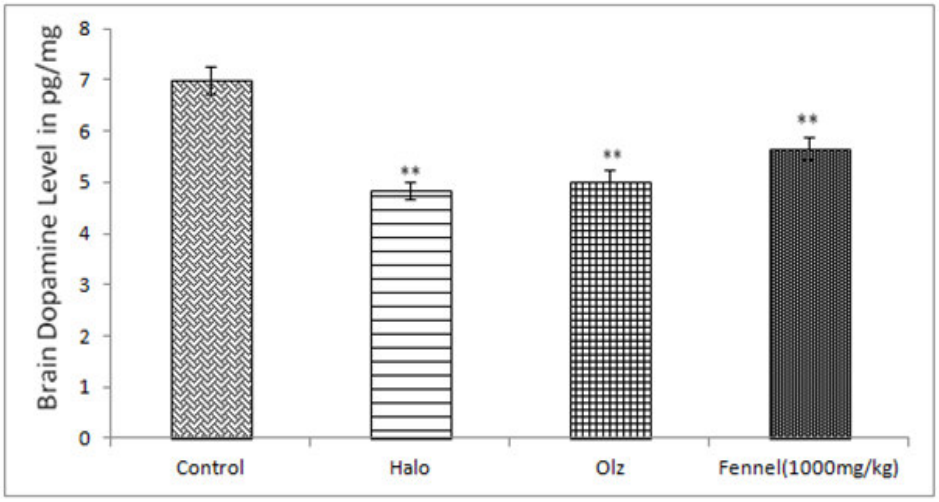

Figure 7
Effect of Fennel on brain Dopamine levels of rodents

Values are in mean ± SEM (n = 6).
***** denotes p<0.01 as compared to control group.***
Halo = Haloperidol, Olz = Olanzapine
Fennel was administered at 1000 mg/kg per orally for 21 days.
Statistical analysis was carried out by one way ANOVA followed by Dunnett's t-test.

Effect of Fennel on brain acetyl cholinesterase (AchE) activity

Administration of Fennel (p.o) at the concentration of 1000 mg/kg for 21 consecutive days showed significant ($p<0.05$) decrease in brain Acetyl cholinesterase activity of rodents as compared to the control group (See Fig 8)

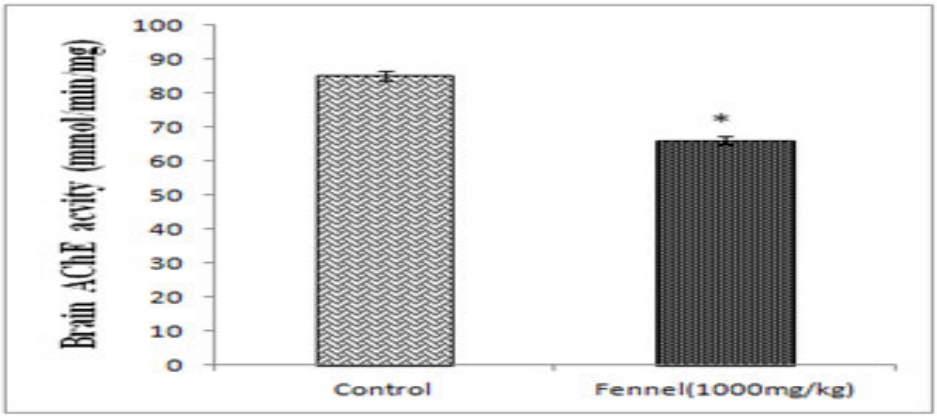

Figure 8
Effect of Fennel on brain AchE activity of rodents

Values are in mean ± SEM (n = 6).
**** denotes p<0.05 as compared to control group.***
Fennel was administered at 1000 mg/kg (p.o) for 21 days.
Statistical analysis was carried out by one way ANOVA followed by Dunnett's t-test.

Effect of Fennel on brain glutathione levels
Administration of Fennel (p.o) at the concentration of 1000 mg/kg for 21 consecutive days showed remarkable (p<0.01) increase in brain Glutathione levels of rodents as compared to control group (See Fig 9).

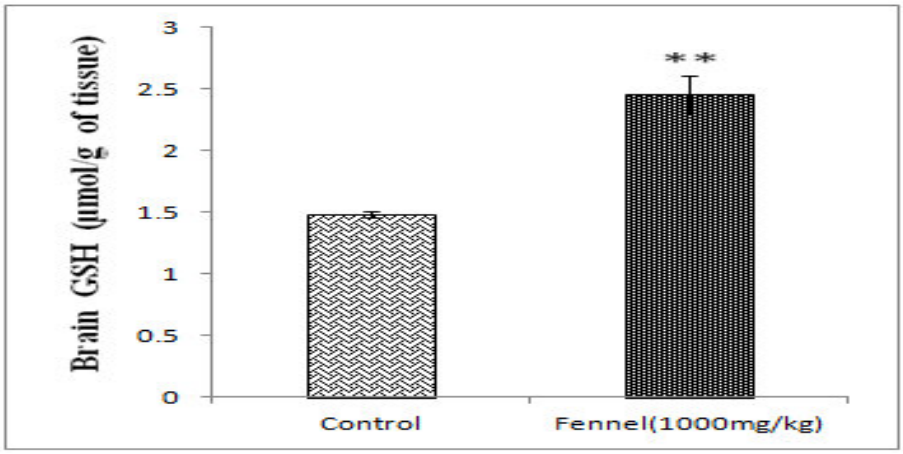

Figure 9
Effect of Fennel on brain GSH levels of rodents
Values are in mean ± SEM (n = 6).
***** denotes p<0.01 as compared to control group.***
Fennel was administered at 1000 mg/kg per orally for 21 days.
Statistical analysis was carried out by one way ANOVA followed by Dunnett's t-test.

DISCUSSION

Schizophrenia is a devastating illness that attacks some of the most advanced functions of the human brain. The origin of schizophrenia can be attributed to structural and behavioural abnormalities arising from malfunctioning genes or non-genetic factors such as substance abuse, stressful life style, pre-natal and neonatal infections, maternal malnutrition, non-cooperative supervisor, life setbacks / shocks, loss of spouse, accidents etc.[13] By inducing cellular metabolic stress these factors appear to increase the possibility of neuronal damage. Oxidative stress is the condition arising from imbalance between oxidant and antioxidant systems. Low level of antioxidants and increased production of free radicals results in oxidative damage of cell lipids, proteins, enzymes, carbohydrates and DNA.[14] Irregular cellular functions in the brain may produce enormous concentrations of reactive oxygen species (ROS), which cause brain damage. The state of oxidative imbalance found during neurodegenerative processes is triggered by one or more factors such as brain ageing, genetic predisposition, mitochondrial dysfunction, free radical production, and environmental toxins. Cells in the central nervous system (CNS) are more vulnerable to the toxic effects of reactive oxygen species than those in other organs of the body.[15] Therefore, antioxidants could serve as useful agents to prevent free radical-mediated tissue destruction and inhibit some of the early degenerative events trafficking in the central nervous system that lead to neuro-chemical imbalance and brain damage. Antioxidant

substances protect the neuronal cells by scavenging free radicals.[16] Antioxidants are exogenous (such as Fennel in the present study) or endogenous molecules that act against any form of oxidative stress and associated ill effects on cellular systems. Fennel, when consumed as a part of normal diet, serves not only as a source of energy, but may also provide additional health benefits beyond basic nutritional functions, by virtue of its medicinally useful phytoconstituents. When a specific anti-oxidant meets a free radical at its appropriate activity site, it naturally combines with it and coverts the free radical to harmless products, *viz.* water and oxygen.[17] Fennel is rich in different kinds of antioxidants such as vitamin C, vitamin E, polyphenols, quercetine, glutathione etc. [2-3] , which may account for the anti-psychotic effect observed in the present study. Fennel contains glutathione, the major soluble anti-oxidant in fairly high amounts, which in fact is a component of all cell compartments. Ratio between oxidized glutathione (GSH) and reduced GSH is one of the important determinants of oxidative stress in the body [17]. Therefore, higher the concentration of reduced GSH, lower is the oxidative stress. In the present study, Fennel, when administered for 21 days remarkably enhanced reduced glutathione levels in the brains of mice, thus diminishing overall oxidative stress. Fennel contains, Quercetine, as a major flavonoid, which has been reported to possess anti-tumour, anti-thrombotic, anti-inflammatory, anti- apoptotic, apart from antioxidant activity. Quercetine was found to be neuroprotective not only in a zebra fish model, but also was beneficial in reducing ischemia related brain swelling and brain injury [18] . Moreover, carotenoids found in Fennel appear to neutralize peroxyl, hydroxyl, and superoxide radicals [19] and deactivate sensitizer molecules, which are involved in the generation of ROS. These findings indicated that Fennel enhanced scavenging of free radicals in the brain, thereby preventing occurrence of psychotic attack. NADPH oxidase, a membrane bound enzyme, produces superoxide radical in the brain, which is identified as one of the major contributors to oxidative stress. Natural polyphenols present in Fennel not only inhibit this NADPH oxidase enzyme, but also activate endothelial nitric oxide synthase (eNOS) in brain. This activated endothelial nitric oxide synthase produces nitric oxide, which further inhibits NADPH oxidase. This protective effect of natural polyphenols may be important in the prevention of brain damage due to ischemic stroke, neuronal apoptosis and neurodegenerative diseases. [20]Currently, extensive research showed that glutamate concentrations were reduced in the CSF of patients suffering with schizophrenia. Brain stem cortical projections communicate with mesolimbic dopaminergic pathway through GABA interneurons of ventral tegmental area (VTA), which is known as indirect pathway. Glutamatergic stimulation of interneuron NMDA receptors causes the release of GABA, which in turn inhibits dopamine release in mesolimbic dopaminergic pathway. If the NMDA receptors residing on GABA interneurons become hypoactive, no descending effect of tonic inhibition will occur. The net result is being hyperactivity of the dopaminergic pathway. [21] Ketamine (an established NMDA antagonist) -induced stereotypic behaviour such as falling, head-bobbing, weaving and turning counts were remarkably diminished, when the animals were pre-treated with Fennel for 21 days. As Fennel contains glycine, which is an agonist of NMDA receptors, may be interfering with the binding of Ketamine thereby enhancing NMDA mediated dopaminergic hypoactivity. Glutamic acid present in Fennel can also contribute to increased concentration of glutamate in the brain. Both of these mechanisms may be responsible for remarkable decrease in concentration of dopamine thereby curing bizarre behaviour of schizophrenics. Fennel contains choline, which is a precursor of Acetylcholine. In schizophrenic patients there areevidences of decrease in number of muscarinic receptors.[21] Cholinesterase inhibitors improved cognitive functions of the patients by enhancing cholinergic transmission. In the present study, when Fennel administered to mice for 21 days, showed remarkable decrease in acetyl cholinesterase activity, thereby enhancing cholinergic transmission in turn. This effect of Fennel would probably be beneficial in managing cognitive dysfunctions of schizophrenia. The net consequence of all these findings reflects usefulness of Fennel in the management of bizarre and cognitive symptoms of schizophrenia.

CONCLUSION

The outcome of present investigation exhibited significant anti-psychotic potential of Fennel for the first time in pre- clinical studies. Furthermore, Fennel possesses strong anti-inflammatory as well as anti-oxidant properties, which would be beneficial in preventing psychotic attacks. The anti-psychotic effect observed in the present study can be attributed to the presence of antioxidants like glutathione, Vitamin C, Vitamin E, flavonoids, and polyphenolic compounds, which protect brain cells from the oxidative stress. The presence of glycine and glutamic acid in Fennel probably activates NMDA receptors ultimately resulting in diminished dopaminergic activity via GABA mediated indirect pathway. This beneficial effect of Fennel could be helpful in alleviating bizarre symptoms of psychosis. Furthermore both, inhibition of AchE activity by chronic consumption of Fennel and availability of choline in Fennelenhance cholinergic transmission in brains of rodents, which is desirable for reversing cognitive dysfunctions. Thus, chronic consumption of Fennel appears to be beneficial in reversing bizarre symptoms and managing cognitive dysfunctions of psychosis due to its multifaceted actions.

CONFLICT OF INTEREST

Conflict of interest declared none.

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