Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.216419.2809 Volume 30, Issue 1, January 2024

Manuscript ID ZUMJ-2306-2809 (R1)
DOI 10.21608/ZUMJ.2023.216419.2809

Original article:

Effect of Genistein on Scopolamine Induced Dementia in Mice

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Submit Date 2023-06-12
Revise Date 2023-06-18
Accept Date 2023-06-20

ABSTRACT

Background: Dementia is a neurological disorder that is manifested by an impairment of one or more cognitive abilities that is severe enough to interfere with daily living. The current work aims to determine how caveolin-1, NSD2, which stands for nuclear receptor binding SET domain protein 2, cellular senescence, and scopolamine-induced dementia are related. It also seeks to clarify how Genistein protects against scopolamine-induced dementia.

Methods: The 40 male mice used in this study were separated into four groups. Each group comprised ten mice: group I was used as the control group, group II represented the scopolamine group, group III was designated as the genistein/scopolamine group, and group IV represented the donepezil/scopolamine group. Also, caveolin-1, NSD2 levels, beta-galactosidase activity in brain tissue homogenates, and serum sialic acid levels were measured.

Results: In comparison to the control group, the scopolamine group demonstrated a statistically significant increase in serum sialic acid, brain tissue caveolin-1 levels, and activity of senescence-associated beta galactosidase, as well as a significant decrease in NSD2 levels and the discrimination index of the object location recognition test. There was a statistically significant reduction of caveolin-1, serum sialic acid levels, and senescence-associated beta-galactosidase activity concomitantly with a significant increase in NSD2 level and discrimination index in the genistein/scopolamine group and donepezil/scopolamine group as compared to the scopolamine group.

Conclusions: These elaborated data indicate that cellular senescence, caveolin-1, NSD2, and sialic acid are key players in the pathophysiology of dementia. The neuroprotective effect of genistein against this illness was also demonstrated by this study.

Keywords: Alzheimer's Disease; Scopolamine; Genistein; Senescence.

INTRODUCTION

The hallmark of dementia, including Alzheimer's disease (AD), is deterioration in one or more cognitive functions that has an impact on day-to-day activities [1]. Caveolin-1 is a structural protein of caveolae in the plasma membrane. It has been suggested that caveolin-1 plays a critical role in the pathogenesis of AD as it induces the proteolytic cleavage of APP (amyloid precursor protein) through activation of β-secretase, thus generating Aβ (amyloid beta) peptides, which are deposited into extracellular plaques in AD [2]. Cellular senescence is a condition in which the cell cycle is permanently arrested. It causes a proinflammatory environment, which is ideal for dementia onset [3]. It has been reported that senescent astrocytes

produce fewer neurotrophic factors, which may cause increased neuronal death in dementia [4]. In addition, it has been observed that the accumulation of senescent endothelial cells is associated with impaired blood-brain barrier integrity, which may adversely affect neuronal and glial survival [5]. Senescence-associated beta-galactosidase is frequently used as a marker of cellular senescence [6]. The nuclear receptor-binding SET domain protein 2 (NSD2), which is an epigenetic regulator, modulates the cell cycle. It is a histone methyltransferase that leads to the monomethylation and dimethylation of the lysine 36 residue on histone H3 (H3K36), resulting in active transcription of the genes responsible for the progression of the cell cycle, thus preventing cellular senescence and dementia [7]. Sialic acid is most abundantly found in the brain within gangliosides, where it regulates important brain functions, including axon myelination and synaptic transmission. Gangliosides are sialic acid-containing glycosphingolipids that are highly abundant on the surfaces of nerve cells. It has been suggested that Aβ can bind to gangliosides, causing the conversion of soluble α-helix-rich Aβ into aggregated β-sheet-rich structures, leading to Aβ accumulation [8]. Moreover, serum sialic acid might indicate chronic inflammation and oxidative stress in AD [9]. Genistein is an isoflavone with many therapeutic effects [10]. Therefore, this study aims to illustrate how caveolin-1, NSD2, cellular senescence, and scopolamine-induced dementia are related. It also seeks to elucidate how genistein protects against scopolamine-induced dementia.

METHODS

Animals:

The forty male mice used in the current study had a weight of 20–25 g. Throughout the study, wire mesh cages were used to provide the animals with an unrestricted supply of food and water. They were maintained under stable environmental circumstances, which were: a temperature of 23±2ºC, a relative humidity of 55 ± 5%, and a 12-hour cycle of darkness and light. In accordance with the recommendations of the Medical Research Ethical Committee at the Faculty of Medicine at Tanta University in Egypt (approval code: 35046/11/21), the care of the animals and the experimental techniques were achieved at the Medical Biochemistry Department of the Faculty of Medicine. Also, this study was carried out in accordance with ARRIVE guidelines, the U.K. Animals (Scientific Procedures) Act, 1986, and associated guidelines.

Chemicals:

All chemicals were highly pure and were purchased, except as mentioned elsewhere, from Acros Organics (New Jersey, USA).

Experimental design:

Mice were given a week to acclimatize before being randomly assigned into four groups. Each group consisted of ten mice. Throughout the trial, distilled water was administered orally to Group I (the control group) [11]. For 14 days, Group II (the Scopolamine group) received distilled water orally. Then, scopolamine was injected for 7 consecutive days [12]. Group III (Genistein/Scopolamine group) received oral pretreatment with genistein in the amount of 15 mg/kg in 0.5 ml dimethyl sulfoxide (DMSO) for 14 days. Then, mice received genistein, followed by injections of scopolamine for 7 consecutive days [13]. Group IV (donepezil/scopolamine group): received oral pretreatment with donepezil (1.60 mg/kg) for a period of fourteen days. Then, mice received donepezil, followed by scopolamine injections once daily for 7 consecutive days [14].

Induction of experimental dementia:

Scopolamine was injected intraperitoneally for seven days sequentially at a dosage of 1 mg/kg to cause dementia. Scopolamine was dissolved in saline (0.9% NaCl) [15]. It is a muscarinic antagonist, leading to cholinergic dysfunction and cognitive decline [16].

Behavioral assessment by object location recognition test [14]:

The object location recognition test evaluates the short-term, spatial object recognition memory. After the third week had ended, the groups were subjected to the test. Two plastic items, which had the same size and shape but different colors, were put inside a plastic box (60×40×80). Mice were allowed to spend 10 minutes exploring the empty box daily for a period of three successive days. On the fourth day, the two items in the box were freely explored by mice for five minutes per trial. Then, after a 30-minute interval, one of the items had been moved to a new place in the box (a novel). The second item, however, stayed in its original location (familiar). Then the mice were free to discover the objects. The exploratory behavior was taken into consideration only when the mice were touching or smelling the item. 70% ethanol was used to clean the box between each trial. The duration of

exploration for novel and familiar objects as well as the total time of exploration were calculated.

The formula used to determine the discrimination index (DI) was:

$$DI = \frac{TN - TF}{TN + TF}$$

DI= discrimination index

TN = exploratory period for the "novel" item

TF= exploratory time for the "familiar" item

Mice with normal cognitive skills have a natural affinity to spend more time exploring an object moved to a new location for a longer period of time than the non-moved object [17]. Since they spend more time examining the familiar item (TF) than the new object (TN), mice with impaired cognitive abilities exhibit DI with a negative value, suggesting that they are unable to distinguish between the two objects [18].

Blood and tissue sampling:

Under anesthesia, mice were decapitated. Blood samples were collected in non-coated tubes, which remained at room temperature for 30 minutes to allow clotting. After that, centrifugation of the samples was performed at 3000 rpm for a period of 20 minutes. Sera were drawn out, placed in Eppendorf tubes, and immediately frozen at -20 °C for future assessment. The entire brain was taken out of the skull, was washed in cold saline, and was split into two specimens for histopathological examination and biochemical testing.

Histopathological study:

The samples of brain tissue were embedded in paraffin after their fixation in 10% formalin. Then, staining of 5-µm slices using H&E (hematoxylin and eosin) was performed. After that, photomicrographs at 200x and 400x were taken.

Preparation of brain tissue homogenate:

Brain tissue was weighed and homogenized using a Potter-Elvehjem tissue homogenizer (Omni International, USA) at a weight-to-volume ratio of 1/10 in 0.1M ice-chilled phosphate buffer saline (pH 8). Centrifugation of the crude homogenate was carried out at 3000 revolutions per minute for a period of ten minutes at 4°C, then the supernatant was gathered, split into three aliquots, and kept at -80°C [19].

Biochemical assay:

1) **Assay of Caveolin-1 level in brain tissue homogenate:**

Using an ELISA commercial kit (Catalogue number 201-02-1290) purchased from Sun Red Biotechnology Company, USA, the level of caveolin-1 was measured. The values of caveolin-1 were determined as ng/mg protein.

2) Colorimetric assay of senescence associated beta galactosidase activity in brain tissue homogenate [20]**:**

Ortho-Nitrophenyl- β-galactoside (ONPG) buffer was made by dissolving 40 mM NaH_2PO_4, 60 mM Na_2HPO_4, 1 mM $MgCl_2$, 10 mM KCl, 0.4% β -mercaptoethanol, and 4 mg/ml ONPG. An aliquot (20 µl) of brain tissue homogenate was added to 150 µl of ONPG buffer. It was freshly prepared at pH 4 and pH 6, blended, and then incubated at 37°C till a pale-yellow color developed. A stop solution of 60 µl of 1 M Na_2CO_3 was used to stop the reaction and the optical density (OD) was measured at 420 nm by BTS-350 spectrophotometer (Biosystems, Spain). Beta galactosidase activity was determined as nmoles of beta galactose produced per min per mg protein at 37 °C [21].

1) OD 420/0.0045 = nmoles formed per ml

2) nmoles/ml × total assay volume (lysate, ONPG buffer and stop solution) = nmoles

3) nmoles/time of 37°C incubation = nmoles/min (units)

4) Units/µl of lysate used in the assay/protein concentration of 1 µl lysate in mg = Units/mg of protein

3)Assay of NSD2 level in brain tissue homogenate:

An ELISA commercial kit (Catalogue number 201-02- 2897), purchased from Sun Red Biotechnology Company, USA, was used to measure the level of NSD2. The values of NSD2 were evaluated as ng/mg protein.

4) Assay of serum sialic acid [22]**:**

To 0.5 ml of 10% trichloroacetic acid, 0.5 mL of serum was added. The tubes remained for 10 minutes in a bath of boiling water, were cooled in tap water, placed in the refrigerator for 15 minutes, and centrifuged for 10 minutes. 2.5 mL of sulfuric-acetic acid reagent was added to 0.2 ml of the supernatant solution of the unknown and to 0.2 ml of the working standard and were mixed. The tubes stayed for 30 min in a bath of boiling water followed by cooling in tap water, and OD was calculated by a BTS-350 spectrophotometer (Biosystems, Spain) at 530 nm within 40 min against a blank (sulfuric acetic acid reagent).

Statistical analysis:

The results of the present study were statistically analyzed by the Statistical Package for the Social Science (SPSS) computer program; version 23, and the data were shown as mean ± standard deviation

(SD). Analysis of variance (ANOVA), Tukey tests, and Pearson's correlation test were used. P-values < 0.05 were considered significant.

RESULTS

The comparative statistics of the studied parameters between all groups are summarized in Table 1. There was a statistically significant increase in caveolin-1 level, activity of beta galactosidase, and serum sialic acid level in the scopolamine group when compared to the control group, as indicated by Figures 1, 2, and S1, respectively. Also, there was a significant decrease in NSD2 and the discrimination index of the object location recognition test in the scopolamine group when compared to the control group, as shown in Figures 3 and 4, respectively. On the other hand, there was a significant decrease in caveolin-1 level, activity of beta galactosidase, and serum sialic acid level in the genistein/scopolamine group and donepezil/scopolamine group as compared to the scopolamine group, as shown in Figures 1, 2, and S1, respectively. In addition, there was a significant increase in NSD2 and discrimination index in the genistein/scopolamine group and the donepezil/scopolamine group as compared to the scopolamine group, as indicated by figures 3 and 4, respectively. The histopathological examination (Figure 5) showed Aβ peptide accumulation in the brain which is characteristic to dementia of Alzheimer's type.

Table 2 shows Pearson Correlation between the activity of beta-galactosidase and the studied parameters. The activity of beta-galactosidase in brain tissue homogenate showed a significant positive correlation with both the brain tissue caveolin-1 level and the serum sialic acid level. However, the activity of beta-galactosidase in brain tissue homogenate showed a significant negative correlation with both brain tissue NSD2 level and DI.

Table 1: Comparative statistics of studied biomarkers between all groups

	Group I (n=10)	Group II (n=10)	Group III (n=10)	Group IV (n=10)	ANOVA	
					F	P-value
Caveolin-1 (ng/mg protein)	0.109±0.041	0.219±0.123[a]	0.110±0.063[b]	0.114±0.050[b]	5.031	0.005*
Activity of beta-galactosidase (units/mg protein)	0.013±0.006	0.030±0.008[a]	0.014±0.006[b]	0.015±0.007[b]	14.352	<0.001*
NSD2 (ng/mg protein)	0.019±0.004	0.004±0.001[a]	0.018±0.010[b]	0.013±0.001[b]	14.457	<0.001*
Sialic acid (mg/dL)	46.838±20.041	117.829±34.009[a]	52.836±23.034[b]	53.422±24.713[b]	16.659	<0.001*
DI	0.588±0.109	-0.511±0.084[a]	0.567±0.084[b]	0.496±0.068[b]	369.201	<0.001*

*: Statistically significant at $p \leq 0.05$. (n) number of mice =10 in each group. [a,b]significant differences between groups: [a]significance from group I, [b]significance from group II. **Group I** (control group), **group II** (scopolamine group), **group III** (genistein/scopolamine group) and **group IV** (donepezil/scopolamine group).

Table 2: Pearson Correlation between activity of beta-galactosidase and the studied parameters

Correlation Study		
Parameters	**Activity of beta-galactosidase (units/mg protein)**	
	r	**P-value**
Caveolin-1(ng/mg protein)	0.646	<0.001*
NSD2 (ng/mg protein)	-0.366	0.020*
Sialic acid (mg/dl)	0.510	0.001*
DI	-0.712	<0.001*

*: Statistically significant at $p \leq 0.05$.

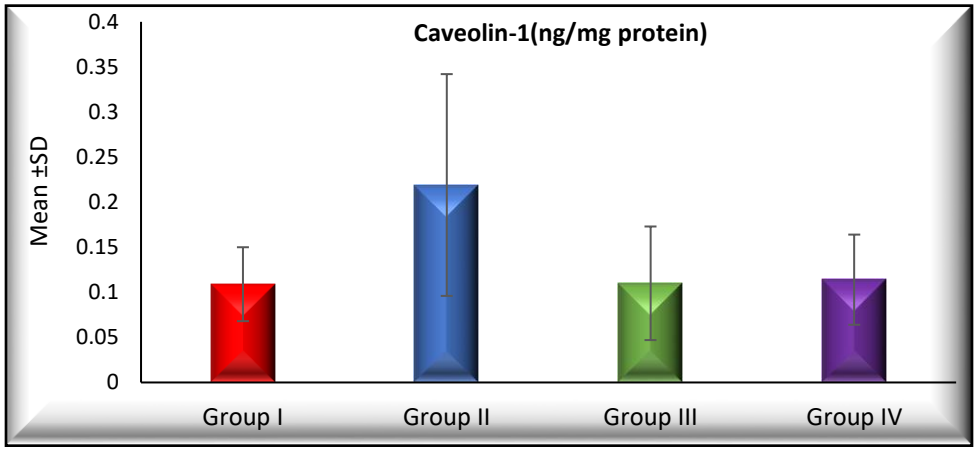

Figure 1: Comparison among all the studied groups as regard caveolin-1 level (ng/mg protein) in brain tissue homogenate.

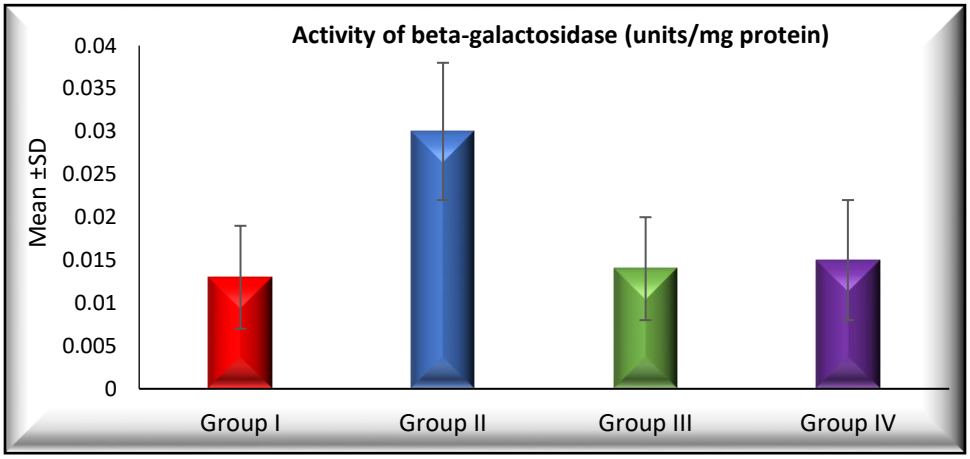

Figure 2: Comparison among all the studied groups as regard activity of beta-galactosidase (units/mg protein) in brain tissue homogenate.

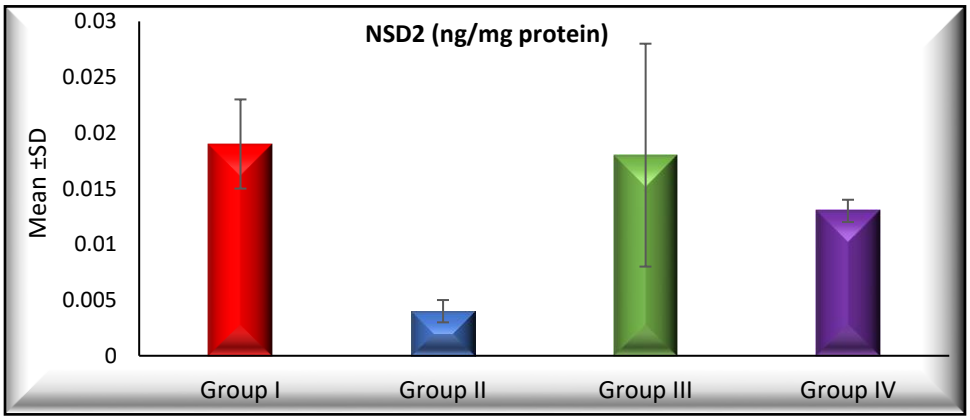

Figure 3: Comparison among all the studied groups as regard NSD2 level (ng/mg protein) in brain tissue homogenate.

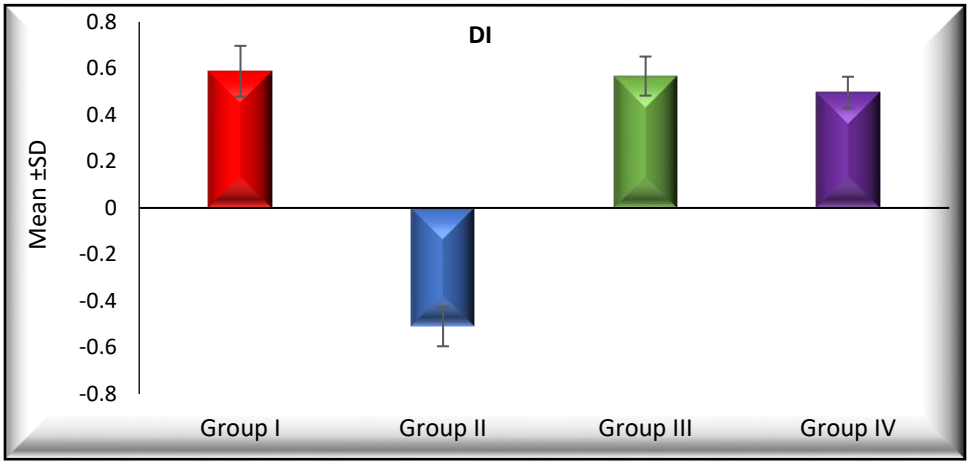

Figure 4: Comparison among all the studied groups as regard DI (discrimination index).

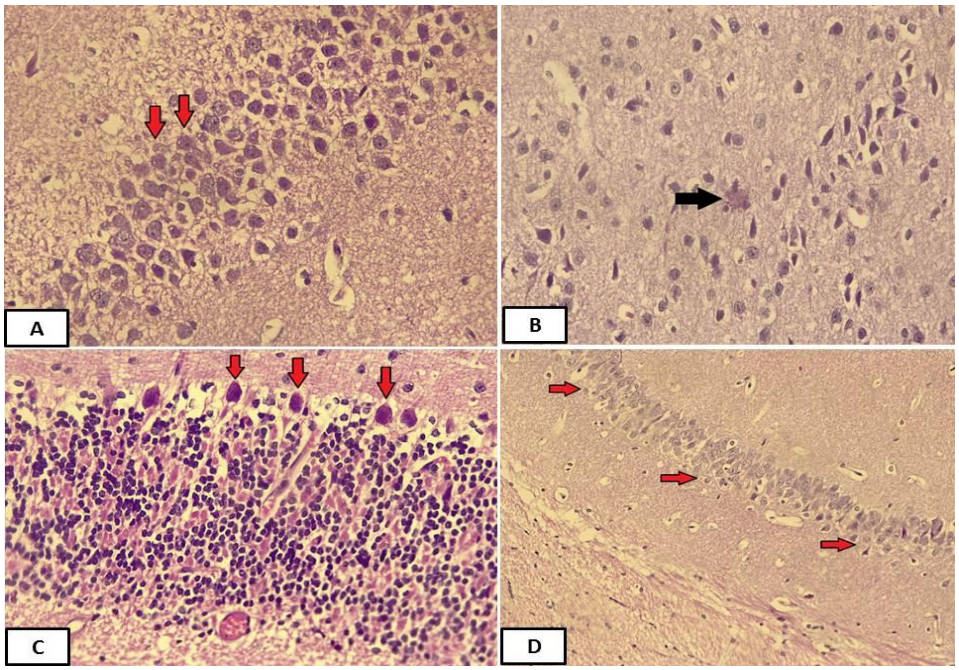

Figure 5: Histopathological examination. **A:** Section from brain of control group showing normal grey matter with normal soma of neurons as indicated by arrows (H&E x400).**B:** Section from brain of scopolamine group showing abnormal grey matter with extracellular accumulation of senile plaques composed of Aβ peptide as indicated by arrow (H&E x400).**C:** Section from brain of genistein /scopolamine group showing normal grey matter with normal soma of neurons as indicated by arrows and with no remarkable pathological changes (H&E x 400).**D:** Section from brain of donepezil/scopolamine group showing normal grey matter with normal soma of neurons as indicated by arrows and normal white matter without notable pathological changes (H&E x200).

DISCUSSION

In the current study, dementia was induced in mice by the intraperitoneal injection of scopolamine, which is a muscarinic blocker. The mice were exposed to the object location recognition test to assess their short-term spatial object recognition memory, and then a set of biochemical and histopathological assessments were performed. Scopolamine-injected mice showed memory decline, as indicated by poor performance in the object location recognition test. The histopathological examination showed Aβ peptide accumulation in the brain, which is characteristic of dementia of Alzheimer's type. Also, the scopolamine group showed changes in the measured biochemical parameters, which are related to cognition.

This study revealed a significant decrease in the DI of the scopolamine group when compared to the DI of the control mice. These findings came in

congruence with those of Lu et al. [14], who showed that scopolamine administration significantly reduced the DI compared to the control group, suggesting that scopolamine effectively induced memory deterioration, hence the negative value of DI.

Histopathological examination in the present study showed extracellular accumulation of senile plaques of Aβ peptide in the brain of the scopolamine group when compared to the control group. This finding came in accordance with that of Patel et al. [23], who reported the deposition of Aβ peptide in the brains of scopolamine-treated mice.

The present study showed a significant increase in caveolin-1 level in brain tissue homogenate in the scopolamine group when compared to the control group. In agreement with the attained findings, Sun et al. [24] found that the brains of AD mice showed overexpression of caveolin-1 when compared to the control group. One hypothesis to explain this finding might be based on the fact that caveolin-1 induces activation of β-secretase, leading to proteolytic cleavage of APP (amyloid precursor protein), thus increasing the production of Aβ peptide.

On the contrary, Wang et al. [25] found that there was decreased expression of caveolin-1 in AD mice when compared to the control mice. This might be due to the neuroprotective effect of caveolin-1, as it could preserve synaptic integrity.

Senescence-associated beta-galactosidase (SA-β-gal) is a well-known marker that is used to detect cellular senescence. The present study showed a significant increase in SA-β-gal activity in brain tissue homogenate in the scopolamine group when compared to the control group. These findings were compatible with those of Dorigatti et al. [26], who showed that the activity of SA-β-gal was significantly increased in the brains of AD mice, thus providing convincing evidence for the involvement of senescent cells in the pathogenesis of AD.

The present study revealed that the NSD2 level was significantly decreased in the brain tissue homogenate of the scopolamine group when compared to the control group. In harmony with the attained findings, Wang et al. [27] found that the expression of methylated H3K36, the characteristic epigenetic mark of NSD2, was decreased in the brain of a dementia mouse model. This might be justified by the fact that H3K36 methylation leads to active transcription of cell cycle-promoting genes. Thus, NSD2 prevents cellular senescence. Moreover, Gräff et al. [28] observed low DI, which indicates impairment of memory in mice, after administration of the NSD2 inhibitor, as it causes a significant decrease in the methylated H3K36.

Wolf-Hirschhorn syndrome (WHS) is a chromosomal abnormality that is characterized by deletion of the short arm of chromosome 4. Moshe et al. [29] showed that a patient with WHS had six dementia-like episodes and a deletion of the NSD2 gene in the WHS region, which is found on the short arm of chromosome 4.

Sialic acids occupy the terminal position in the oligosaccharide chains of glycolipids and glycoproteins [30]. The current study revealed a significant increase in serum sialic acid level in the scopolamine group when compared to the control group. These findings come in harmony with those of Yadav et al. [9], who reported significantly higher levels of plasma sialic acid in AD patients. These findings could be justified by increased oxidative stress in AD, which causes lipid peroxidation and neuronal membrane damage, leading to the liberation of free sialic acid in plasma. Concomitantly, Baboolal et al. [31] demonstrated that the sialic acid level in the serum of AD patients was significantly higher than that in the control group. This finding might be related to inflammation, which is an important aspect of the pathogenesis of AD, as many of the acute-phase reactants are glycoproteins, which have sialic acid as a terminal residue on their carbohydrate chains.

In the present study, mice received oral pretreatment with genistein, which has been reported to have neuroprotective effects involving anti-amyloid β and anti-tau properties, before intraperitoneal injection of scopolamine. Genistein pretreatment significantly ameliorated the scopolamine group's cognitive performance in the OLR test and reduced the histopathological alterations evidenced by normal neuronal appearance on histopathological examination, which was compatible with the findings of Bonet-Costa et al. [32], who reported a decreased number of Aβ plaques in AD mice treated with genistein when compared to the untreated AD mice.

Genistein administration resulted in a significant increase in the DI of object location recognition tests in the genistein/scopolamine group when compared to the scopolamine group. These findings came in accordance with those of Lu et al. [14], as treatment with genistein significantly increased the DI compared with the scopolamine group. This could be justified by the memory enhancement

effects of genistein, which resulted in an improvement in spatial object recognition memory, hence the significant increase in DI.

The present study revealed a significant decrease in caveolin-1 levels in the genistein/scopolamine group when compared to the scopolamine group. In agreement with the attained findings, Sardar Sinha et al. [33] reported that genistein inhibited caveolin-1 as it inhibited the uptake of Aβ peptide-containing exosomes by nerve cells through caveolae-mediated endocytosis in comparison with the nerve cells without genistein treatment.

The current study revealed that SA-β-Gal levels were significantly reduced in the genistein/scopolamine group as compared to the scopolamine group. This finding came in accordance with that of Wu et al. [34], who showed that genistein had a protective effect on H_2O_2-induced senescence in the endothelial cells of the human umbilical vein. H_2O_2 caused a significant increase in SA-β-gal-positive cells. However, the number of SA-β-gal-positive cells in the genistein-treated group was lower than in the H_2O_2 group without genistein.

The present study revealed that genistein pretreatment caused a significant decrease in serum sialic acid levels in the genistein/scopolamine group as compared to the scopolamine group. To our knowledge, there have been no reports about the effect of genistein on serum sialic acid in dementia models. However, some studies were done to illustrate the relationship between genistein and serum sialic acid in other diseases. For instance, Abbasi et al. [35] reported that administration of soy milk containing genistein caused a significant decrease in serum sialic acid level in diabetic patients as compared to the control group.

Donepezil is an acetylcholinesterase inhibitor, which improves cognitive functions. It was used as a standard anti-amnestic drug for comparison with genistein [36]. In the current study, mice received oral pretreatment with donepezil before intraperitoneal injections of scopolamine. The results of both genistein and donepezil-treated groups were closely similar to each other, with non-significant changes between them, thus emphasizing the neuroprotective potential of genistein.

In harmony with the elaborated findings, Lu et al. [14] reported that the ameliorative effect of genistein on the cognitive performance of AD mice in the OLR test was analogous to that of donepezil, as indicated by the closely related increase in DI in both genistein and donepezil groups.

CONCLUSIONS

The present study elaborates on the critical role of increased caveolin-1, decreased NSD2, and cellular senescence in the pathogenesis of dementia. Also, this study provided evidence for the promising neuroprotective and memory enhancement effects of genistein on scopolamine-induced dementia. Further research is warranted to find the most effective dosage of genistein with the fewest side effects in humans and to elucidate the effectiveness of caveolin-1 inhibitors, NSD2 activators, and senolytics in the treatment of dementia.

Declaration of interest:

The authors report no conflicts of interest.

Funding information:

Nil.

Supplementary figure:

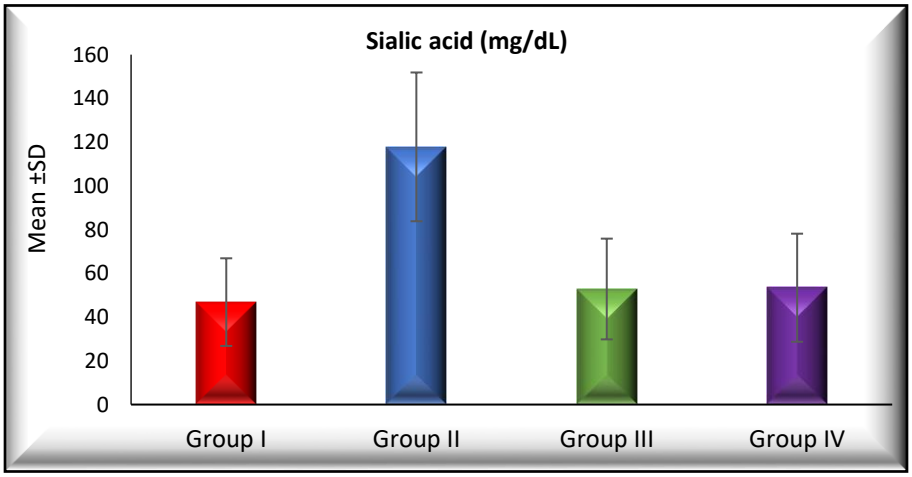

Figure S1: Comparison among all the studied groups as regard serum sialic acid level (mg/dl).

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To Cite:

Rofaeel, M., Ayad, N., Abou El-Noeman, S. E., Gaber, R. Effect of Genistein on Scopolamine Induced Dementia in Mice. *Zagazig University Medical Journal*, 2024; (154-163): -. doi: 10.21608/zumj.2023.216419.2809