



## **Antidepressant and Antiamnesic Potential of *Foeniculum vulgare***

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### **Authors' contributions**

All authors worked in collaboration for this study. Author AA designed the study, wrote the protocol and wrote the first draft of the manuscript. Author RI proposed the study, literature research and helped in writing final draft of manuscript, Author AA managed the analyses of the study. Author UN performed the statistical analysis. Author QUA managed the literature searches. All authors read and approved the final manuscript.

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### **ABSTRACT**

**Aim:** To evaluate the antiamnesic and antidepressant effect of *Foeniculum vulgare* whole crushed seeds.

**Study Design:** Laboratory based randomized control study.

**Place and Duration of Study:** Department of Pharmacology, University of Karachi between January 2018 to August 2018.

**Methodology:** Thirty swiss albino mice and wistar rats were divided equally in three groups. Control group was fed on standard rodent diet, group 2 was fed on 2% *Foeniculum vulgare* diet and group 3 was given 4% *Foeniculum vulgare* diet. Antidepressant activity was assessed using forced swimming test. Memory enhancement effect was evaluated by stationary rod test, passive avoidance test and water maze test.

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**Results:** Increased duration of struggling time was noted in both group 2 and group 3 as compared to control in forced swimming test. Decrease in time to reach platform in both water maze and stationary rod test was recorded in both the study group (group 2 & 3). Increase in step through latency was also seen in group 2 and group 3 as compared to control group.

**Conclusion:** The results showed the memory enhancing and antidepressant actions of *Foeniculum*.

**Keywords:** Antiamnesic; antidepressant; *Foeniculum vulgare*; mice; rats.

## 1. INTRODUCTION

The brain's ability to save and recall data, information and experiences is memory. Multiple factors like aging, anxiety, alteration in hormones, medication, lack of sleep etc may influence memory. The learning ability is mostly dependent upon proper working of cholinergic system and concentration of acetylcholine in brain [1]. Increase in acetylcholine by inhibition of acetylcholinesterase enhances memory [2]. Adrenaline, noradrenaline and dopamine are also found to have role in memory as documented in previous studies [3,4]. Prefrontal cortex is related to numeric learning while hippocampus is linked to spatial recall [5,6,7].

Psychiatric disorder like depression also affects memory. Depression is a common term with prevalence of 10-15% worldwide [8]. It is characterized by lack of sleep, low mood, decreased appetite and loss of interest in life. Increasing number of people are taking their lives due to this ailment [9]. Alteration in levels of certain neurotransmitters, such as, dopamine, norepinephrine and serotonin is noted in patients of depression [10]. Many drugs are developed for this common disorder such as selective serotonin reuptake inhibitors and tricyclic antidepressants. The side effects associated with these drugs has reverted attention of researchers to natural and herbal sources [11].

*Foeniculum vulgare* is one of the many herbs investigated as remedial agent for different diseases. Being member of Apiaceae family, it grows in most parts of the world [12]. It has small yellow flowers arranged in groups or bunches and slender leaves [13]. Aromatic property of *Foeniculum vulgare* is responsible for its utilization in cosmetic industry as well as food and beverages [14]. Though leaves and stalks of herb are consumed as vegetable, but seeds are considered as most useful [15].

It has been found to be effective in disorders of gastrointestinal tract as carminative and anti-

colic. Its antioxidant potential has found its use as anxiolytic [16]. Moreover fennel seeds are utilized as analgesic, anti-inflammatory, antispasmodic, diuretic, galactagogue, hepatoprotective, secretomotor and in eye lotions in European and Mediterranean regions. Menopausal symptoms, nausea, obesity and renal calculi are also treated by fennel seeds [17]

The major components of essential oil of this herb are  $\alpha$ -phellandrene estragole, fenchone and tansanethole [18], camphene, cymene,  $\alpha$ -pinene,  $\beta$ -pinene, myrcene,  $\gamma$ -terpinene and P-anisaldehyde [15].

The aim of this study is to evaluate anti-amnesic and antidepressant potential of *Foeniculum vulgare*.

## 2. MATERIALS AND METHODS

### 2.1 Study Design

This laboratory centered randomized controlled trial was done in the Pharmacology Department of University of Karachi. The Study protocol was approved by Board of Advanced Studies and Research (BASR), University of Karachi, Resol. No. 10(P)14.

**Herb material:** Seeds of *Foeniculum vulgare*, bought from a local departmental store and identified from the Pharmacognosy Department, Faculty of Pharmacy and Pharmaceutical Sciences University of Karachi, and given the voucher no. FVF-02-15/17.

### 2.2 Animals

Adult, healthy, Swiss albino mice (weight 20-25 gram) and wistar rats (weight 220-250 gram) of either sex, were taken from the Animal house of Pharmacology department of University of Karachi. Mice were housed in transparent cages having saw dust spread on floor. For these rodents, the temperature was maintained at 22-25°C and humidity of 50-60% with 12 hour light and dark cycle [19].

## 2.3 Grouping and Dosing

Thirty mice and rats were divided equally into three groups.

Group 1 was named Control-group and animals were fed on standard rodent diet.

Group 2 and Group 3 were taken as treated-group 2% *Foeniculum vulgare* (2%FV) and treated-group 4% *Foeniculum vulgare* (4%FV), respectively, and given specially prepared diet pellets. To prepare these special diet pellets, *Foeniculum vulgare* whole seeds were crushed (moulinex grinder model number 02029-221), and mixed in ratio of 2% and 4% with standard diet of mice. These special diet pellets were kept under hygienic condition in store for animal food of Animal house of Faculty of Pharmacy, University of Karachi. Standard rodent diet contained fish meal (11.1%), corn gluten (11.1%), wheat flour (44.4%), gram flour (11.1%), barley flour (22.25) and milk powder (1%) [20].

Dosing continued for sixty days and all rodents were provided water adlibitum. Tests for anti-amnesic and antidepressant activity.

## 2.4 Stationary Rod Crossing Activity

It was utilized to note balance and memory of mice of both sexes. The stationary rod apparatus was an elevated and fixed steel rod (elevation: 18 inches, length: 2 feet and diameter: 5/8 inch) with platforms at ends. All mice of three groups were trained before start of study to walk across rod to platform. For fortnightly observations, each selected mouse was placed on rod's mid-point individually and was made walk across rod to platform [21]. Time taken to reach the platform from mid-point was noted for each mouse.

## 2.5 Water Maze Test

This test and apparatus was designed by Richard Morris and was used to assess spatial learning and recall. The apparatus, a perspex tank (122 x 122 cm) with a central platform. Tank was filled with water to 24 cm with platform submerged 2 cm below water surface. Starch was mixed in water to make it opaque. Rats were trained individually, before start of study, to reach submerged platform [22]. Time to reach the platform was noted for each rat at interval of 15 days for two months.

## 2.6 Passive Avoidance Test

This apparatus comprised of rectangular box divided in two unequal chambers; larger chamber

was lightened and smaller chamber was dark with a grid floor linked to electricity source. Individually, each rat was trained by placing in lightened chamber and whenever the animal entered darkened chamber electric shock of 1.5 mA and 50 hertz was given to foot of rat for 1 second. After 24 hours of training first reading was taken for each rat. Step through latency was the time taken by rat to enter darker chamber and it was noted during its placement in apparatus for 5 minutes [23]. Poor memory was indicated by decrease in step through latency. The test was conducted on day 1, 7, 21, 30 and 45.

## 2.7 Forced Swimming Test

This test is considered as a standard for assessment and comparison of antidepressant as it induces depression in rats. The rodents were placed in water filled (up to 30 cm) glass cylinder of 45 cm height and 20 cm diameter. Temperature of water was maintained at 23-25°C. Struggling time and immobility time showing sign of depression were noted for period of 5 minutes for each selected rat [24].

## 2.8 Statistical Analysis

SPSS 17.0 was used to analyse data. All values were expressed as mean±SD. Values were compared by Analysis of variance (ANOVA) followed by post hoc Tukey's test.

## 3. RESULTS AND DISCUSSION

### 3.1 Stationary Rod Crossing Activity

The stationary rod crossing time of both treated groups decreased from day 1 to end of study. Statistically significant decrease in time to cross stationary rod was seen in both 2% *Foeniculum vulgare* and 4% *Foeniculum vulgare* group on all observation days in comparison to control. Similarly, statistically significant difference was seen in time to cross stationary rod among the two study groups from day 15 to day 60. Within each treated group stationary rod crossing time decreased from day 1 to day 60 (Table 1).

### 3.2 Water Maze Test

The time to reach platform decreased significantly in both treated groups as compared to control group throughout the study period. Statistically significant difference was noted among 2% and 4% *Foeniculum vulgare* groups

on day 15, 30 and 45. Within 2% *Foeniculum vulgare* group time to reach platform decreased significantly on all study days; whereas in 4% *Foeniculum vulgare* group statistical significant decrease was observed only from day 1 to day 15 (Table 2).

### 3.3 Passive Avoidance Test

Animals in both the treated groups showed statistically significant increase in step through latency from beginning to end of study as compared to control. Among study groups significant difference was noted on day 15, 21

and 30. Within both treated groups step through latency increased from beginning to end of study (Table 3).

### 3.4 Forced Swimming Test

Statistically significant increase in struggling time was observed in both treated groups as compared to control on all observation days. On day 15 and 30 significant difference was noted among 2% *Foeniculum vulgare* and 4% *Foeniculum vulgare* groups. Increase in struggling time was seen within each group (treated) on day 15, 30 and 45 (Table 4).

**Table 1. Effect of *Foeniculum vulgare* diet in different ratio on stationary rod crossing test**

Groups	Time to cross stationary rod (Seconds)				
	Day 1	Day 15	Day 30	Day 45	Day 60
Control	43.80±4.73	34.30±3.09	31.21±3.69	29.43±1.42	28.50±2.25
2% FV	42.40±5.50	10.20±2.4***\$\$\$	7.68±1.22***	5.54±1.63***	4.61±2.21***
4% FV	41.10±5.08	19.23±2.28***!!\$\$\$	17.50±1.87***!!	12.15±1.81***!\$\$	11.98±1.32***!!

10 Values are mean ± SD, data analysed by one way ANOVA followed by multiple comparison (post hoc Tukey's test)

\*\*\* p=0.001 is considered significant as compared to control

!!p=0.01 is considered significant when both study groups are compared

!!!p=0.001 is considered significant when both study groups are compared

\$\$ p=0.01 is considered significant when days within a study group are compared

\$\$\$ p=0.001 is considered significant when days within a study group are compared

**Table 2. Effect of *Foeniculum vulgare* diet in different ratio on water maze test**

Groups	TIME (Seconds) taken to reach platform				
	Day 1	Day 15	Day 30	Day 45	Day 60
CONTROL	41.79±1.48	42.58±2.38	41.13±2.59	39.03±1.35	38.10±1.19
2% FV	38.80±2.55	16.73±2.31***\$\$\$	11.77±1.47***\$	6.08±1.90***\$	1.83±1.15***\$
4% FV	39.24±1.83	6.46±1.74***!!\$\$\$	2.26±1.23***!!	1.89±1.54***!	1.30±2.84***

10 Values are mean ± SD, data analysed by one way ANOVA followed by multiple comparison (post hoc Tukey's test)

\*\*\* p=0.001 is considered significant as compared to control

! p=0.05 is considered significant when both study groups are compared

!!!p=0.001 is considered significant when both study groups are compared

\$ p=0.05 is considered significant when days within a study group are compared

\$\$\$ p=0.001 is considered significant when days within a study group are compared

**Table 3. Effect of *Foeniculum vulgare* diet in different ratio on passive avoidance test**

Groups	Step through latency (Seconds)				
	Day 1	Day 7	Day 21	Day 30	Day 45
Control	18.79±2.53	20.57±2.05	22.04±1.34	20.46±1.52	21±2.52
2% FV	20.18±1.58	275.03±2.30***\$\$\$	280.95±1.69***\$	286.82±1.18***\$	297.4±3.8***\$\$\$
4% FV	21.21±1.64	280.21±3.25***!!\$\$\$	287.77±2.57***\$	291.55±1.74***!	298.44±3.85***\$

10 Values are mean ± SD, data analysed by one way ANOVA followed by multiple comparison (post hoc Tukey's test)

\*\*\* p=0.001 is considered significant as compared to control

! p=0.05 is considered significant when both study groups are compared

!!!p=0.001 is considered significant when both study groups are compared

\$ p=0.05 is considered significant when days within a study group are compared

\$\$\$ p=0.001 is considered significant when days within a study group are compared

**Table 4. Effect of *Foeniculum vulgarediet* in different ratio on forced swimming test**

Groups	Struggling time (Seconds)				
	Day 0	Day15	Day30	Day 45	Day 60
Contrl	90.46±3.16	90.47±1.91	90.48±0.81	89.79±2.80	91.44±1.48
2% FV	91.44±2.67	166.56±3.04 ***\$\$\$	248.21±1.40 ***\$\$\$	289.30±1.49 ***\$\$\$	288.68±1.32 ***
4% FV	88.84±3.77	177.85±1.00 ***!\$\$\$	253.98±2.45 ***!\$\$\$	291.50±1.35 ***\$\$\$	291.14±2.94 ***

10 Values are mean ± SD, data analysed by one way ANOVA followed by multiple comparison (post hoc Tukey's test)

\*\*\* p=0.001 is considered significant as compared to control

!!p=0.001 is considered significant when both study groups are compared

\$\$\$ p=0.001 is considered significant when days within a study group are compared

#### 4. DISCUSSION

Ability of a person to retain and recall sensory data is memory. It relates to retaining of the learned knowledge. Apart from aging, many pathological conditions such as alzheimer's, attention deficit hyperactivity disorder, brain injury, lack of oxygen and psychiatric disorders like anxiety and depression have negative effect on memory. Memory deficit may temporary or permanent and vary in severity. It is usually associated with injury to neurons especially of cholinergic nervous system which have a basic role in memory and cognitive functions [25].

We used three tests to assess memory enhancing effect of *Foeniculum vulgare* whole seeds. These tests are considered as gold standard for evaluation of memory status especially water maze test which analyze spatial memory. Spatial memory is dependent upon acetylcholine concentration in hippocampus. Inhibition of acetylcholine esterase activity by *Foeniculum vulgare* aqueous extract has been noted in a study which supports our results. Two compounds coumarin and 1,8-cineole found in *Foeniculum vulgare* may exhibit anticholinestrase action [26]. Rodents fed on *Foeniculum vulgare* containing diet in our study, showed significant improvement in memory and similar results were found in other studies where extract of *Foeniculum vulgare* was used [27,28].

It is a known fact that depression being a behavioral illness markedly affects quality of life of an individual and its prevalence is on the increase. Changes in major neurotransmitters of brain namely dopamine, noradrenaline and serotonin is associated with major depression [11]. Unwanted effects of currently available medicines for this disorder have directed patients towards herbal therapies and aromatherapy. Aromatherapy is being utilized for treatment and management of chronic pain, insomnia, neurological and psychiatric disorders [29].

Aromatic essential oil of *Foeniculum vulgare* has been used successfully for management of depression [30]. The results of our study using forced swimming test are in accordance with study conducted by Jamwal and Kumar, where methanolic extract was used [31], as well as with the study done by Perveen et al. using oil of *Foeniculum vulgare* [8].

It has been noted recently that depressive disorders are related to oxidative stress and inflammation as patients of depression show increased levels of cytokines and other inflammatory markers in blood which reach brain and effect regions related to depression [32]. Extensive research has been done to find the link between psychiatric illness and oxidative stress and free radicals are found to be a key factor in development of depression [33,34]. Hazardous effect of oxidative stress in these disorders could be due to neuro-inflammation, neuroplastic deterioration and deficit in signalling [35,36]. Patients having elevated inflammatory biomarkers tend to show resistance to treatment [31].

Anethole, a compound found in *Foeniculum vulgare* has shown anti-inflammatory and antioxidant potential [37]. Anethole exhibit antioxidant effect by inhibition of lipid peroxidation and free radical scavenging. Moreover, it also has inhibitory action on monoamine oxidase B, therefore, prevent breakdown of monoamines and decrease oxidative stress [38,39].

Furthermore, kamferol and coumarin, found in *Foeniculum vulgare* also inhibit monoamine oxidase enzymes A and B, thus producing anti-inflammatory and antioxidant action [26,40].

Nowadays, selective serotonin reuptake inhibitors (SSRI) are considered as preferred treatment of depression with the drawback of causing unwanted weight gain and sexual

dysfunction [41]. Hyperlipidemia, may also result from long term usage of these drugs which may be caused by up-regulation of genes of lipid synthesis [42]. This hyperlipidemia results in decreased therapeutic response to SSRI.

Numerous studies documented hypolipidemic action of *Foeniculum vulgare*, caused by lowering of peroxidative damage, enhancing beta oxidation and decreasing lipid absorption [43,44,45] thus contributing to antidepressant action of *Foeniculum vulgare*.

## 5. CONCLUSION

Antiamnesic and antidepressant action of seeds of *Foeniculum vulgare* are shown in our study. This action should be explored in clinical studies as raw form of *Foeniculum vulgare* seeds is easy to use and available for all.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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