Vol. 18(5), pp. 81-87, June 2024
DOI: 10.5897/AJPP2024.5386
Article Number: 39CC3CF72266
ISSN 1996-0816

http://www.academicjournals.org/AJPP

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African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Effect of flavonol from chamomile (*Matricaria recutita*) flavonoids on memory disorders and determination of oxidative stress in Alzheimer's rats

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Received 12 March, 2024; Accepted 9 May, 2024

Alzheimer's disease is one of the most common neurodegenerative diseases characterized by beta-amyloid plaques and neurofibrillary tangles. Alzheimer's is associated with various cellular changes including oxidative stress, neuronal inflammation, and mitochondrial disorders, ultimately leading to neuronal death. Flavonols found in the chamomile plant (*Matricaria recutita*) exert beneficial effects on brain disorders like Alzheimer's disease owing to their antioxidant properties. In this study, the flavonoids from the methanolic extract of chamomile (*M. recutita*) were isolated and purified using column chromatography and TLC methods. Flavonols from the flavonoid compounds were then extracted, separated, and identified using spectroscopic methods such as 1H-NMR, 13C-NMR, Mass, and IR. 56 adult male rats were divided into 7 groups, including control (vehicle 1, solvent of flavonol, and solvent of streptozotocin drug), Alzheimer's, and flavonoid doses of 120, 250, and 400 mg/kg. Diabetes was induced by a single intraperitoneal injection of streptozotocin at a dose of 60 mg/kg, and flavonols were administered for 15 days. Memory and learning were assessed using the shuttle box device. Data analysis was conducted using SPSS 22 software, ANOVA, and Tukey tests, with significance set at $p \leq 0.05$. The results indicated that doses of 250 and 400 mg/kg of flavonol extracts from chamomile caused significant changes, compared to the control group, ultimately improving avoidance memory in rats. Additionally, oxidative stress parameters were significantly reduced in the Alzheimer's groups treated with chamomile flavonol. Plant flavonols demonstrated the ability to restore spatial memory function and normalize oxidative stress parameters in streptozotocin-treated groups.

Key words: Alzheimer, Flavonoid, Flavonol, learning, rat.

INTRODUCTION

Learning and memory are fundamental functions of the central nervous system, representing the processes through which animals interact with their environment. Memory encompasses the encoding, storage, and retrieval of learned information (Josselyn and Tonegawa, 2020). Alzheimer's disease, a neurodegenerative condition associated with aging, is characterized by various cognitive impairments, including memory deficits (Tamagno et al., 2021), speech impairments (Teleanu et al, 2022), visual-spatial impairments (Cammisuli, 2024), and sensory and motor deficits (Brewer et al, 2020). This disease arises from the accumulation and increased levels of beta-amyloid protein, leading to the formation of brain plaques and the degeneration of nerve cells in the neocortex and

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other brain regions (Pfundstein et al., 2022). Free radicals, generated as active forms of oxygen, contribute to the destruction of brain tissue and the disruption of brain neurotransmitter function. Antioxidants are essential for neutralizing free radicals in the brain. Oxidative stress, a hallmark frequently observed in Alzheimer's disease and related dementias, is often overlooked or considered a consequence of the disease's main histopathological features. Notably, oxidative stress is directly or indirectly associated with each of Alzheimer's disease's common features, and signs of oxidative stress are evident from the earliest stages of the disease (Mayne et al., 2020). Clinical studies indicate that oxidative stress plays a significant role in the pathophysiology of dementia (Teleanu et al., 2022) and can contribute to the development of the disease by disrupting the balance between free radicals and the antioxidant system (Dufour et al., 2022). Oxygen free radicals have the potential to damage proteins, nucleic acids, and lipid membranes, thereby disrupting cellular function (Teleanu et al., 2022; Butterfield and Mattson, 2020).

Brain tissue contains a significant amount of unsaturated fatty acids, making it highly susceptible to attacks by free radicals. Lipid peroxidation, considered a destructive form of oxidative damage in neurons, compromises membrane integrity and generates neurotoxic secondary products (Pohl and Lin, 2018). The balance of oxidative stress in biological systems is determined by the interplay between free radical production and antioxidant mechanisms, including enzymes like superoxide dismutase, glutathione peroxidase, and catalase, as well as molecules such as glutathione and ascorbate (Teleanu et al., 2022). For instance, increased levels of malondialdehyde serve as a marker for lipid oxidation (Teleanu et al., 2022; El Joumaa and Borjac, 2022).

Memory and learning disorders can be induced in animal models by intraperitoneal injection of streptozotocin, leading to diabetes. Streptozotocin at 40 mg/kg significantly raises glucose levels in rats compared to the normal group. The mechanism involves the destruction of beta cell membranes, DNA fragmentation, and inhibition of enzymes like glucokinase, ultimately leading to increased blood glucose and diabetes (Furman, 2021). Diabetes induces free radical production and oxidative stress, resulting in lipid, protein, and DNA oxidation, ultimately damaging brain cells and causing memory and learning impairments.

Beta-amyloid accumulation is central to Alzheimer's disease pathology, with oxidative stress playing a significant role. Beta-amyloid peptides directly and indirectly induce oxidative stress by acting as enzymes to produce hydrogen peroxide and free radicals, which in turn trigger neuronal inflammation (Grimm and Eckert, 2017; Ansari, 2023). Neuronal inflammation has been extensively studied in Alzheimer's disease pathogenesis, with increased microglial and astrocytic activity, along with elevated cytokine levels, directly associated with aging plaques in Alzheimer's patients. Despite microglia's phagocytic abilities, the presence of inflammatory cytokines and extracellular matrix proteins hinders beta-amyloid clearance (Jung et al., 2022).

Recent research suggests promising effects of herbal medicines with antioxidant properties in treating or preventing brain diseases such as memory impairments (Namazi, 2022), strokes (Hong et at., 2023), and various other conditions. These effects are attributed not only to specific ingredients but also, predominantly, to their antioxidant properties.

Chamomile, a flowering plant found across Europe, Asia, and Africa, possesses antioxidant properties. Flavonols, which are polyphenolic compounds abundant in chamomile, exhibit potent antioxidant effects. Chamomile contains various biologically active substances, including volatile oil and flavonols, with flavonols representing the highest percentage among these compounds (El Joumaa and Borjac, 2022). Polyphenols, including flavonols, have been recognized as neuroprotective agents due to their ability to modulate cellular processes such as the formation of neuronal tangles and beta-amyloid plaques. Epidemiological and experimental studies have suggested that a diet rich in flavonols improves cognitive function and protects against neuronal degeneration in humans. Quercetin, the primary compound in the flavonoid subgroup, constitutes 60 to 75% of flavonols and is found in foods such as onions, leeks, broccoli, apples, and chamomile (Hwang et al., 2018).

This study aimed to investigate the therapeutic effects of flavonols on memory and learning disorders and to assess oxidative stress in male rats with Alzheimer's disease.

MATERIALS AND METHODS

In this study, 56 white male Wistar rats weighing 230-250g (obtained from Pasteur Institute, Marand Serum Company) were utilized. All animals were housed in groups of 8 rats per cage at a temperature ranging from 21 to 23°C.

Throughout the 6-week experimental period, the rats had ad libitum access to both food and water. The adult male rats were then divided into 7 groups, comprising a control group, vehicle 1 (solvent of flavonol), vehicle 2 (solvent of streptozotocin), Alzheimer's group, and three different doses of flavonol treatment groups: 120, 250, and 400 mg/kg.

Preparation of chamomile hydroalcoholic extract

First, chamomile were collected from different regions of Marand region and the identity was confirmed by botanists, The material vegetal was dried and was used for preparation of the hydroalcoholic extract in 70% ethanol by maceration for 48 h in two shifts. The dry extract was prepared using a rotary evaporator at low temperature (El Joumaa and Borjac, 2022).

Determination of flavonoid compounds

To measure the flavonoid compounds, 0.5 ml of each extract solution

(0.01 g in 10 ml methanol of 60%) 0.5 ml of 2% aluminum chloride and 3 ml of 5% potassium acetate were added. After 40 min, the absorbance of the samples was read against distilled water at 415 nm (Liang et al., 2022).

Determination of flavonol compounds

In order to measure the flavonol compounds, 0.5 ml of each extract solution (0.01 g in 10 ml of methanol 60%), 0.5 ml of 2% aluminum chloride and 3 ml of 5% sodium acetate were added. After 2.5 h, the absorption of the samples against distilled water at 440 nm was read. At the same time as the experiment, different dilutions were prepared and a standard curve was prepared. The absorption of the samples was compared with the standard curve. And the amount of flavonol of each extract was calculated in terms of mg per gram of dry extract (Hwang et al, 2018).

HPLC analysis

All standards, hydro alchol extracts of chamomile were analyzed on Agilent 1200 HPLC system (Agilent Technologies, Santa Clara, CA) using C-18 column. The mobile phase consists of acetonitrile and water as isocratic solvent (30:70 v/v) maintained at a flow rate was 1 ml/min with injection volume of 5 µl and run time of 8 min, respectively. Data were collected at 335 nm (λ max for the majority of the flavonol glucosides).

Mass spectrometric analysis of flavonol

Electrospray ionization tandem mass spectrometry was used to identify apigenin and its derivatives in aqueous and methanolic extracts. In brief, chamomile fractions were dissolved in 50% methanol and introduced onto a Quattro Ultima triple quadruple mass spectrometer (Micromass, Inc., Beverly, MA) at the rate 50µl/min and analyzed using electrospray ionization both in negative and positive-ion modes and its derivatives were identified using both full and product scans. The capillary and cone voltages were set at 3.5 kV and 50V respectively. The desolvation and cone temperatures were set at 250°C and 120°C respectively. The nitrogen gas flow rate for desolvation and cone was 600 L/h and 80 L/h respectively. Collision-induced dissociation was obtained using argon gas (Reis et al, 2020).

Experimental design

The chamomile extract, rich in flavonoids, was diluted with double-distilled sterile water and administered intraperitoneally daily for 2 weeks, starting seven days after streptozotocin injection. Streptozotocin (Sigma, USA) at a dosage of 60 mg/kg dissolved in sterile normal saline was intraperitoneally administered to induce Alzheimer's disease in the rats. One week post-injection, the animals' free blood sugar (FBS) levels were measured to confirm diabetes induction, with only diabetic animals exhibiting FBS levels higher than 250 mg/dL proceeding to subsequent stages.

Over the following days, characteristic signs of polyphagia, polydipsia, diuresis, and weight loss gradually manifested in the rats. Weight loss was observed in all rats by the end of the experiments. The animals' weights were recorded both before and during the experiments. Additionally, FBS levels were measured using glucose oxidase enzyme (from Biochemical Company, Tehran), in addition to glucometry. Memory and learning abilities were assessed using the shuttle box device. Following the final behavioral test with the passive avoidance test, the rats were anesthetized with chloroform, their heads were severed using a guillotine, and placed on an ice board. The hippocampus was isolated from the brain and promptly stored in a freezer at -80°C. Tissue homogenate was prepared using a mechanical homogenizer and centrifugation at 3000 rpm for 10 min at 4°C, with the supernatant solution separated from the bottom sediment and utilized for biochemical analysis (Alahmady, 2024).

Evaluation of antioxidant potential with DPPH method

In this method, DPPH (1,1-diphenyl-2-picrylhydrazyl) was employed as a reagent to measure stable radical compounds. Initially, 50 ml of extracts at concentrations of 10, 15, 20, 25, 30, 40, 50, 60, 70, and 80 mg/ml in methanol were added to 5 ml of 0.004% DPPH solution in methanol. After 30 minutes, the optical absorption of the samples was measured at 517 nm compared to the blank. The percentage inhibition of DPPH free radicals was calculated using the formula I (%) = 100 × (A_control - A_sample) / A_control. Subsequently, the concentration of the extract that exhibited 50% radical inhibition was determined from the graph. It is noteworthy that a lower concentration indicates greater antioxidant power or inhibition of free radicals. In this experiment, butylated hydroxytoluene (BHT) was used as a positive control for antioxidant synthesis, and all experiments were performed in triplicate (Alahmady, 2024).

Statistical analysis

The obtained data were statistically analyzed in the latest version of SPSS29 software. One-way analysis of variance was used to compare the effects of different doses of each sample with the corresponding group, and two-way analysis of variance was used to investigate the interaction effects between drugs. The results were presented as mean ± standard error. After the differences were significant, Tukey's post-test was used to compare the differences between the experimental groups. $P<0.05$ was considered as a significant difference between the groups. Graphs were drawn using Excel 2021 software.

RESULTS

Streptozotocin administration

The FBS levels in the streptozotocin (60 mg/kg i.P) groups during the first and second weeks exhibited a significant difference ($p < 0.005$) compared to the control and vehicle groups (Figure 1A). Specifically, the results indicated that the FBS levels in the control and vehicle groups remained low, approximately 150 mg/dL. However, in the streptozotocin-treated groups, FBS levels increased to 250 mg/dL, confirming the induction of diabetes in the rats. Prior to the experiment, FBS levels of all rats were measured using the Accu-check glucometer by obtaining a blood drop from the tail. FBS levels were monitored up to 3 days after diabetes induction and then at the end of each week following an 8-hour fasting period. Additionally, to ensure accuracy, serum glucose measurement was repeated using the enzyme-colorimetric method with glucose oxidase-peroxidase by an auto analyzer model RA1000 from Tichinco USA with Pars Azmoun (Iran) company kit. Data were analyzed using one-way analysis

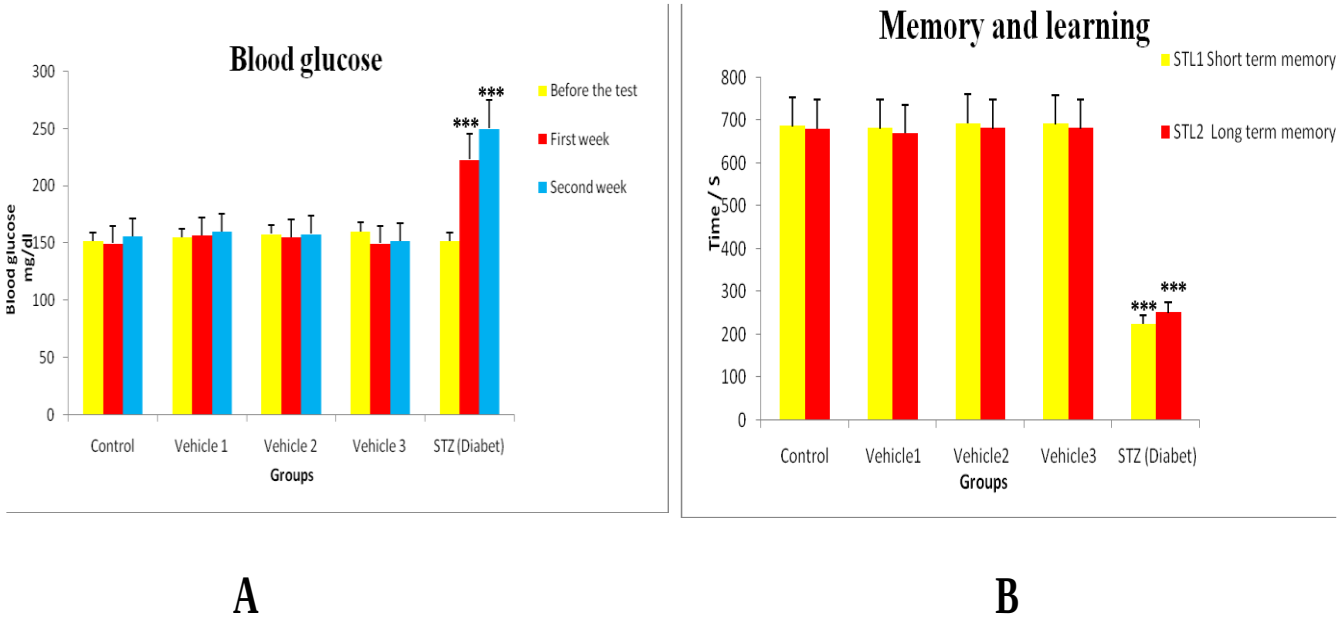

Figure 1a. Changes of FBS in the first and second weeks of the experiments after streptozotocin injection compared to control and vehicle rats (P<0.005)***, (b)The results of passive avoidance test STL1 (short-term memory) and STL2 (long-term memory) of the control, vehicles and the streptozotocin groups, each histogram shows the mean ± standard deviation (mean ± SD) of the time of STLs. The number of rats in each group is 8 and the changes are significant (p<0.01) compared to the control group.

of variance (ANOVA) followed by Tukey's post hoc test.

Additionally, the results of the passive avoidance test, specifically STL1 (short-term memory) and STL2 (long-term memory) of the control and vehicle groups, demonstrated significant changes compared to the streptozotocin group. Each histogram represents the mean ± standard deviation (mean ± SD) of STLs, with 8 rats in each group, and the observed changes are significant at $p < 0.01$ compared to the control group (Figure 1b). The findings of this study indicate that diabetes leads to impairment in learning and memory processes, as evidenced by a significant decrease in the average duration of STL1 and STL2 in the diabetic group compared to the control group, reflecting diminished performance and reduced learning ability in diabetic rats. The performance defects observed in diabetic rats treated with streptozotocin may be attributed to alterations in glucose levels or neurotoxic hyperglycemia associated with the action of the acetylcholine neurotransmitter.

Flavonol administration

According to the statistical analysis depicted in Figure 2, the impact of different doses of flavonol, as well as vehicle 1 (aqueous solvent), vehicle 2 (ethanol solvent of the flavonol), and vehicle 3 (streptozotocin solvent), did not show significant differences compared to the control group. This lack of effect observed in the control group suggests that the vehicles themselves were insufficient to increase the duration of STL1 and STL2, while only flavonol demonstrated the ability to enhance both short-term and long-term memory. The control group served primarily for comparison with the other experimental groups to evaluate the effect of chamomile flavonol. Notably, the control group exhibited elevated values of both STL1 and STL2 (Figures 1 and 2). Regarding the statistical findings concerning the impact of flavonol at a dosage of 120mg/kg on the diabetic group, it was observed that this dosage did not significantly alter short-term or long-term memory performance compared to the diabetic group. Flavonol at 120mg/kg did not effectively improve memory and learning disorders in the diabetic group.

On the other hand, statistical analysis pertaining to the effects of flavonol at a dosage of 250mg/kg on the diabetic group revealed significant improvements ($P \leq 0.01$) in both STL1 and STL2 performance compared to the diabetic group. This indicates that the detrimental effects of hyperglycemia on cognitive performance, memory, and learning in the flavonol-treated groups at 250mg/kg were significantly mitigated, leading to improved memory and learning compared to the diabetic group. Furthermore, the statistical results associated with the diabetic group treated with flavonol at a dosage of 400 mg/kg demonstrated a significant increase ($P \leq 0.001$) in both short-term and long-term memory performance compared to the diabetic group. Importantly, the clinical symptoms related to memory and learning disorders were alleviated in this group; indicating a

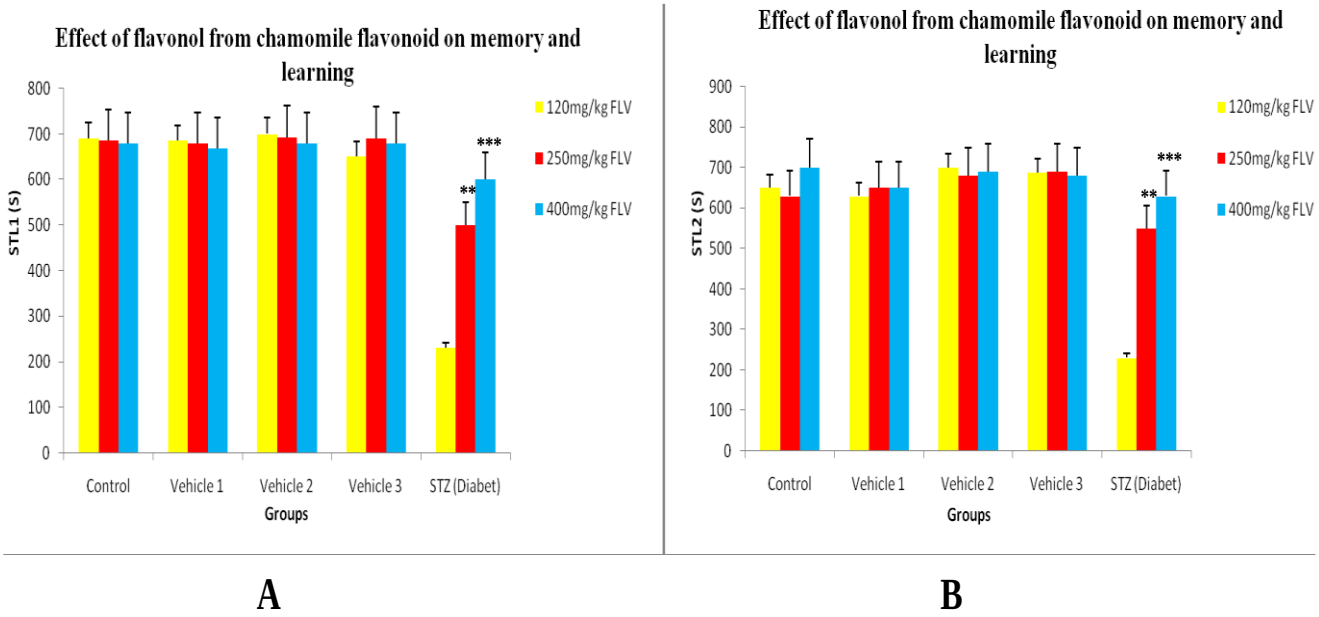

Figure 2. The effect of flavonol in control, diabetic and vehicle groups. (a) The results of passive avoidance test STL1 (short-term memory), (b) The results of passive avoidance test long-term memory (STL2).
The data are in the form of SEM Mean and n=8 animals in each group. (P≤0. 001)*** (P≤0. 01)** in comparison with diabetic group, cut of time = 900s.

substantial improvement in memory and learning outcomes (Figure 2a and b).

Standardization of ethanol chamomile extract

The amount of phenolic, flavonol and flavonoid compounds in chamomile extract is 26.5, 78.4 and 47.6 mg per dry gram of chamomile plant extract. In relation to the antioxidant activity of the chamomile plant, the IC_{50} value for the radical scavenging activity of the chamomile plant extract is shown in Table 1.

DISCUSSION

Alzheimer's disease is a neurodegenerative condition characterized by the degeneration of various neural regions, notably the cerebral cortex, particularly impacting cholinergic neurons in areas such as the hippocampus and frontal cortex (Grimm and Eckert, 2017). This disease manifests with memory and learning impairments, including deficits in spatial memory, short-term memory, and long-term memory (Petersen, 2019). In this study, the impact of the active compounds found in chamomile hydroalcoholic extract, specifically flavonol was investigated concerning memory and learning disorders in streptozotocin-induced diabetic rats, commonly employed as an experimental model for Alzheimer's disease induction (Furman, 2021). Streptozotocin is known to exert its effects both centrally and peripherally (de Oliveira et al, 2021), and it was initially utilized to induce an experimental model of Alzheimer's disease in rodents, resulting in memory and learning disturbances within a two-week period (Qi et at, 2021), a finding consistent with the results obtained in this study.

Research in this area suggests that intraperitoneal administration of streptozotocin disrupts brain insulin receptor function, leading to impaired glucose utilization, mitochondrial dysfunction, reduced ATP production, and ultimately, dysregulation of energy metabolism, mirroring early Alzheimer's disease pathology (Saleh et al., 2020). These actions contribute to disturbances in cellular membrane activity, promoting the accumulation of amyloidogenic processes and hyperphosphorylation of tau protein, key hallmarks observed in Alzheimer's disease pathology.

As indicated by the aforementioned research, low doses of streptozotocin disrupt and damage signaling pathways associated with brain insulin receptors, akin to type 2 diabetes mellitus. Conversely, high doses of streptozotocin impair the structural integrity of beta cells within the pancreatic islets of Langerhans, resulting in decreased insulin production and the onset of type 1 diabetes mellitus (Ureliano et al., 2022; de Oliveira et al., 2021). Additionally, streptozotocin induces the generation of free radicals, nitric oxide, and hydrogen peroxide in neurons, contributing to structural, neurochemical, and behavioral alterations reminiscent of those observed in Alzheimer's disease (de

Table 1. Antioxidant activity of flavonol from chamomile plant with butylated hydroxytoluene as a positive control in DPPH method.

Sample	µg/ml	DPPH radical inhibition percent (IC_{50}%)
Flavonol	10	5.8
	15	18
	20	22.5
	25	27.5
	30	32.4
	40	41.29
	50	49.2 IC_{50}
	60	56.9
	70	63.5
	80	74.8
Butylated hydroxytoluene	20	8.8
	50	14.4
	100	30.7 IC_{50}
	250	68.2
	500	79.3
	700	95.3

Oliveira et al., 2021).

The results of the passive avoidance test in the streptozotocin group demonstrate a significant decrease in STL1 and STL2 compared to the control and vehicle groups. Figure 1b illustrates that diabetes leads to the impairment of learning and memory processes, as evidenced by the significant reduction in short-term and long-term memory duration in this group compared to the control group. Cognitive deficits observed in diabetic animals may arise from alterations in glucose levels or neurotoxic hyperglycemia affecting cholinergic neurons and acetylcholine neurotransmitter secretion.

Beta-amyloid accumulation is a crucial factor in the pathogenesis of Alzheimer's disease. While oxidative stress is known to play a significant role in the disease's development, its occurrence is widespread in Alzheimer's pathology. Beta-amyloid peptides directly and indirectly induce oxidative stress; enzymatically, beta amyloid can catalyze iron reduction, leading to hydrogen peroxide and free radical production. Moreover, beta amyloid binding to mitochondrial proteins triggers free radical generation and neuronal inflammation, exacerbating oxidative stress. Consequently, oxidative stress contributes to cell membrane degradation, DNA damage, protein oxidation, and ultimately, apoptosis, which is the primary mechanism of neuronal death in Alzheimer's disease.

Laboratory analyses and pharmacological tests have revealed that chamomile flowers contain terpenoid compounds in essential oils such as azulene, chamazulene, and bisabolene oxide. Additionally, the flowers contain flavonoid compounds like apigenin, kaempferol, chrysin, luteolin, quercetin, coumarins, and mucilaginous substances (El Joumaa and Borjac, 2022). Chamomile extract has demonstrated neuronal protective effects in cerebral ischemia, as well as protection against oxidative stress induced by aluminum fluoride (El Joumaa and Borjac, 2022).

Statistical analysis in Figure 2 indicates that plant flavonol at doses of 250 and 400 mg/kg significantly alters short-term and long-term memory performance in the diabetic group compared to the diabetic group alone. The effects of chamomile extract mitigate the deleterious effects of hyperglycemia, leading to improved memory and learning outcomes in this group relative to the diabetic group. To definitively ascertain the effects of flavonol on memory and learning disorders, histological examinations of various brain regions, especially the hippocampus, and subsequent clinical trials are warranted.

Conclusion

The findings of this study demonstrate that chamomile extract enhances both short and long-term memory in rats, attributing this effect to the presence of its bioactive compounds.

ACKNOWLEDGMENT

The author wishes to thank the Director of Islamic Azad University and the Research Vice-Chancellor of Marand University for their support in conducting this study.

CONFLICT OF INTERESTS

The author has not declared any conflict of interests.

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