

Antidepressant Activity of Methanolic Extract of *Foeniculum Vulgare* (Fennel) Fruits in Experimental Animal Models

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ABSTRACT

The present study was undertaken to investigate the effects of methanolic extract of *Foeniculum vulgare* fruits (family: umbellifereae), popularly known as fennel, on depression using force swim test in rats, potentiation of norepinephrine toxicity in mice and haloperidol induce catalepsy in mice. The extract of *F.vulgare* (250 and 500 mg/kg) was administered orally to rats used in FST and 500mg/kg was administered in HIC and same dose administered in NE toxicity in mice. The dose of 250mg/kg and 500mg/kg of extract significantly ($p<0.001$) reduced the immobility times in rats but dose of 500 mg/kg showed more potent effect than imipramine (30mg/kg). So this dose was used in HIC and NE toxicity in mice. But in NE toxicity model it was observed that MEFV is not good adrenergic component. A significant ($P<0.001$) reduction in the duration of catalepsy was observed in the MEFV treated group and Fluoxetine group as compared to the haloperidol treated group. In HIC, mice were sacrificed on the seventh day and TBARS, glutathione, nitrite activities were estimated. Monoamine oxidase inhibiting effect and anti-oxidant effect of *Foeniculum vulgare* may be contributing favorably to the antidepressant-like activity. Thus, it is concluded that *Foeniculum vulgare* extract may possess an antidepressant-like effect.

INTRODUCTION

Depression is considered as affective mood disorder which is characterized by change in mood, lack of confidence, lack of interest in surroundings, has been estimated to affect 21% of world's population and it may range from mild to severe depression, which is called as psychotic depression (WHO, 1998). According to the World Health report, approximately 450 million people suffer from a mental or behavioral disorder (WHO, 2001). Today depression is the leading cause of suicides. It is to be estimated that 3000 people lost their lives in each day and 1 million people lost their lives yearly due to suicide (WHO, 2002). Depression is the most prevalent disorder and the symptoms associated with depression changes the neurotransmitter levels in brain such as norepinephrine, serotonin and dopamine (Gold *et al.*, 1988). There are various synthetic drugs are available for the treatment of depression are SSRI (Selective serotonin reuptake inhibitors)- Fluoxetine, Fluvoxamine, Sertraline, Paroxetine, TCA (Tricyclic antidepressants)- Imipramine, Amitriptyline,

Clomipramine, Desipramine, Doxepin, MAOIs (Monoamine oxidase inhibitors)- Selegiline, Atypical antidepressant- Bupropione, Duloxetine, Venlafaxine, Mirtazapine, Trazodone and many more drugs (Ayflegül *et al.*, 2002). But with their effective treatment these drugs also associated with side effects such as sexual dysfunction (Csoka *et al.*, 2007), nausea (MacKay *et al.*, 1997), insomnia (MacKay *et al.*, 1997), mania (Settle *et al.*, 1984), tremor (Chouinard *et al.*, 1986), dystonia (Lavin *et al.*, 1993), dry mouth, hypertension (Aubin *et al.*, 2002). Among these medicinal plants, fennel is also known for its medicinal properties. *Foeniculum vulgare* is known as "Saunf" in hindi and "Madhurika" in Sanskrit. *Foeniculum vulgare* has been scientifically proved to possess various pharmacological activities, which include antidiabetic (Abou *et al.*, 2011), antioxidant (Singh *et al.*, 2006), hepatoprotective (Ozbek *et al.*, 2006), antifungal (Singh *et al.*, 2006), antimicrobial (Janseen *et al.*, 1986), antithrombotic (Tognolini *et al.*, 2007), antispasmodic (Forster *et al.*, 1980), antiosteoporotic (Fariba *et al.*, 2006) and toxicology (Mokkhasmit *et al.*, 1971). *Foeniculum vulgare* is monoamine inhibitor and the previous evidences indicate that monoamine inhibitors increase the level of norepinephrine, serotonin and dopamine in brain.

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Though the fruits of *Foeniculum vulgare* traditionally use in depression so the present study was undertaken to evaluate the antidepressant activity of *Foeniculum vulgare* fennel (fruits) by employing force swim test in rats, potentiation of norepinephrine toxicity in mice and haloperidol induce catalepsy in mice.

MATERIAL AND METHODS

Animals

Wistar albino rats and Swiss albino mice of either sex, weighing 150-180g and 20-30g procured from CPCSEA registered source.

They were housed in polypropylene cages under standard light/dark cycle, with food and water provided ad libitum. The experiments were performed between 09:00 and 16:00 h. The experimental protocols were approved by the Institutional Animal Ethics Committee and conducted according to the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India.

Chemicals

Imipramine tablets, Haloperidol ampoules and Fluoxetine capsules were purchased from the local market of Ropar, Punjab. Norepinephrine ampoules were purchased from IGMC Shimla (H.P). 5,5'-Dithio-bis (2-nitrobenzoic acid) (DTNB) Reduced Glutathione standard was purchased from Sanjay biological Amritsar, India.

NEDA and TCA was purchased from (SDFCL) S D Fine-Chem Ltd, Mumbai. TBA was purchased from Loba Chemie Pvt Ltd., Mumbai and Sulfanilamide was purchased from Titan Biotech Limited. All the reagents and chemicals used in the study were of analytical grade and were procured from Spruce Enterprises (Ambala, Haryana).

Plant material

Fruits of *Foeniculum vulgare* were procured from local market of Ropar, Punjab, India in December 2012. Authentication of plant was carried out by Dr. H.B. Singh, Chief Scientist & Head of Raw Materials Herbarium & Museum (RHMD), National Institute of Science Communication and Information Resources (NISCAIR) New Delhi.

Preparation of extract

The collected plant fruits were made dried by fan aeration in shade. The air dried plant material was then grinded to reduce them into coarse powder with the help of a suitable grinder. The powder was then subjected to extraction with methanol in Soxhlet extractor. After the complete extraction, the solvent was distilled off and concentrated on a water bath to a dry residue. The extract was concentrated by distilling of the solvent and then evaporated to dryness on water bath. A gummy concentrate of dark chocolate black color obtained was designated as methanolic extract of *Foeniculum vulgare* (MEFV). The yield of extract was found to be 7.2%.

Phytochemical evaluation

The phytochemical evaluation of methanolic extract of *Foeniculum vulgare* (MEFV) fruits was carried out as per standard methods (Khandelwal, 2004). The presence of flavonoids was determined by lead acetate test, tannins by acetic acid test, saponins by foam test and steroids was determined by Salkowski reaction.

Methodology

Overnight fasted animals were selected randomly on the day of experiment for administration of vehicle, standard drug and study drug.

Force swim test (FST)

Method of behavior despair or force swim test use as a model was proposed by (Porsolt *et al.*, 1977, 1978) to evaluate antidepressant activity. Rats were forced to move in open cylindrical container (diameter of 15cm, height 25 cm), containing fresh water of 15cm height and maintained at 25^oc. All the rats were divided in to three groups of six animals in each. Group I represented as control group that received normal saline, NaCl (5ml/kg, i.p). Group II is standard group that received imipramine (30mg/kg, i.p). Group III was represented as drug treated group which was further divided in to two groups IIIa, IIIb that received two different doses (250, 500mg/kg, p.o) of MEFV. In total time period of 10 min, the duration of immobility was recorded during the last 6 min (Thamarai *et al.*, 2012). After an initial 4 min period of vigorous activity, each animal assumed a typical immobile posture. A rat was considered to be immobile when it remained floating motionless in the water, ceased for struggling and making only minimum movements of its limbs necessary to keep its head above water. Changes in duration of immobility of each group were studied in this model.

Potentiation of norepinephrine toxicity in mice

This model is proposed by (Sigg, 1959) to evaluate antidepressant activity based on mechanism of action (Vogel, 2002). Mice were divided into four groups of six animals each. Group I animals received Normal saline (5ml/kg, i.p) and this group used as control group. Group II animals received norepinephrine (4mg/kg, i.p) and this group used as NE group. Group III animals received Imipramine (40mg/kg x 2) and norepinephrine (4mg/kg, i.p) this group used as standard group. Group IV animals received dose of MEFV (500mg/kg x 2) and norepinephrine (4mg/kg, i.p) this group used as drug treated group. In this model, imipramine and MEFV administered p.o twice 24 hr and 30 min prior to norepinephrine. Within 48 hrs after norepinephrine injection, number of lethalties or mortalities were recorded and calculated.

Haloperidol induce catalepsy (HIC) in mice

In this method catalepsy was induced by haloperidol. Mice were divided into four groups of six animals each. Group I served as normal control that received normal saline (5ml/kg, i.p).

Group II served as negative control that received haloperidol (1mg/kg, i.p). Group III served as standard group that received 5mg/kg flouxetine, i.p (Pires *et al.*, 2005) and haloperidol (1mg/kg, i.p). Group IV served as drug treated group that received MEFV (500mg/kg, p.o) and haloperidol (1mg/kg, i.p). All these doses were given to mice for seven days. The duration of catalepsy was measured at 30, 60,90,120,150,180 min. Catalepsy was assessed by means of standard bar test on every 3rd, 5th and 7th day of the drug treatment (MD *et al.*, 2012). The catalepsy was measured in time for which the mouse maintained an imposed posture with both the front limbs extended and resting on a 4 cm high wooden bar (1.0cm diameter). The end point of the catalepsy was considered to occur when both the front paws were removed from the bar or if the animal moved its head in an exploratory manner. A cut-off time of 200 seconds was applied. The effects of the test drug MEFV (500 mg/kg, p.o) and the standard drug flouxetine (5mg/kg, i.p) were assessed after their repeated dose administration in mice for seven days, 30 minutes prior to the administration of haloperidol. The mice were sacrificed on the 7th day and the TBARS, glutathione and nitrite estimations were estimated.

Biochemical parameters

Preparation of Brain homogenate

On 7th day of dosing of all groups, for the biochemical analysis, animals were scarified by anesthetized with diethyl ether immediately after behavioral assessment. The brains were removed and rinsed with 0.9%Nacl solution and weighed. Tissue was homogenized with phosphate buffer solution (ph-8) for 1 minute and then centrifuged the homogenized mixture for 10 min at 2000 rpm. An aliquot supernatant phase was collected and stored at 2-8^o C (Habibur *et al.*, 2008).

Estimation of TBARS

Lipid peroxidation was estimated spectrophotometrically in brain tissue by quantifying TBARS. In brief, for the estimation of TBARS the supernatant of the tissue homogenate was treated with 10 % TCA reagent and kept the solution in ice bath for 15 minutes. Then centrifuged the ssolution for 5 min utes at 2000 rpm. Then 2 ml of supernatant was taken out and mixed with freshly prepared 2 ml of 0.67% TBA solution. The mixture was kept in boiling water bath for 15 minutes. After cooling, the tubes were centrifuged for 10 minutes and the supernatant taken for measurement. The developed color was read at 532 nm using a UV spectrophotometer (Shimadzu UV-1700, UV-VIS double-beam Spectrophotometer) against a reagent blank and expressed as nM/mg of protein (J.Stocks *et al.*, 1974).

Estimation of Reduced glutathione

The supernatant of brain homogenate was mixed with trichloroacetic acid (10% w/v) in 1:1 ratio. The tubes were centrifuged at 10000 rpm for 10 min at 4^oC. The supernatant obtained (0.5 ml) was mixed with 2 ml of 0.3 M disodium

hydrogen phosphate. Then 0.25 ml of 0.001 M freshly prepared DTNB [5, 5-dithiobis (2-nitrobenzoic acid) dissolved in 1% w/v sodium citrate] was added and absorbance was noted spectrophotometrically (Shimadzu UV-1700, UV-VIS double-beam Spectrophotometer) at 412 nm. A standard curve was plotted using 10-100 μ M of reduced form of glutathione and results were expressed as micromoles of reduced glutathione per mg of protein (Beutler *et al.*, 1963).

Estimation of nitrite:

The accumulation of nitrite in the supernatant is an indicator of production of nitric oxide (NO), which has produced due to oxidative stress occurring in the brain. Production of NO was determined by spectrophotometric assay with Griess reagent (0.1% N-1-naphthyl ethyleneamine dihydrochloride, 1% sulphanilamide and 2.5% phosphoric acid). Equal volumes of brain homogenate and Greiss reagent were mixed, the mixture was incubated for 10 min at room temperature and the absorbance was measured at 546 nm.

The concentration of nitrite in the supernatant was determined from the standard curve and expressed in nM/mg of protein (Lidija *et al.*, 2007).

RESULTS

Phytochemical screening

The results of the preliminary phytochemical screening of methanolic extract of *Foeniculum vulgare* (MEFV) showed the presence of flavonoids, tannins, saponins and steroids.

Effect of MEFV on FST induce immobility in rats

Animals administred with imipramine 30mg/kg showed the decreased duration of immobility. Thus showing the significant (p<0.001) difference as compared to control . There was a significant (p<0.001) dose dependent decrease in duration of immobility in animals treated with 250 and 500 mg/kg doses of MEFV. MEFV showing a greater effect at 500 mg/kg dose when compared to vehicle control group. Where as, MEFV at 500mg/kg showed a significant (p<0.01) potent effect when compared to imipramine treated group. Animals treated with MEFV 250 mg/kg and 500mg/kg showed average duration of immobility respectively for a period of 6 min after 1 hr of MEFV treatment (Table 1)

Table 1: Effect of MEFV on FST induced duration of immobility in rats.

Group	Treatment	Duration of immobility (Sec) Mean \pm SEM
I (Control)	Normal saline (5ml/kg, i.p)	183.5 \pm 3.885
II (Standard)	Imipramine (30 mg/kg, i.p)	124.5 \pm 1.897 ^{a***}
IIIa (Test 1)	MEFV (250 mg/kg, p.o)	135.1 \pm 2.786 ^{a***, b*}
IIIb (Test 2)	MEFV (500 mg/kg, p.o)	104.8 \pm 3.798 ^{a***, b**}

Data are mean \pm SEM values, n=6. Data were analyzed by One way ANOVA followed by Dunnett's Multiple Comparison Test. *P < 0.05, **P < 0.01, ***P<0.001.

^acompared with control,

^bcompared with Imipramine.

Table 2: Effect of MEFV on norepinephrine potentiation toxicity in mice.

Group	Treatment	Death number of animals	Lethality (%)
I (Control)	-	0	0.0
II (NE treated)	NE (4.0 mg/kg, i.p)	2	33.3
III (Standard + NE)	Imipramine (40 x 2 mg/kg, i.p) + NE (4.0 mg/kg, i.p.)	5	83.3
IV (Test + NE)	MEFV (500 x 2 mg/kg, p.o) + NE (4.0 mg/kg, i.p)	2	33.3

Table 3: Effect of MEFV on Haloperidol induce catalepsy in mice.

Group	Treatment	Duration of Catalepsy (Sec.)		
		3 rd day	5 th day	7 th day
I (Control)	Normal saline (5ml/kg, i.p)	2.667±0.715	3.167±0.703	4.500±0.719
II (Negative control)	Haloperidol (1mg/kg, i.p)	179.00±3.337 ^{a***}	182.500±2.790 ^{a***}	185.833±2.272 ^{a***}
III (Standard)	Flouxetine (5mg/kg, i.p) + Haloperidol (1mg/kg, i.p)	80.500±2.232 ^{b***}	84.000±2.490 ^{b***}	89.000±2.378 ^{b***}
IV (Test drug)	MEFV (500mg/kg, p.o) + Haloperidol (1mg/kg, i.p)	116.117±2.971 ^{b***}	121.167±2.664 ^{b***}	125.167±2.442 ^{b***}

Data are mean ± SEM values, n=6. Data were analyzed by One way ANOVA followed by Dunnett's Multiple Comparison Test. *P < 0.05, **P < 0.01, ***P<0.001.

^acompared with control group.

^bcompared with haloperidol treated group.

Table 4: Effect of MEFV on the TBARS level in mice brain.

Group	Treatment for 7 days	TBARS level (nM/ mg protein) [Mean ± SEM]
I (Control Group)	Normal Saline (5 ml/kg, i.p)	6.22 ± 0.56
II (Negative Control)	Haloperidol (1 mg/kg, i.p)	15.83 ± 0.22 ^{a***}
III (Standard Group)	Flouxetine (5 mg/kg, i.p) + Haloperidol (1 mg/kg, i.p)	8.88 ± 0.393 ^{b***}
IV (Test drug)	MEFV (500 mg/kg, p.o) + Haloperidol (1 mg/kg, i.p)	10.573 ± 0.414 ^{b***}

Data are mean ± SEM values, n=6. Data were analyzed by One way ANOVA followed by Dunnett's Multiple Comparison Test. *P < 0.05, **P < 0.01, ***P<0.001.

^acompared with control group.

^bcompared with haloperidol treated group.

Table 5: Effect of MEFV on Nitrite level in mice brain.

Group	Treatment for 7 days	Nitrites level (µM/ mg protein) [Mean ± SEM]
I (Control Group)	Normal Saline (5ml/kg, i.p)	6.441 ± 0.415
II (Negative Control)	Haloperidol (1 mg/kg, i.p)	22.016 ± 0.728 ^{a***}
III (Standard Group)	Flouxetine (5mg/kg, i.p) + Haloperidol (1mg/kg, i.p)	11.673 ± 0.739 ^{b***}
IV (Test drug)	MEFV (500 mg/kg, p.o) + Haloperidol (1 mg/kg, i.p)	16.599 ± 0.510 ^{b***}

Data are mean ± SEM values, n=6. Data were analyzed by One way ANOVA followed by Dunnett's Multiple Comparison Test. *P < 0.05, **P < 0.01, ***P<0.001.

^acompared with control group.

^bcompared with haloperidol treated group.

Table 6: Effect of MEFV on the GSH level of mice brain.

Group	Treatment for 7 days	Reduced GSH level (µM/ mg protein) [Mean ± SEM]
I (Control Group)	Normal Saline 5ml/kg i.p	30.096 ± 1.232
II (Negative Control)	Haloperidol 1 mg/kg i.p	8.363 ± 0.441 ^{a***}
III (Standard Group)	Flouxetine 5mg/kg i.p + Haloperidol 1mg/kg i.p	20.522 ± 2.056 ^{b***}
IV (Test drug)	MEFV 500 mg/kg p.o + Haloperidol 1 mg/kg i.p	17.167 ± 1.279 ^{b**}

Data are mean ± SEM values, n=6. Data were analyzed by One way ANOVA followed by Dunnett's Multiple Comparison Test. *P < 0.05, **P < 0.01, ***P<0.001.

^acompared with control group.

^bcompared with haloperidol treated group.

Effect of MEFV on norepinephrine potentiation toxicity in mice

Animals of Group I received normal saline showed no mortality in mice. Group II animals received NE (4 mg/kg i.p) showed 2 mortality in mice, Group III animals receive imipramine (40 x 2 mg/kg i.p) twice daily 30 min before NE administration showed significant increase in mortalities of mice. And in IV group animals receive MEFV (500 x 2 mg/kg p.o) twice daily 30 min before NE administration showed only 2 mortalities in mice. Imipramine potentiated markedly NE toxicity in mice but MEFV did not show potentiated markedly NE toxicity in mice (Table 2.)

Effect of MEFV on Haloperidol induce catalepsy in mice

The cataleptic behavior (inability to correct abnormal posture) of haloperidol (1mg/kg, i.p) treated animal was found to increase significantly on 3rd or 5th day and also on the 7th day of treatment when compared to control group animals.

Administration of Flouxetine (5mg/kg, i.p) and MEFV (500 mg/kg, p.o) to haloperidol (1mg/kg, i.p) treated animals significantly (p < 0.001) prevented the increase in catalepsy when compared to haloperidol treated group on 7th day (Table 3).

Biochemical parameters

Effect of MEFV on TBARS level in mice brain

Haloperidol treatment to mice for 7 days induced lipid peroxidation as indicated by a significant ($P < 0.001$) rise in brain MDA levels compared with the vehicle treated mice.

Administration of Fluoxetine (5mg/kg, i.p) and MEFV (500mg/kg, p.o) to haloperidol treated animals significantly ($P < 0.001$) respectively reversed the extent of lipid peroxidation compared with haloperidol treated mice (Table 4).

Effect of MEFV on Nitrites levels in mice brain

As shown in table 5 the brain nitrite levels in haloperidol treated group significantly ($p < 0.001$) increase as compared to control group. Administration of Fluoxetine (5mg/kg, i.p) and MEFV (500mg/kg, p.o) to haloperidol treated animals significantly ($P < 0.001$) decrease the nitrite level as compared to haloperidol treated group (Table 5)

Effect of MEFV on GSH levels in mice brain

Statistical analysis of brain GSH levels showed a significant difference ($P < 0.001$) between the vehicle treated and haloperidol treated mice. Administration of Fluoxetine (5mg/kg, i.p) and MEFV (500mg/kg, p.o) to haloperidol treated animals significantly ($P < 0.001$) and ($p < 0.01$) increase GSH levels as compared to haloperidol treated group (Table 6)

DISCUSSION

Depression is a mood disorder which is the most common illness, which affects the mood, lack of interest in surroundings, decreased energy level, lack of confidence, poor concentration, disturbed sleep and the arousal of negative thoughts. It is mainly associated with anxiety. Ayurveda provides lot of medicinal plants to counteract these side effects. *Foeniculum vulgare* is one of the important medicinal plant knowing for its various medicinal properties.

The most widely used model for antidepressant screening is FST. And the other models which are used in this study is potentiation of norepinephrine toxicity in mice and haloperidol induce catalepsy in mice. FST is quite sensitive and relatively specific to all major classes of antidepressants (Porsolt *et al.*, 1977). In FST, Results showed that the administration of *Foeniculum vulgare* produce antidepressant activity at a dose of 250 and 500 mg/kg body weight in a dose dependent manner as compared to control group and imipramine group. *Foeniculum vulgare* at a dose of 500mg/kg showed potent effect to decrease the immobility period as compared to imipramine (30 mg/kg). Numerous studies have demonstrated that antidepressant drugs such as imipramine stimulated the action of serotonin and act by inhibiting the reuptake of biogenic amines in CNS.

There is another model potentiation of norepinephrine toxicity in mice is used. This model reveals an adrenergic component of pharmacological activity of antidepressants. In the present study imipramine potentiated markedly NE toxicity in

mice but MEFV did not potentiated markedly NE toxicity in mice. So results showed that imipramine is a good adrenergic component but MEFV may not be good adrenergic component.

In Haloperidol induce catalepsy, administration of *Foeniculum vulgare* at dose 500 mg/Kg p.o. for 7 days and the duration of catalepsy were observed on 3rd 5th and 7th day showed to decrease the duration of catalepsy as compared to haloperidol treated group. The standard drug Fluoxetine (5mg/kg) also showed significant reduction in duration of catalepsy as compared to haloperidol treated animals. From various previous research showed that the treatment with haloperidol induces the production of free radical but the exact mechanisms by which haloperidol increased free radical production were not clear. With chronic dosing in mice for 7 days, haloperidol is associated with the greatest level of oxidative stress. The oxidative stress was measured through determination of levels of TBARs (or MDA), reduced glutathione and nitrite. Also generation of oxidative stress, indicated by decrease in levels of endogenous antioxidant marker(GSH) and increase in the extent of lipid peroxidation (TBARs) and increase in nitrite levels was found to be the cause of depression and catalepsy. In the present study treatment of mice for seven days with Fluoxetine at the dose of 5 mg/kg (i.p) and MEFV (500 mg/kg) significantly ($p < 0.001$) decreased the levels of TBARs and nitrites whereas increase the level of GSH revealed the antioxidant nature of the extract and also an indication of effective herbal antidepressant. In the present study, preliminary phytochemical studies of the methanolic extract of *Foeniculum vulgare* showed the presence of flavonoids, saponins, tannins and steroids. It has been reported that flavonoids may be responsible for antidepressant activity in experimental animal models.

CONCLUSION

The present study thus proves that the methanolic extract of *Foeniculum vulgare* possess significant antidepressant activity due to its reduction in the immobility period in FST and reduction in the duration of catalepsy in haloperidol induce catalepsy. But MEFV does not potentiate markedly NE toxicity in mice. The study though supports the traditional claim, further studies are needed to identify the chemical constituents that are responsible for the antidepressant effect.

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