



## **Protective Role of *Foeniculum vulgare* Mill. in Brain Disorders; A New Window**

**Afshan Abbas<sup>1\*</sup>, Rahila Ikram<sup>2</sup>, Faiza Hasan<sup>3</sup>, Saadia Iftikhar<sup>4</sup>,  
Qurrat ul Ain Bukhari<sup>1</sup>, Uzair Nisar<sup>2,5</sup> and Abeer Adil<sup>6</sup>**

<sup>1</sup>Sir Syed College of Medical Sciences for Girls, Rojhan Street, Block 5, Clifton, Karachi, Pakistan.

<sup>2</sup>University of Karachi, Gulshan-e-Iqbal, Karachi, Pakistan.

<sup>3</sup>Fatima Jinnah Dental College, 100 Foot Road, Azam Town Adjacent to D.H.A. Phase 1 Defence Housing Authority, Karachi, Pakistan.

<sup>4</sup>Bahria University, 13 National Stadium Road, Karachi, Pakistan.

<sup>5</sup>Ziauddin University, Clifton, Karachi, Pakistan.

<sup>6</sup>Jinnah University for Women, Street 1, 5-C, Nazimabad, Karachi, Pakistan.

### **Authors' contributions**

This work was carried out in collaboration among all authors. Author AA designed the study, performed the statistical analysis and wrote the protocol. Author RI reviewed and edited the final draft. Author FH managed the analyses of the study. Author SI wrote the first draft of the manuscript. Author QAB managed the literature searches. Author AA supervised. Author UN verified the analysis. All authors read and approved the final manuscript.

### **Article Information**

DOI: 10.9734/JPRI/2020/v32i1330593

#### Editor(s):

(1) Dr. Takashi Ikeno, National Center of Neurology and Psychiatry, Japan.

#### Reviewers:

(1) Dorge Marmitt, University of Taquari Valley, Brazil.

(2) Baraa al-Mansour, Syria.

(3) G. Lal, ICAR-National Research Centre on Seed Spices, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/59445>

**Original Research Article**

**Received 20 May 2020**  
**Accepted 25 July 2020**  
**Published 06 August 2020**

### **ABSTRACT**

**Aims:** Alzheimer disease and epilepsy are two of the central nervous system (CNS) disorders that not only affect the quality of life of patients but also of family members and caretakers. Remedies for these illnesses are available in allopathic medicines but not without side effects. Herbal products are being investigated for these ailments. Protective role of *Foeniculum vulgare* Mill. was assessed in this study.

**Study Design:** Laboratory based randomized controlled trial.

**Place and Duration of Study:** Conducted in Pharmacology Department of University of Karachi, between March 2018 and April 2018.

**Methodology:** Mice and rats were divided in three groups, control, 2% and 4% *F. vulgare* groups, each containing 10 rodents. Control group was fed standard rodent diet, whereas, study groups were given 2% and 4% *F. vulgare* seeds (crushed) incorporated in standard rodent diet. Epilepsy model was made for mice and Alzheimer disease study was done using rats and passive avoidance test.

**Results:** Lower incidence of seizures and mortality in both study groups as compared to control in epilepsy model and memory retaining effect in both treated groups in Alzheimer disease model was recorded with statistical significance.

**Conclusion:** Clinical studies should be conducted to validate the protective role of this herb in these disorders.

**Keywords:** Alzheimer disease; epilepsy; *Foeniculum vulgare*; mice; rats.

## 1. INTRODUCTION

Alzheimer disease is considered as most common cause of dementia in elderly [1-3]. Almost 30 million people are affected by this disease world over [4]. It is said to be a main reason of handicap and incapacity in elderly [5]. Alzheimer disease patients and their families face stigma as documented in 2016 World Alzheimer report. Caretaking of Alzheimer disease patient is a stressful task. To provide support Alzheimer associations are formed world over [6,7]. Genetic risk factor, vascular risk factors such as hypertension, diabetes and hypercholesterolemia plus life style risk factors like smoking, dietary habits and use of insecticides contribute to pathogenesis of this disease [8,9]. Microglia are responsible healthy central nervous system (CNS) as these cells remove debris and pathogenic elements or tissue as well as, also contribute to repair process [10]. Inflammation plays a pivotal role in pathogenesis of this neurodegenerative disorder [11]. Donepezil is used as one of the standard drugs for treatment of Alzheimer disease [12].

Another common brain disease is epilepsy which is a persistent disorder, causing seizures [13]. Genetic predisposition and acquired factors like head injury, stroke and infections contribute to pathogenesis of epilepsy. This disease is common in developing countries [14] exhibiting more prevalence in rural areas [15]. Excessive and sustained neuronal discharge is salient feature of all types of seizures [16]. Patients suffering from seizure disorders often complain about quality of life [17]. Ketogenic diet is being investigated as treatment and management of epilepsy [18]. Though multiple drugs are available for management of this disease but with side effects and do not promote the cure of the disease [19].

To provide an alternative to synthetic medicines, for decades herbal medicines are being evaluated for their therapeutic and protective potential against many ailments especially chronic disorders [20,21] that negatively affect the quality of life of patients as well as caregivers. *F. vulgare* is a herb, belonging to Apicaceae family, growing all around the globe. All parts of herb are consumed as condiment, flavoring agent and remedial agent. Traditional use of this plant has proven its beneficial effect as diuretic, antihypertensive, lipid lowering, stress relieving and in multiple other ailments. Anxiolytic, antidepressant and anti-amnesic potential have also been assessed [22-24]. We used seeds of this herb to evaluate protective role in Alzheimer disease and epilepsy.

## 2. MATERIALS AND METHODS

### 2.1 Study Design

It was a laboratory based randomized controlled study conducted in the Pharmacology Department of University of Karachi. The ethical standards were based on the Interdisciplinary Principles and Guidelines for the Use of Animals in Research, Testing, and Education issued by the New York Academy of Sciences Adhoc Committee on Animal Research and the study design and protocol was authorized by Board of Advanced Studies and Research (BASR), University of Karachi, Resol. No. 10(P)14 [22].

### 2.2 Plant Material

*Foeniculum vulgare* dried fruits were bought from a local departmental store and identified from the Pharmacognosy Department, Faculty of Pharmacy and Pharmaceutical Sciences University of Karachi, and assigned voucher no. VVF-02-15/17.2.2 [23].

### 2.3 Animals

Healthy, adult albino mice (weight 20-25 gram) and wistar rats (weight 220-250 gram) of either sex, taken from the Animal house of Pharmacology department of University of Karachi were used for the study. Mice and rats were kept in transparent cages with saw dust covered floor. For these animals, temperature and humidity was maintained at 22-25°C and 50-60%, respectively, along with 12 hourly light and dark cycle [22,23].

Animals were segregated equally in four groups; control, 2% and 4% *F. vulgare* and standard groups. Mice groups were employed for epilepsy study and rat groups for Alzheimer model. Mice and rats of control and standard groups were provided standard rodent diet while *F. vulgare* groups were given especially formulated diet pellets containing *F. vulgare* coarsely crushed seeds in 2% and 4% proportion [25]. These diet pellets were stowed hygienically in storeroom 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%) [22]. All rodents were provided water ad libitum.

### 2.4 Epilepsy Model

For this model seizures were induced by using strychnine (1 mg/kg) given intraperitoneally and diazepam was used as standard drug. Study groups (2% and 4% *F. vulgare*) were fed their special dietary pellets an hour (60 minutes) before strychnine. In control and standard group mice, distilled water 0.1 ml and intraperitoneal injection of diazepam 5mg/kg respectively, was given half an hour before injecting convulsion inducing drug. After strychnine injection all mice were placed separately in transparent boxes and were observed for next 30 minutes. Time to seizure onset, frequency and duration of jerks was recorded of all mice using a stopwatch and a counter. The rodents were considered protected if they were alive after half an hour [26,27].

### 2.5 Alzheimer Disease Model

It was same as explained by Georgieva-Kotetarova and Kostadinova [28]. Diazepam was used to induce dementia and donepezil 5mg/70kg was used as standard drug. All animals of four groups were given respective diets and drug (donepezil for standard group

only) for 12 days and after half an hour each rat was injected intraperitoneally 2.5 mg/kg diazepam daily. Passive avoidance test was conducted on day 9 and day 12 [29] of the study to note the protective effect of *F. vulgare* as compared to control and standard as memory retaining agent.

### 2.6 Passive Avoidance Test

It was done using special apparatus having larger lit zone and a smaller darker chamber having grid floor linked to an electric source. Each animal was trained before start of dosing by placement in lit chamber. Whenever rodent stepped in darker part an electric shock of 1.5 mA and 50 Hz was sent in grid floor for 1 second. During study period step-through latency that is, time passed before each rat stepped in darker chamber was noted. Each selected rat was kept in passive avoidance apparatus and observed for duration of 5 minutes [29,23].

The apparatus of this test comprised of a box with a bigger lightened section and a smaller unlit chamber. The unlit chamber is closed and had a grid floor connected to an electric shock source. During training period each rat was positioned in the lit chamber. As soon as the rat stepped in the unlit section, an electric foot shock was passed in grid floor [30]. Electric shock of 1.5mA and 50 Hz was passed for a second. Memory was tested 24 h after foot shock given in training period for test phase. In test period, the time elapse before each animal entered the unlit zone called step-through latency was recorded. Each rat was observed for 5 minutes after placement in apparatus. Reduction in the step- through latency is taken as bad memory retention [29].

All rodents were sacrificed at the end of study (day 12) and histopathology was done of animals' brain tissue at Panjwani Center For Molecular Medicine and Drug Diagnostic lab, University of Karachi.

### 2.7 Statistical Analysis

Results were analyzed using statistical package for social sciences (SPSS) 17.0 [22]. All readings were shown as mean  $\pm$  standard deviation (SD) and were compared by Analysis of variance (ANOVA) followed by post hoc Tukey's test. *P* value = 0.05 was considered significant, *P* value = 0.01 was considered very significant and *P* value = 0.001 was considered as highly significant.

### 3. RESULTS

#### 3.1 Epilepsy Study

It was evident from results that mice fed on *F. vulgare* diets both 2% and 4% showed significant protection against strychnine induced seizures in comparison to both control and standard groups. Mice given 4% *F. vulgare* diet developed seizures later than those given 2% *F. vulgare* diet. Similarly, frequency and duration of seizures was also lesser in 4% *F. vulgare* group. Safety factor noted in *F. vulgare* groups was comparable and nearer to standard group (Tables 1, 2, 3 and 4).

#### 3.2 Alzheimer Study

In Alzheimer disease model memory retaining effect of *F. vulgare* groups was matching that of standard group. Step through latency increased more after 12 days in both of the treated groups (Table 5).

#### 3.3 Microscopic Findings of Alzheimer Study

Histopathology of brain tissue also showed protective effect of *Foeniculum vulgare* (Figs. 1, 2, 3 & 4).

**Table 1. Effect of *F. vulgare* diet in different ratio on seizure onset in strychnine induced seizure model**

Groups	Seizure onset in sec (Latency)	P value
Control group (Distilled water + Strychnine)	104.94±3.87	
2% <i>F. vulgare</i> group (2% FV diet + Strychnine)	183.96±2.28	0.001 <sup>a</sup> 0.001 <sup>b</sup>
4% <i>F. vulgare</i> group (4% FV diet + strychnine)	281.64±1.55	0.001 <sup>a</sup> 0.001 <sup>b</sup> 0.001 <sup>c</sup>
Standard group (Diazepam+ Strychnine)	384.17±2.87	0.001 <sup>a</sup>

*n*=10. Values are mean ± SD, data analyzed by one way ANOVA followed by multiple comparison (Post hoc Tukey's test)

<sup>a</sup>P-value is highly significant in comparison to control

<sup>b</sup>P-value is highly significant compared to standard group

<sup>c</sup>P-value is highly significant among the study groups

**Table 2. Effect of *F. vulgare* diet in different ratio on number of convulsions in strychnine induced seizure model**

Groups	No. of Convulsions (Frequency)	P value
Control group (Distilled water + Strychnine)	20.44±3.12	
2% <i>F. vulgare</i> group (2% FV diet + Strychnine)	8.02±3.85	0.001 <sup>a</sup> 0.001 <sup>b</sup>
4% <i>F. vulgare</i> group (4% FV diet + strychnine)	5.64±2.17	0.001 <sup>a</sup>
Standard group (Diazepam+ Strychnine)	2.99±2.01	0.001

*n*=10. Values are mean ± SD, data analyzed by one way ANOVA followed by multiple comparison (Post hoc Tukey's test)

<sup>a</sup>P-value is highly significant in comparison to control

<sup>b</sup>P-value is highly significant compared to standard group

**Table 3. Effect of *F. vulgare* diet in different ratio on total duration of seizure in strychnine induced seizure model**

Groups	Total duration of seizures (sec)	P value
Control group (Distilled water + Strychnine)	89.93±3.59	
2% <i>F. vulgare</i> group (2% FV diet + Strychnine)	12.11±3.81	0.001
4% <i>F. vulgare</i> group (4% FV diet + strychnine)	10.95±2.94	0.001
Standard group (Diazepam+ Strychnine)	9.6±2.19	0.001

*n*=10. Values are mean ± SD, data analyzed by one way ANOVA followed by multiple comparison (post hoc Tukey's test)

P-value is highly significant in comparison to control

**Table 4. Effect of *F. vulgare* diet in different ration fatality rate in strychnine induced seizure model**

Groups	Animals		Mortality (%)	Safety (%)
	Alive	Dead		
Control group	1	9	90	10
2% <i>F. vulgare</i> group	8	2	20	80
4% <i>F. vulgare</i> group	9	1	10	90
Standard group (Diazepam)	10	0	0	100

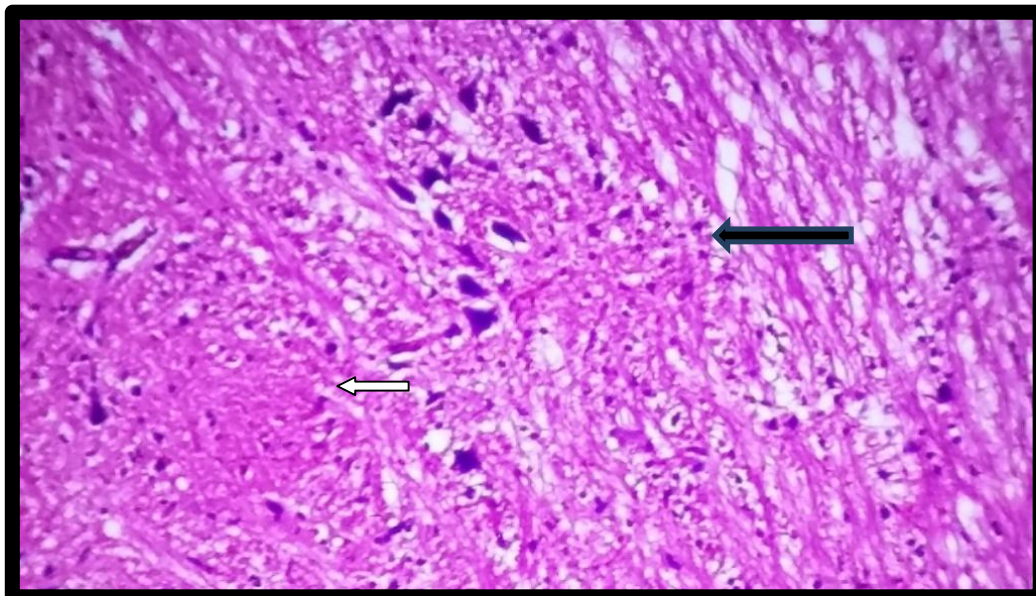
**Table 5. Effect of *F. vulgare* diet in different ratio on alzheimer induced dementia**

Groups	Step Through Latency (Seconds)			
	Day 9	P-value	Day 12	P-value
Control group	27.95±1.12		28.14±1.60	
2% <i>F. vulgare</i> group	295.68±1.73	0.001 <sup>a</sup>	300.12±2.87	0.001 <sup>a</sup> 0.01 <sup>b</sup>
4% <i>F. vulgare</i> group	299.5±3.95	0.001 <sup>a</sup>	300.66±1.21	0.001 <sup>a</sup>
Standard group (Donezepil 5 mg/70 kg)	299.27±1.15	0.001 <sup>a</sup>	301.09±1.75	0.001 <sup>a</sup>

*n*=10. Values are mean ± SD, data analyzed by one way ANOVA followed by multiple comparison (Post hoc Tukey's test)

<sup>a</sup>P-value is highly significant in comparison to control

<sup>b</sup>P-value is very significant within the group



**Fig. 1. 2% *F. vulgare* group**

Histological section showing brain tissue with intact histological architecture. Scattered lymphocytic infiltration (Mild to Moderate black arrow). Gliosis and edema present. No necrosis seen. Clusters of neurons are intact

#### 4. DISCUSSION

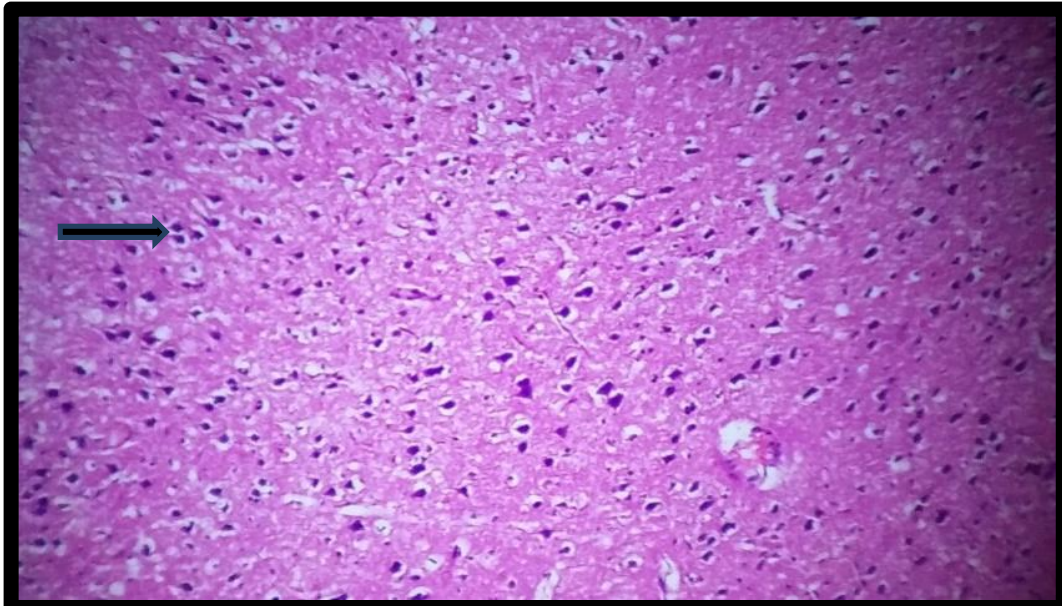
Alzheimer disease is a prevalent and progressive neurodegenerative disease, showing troublesome deterioration of memory and cognitive system of elderly population, around the globe. It is a chronic disorder with behavioral and personality alteration and deprivation of

thought process [31]. It is said to be one of the main etiology of dementia of old age, spreading over duration of almost 8.5 years from appearance of clinical manifestations to death [32]. It usually starts with deficit of short term memory, unable to recall names and addresses, later as the disease progresses, the memory loss increases and



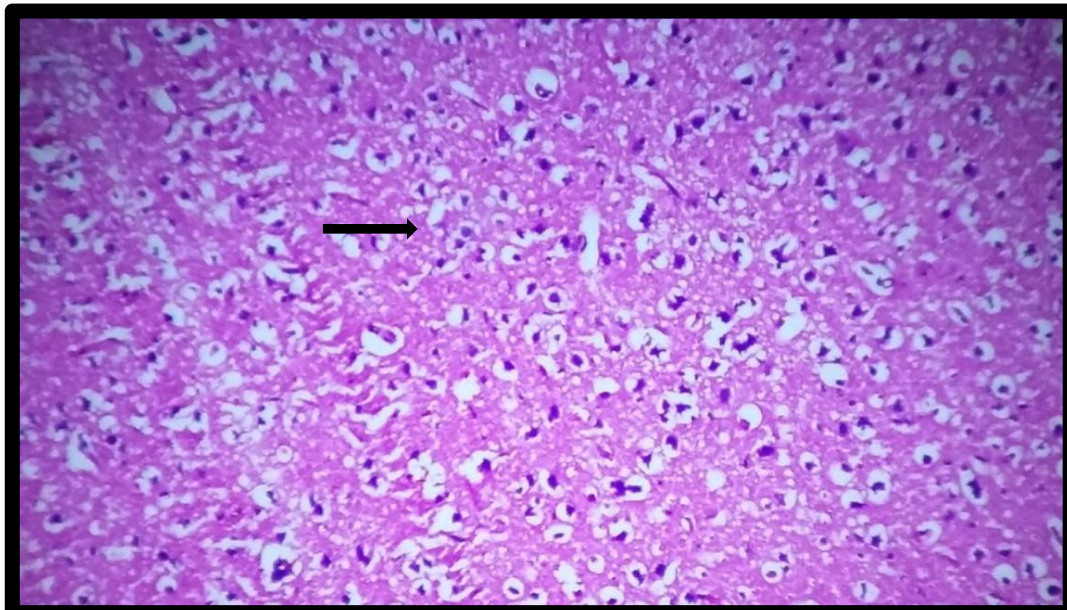
patients tend to forget their way to home. Unfortunately, this disease is not remediable but could be slowed down. Central nervous system zones associated with cognitive ability, mainly, the neocortex and hippocampus,

are mostly affected. Scientific research has shown beneficial effects of the herbal medicines in regard to the management of several disorders including linked with memory problems [33].



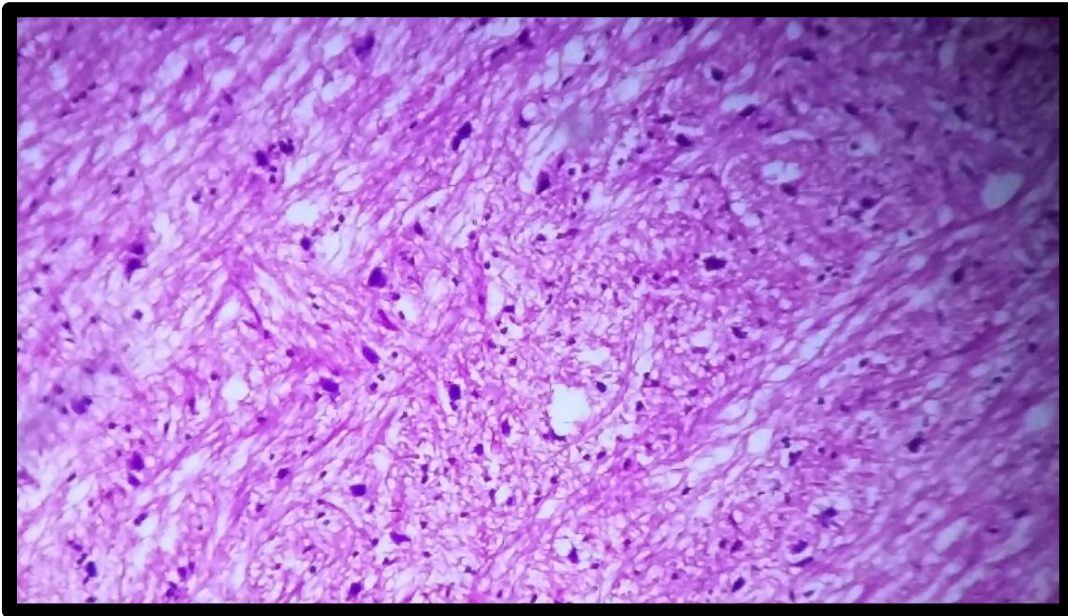
**Fig. 2. 4% *F. vulgare* group**

*Histological section reveals scattered / mild lymphocytic infiltration. Focal gliosis seen, prominent neurons but no remarkable or neurofibrillary tangles noted*



**Fig. 3. Control group**

*Intermediate magnification showing brain tissue having largely intact architecture. Gliosis is present. Scattered lymphocytes are seen around the lesion*



**Fig. 4. Standard group**

*Histological view reveal brain tissue with intact architecture. No gliosis was observed. No remarkable changes in meningeal layer coverings*

Passive avoidance test, a penalty paradigm is utilized for assessing memory, a salient feature of Alzheimer disease. Our results demonstrated a protective action of *F. vulgare* in retention of memory in rodents since the time to enter darker chamber (step through latency) increased notably in both of the treated groups. A study done by Joshe and Parle [34] support our results by showing increase in step through latency on day 9 of study. They used extract of *F. vulgare* in 50 mg, 100 mg and 200 mg doses in mice. Best results were observed in mice receiving 200 mg of extract.

It is believed that *F. vulgare* improves learning capacity and recall by positively influencing cholinergic system. Anti-inflammatory potential of this herb is an additional element for neuro-protection, since chronic inflammation is seen in different areas of brains of these patient brains [35]. Limonene, a constituent of *F. vulgare* act as analgesic and anti-inflammatory agent by decreasing synthesis and release inflammatory mediators [36-38]. Part played by polyunsaturated fatty acids (PUFA) in preservation of central nervous system architecture and functioning is a known fact. PUFA deficient diet may cause disorders of central nervous system.  $\alpha$ -Linolenic acid an important PUFA, found in *F. vulgare*, has role in learning and memory plus it may play a basic

part in maintenance of dopamine and norepinephrine levels in brain areas linked to recall and cognitive abilities, such as cerebral cortex, hippocampus and striatum. Epidemiological studies showed reduction in risk of developing this disease in people who consume mainly fruits and vegetables in their diet [39].

Almost, 1% population of the world is suffering from epilepsy. Epilepsy is neurological ailment, with recurrent loss of consciousness [40]. It is a disease of central nervous system which have both motor and sensory components, displaying abnormal automatic motor and sensory movements [41]. In our study remarkably reduced onset, duration and frequency of convulsions was noted in both 2% and 4% *F. vulgare* treated groups. This herb also possesses a protective effect as evident by its safety effect as seen in our study. These results are supported by the study in which *F. vulgare* methanolic extract and essence were evaluated for anticonvulsive effect in mice using different doses ranging from 100 to 1000 mg and 100 to 600 mg respectively. Both extract and essence (essential oil) showed anticonvulsive action in dose dependent manner as observed in our study [42]. Another earlier study showed that *F. vulgare* reduced the neurotoxic action of strychnine. They assessed effect of *F. vulgare*

along with other spices on liver microsomal monooxygenase activity by alteration of hexobarbital narcosis and strychnine mortality in mice. Significant reduction was noted in toxicity due to strychnine [43] as recorded in our study where latency, duration and frequency of seizures reduced as well as fatality rate.

It was noted in a study that daily intake of *F. vulgare* seed extract 300 mg/kg body weight enhances concentration of catecholamines like dopamine, norepinephrine and serotonin in various regions of brain and lowers the sodium levels in the same areas of brain [44]. Similarly, an earlier study showed that linolenic acid, a constituent of *F. vulgare*, elevates the amount of neurotransmitters in brain [45]. Quercetin, is found in *F. vulgare*. Previous studies indicate that antiepileptic action of quercetin is via activation of GABA<sub>A</sub> receptors and by inhibition of NMDA receptors [46]. Furthermore, it is suggested that thymol may cause partial blockage of voltage gated sodium channels [47] required for nerve impulse propagation and membrane excitability [48]. It could be said that *F. vulgare* exert anti-convulsive effect through activation of GABA receptors, Partial blockage of voltage gated Na channels and inhibition of NMDA receptors as also suggested by Eghbali et al [42] by utilizing its mentholic extract.

## 5. CONCLUSION

Results of this trial showed protective role of *F. vulgare* in Alzheimer disease and epilepsy in experimental animals. Further suggestion is that clinical studies should be done in this regard, as utilizing seeds of this herb would be cost effective and within the reach of every individual.

## 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 Resol. No. 10(P)14.

## ACKNOWLEDGEMENTS

We are extremely thankful to Mr. Kashif for his support in conducting this study.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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