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EFFECTS OF THE MIXTURE DRIED FIGS (FICUS CARICA) AND OLIVE OIL ON AMNESIA MODEL OF ALZHEIMER'S INDUCED BY SCOPOLAMINE IN MALE ALBINO RATS

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ABSTRACT

Alzheimer disease is a neurodegenerative problem that progressively results in the impairment of cognitive functions in the brain. This research aimed to define neural influences of the chronic administration of the mixture Figs (Ficus carica) and Olive oil (Olea europaea) as medicinal plants to delay cholinergic abnormality and oxidative stress in amnesia induced by Scopolamine as a model of Alzheimer's disease in the hippocampus region of male Albino Rats. The rats were divided into five equal main groups (ten rats for each group): the first main group was labeled negative control receiving normal saline, rats in the second group received a dose of mixture dried Figs (F. carica) and Olive oil (4ml/kg) orally for four weeks (experientially period), the third group produced memory deficits by scopolamine (2 mg/kg , i.p at daily), the fourth group was treated using a mixture of Figs and Olive oil at daily oral dose of (4 ml/kg) followed by the intraperitoneal dose of scopolamine (2 mg/kg) for four weeks, finally, the fifth group was given an oral dose daily of (1 mg/kg) Rivastigmine and Scopolamine (2 mg/kg at daily). At the end of the experimental period (four weeks); the changes of behavioral activities and the acetylcholinesterase (AchE) levels in the homogenate hippocampus of the rats' brains were investigated. This research was to assess the efficacy of Ficus carica and Olive oil mixture on cognitive functions. The findings showed that the combination of dried Figs and Olive oil produced a considerable decrease in AchE levels in the hippocampus. The outcomes suggested that the daily administration of the mixture F. carica and Olive oil resulted in the enhancement of behavioral activities and reduction in the levels of AchE due to the antioxidant properties and protective benefits of the mixture.

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Introduction

One of the most considerable global health problems facing the generation is dementia, including Alzheimer's disease (AD). AD has been considered the main reason for dementia [1]. Alzheimer is a chronic, progressive disorder defined by deterioration in the symptoms of behavioral and cognitive abilities [2]. The disease has been shown to be the sixth major reason for death [3]. AD is differentiated by memory loss, behavior deterioration, performance weakness, and cognitive decline [4]. Amnesia, or lack of memory, predominantly is an initial characteristic of the cognitive degradation or dementia [5]. By 2050, the worldwide prevalence of AD disease could be quadruple, by that time, 1 in 85 persons might be struggling with the disease [6]. It has been suggested that oxidative stress is participated in neurodegeneration leading to cell death [7]. Loss of memory is one of the main changes that occur in AD, and it is due to the loss of acetylcholine (Ach) [8]. The neurotransmitters such as ACh play a vital role in learning and memory. ACh activates muscles, and assists with stimulation memory and learning. In fact, patients with AD lack the levels of ACh. Some studies reported that plaques may be one of the causes for elevating the activity of acetylcholinesterase which is involved in breaking down ACh contributing to developing the symptoms of AD [9].

Scopolamine, a muscarinic antagonist, is a widely used experimental model that mimics AD induced memory dysfunction. The model is beneficial in screening for new drugs for AD management [10]. Amnesia can be induced in rats by administration of scopolamineby blocking presynaptic muscarinic receptors [11].

Natural bioactive compounds from herbal origin provide a probable therapeutic alternative for AD management [12, 13]. The natural antioxidants have awarded distinctive concern as food complements. Besides, many previous researches reported the suppression of amyloid beta (Aβ) plaque synthesis in vitro and in vivo by multiple medicinal herbs and their active

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constituents [14]. Some medicinal plants including Figs and Olive oil involved in the treatment of AD and enhancing general health.

Ficus carica (Figs) belongs to the family of Moracae. This plant contains natural chemicals that play a significant function in memory deficit and AD due to its antioxidant activity [15]. The nutritional value of this fruit was high that associated with lowering the risk of various diseases. *Ficus carica*, at lower doses, causes a mild memory enhancing effect. Furthermore, at higher doses, *F. carica* increases learning abilities and behavioral changes [15]. Some research studies have observed that *Ficus* species show anticholinesterase characteristics, capacity to promote acetylcholine levels and anti-dementia activity in rats [16]. The fruit extract of *F. carica* enhanced learning and memory activity in comparison to scopolamine treated rats [17].

The olive (*Olea europaea*) is from Oleaceae family. The regular consumption of virgin olive oil is beneficial in combating oxidative stress concerning diseases [18]. Olive oil has been shown to have a protective effect against some age-related pathologies and neurological diseases such as Alzheimer's disease [19-21].

The target of the present research was to examine the influences of mixture Figs and Olive oil on memory tasks in rats. In the present research, the maze test and AchE assay were used for the assessment of memory functions.

Materials and Methods

Materials

Animals

Male albino rats (fifty rats) were obtained from King Fahd Medical Research Center (KFMRC), King Abdul-Aziz University, Jeddah, animal house, and weighing 140–160 g. The rats were divided in groups and housed in cages with relative humidity of 70%, in a stable temperature (24±1°C) and light-controlled room on an alternating 12:12 h light/dark cycle with given free access to food and water. The rats were acclimatized to the laboratory environment for one week before starting the experiment.

Chemicals

Scopolamine was ordered from Sigma chemical company (St. Louis, USA). Rivastigmine (Exelon®) 1.5mg capsule was obtained from (Novartis Company, Basel, Switzerland). Dried Figs (*Ficus carica*) were purchased from local store Abazeer, Jeddah. Olive oil for Ergon Greece was purchased from Abazeer store, Jeddah. Sodium chloride (NaCl) and sodium hydroxide (NaOH) were obtained from (Panreac, Barcelona, Spain). Potassium chloride (KCl), disodium phosphate (Na_2HPO_4), potassium dihydrogen phosphate (KH_2PO_4), and AchE Enzyme Linked Immunosorbent Assay (ELISA) kit.

Experimental Design

The rats of the experimental animals were randomly assigned to five groups of 10 rats each (n=10/group) as the following:

Group I: the rats of this group were orally given 0.9 ml of saline solution (0.9% NaCl) daily for four weeks.

Group II: this group was given a dose of the mixture dried Fig (*Ficus carica*) and Olive oil (4ml/kg) daily for 4 weeks [22].

Group III: the rats in this group were injected a dose of Scopolamine (2 mg/ kg, i.p) dissolved in saline daily for 4 weeks [23].

Group IV: This group was treated by the extract of mixture dried Fig *(F. carica)* and olive oil at an oral dose of (4 ml/kg), followed by the injection of Scopolamine (2 mg/kg, i.p) after 40 minutes [22, 23].

Group V: the rats were given a dose of Rivastigmine at an oral dose of (1 mg/kg), followed by Scopolamine (2 mg/kg, i.p) after 40 minutes daily for 4 weeks [23].

Behavior Study (Maze learning test)

The maze test is a useful method for studying learning and memory by measuring the time spent and the memory error. The maze measuring was 100x 60 cm (L x W), and the walls were 20 cm high. The maze was constructed of wood, and consisted of a glass cover at the top of the maze to prevent the rats from escape and to do the investigation. There was no need for learning the rules of this trial test. The procedures focused on the food restriction during the performance and appetitive motivation tasks that utilized food as a reward. Before the beginning of the test, the male albino rats were prevented from access to the food for 23 h. Then, the rats were motivated by providing the food at the end of the maze. The rats were given one trial per day for five days. The spending time to successfully reach the food (minutes), and the number of errors (passage in blind alleys) were recorded [24].

Biochemical assay

ELISA kits for the measurement of hippocampus tissues homogenate for Acetylcholinesterase (AchE) (Catalog Number # MBS038896).

Principle of the test

This kit was used for quantitative determination of AchE level in the sample, adopt clarified rat AchE coat micro ELISA strip plate wells were used to make solid-phase antibody, AchE and AchE antibody which has been labeled with horseradish peroxidase (HRP) was added to wells to form antibody-antigen-antibody-enzyme complex, after that, they were washed completely, the reaction antibody Tetramethylbenzidine (TMB) substrate solution was added , TMB substrate became blue under HRP enzyme-catalyzed, the reaction was terminated by the addition of stop solution, and the alternative color was

measured at a wavelength of 450 nanometer (nm). The concentration of AchE in the samples was then determined by comparing the optical density (O.D.) of the samples to the standard curve [25].

Assay procedure

1) All reagents and samples must be at room temperature (18°C-25°C) naturally for 30 mins before starting the assay procedure.
2) Add standard 50 microliter (µl) to each standard well, add sample 50 µl to each sample well, add sample diluent 50 µl to each blank/control well.
3) Add 100 µl of HRP-conjugate reagent to each well, cover with an adhesive strip, and incubate them for 60 mins at 37°C.
4) Wash the microtiter plate 4 times.
5) Add chromogen solution A 50 µl and chromogen solution B 50 µl to each well. Gently mix and then protect from light to incubate for 15 mins at 37°C.
6) Add 50 µl stop solution to each well.
7) Read the O.D. at 450 nm using a microelisa stripplate reader within 15 mins (the concentration of AchE was expressed in U/mg tissue weight).

Statistical analysis

The data were analyzed by using One-way ANOVA analysis of variance (Tukey's test). The results of values were expressed as mean ± standard error (SD). P-value <0.05 was recognized as a significant value. The statistical analysis was made by Statistical Package for Social Science (SPSS program, version 25) (SPSS Inc., Chicago, IL, USA).

Results:

Behavior study (Maze learning test)

The elapsed time through maze

Table (1) and Figure (1) showed that the effect of the mixture dried Figs (*Ficus carica)* and Olive oil on protection from scopolamine induced amnesia model of AD in rats by utilizing maze learning test (the spent time through the maze). At the first day, in the maze for scopolamine group, there was a significantly increase of the time spent for the rats against the control group (P <0.05). Moreover, the elapsed time in the maze significantly decreased in groups (*Ficus carica*and Olive oil mixture with Scopolamine) and (Rivastigmine with Scopolamine) group comparing to the Scopolamine group (P <0.05). At the day 2,3,4 and 5, the duration of elapsed time in the maze was considerably prolonged in scopolamine group than to (control group), (*Ficus carica* and olive oil mixture with Scopolamine) and (Rivastigmine with Scopolamine) (P <0.05).

Number of errors in maze test

Table (2) and **Figure (2)** showed the mixture effect of dried Figs (*Ficus carica*) and Olive oil on protection from Scopolamine cause amnesia model of AD in rats by utilizing maze learning test (number of errors in maze). At the day 1, 2, 3, 4 and 5 of the maze tests, the number of errors in the maze was remarkably higher compared with the negative group (P <0.05). However, at the day 1, 3, 4 of the maze tests, the number of errors was significantly decreased at (*Ficus carica* and Olive oil mixture with Scopolamine) than to the Scopolamine group (P <0.05). The (Rivastigmine with scopolamine) groups showed a considerable decrease at the five days versus Scopolamine group (P <0.05).

Table 1: Evaluation of the mixture protective effects of dried Figs *(Ficus carica)* and Olive oil on scopolamine induced amnesia model of Alzheimer's disease in rats by utilizing maze learning test (the elapsed time through maze) for 5 days.

Treatment groups	**Elapsed time in maze (min)**				
	Days				
	Day 1	Day 2	Day 3	Day 4	Day 5
Control	3.50 ± 0.18	2.31 ± 0.30	2.01 ± 0.36	1.34 ± 0.07	0.30 ± 0.05
Mixture of dried Figs *(Ficus carica)*and Olive oil	2.41 ± 0.30	1.91 ± 0.38	1.86 ± 0.40	1.56 ± 0.09	0.87 ± 0.29
Scopolamine	10.93 ± 0.91 [a]	7.15 ± 0.36 [a]	6.70 ± 0.26 [a]	5.21 ± 0.03 [a]	5.69 ± 0.22 [a]
Mixture of dried Figs *(Ficus carica)*and Olive oil + Scopolamine	2.5 ± 0.84 [b]	1.28 ± 0.04 [b]	1.98 ± 0.22 [b]	3.02 ± 0.22 [b]	1.34 ± 0.05 [b]
Rivastigmine + Scopolamine	3.74 ± 0.43 [b]	3.49 ± 0.41 [b]	3.29 ± 0.44 [b]	3.22 ± 0.03 [b]	1.89 ± 0.21 [b]

The values were expressed as means ± S.E of 10 animals. P<0.05 (significant)

a = Significant difference comparing to the control group.

b = Significant difference comparing to scopolamine group.

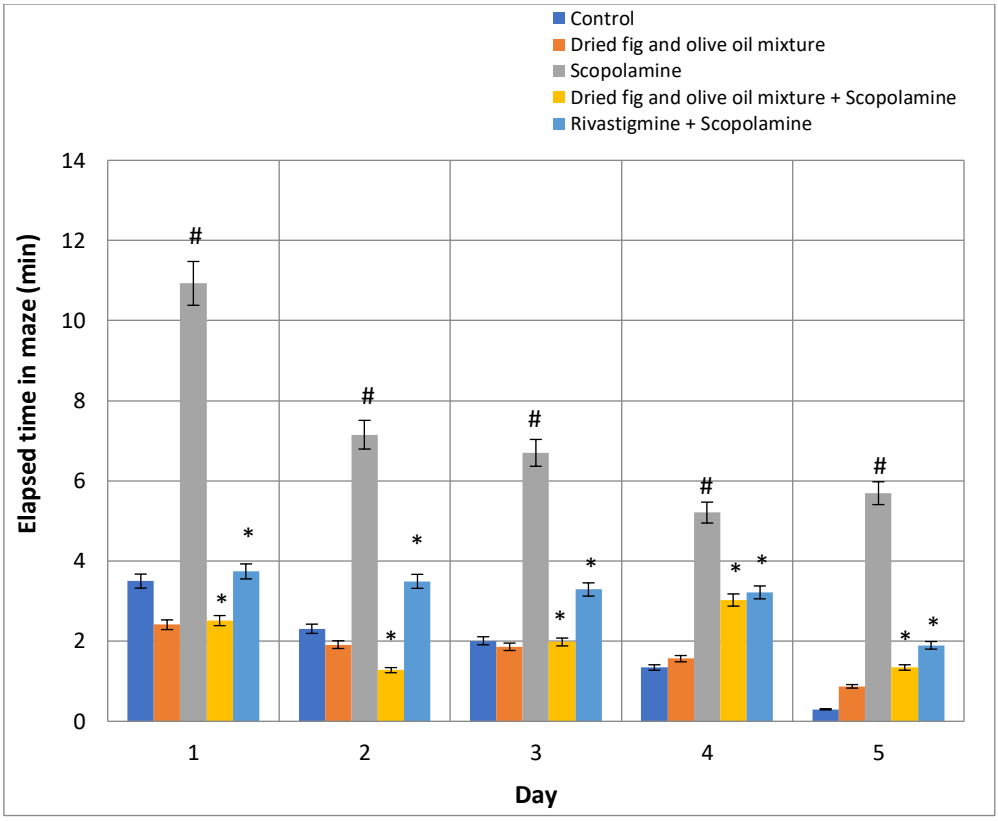

Figure 1: The mixture protective effects of dried Figs *(Ficus carica)* and Olive oil on scopolamine induced amnesia model of Alzheimer's disease in rats by utilizing maze learning test (the elapsed time through maze) for 5 days.
Data was expressed as mean+/- standard error.
*: significance versus scopolamine (P <0.05)
#: significance versus control (P <0.05)
Significance was made using One Way ANOVA test (Tukey test).

Table 2: Evaluation the mixture protective effects of dried Figs *(Ficus carica)* and Olive oil on scopolamine induced amnesia model of Alzheimer's disease in rats by using maze learning test (number of errors in maze) for 5 days.

Treatment groups	**Number of errors in maze**				
	Days				
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Control	3.5 ± 0.67	1.0 ± 0.44	1.5 ± 0.22	0.0 ± 0.0	1.0 ± 0.0
Mixture of dried Figs *(Ficus carica)*and Olive oil	3.0 ± 0.0	2.0 ± 0.37	1.7 ± 0.42	2.0 ± 0.37	1.7 ± 0.21
Scopolamine	8.7 ± 0.21 [a]	5.3 ± 0.56 [a]	4.7 ± 0.42 [a]	3.7 ± 0.42 [a]	3.0 ± 0.73 [a]
Mixture of dried Figs *(Ficus carica)*and Olive oil + Scopolamine	5.3 ± 0.42 [b]	4.0 ± 0.37	2.3 ± 0.21 [b]	1.3 ± 0.21 [b]	1.7 ± 0.42
Rivastigmine + Scopolamine	5.0 ± 0.63 [b]	3.3 ± 0.21 [b]	2.7 ± 0.42 [b]	1.7 ± 0.21 [b]	1.0 ± 0.0 [b]

The values were expressed as means ± S.E of 10 animals. P<0.05 (significant)
a = Significant difference comparing to the control group.
b = Significant difference comparing to scopolamine group.

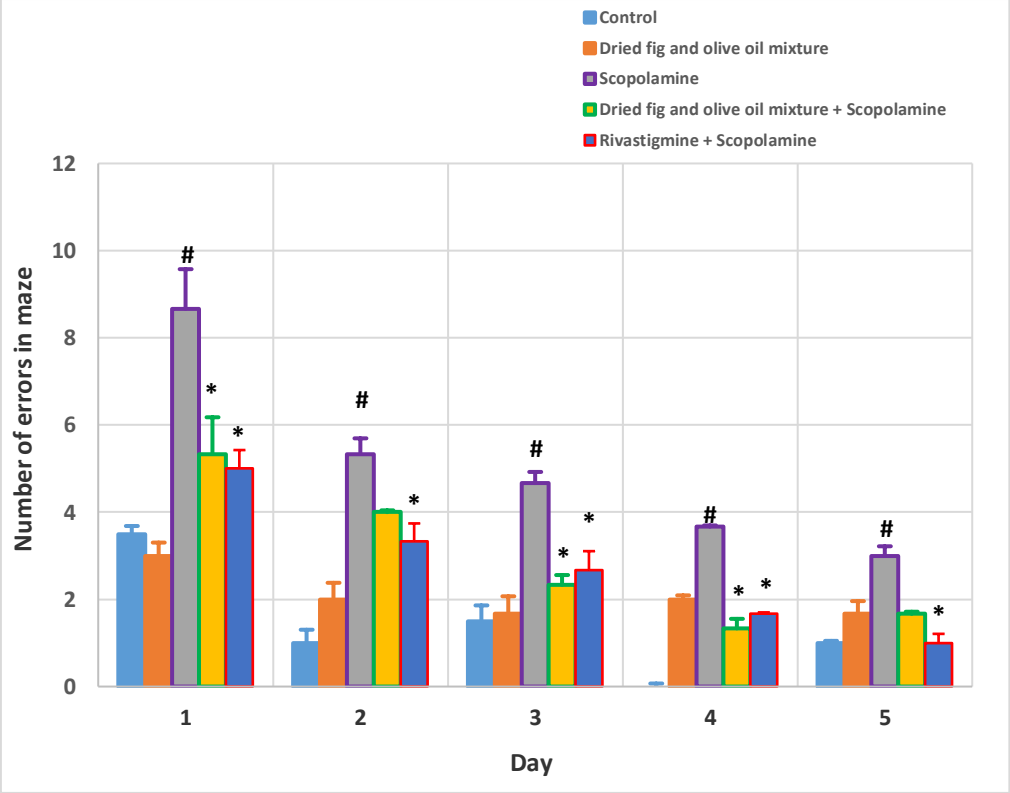

Figure 2: The mixture protective effects of dried Figs *(Ficus carica)* and Olive oil on scopolamine induced amnesia model of Alzheimer's disease in rats by using maze learning test (number of errors in maze) for 5 days.
Data was expressed as mean+/- standard error.
*: significance versus scopolamine (P <0.05)
#: significance versus control (P <0.05)
Significance was made using One Way ANOVA test (Tukey test).

Biochemical Analysis

Hippocampus homogenate levels of Acetylcholinesterase (AchE)

(Table.(3) and (Figure. 3) showed the effects of the mixture dried Figs(*Ficus carica*) and Olive oil on the AchE levels. The hippocampus homogenate of AchE levels was considerable elevated in Scopolamine group than the negative group ($p<0.05$). AchE levels were significantly decreased in (mixture of dried Figs and Olive oil with Scopolamine) group and (Rivastigmine with Scopolamine) group than the scopolamine group ($p<0.05$).

Table 3: Evaluation of the mixture protective effects of dried Figs *(Ficus carica)* and Olive oil on Acetylcholinesterase (AchE) levels in hippocampus homogenate (umol/mg) from scopolamine induced amnesia model of Alzheimer's disease in rats for 4 weeks.

Parameter / Groups	Hippocampus homogenate levels ofAchE (umol/mg) for 4 weeks
Control	1.891± 0.110
Mixture of dried Figs(*Ficus carica*) and Olive oil	1.498± 0.127
Scopolamine	3.023± 0.211[a]
Mixture of dried Figs(*Ficus carica*) and Olive oil +Scopolamine	1.955± 0.286[b]
Rivastigmine +Scopolamine	1.792± 0.241[b]

The values were expressed as means ± S. E of 10 animals. P<0.05 (significant)
a = Significant difference comparing to the normal control group.
b = Significant difference comparing to scopolamine group.

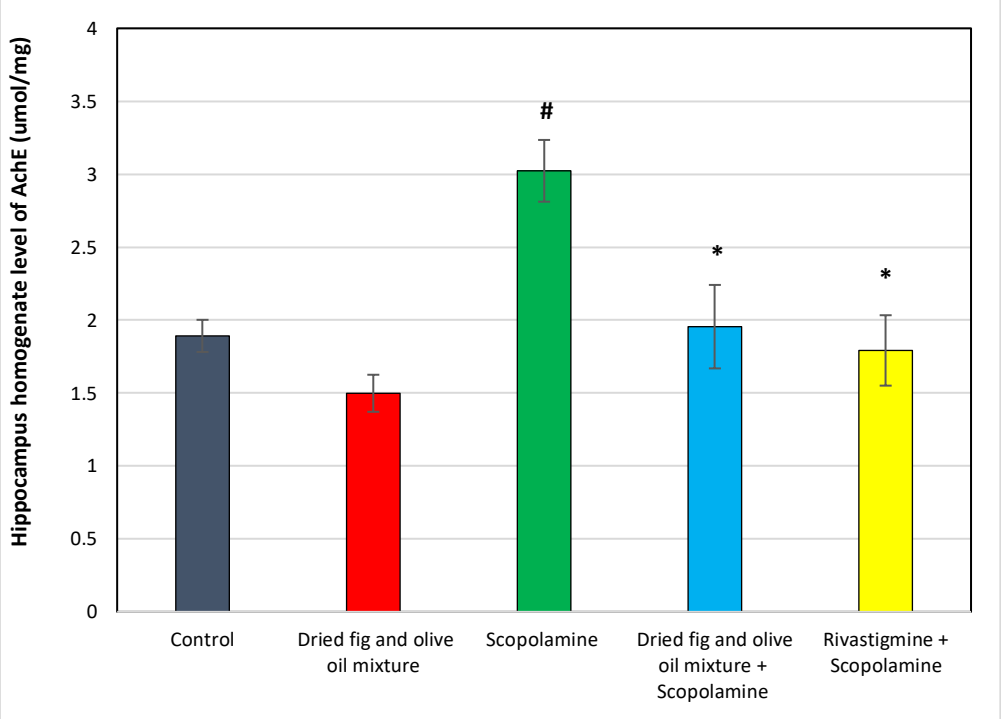

Figure 3: The mixture's protective effects of dried Figs *(Ficus carica)* and Olive oil on Acetylcholinesterase (AchE) levels in hippocampus homogenate (umol/mg) from scopolamine induced amnesia model of Alzheimer's disease in rats for 4 weeks.
Data was expressed as mean+/- standard error.
#: significance versus control (P <0.05)
*: significance versus scopolamine (P <0.05)
Significance was made using One Way ANOVA test (Tukey test).

Discussion

AD disease is a chronic neurodegenerative disease that begins slowly and gets worse over time on memory, thinking skills and even the ability to perform daily functions [26]. Natural medicines display multiple options to minimize the progression and the appearance of numerous types of disease including AD disease [27]. From the current results, the mixture of (Figs and Olive oil) could potentially represent an important alternative drug for addressing amnesia in Alzheimer's patients.
The findings of the maze test in the study revealed that 4 weeks injection of scopolamine (2 mg/kg/ day) in rats led to the impairment of the learning and memory abilities compared with the normal rats that were manifested by the increase in the elapse time and the increase in the number of errors in the maze learning test to get the food.
Behavioral studies have also shown that scopolamine induced a marked rise in memory errors. Almost the same findings were reported by [28]. It was documented that the impacts of chronic scopolamine injection on learning and memory might be linked to permanent alterations in the cascades that were implicated in the behavioral function and were modified by the cholinergic system [29].
It was noticed that the mixture (Figs and Olive oil) improved the performance of the spatial learning by decreasing the spent time in the treated rats compared to Scopolamine group. It was reported that the supplementation of figs in the diet for mice caused positive behaviors alterations which could reduce Aβ deposition and oxidative stress [30]. The analysis of the results obtained by the maze test for the *Ficus carica* treated male albino rats indicated a gradual improvement in memory formation as their latency to reach the food at the end decreased. The findings of this work obviously described that feeding Figs markedly improved learning and memory disorders induced by scopolamine. [30] supported the current findings that the beneficial influences of Figs appeared in reducing the disturbances in cognitive and behavioral tasks in AD which might be caused by the presence of high antioxidant active constituents.
Many research studies reported that adherence to the Mediterranean diet, that contain olive oil, is linked to reducing the risk of Alzheimer's disease [31, 32]. The present study consistently supported that virgin olive oil enhances memory functions. Memory of olive oil treated rats was significantly improved in water maze test according to [33]. Present study therefore suggested the use of olive oil for reducing cognitive decline in aging.
Long term application of olive oil improved the cognitive function in various types of maze [34]. Furthermore, the low doses of olive oil administration showed the increase of the exploratory efficiency [35].

As confirmed by the results of the maze trial, rivastigmine had an anti-amnesic effect on scopolamine-treated rats due to the cholinesterase inhibitors leading to increase ACh concentration in the hippocampus as it was mentioned [36, 37].
The current research also documented an increase in the level of AchE in Scopolamine group against the combination of (*Ficus carica* and Olive oil) and Rivastigmine treated rats.
Moreover, in the current research, Scopolamine considerable increased AChE activities, an enzyme responsible for degradation of Ach, compared with the control group. Several reports indicated receiving scopolamine lead to produce amnestic effects, impair learning and memory processes in rodents [38]. Moreover, the study finding was consistent with [39] that reported Scopolamine inhibiting the cholinergic system, which led to the performance shortage of learning and memory functions. It has been demonstrated that the anticholinergic drug, Scopolamine competes with acetylcholine neurotransmitter on the muscarinic receptors with a great affinity, and low activity as well as enhancement of brain AChE action [40]. Moreover, it enhanced free radicals' formation, lipid peroxidation, and decreased enzymatic and non-enzymatic antioxidant activities resulting in neuronal membrane damage [41].
In tune with earlier reports [42], the administration of Scopolamine produced neuroinflammation through induction of oxidative stress state in the hippocampus. It has been confirmed that scopolamine linked with a raise in the concentration of amyloid precursor protein (APP) and Tau protein, both are AD disease characteristic [12].
However, the findings indicated that the oral consumption of the mixture Figs and Olive oil along 4 weeks period markedly reduced the action of AchE in (the mixture of Figs and olive oil with scopolamine groups).
The present results were in agreement with many studies [43, 44] that learning and memory enhancing activity of *Ficus carica*, may be due to its antioxidant activity and some compounds. Polyphenolic contents that were found in *Ficus carica* were responsible for AChE inhibition as it was mentioned [45]. Hence, AchE inhibitory activities of the mixture (Figs with Olive oil) could be a possible source of emerging accepted medications for Alzheimer's disease [46]. The current work on *Ficus carica* extract has revealed significant AChE inhibitory effects. *Ficus carica* fruit exhibited the potential for the treatment of Alzheimer's disease [47].
The recorded data were in accordance with the study that was carried out by [48, 49] and suggested the protective effects of Olive oil could be mediated by a direct inhibitory effect of the natural antioxidants in olive oil such as hydroxytyrosol, oleuropein, caffeic and chlorogenic acids to inhibit AchE enzyme. Olive oil had contained different compounds capable of inhibiting AChE leading to elevate acetylcholine levels which is a significant neurotransmitter in maintaining cognitive roles such as learning and memory, assisting to maintain the normal synaptic activity [50].
Previous in vitro studies have shown that chronic administration of a diet enriched with extra virgin olive oil would lead to the improvement of memory, learning, and synaptic histology. In addition, olive oil provided a marked lowering in the level of Aβ peptides and tau protein [51]. Additionally, olive oil has the ability to preserve the neurons as estimated by the regeneration of cerebral cortex fatty acid contents. This research suggested that olive oil would supply new visions of neuroprotection which might progress to the emergence of efficient medicinal plans [52].
Furthermore, the findings of this work showed that the oral intake of Rivastigmine with scopolamine for 4 weeks produced a marked decrease in AchE activities in the hippocampus homogenate. These findings reflected prior data showing that AchE inhibitors including Rivastigmine was shown to reverse the effects of the enzyme [53]. Anticholinesterase drugs were the agents which suppressed the AChE work, protected acetylcholine from hydrolysis, and preserved its concentration [54].

Conclusion

The results from the current study exposed that amnesia model AD induced by scopolamine in albino male rats showed elevated levels of the acetylcholinesterase enzyme leading to oxidative stress in the hippocampus. However, this research supplied proof supporting that the extract combination of *Ficus carica* and Olive oil had a significant neuroprotective influence on memory and learning in the rats with AD induced by scopolamine. Themixture *F. carica* and Olive oil improved the nerve functions in rats, and enhanced the memory performance by the inhibition of oxidative activity shown by the reduction in the levels of AchE compared with the untreated Alzheimer's rats. According to the obtained results from this study, it could be recommended using the combination of *F. caria* and Olive oil as herbal medicine that was anticipated to control AD progression and help to relieve the symptoms related to AD, and improve the life quality of patients with AD and memory deficits. As the combination of figs and olive oil is completely safe, clinical trials are needed in humans to ensure the neuroprotective activity.

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