SITAGLIPTIN MITIGATES SCOPOLAMINE-INDUCED NEUROCOGNITIVE DEFICITS VIA ACTIVATION OF Nrf2/HO-1 PATHWAY AND IMPROVED MITOCHONDRIAL ACTIVITY

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ABSTRACT

Background: Rats' memory is hampered by the muscarinic receptor antagonist scopolamine (Scop), which inhibits cholinergic neurotransmission. ***Objective***s: to assess the protective impact of sitaglibtin and its underlying processes in neurocognitive impairments brought on by Scop. ***Methodology*:** Thirty adult male albino rats were divided into three groups: control, Scop, and Scop+STG (10/group). Rats were evaluated neurocognitively. The following were measured: BDNF, Nrf2, HO-1, citrate synthase (CS) activity, acetylcholine, MDA, SOD, TNF-α, interleukin (IL)-6, IL-10, and amyloid β 42 (Aβ42). Additionally, hippocampal histological and immunohistochemical analyses were performed. ***Results*** Along with significantly greater levels of MDA, TNF-α, IL-6, acetylcholine, and Aβ 42, as well as GFAP and Caspase-3 hippocampus immunoreaction, the Scop group also showed a decline in cognitive performance compared to control. Additionally, it down-regulated BDNF, Nrf2, and HO-1 gene expression in the hippocampus and markedly decreased IL-10, SOD, and CS activity. The Scop+STG showed a considerable amelioration in the

neurocognitive deficits caused by Scop. ***Conclusion***: In addition to up-regulating Nrf2 and HO-1 gene expressions, sitagliptin has a beneficial protective impact against Scop-induced cognition impairments through anti-oxidant, anti-inflammatory, enhanced mitochondrial activity, prevention of apoptosis, and neurotrophic actions.

KEYWORDS
BDNF, Caspase-3, HO1, Nrf2, Scopolamine, Sitagliptin

INTRODUCTION

Alzheimer's disease (AD) is a gradual, irreversible neurological illness characterized by memory loss, confusion about one's surroundings, and a decline in cognitive function. 80% of dementia cases are diagnosed with this most prevalent type of neurodegenerative disease, which is also rapidly rising to the top of the list of costly, debilitating, and burdensome illnesses (Lopez, and Kuller, 2019).Glial responses, neuronal and synaptic loss, and the placement of amyloid beta plaques are important pathology markers for the diagnosis of AD (Congdon and Sigurdsson, 2018).Oxidative stress is another important element that starts the pathogenesis of AD (Zhao and Zhao, 2013). Amyloid beta plaques cause the generation of these species (Gul et al., 2023). Synaptic dysfunction is the first pathogenic event in Alzheimer's disease and a strong predictor of cognitive decline (Gul et al., 2023).

Furthermore, studies have shown that the development of Alzheimer's disease is significantly influenced by neuroinflammation, which is typified by the aggregation of Aβ. This neuroinflammation may cause synaptic impairment by initiating a mitochondrial apoptotic pathway (Salahuddin et al., 2023).

Acetylcholine, a neurotransmitter that is extensively distributed throughout the nervous system and is essential for memory and learning processes, is associated with cognitive function and the cholinergic system (Ghias et al., 2019). AChE breaks down acetylcholine in the synaptic cleft, converting it to choline and acetic acid. Cognitive impairment and an ACh deficiency might result from excessive AChE activity activation (Hussain et al., 2022). Research has shown that Scop injection raises AChE levels, which impairs memory (Choi et al., 2021).

A muscarinic receptor antagonist called scopolamine (Scop) impairs cholinergic neurotransmission, which impairs memory in rodents. Scop causes oxidative stress, which impairs memory by elevation of the buildup of reactive oxygen species (Bunadri et al., 2013). Scop affects memory and learning via modulating oxidative stress, amyloid beta formation, and synaptic dysfunction. It has been used to assess the effects of medications and their potential as a treatment for neurodegenerative diseases in animal experimental models (Chen et al., 2014).

The expression of BDNF, a neuronal health indicator, is essential for preserving synaptic plasticity and transmission. Additionally, BDNF has the ability to alter a number of signaling pathways linked to memory and learning. Additionally, neuroinflammation, the development of Aβ plaque, tau protein phosphorylation, and neuronal death have all been connected to the BDNF signaling pathways. The degree of memory impairment depends on decreased plasma BDNF (Gao et al., 2022).

Through the antioxidant response element (ARE), nuclear factor E2-related factor 2 (Nrf2), the primary regulator of the antioxidant response, regulates the expression of many genes that code for antioxidant proteins (Khodir et al., 2021). The oxidant-responsive transcription factor Nrf2 facilitates cytoprotection against oxidative stress by regulating the expression of HO-1 (Luo et al., 2017).

Scop inhibited the expression of Nrf2 and HO-1, two natural antioxidant enzymes, in the mice's brains. On the one hand, Nrf2 increases the production of antioxidant enzymes. It breaks down ROS, and its overexpression raises HO-1 production, which lowers oxidative stress (Krajka-Kuz´ niak and Baer-Dubowska, 2021). Conversely, the antioxidant enzyme HO-1 has anti-inflammatory properties and removes tau protein (Fujita et al., 2012).

As part of a medication repositioning or repurposing approach, dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin (STG), are being investigated for their possible usage for novel therapeutic applications (Pushpakom et al., 2019). Type 2 diabetes mellitus can be efficiently treated with STG (Wang et al., 2021). Furthermore, DPP-4 inhibitors have neuroprotective benefits against neuronal degeneration (Abdelsalam and Safar, 2015). By inhibiting DPP-4 function, STG raises the levels of glucagon-like peptide-1 (GLP-1) in the blood. Therefore, through its positive effects on learning behavior, GLP-1 may have a neuroprotective function (Maniscalco et al., 2015).

Although it is an intriguing option, the possible involvement of STG in Scop-induced dementia has not been assessed to the best of our knowledge. This is because antioxidants are crucial in reducing the symptoms of dementia, whereas free radicals are a key contributor to the pathophysiology of dementia. According to reports, STG may have antioxidant properties (El-Sahar et al., 2015). Therefore, the work objective was to assess the protective impact of sitaglibtin and its underlying processes in neurocognitive impairments brought on by Scop for the first time to the best of our knowledge.

MATERIALS AND METHODS

Experimental animals

Before the study started, thirty male Wister albino rats weighing between 120 and 150 grams each were transported from Theodore Bilharz Research Institute in Giza, Egypt, and acclimated at the animal house of the Menoufia Faculty of Medicine for seven days (5 rats per cage), with unrestricted access to food and water. Environmental parameters were adjusted to a 12-hour light/dark cycle, 22±2 °C, and 40–70% humidity. The Menoufia Faculty of Medicine ethics committee accepted the experiment [IRB No:12/2024BIO14], which complied with the ARRIVE standards and The Guide of Care and Use of Laboratory Animals.

Study design

Rats were randomly divided into three equal groups (10 rats each):

Group I (control): the rats were given 0.5 mL 0.9% sodium chloride (NaCl) administered by i.p. injection to rats during the final 7 days

Group II (Scop-induced cognitive deficit group) [Scop]: During the final 7 days of treatment, a daily i.p injection of Scop (3 mg/kg) was administered (cat. no. S1875; MilliporeSigma). Scop was dissolved in 0.9% NaCl and administered by i.p. injection to rats as described in a previous study (Lin et al., 2016).

Group III (Scop-induced cognitive deficit/ STG treated group) [Scop+STG]: during four weeks, rats were given both Scop (at the same dosage, time, and method of administration as group II) and STG (10 mg/kg) diluted in distilled water and administered orally once daily (Osman et al., 2019). Merck Sharp and Dohme Corp., a division of Merck and Co., Inc., Kenilworth, NJ, USA, was the supplier of STG (JANUVIA 100 mg). Rats were administered it an hour before to the administration of the Scop throughout the previous seven days.

The cognitive capacities of the animals were assessed during the last three days of the study. The rats were sacrificed by cervical dislocation after the behavioral tests. Brain hemispheres were dissected to assess neurodegenerative changes. The right hippocampal tissue was removed and then immediately frozen at -80°C for further biochemical examination. The left cerebral hemispheres were ready for immunohistochemical and histological

examination of the hippocampus (CA1 region).

Novel Object Recognition (NOR) Test. The NOR test was used to evaluate the rats' memory and cognitive performance over the final three days of the experiment (Antunes and Biala, 2012). A rectangular wooden box measuring 65 × 45 × 65 cm was used. The NOR test used a blue ball (a new object) with an opaque cube and two other opaque cubes (familiar objects). The three stages of the NOR test were testing, familiarization, and habituation. Rats were put in the box one at a time and allowed to explore the empty open field arena for three minutes during the habituation period. Twenty hours after the habituation trial, two trials (T1 and T2) were carried out, separated by a 24-hour intertrail interval. During T1 (the familiarization phase), rats were left in the open field to investigate two identical familiar objects (a1 and a2).

The T2 (test phase) was conducted using a novel item (b) and a fresh familiar object (a) after the intertrial period. During T1 and T2, live recordings were captured to document the rats' actions, and the amount of time the rats spent investigating the items was timed using a timer. Rats were considered to be investigating when they touched or pointed their noses two centimeters away from an object. To guarantee the test's sensitivity and comparability, the contact time with the objects (20 seconds) was set in T1 and T2, and the test lasted three minutes. In the familiarization phase (T1), the total amount of time that rats spent investigating comparable items was computed. Furthermore, the recognition index (RI) calculates how much time was spent on the new item compared to how much time was spent on the familiar and new things. During the test, a novel item was used in place of a known one to assess memory performance.

T-Maze Spontaneous Alternation: This test assesses working memory-dependent exploratory behavior. Rats were placed on the T-maze base and given ten consecutive trials to travel in either the right or left arm. When all four paws were in one arm, it was considered an entrance (Lalonde et al., 1986|).

Tissue homogenate preparation

Using a tissue homogenizer (MPW120, MPW Medical Instruments, China), hippocampal specimens were weighted and homogenized independently at the conclusion of the research period. After centrifuging the crude tissue homogenate for 15 minutes at 10,000 rpm in an ice-cold centrifuge, the supernatant was collected and kept at -80°C for further biochemical analysis.

Biochemical analysis

The appropriate rat enzyme-linked immunosorbent assay (ELISA) kits were used to evaluate tissue interleukin 10 (IL-10), tissue interleukin 6 (IL-6), tissue tumor necrosis factor-alpha (TNF-α), citrate synthase (CS), acetylcholine, and amyloid beta 42 (Aβ 42). (IL-10: ERI3010-1, Assaypro LLC, Saint Charles, MO, USA); (TNF-α: ERT2010-1, Assaypro LLC, Saint Charles, MO, USA); (IL-6: ab100772, Abcam, Cambridge, UK); (CS Activity Assay (Catalog No. E-BC-K178-M, Elabscience, Shizishan Ave, Hongshan, China); acetylcholine (Cat.: 201-11-0723, Sunred CO., Shanghai, China); and Aβ 42 rat ELISA Kit (Catalog No.: E-EL-R1402 Elabscience Biotechnology Co., Ltd, China) in accordance with the manufacturer's instructions

in line with the guidelines provided by the manufacturer. Colorimetric kits (Biodiagnostic Company, Dokki, Giza, Egypt) were used to measure tissue superoxide dismutase (SOD) and tissue malondialdehyde (MDA).

Gene expression quantification using RT-PCR

The BDNF, Nrf2, and HO-1 genes' relative mRNA levels in the hippocampal regions were examined using RT-PCR. As directed by the manufacturer, total RNA was extracted from tissues using the TRIzol reagent (Invitrogen-Carlsbad, CA, USA). Until it was used, the isolated RNA was kept at -80 C. The nanophotometer

N60 was used to measure the absorbance of RNA at 260 nm (A260) in order to evaluate its purity and amount. ThermoScript RT reagent kits (Invitrogen) were used for the complementary DNA (cDNA) synthesis (reverse transcription step) phase of the first PCR process. Next, SYBR Green Mix kits (Stratagene, USA) were used for cDNA amplification. A cycle threshold (Ct) value was obtained for every amplification curve. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was the reference gene.

GAPDH primers sequence was: (1) Forward primer: 5 -TATGACTCTACCCACGGCAAGT-3

(2) Reverse Primer: 5 -ATACTCAGCACCAGCATCACC-3.
The BDNF, Nrf2, and HO-1 genes' relative mRNA levels in the hippocampal regions were examined using RT-PCR. Total RNA was extracted from tissues using the TRIzol reagent (Invitrogen). Data analysis was conducted using the 7500 ABI PRISM 2.0.1 version (Applied Biosystems, USA). The comparative ΔΔCt method was used to measure the relative amounts of BDNF, HO-1, and Nrf2 gene expression.

The following primers were used for the BDNF gene:

(1) forward primer : 5-GCTGCCTTGATGTTTACTTTG-3
(2) reverse primer :5-ATGGGATTACACTTGGTCTCGT-3.

The following primers were used for the Nrf2 gene:
(1) Forward primer: 5-AGCAAGACTTGGGCCACTT-3
(2) Reverse primer: 5-GATGGAGGTTTCTGTCGTTTTC-3
The following primers were used for the HO-1 gene were as follows:
(1) Forward primer: 5-AGGTGCACATCCGTGCAGAG-3
(2) Reverse primer: 5-CTTCCAGGGCCGTATAGATATGGTA-3

Histological study:

at the hippocampal location, each cerebral hemisphere was divided coronally into two sections, which were then preserved in 10% formalin. After being cleansed and dehydrated, the samples were embedded in paraffin blocks. For routine histological analysis, serial coronal slices that were 5–7 μm thick were cut and stained with Hematoxylin & Eosin (Hx. & E.) stain.

Immunohistochemical studies:

Blocks of paraffin were deparaffinized and then rehydrated using decreasing alcohol grades. Anti-caspase-3 (rabbit polyclonal antibody, Dako, Carpinteria, California, USA) and anti-glial fibrillary acidic protein (GFAP) (rabbit polyclonal antibody, Midco Trade Company, Giza, Egypt) were added and incubated overnight. A 2% concentration of biotinylated goatpolyvalent secondary antibody was added for 10 minutes, and then the avidin-biotin-peroxidase complex was added.

Statistical analysis

According to the findings of the Shapiro-Wilk test, they were determined to satisfy the parametric assumptions after data collection and analysis. Consequently, post hoc Bonferroni's tests and one-way ANOVA were used to the data. The mean ± standard deviation (SD) was used to illustrate the data. When the p value was 0.05 or below, it was deemed that significance was present. Graph-Pad Prism software (version 9.3.1, San Diego, CA, USA) was used to analyze the data.

RESULTS

The mean value of time in total time of exploration during familiarization phase and recognition index in NOR and percentage of alternation on T maze test in Scop-group were dramatically lower than control ($P< 0.05$). The values of Scop +STG were dramatically higher than Scop ($P < 0.05$). (**Fig. 1 A,B,C)**.

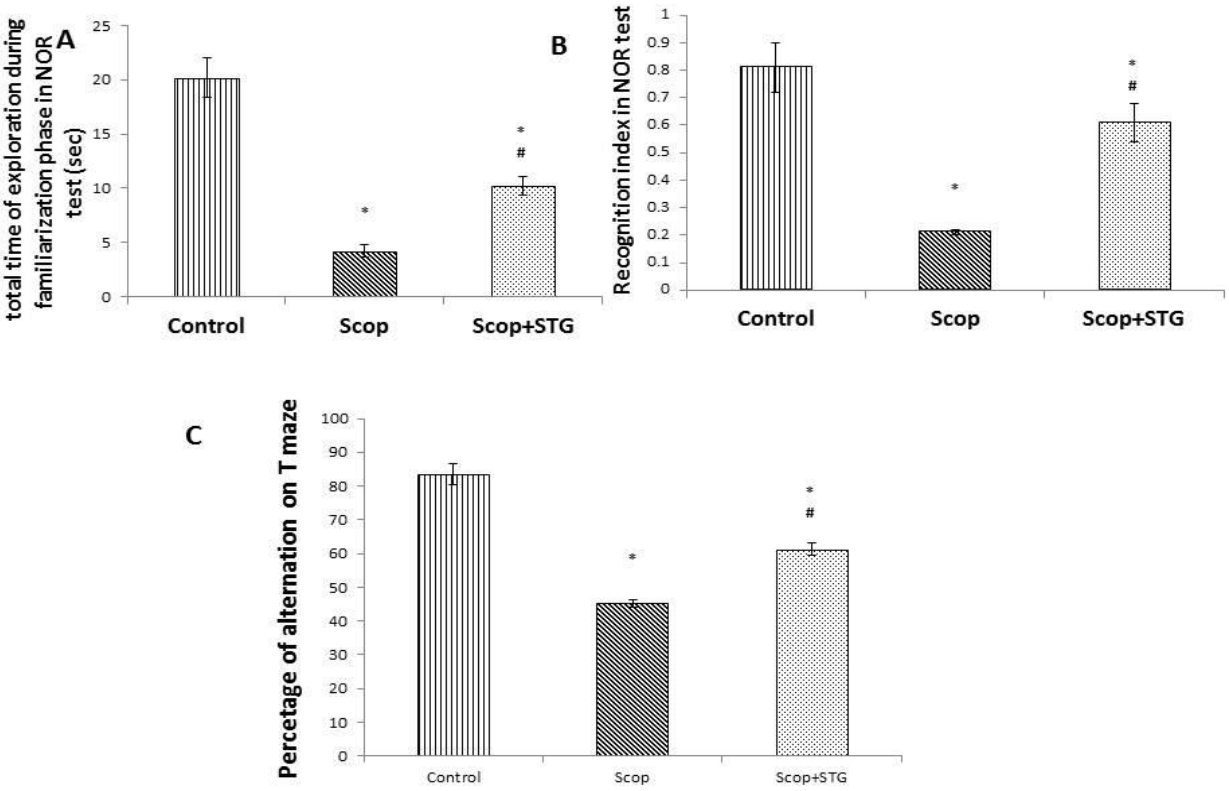

Figure (1): Sitaglibtin impact on (A), (B) Novel object recognition and (C) T maze tests in all studied groups. * Significant compared with control, # Significant compared with STG. Data represented as mean ± SD

There was dramatically elevated hippocampal acetylcholine, MDA, TNF-α, IL-6 and Aβ 42 with substantial decline in SOD, CS activity, IL-10 and hippocampal BDNF, Nrf2 and HO-1 genes expression in Scop group compared to control. Scop+STG group showed dramatically decreased hippocampal acetylcholine, MDA, TNF-α, IL-6 and Aβ 42 with substantial elevation in SOD, CS activity, IL-10 and hippocampal BDNF, Nrf2 and HO-1 genes expression compared to Scop group Table (1).

Table (1): The measured hippocampal acetylcholine, MDA, SOD, Citrate Synthase, TNF-α, IL-6, IL-10, hippocampal BDNF, Nrf2 and HO-1 genes expression in all studied groups

	Control group	Scop group	Scop + STG group
Hippocampal acetylcholine (U/ml)	92.3±2.9	31.1.±0.7 *	49.2±3.2 *#
Hippocampal MDA (nmol/ gm. Tissue)	6.2 ±1.89	23.1± 1.33*	14.5± 2.34*#
Hippocampal SOD (U/gm. Tissue)	5.3±0.09	2.65±0.21*	3.99±0.31*#
Hippocampal Citrate Synthase (U/L)	14.2±0.9	5.9±0.31*	8.67±0.43*#
Hippocampal TNF-α (ng/ml)	23.5±1.59	52.3±2.9*	38.6±2.1*#
Hippocampal IL-6 (pg/mL)	16.2±0.9	4.3±0.31*	7.9±0.1*#
Hippocampal IL-10 (ng/ml)	108.9±6.42	390.1±9. 59*	281±8.1*#
Hippocampal Amyloid beta 42 (***pg/mL)***	61.9±3.22	233±1.25*	149.9±6.1*#
Hippocampal BDNF gene expression	1	2.9±0.02*	0.66±0.08*#
Hippocampal Nrf2 gene expression	1	0.32±0.04*	0.71±0.08*#
Hippocampal HO-1 gene expression	1	0.41±0.07*	0.77±0.09*#

*Significant compared with control, # Significant compared with Scop

Histological results in H&E-stained sections:

Three layers made up the control group's hippocampal structure: molecular, pyramidal, and polymorphic layers. Multiple regular rows of neatly ordered, compact pyramidal cells made up the pyramidal layer. With a big vesicular nucleus, a conspicuous nucleolus, and basophilic cytoplasm, each pyramidal cell had a triangular appearance. Both molecular and polymorphic layers were mostly composed of a dense network of nerve fibers and eosinophilic neuropil matrix. The hippocampal pyramidal layer cell count was significantly lower in the SCOP group. Both molecular and polymorphic layer neurons displayed many vacuolations and dilated, clogged blood channels. The pyramidal cells had perinuclear halos and reduced hyperchromatic nuclei, suggesting degeneration. Both the polymorphic and molecular layers saw an increase in the number of astrocytes. In the The number of pyramidal layer cells appeared to have increased in the SCOP+ STG. With their big vesicular nuclei, prominent nucleoli, and basophilic cytoplasm, many pyramidal cells seemed normal. **Fig (2)**

The number of the pyramidal cells was substantially decreased ($p<0.05$) in the SCOP group as compared to the control group (28.45±0.62 vs. 75.07±0.88). However, the SCOP+ STG group showed a substantially increase ($p<0.05$) of it as compared to the SCOP group (53.23±0.36 vs. 28.45±0.62) but still decreased from the control group

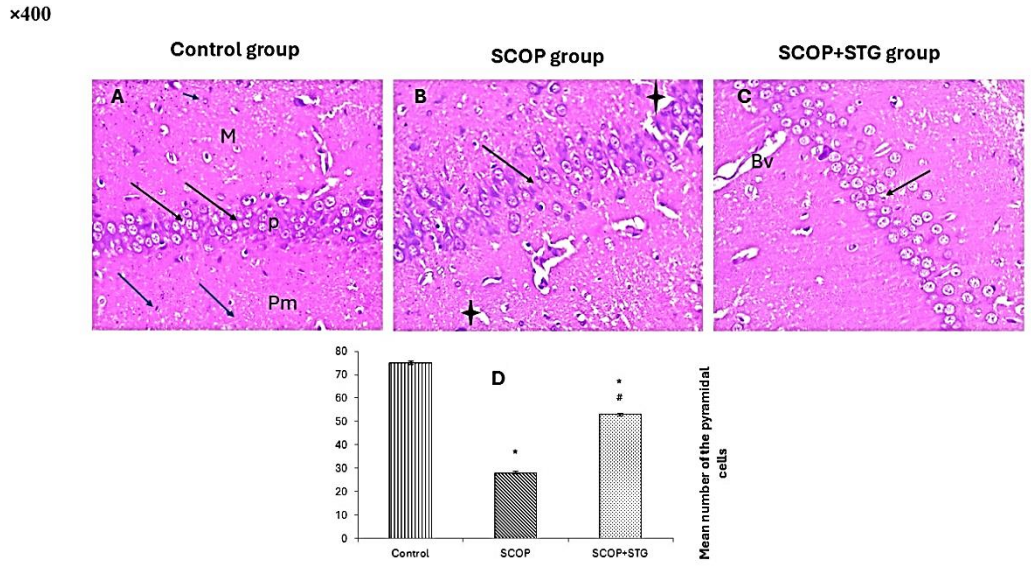

Figure (2): photomicrographs of the hippocampus of the different groups showing the pyramidal (P), molecular (M) and polymorphic (Pm) layers. (A) The control group showed normal small pyramidal cells that appeared triangular with basophilic cytoplasm, large vesicular nucleus (black arrows). Different types of neuroglial cells are observed inside the neuropil matrix of the molecular (M) and polymorphic (Pm) layers (blue arrows). (B) The SCOP group showing loss of tissue integrity (black arrow) with pyknotic pyramidal cells. Many vacuolations (star)) are seen in the neuropil of both molecular and polymorphic layers. (C) SCOP+ STG showing normal appearance of most pyramidal cells (black arrow) with congested blood vessel (BV) (X400), (D) Pyramidal cell counts in all groups.

Immunohistochemical results:

In Caspase-3, the SCOP showed a substantial increase ($p< 0.05$) compared to the control (70.33±3.15 vs. 7.01±0.07). However, the SCOP+ STG showed a substantial decrease in the positive caspase-3 area compared to the SCOP (25.20±0.57 vs. 70.33±3.16) but still increased from the control group.

In GFAP the SCOP showed a substantial elevation ($p< 0.05$) compared to the control (42.23±1.04 vs. 8.06±1.60). However, the SCOP+ STG showed a substantial decrease compared to the SCOP (20.13±1.16 vs. 42.23±1.04) but still increased from the control group. **Fig (3)**

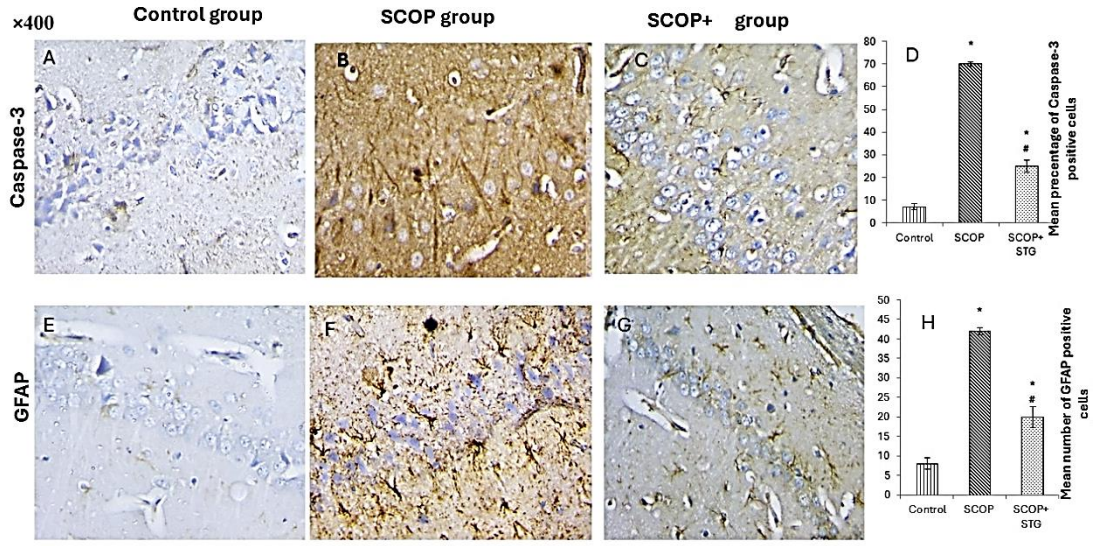

Figure (3): Representative micrographs of the different experimental groups showing a substantial elevation of the Caspase-3 (A-D) and GFAP (E-H) immunoreaction in the SCOP group and a significant downregulation in the SCOP+STG group

DISCUSSION

Scopolamine is frequently used as a model to study dementia-related disorders since it can result in memory and cognitive deficits. This drug has long been used to inhibit muscarinic acetylcholine (ACh) receptors linked to memory (Pezzeو et al., 2017).

This is consistent with our findings, which show that administering scop causes cognitive impairment as shown by the interpretation of NOR and T maze test results.

The cholinergic theory may be implemented by injecting Scopolamine, which causes cognitive abnormalities similar to those seen in AD. The goal of treatment is to suppress the acetylcholinesterase enzyme in order to restore the function of the cholinergic system. Scopolamine decreased the total duration of exploration during the familiarization phase, the recognition index in NOR, and the percentage of alternation on the T maze test, according to the results of the object recognition test. These findings suggested that the learning and recognition processes were impaired. Therefore, as an anticholinergic drug, Scop inhibits muscarinic receptors, which have been shown to impair learning and memory function in both humans and animals. (Sargholi et al., 2015).

When compared to the Scop group, the cognitive deficiency was significantly improved after receiving STG treatment. As a result, STG significantly enhanced memory retrieval and acquisition. This is consistent with other research (Li et al., 2018, Osman et al., 2019, Gault et al., 2015 and Krupina et al., 2016). All things considered, our research points to STG as a possible new medication option for dementia prevention.

Sitagliptin significantly improved the histological changes caused by Scop in the hippocampus and increased the pyramidal layer. This was in agreement with Jiang et al. (2024), who concluded that Sitagliptin improves hippocampal neurogenesis, and Wiciński et al. (2018), who noted that Sitagliptin has a strong neuroprotective effect.

Excessive ROS generation under a variety of circumstances can result in

oxidative stress, which plays a role in the etiology of a number of neurodegenerative diseases, including AD. Research has shown that elevated oxidative stress in the brain is linked to memory impairment caused by scopolamine (Li et al., 2013).

Rats given scopolamine showed decrease in SOD and increase in MDA. Therefore, oxidative stress seems to play a vital role in the cognitive deterioration brought on by scopolamine. Additionally, compared to the control, the current study demonstrated a substantial decrease in citrate synthase activity, a marker for mitochondrial function, and an elevation in Aβ 42. Scopolamine has been linked to increased oxidative stress and Aβ accumulation in the rat hippocampal region (Hernández Rodríguez et al., 2020). According to Gul et al. (2023), oxidative stress caused by Aβ might result in metabolic changes in the brain, including lipid peroxidation and the creation of ROS, which can induce synapse loss and cognitive dysfunction.

When compared to the Scop group, the Scop+ STG group showed a substantial drop in MDA levels, an increase in SOD activity, and enhanced mitochondrial function through an increase in CS activity. This is consistent with other research (Osman et al., 2019 and Kabel et al., 2019). Strong antioxidant and free radical scavenging properties of STG have been demonstrated (Kabel et al., 2019). Additionally, Pintana et al. (2013) showed that STG restored hippocampus mitochondrial activity and reduced brain oxidative stress in rats. Nrf2 was elevated by indirect pathways for STG's antioxidant activities (Hewedy, 2020). One important transcription factor that regulates the production of antioxidants and the stress response to oxidative damage is Nrf2 (He et al., 2020).

Scop+STG showed dramatically decreased level of Aβ 1-42 compared to Scop group The present results agree with Osman et al., (2019).

Previously, vildagliptin and sitagliptin both fully restored brain mitochondrial function and enhanced learning and memory functions (Pintana et al., 2013).

One possible explanation for how sitagliptin medication restores brain mitochondrial function is that it inhibits DPP-4 activity, which prolongs GLP-1 effect. In a variety of cell types, GLP-1 has been demonstrated to provide protection against mitochondrial malfunction. For instance, it has been demonstrated that GLP-1 stimulates mitochondrial ATP production in cultured b-cells and mobilizes intracellular Ca2C (Pintana et al., 2013).

AChE inhibitors may be able to reverse the memory impairment brought on by scopolamine (Thongrong et al., 2024). Nevertheless, it is still unclear how exactly scopolamine raises AChE activity. According to certain data, oxidative stress brought on by scopolamine may be a possible mechanism for raising AChE activity, which in turn causes cognitive impairment (Afzal et al., 2022).

In line with earlier research, the current findings showed that scopolamine-treated rats exhibited significant cholinergic system dysfunction, which was accompanied by memory impairment and a decrease in acetylcholine levels in the hippocampus (Thongrong et al., 2024).

Acetylcholine levels were recovered with sitaglibtin. GLP-1R agonists restore cholinergic marker activity in the basal forebrain of rats treated with ibotenic acid, a rodent model of neurodegeneration (Perry et al., 2002).

In rats treated with ibotenic acid, a rodent model of neurodegeneration, GLP-1R agonists restore cholinergic marker activity in the basal forebrain and stop glutamate-induced death in cultured rat hippocampus neurons (Perry et al., 2002).

Scopolamine lowered IL-10 and increased TNF-α and IL-6 in the hippocampus. According to Shabani et al. (2018), this is consistent. Additionally, when scopolamine was administered, the expression of the NFkB increased (Joseph et al., 2020).

When compared to Scop, Scop +STG group showed a large rise in IL-10 and a significant drop in TNF-α and IL-6. This is in line with earlier research (Kabel et al., 2019) which found that because STG has strong anti-inflammatory properties at both the nuclear and cytoplasmic levels (Wiciński et al., 2018), it was able to reduce proinflammatory cytokines. By affecting the innate immune system, including T cell activation, monocyte/macrophage activation, and the generation of inflammatory factors in vivo, DPP-4 inhibitors contribute to anti-inflammation (Zhong et al., 2013). According to Hu et al. (Hu et al., 2017), STG treatment may reduce both cytokine expression and NF-κB activation. Transcription and the release of cytokines like TNF-α, IL-1, and IL-6 are increased when the NF-κB pathway is activated (Pesarini et al. 2010).

The astrocyte marker, GFAP, may be used to track inflammation and nerve damage (Song et al., 2024). In the current investigation, Scop boosted GFAP immunoreactivity, whereas the STG considerably reduced the number of astrocytes in comparison to the SCOP group. This was in line with Hung et al.'s (2023) findings that gliptins may correct neurogenesis and decrease astrocyte reactivation.

This is in line with earlier findings (Sun et al., 2017), which showed that STG dramatically decreased GFAP in a rat model of febrile seizures. They ascribed that to its ability to reduce inflammation.

The Scop group's hippocampal elevation of Caspase-3 immunoreaction was significantly reduced in the Scop+STG group. This explains STG's antiapoptotic action, which is consistent with You et al.'s (2023) findings that STG causes apoptosis and suppresses growth. According to Kizilay et al. (2021), STG's antiapoptotic function is due to its antioxidant qualities and its capacity to control calcium release from ER, hence preventing ER stress.

One important protein in brain plasticity is BDNF, which has been shown to control neuronal survival and affect cognitive functions (Li et al., 2018) In contrast to Scop, Scop+STG significantly increased the BDNF level, which is consistent with Li et al.'s (2018) discovery that sitagliptin helped PD mice with their memory impairments. Moreover, sitagliptin increased tyrosine hydroxylase (TH) and BDNF expression levels. Furthermore, sitagliptin increased the density of dendritic spines.

Both neurotrophic effects, such as neurogenesis, and neuroprotective benefits, such as decreased apoptotic and necrotic signaling and cell death, are associated with GLP-1R activation (Rondas et al., 2013).

By considerably raising the BDNF level in the hippocampus neurons as compared to the Scop results, sitagliptin (STG) treatment greatly improved hippocampus neurogenesis and neural plasticity. Additionally, by upregulating the production of BDNF, STG helped mice with Parkinson's disease with their memory problems (Yang et al., 2013 and Li et al., 2018). Because of its anti-inflammatory and antioxidant qualities, STG may play a part in neurogenesis. Furthermore, Bachor et al. (2015) linked STG's neurotrophic impact to its function in preventing brain progenitor cell multiplication.

According to Lee et al. (2005), Nrf2 is a key regulator of cellular resistance to oxidants. Under typical circumstances, Kelch-like ECH associated protein (Keap1) suppresses Nrf2. Through the release of Nrf2 from its cytoplasmic Keap1 and the alteration of crucial cysteine thiols of Keap1 and Nrf2, the Nrf2 signaling pathway is activated during oxidative stress. Numerous cytoprotective genes with an antioxidant response element (ARE) in the promoter region are induced to express themselves in the nucleus by Nrf2. Activation of the Nrf2 pathway may reduce oxidative damage in several tissues (Shin, et al. 2013).

A transcription factor called Nrf2 is in charge of controlling the cellular redox equilibrium and the cells' antioxidant defenses (Loboda et al.,2016). One of the main regulators of Nrf2-dependent cellular responses and the main rate-limiting enzyme in heme breakdown events is HO1, the inducible version of heme oxygenase. In addition to playing a vital role in the adaptive response to cell injury, HO-1 and its metabolic products contribute to the maintenance of cellular homeostasis (Nitti et al.,2017).

scopolamine caused oxidative stress and inhibition of Nrf-2/HO-1 in previous study (Gul et al., 2023).

A crucial antioxidant enzyme called HO-1 catalyzes the breakdown of heme, which results in the generation of biliverdin and carbon monoxide and prevents the neurodegenerative illness brought on by oxidative stress. Nrf-2, a redox sensitive transcription factor, induces antioxidants and phase 2 detoxification enzymes such HO-1 (Gul et al., 2023).

On the other hand, sitagliptin significantly increased Nrf2 and HO-1 in the hippocampal region in comparison to the Scop, which is consistent with Hewedy's (2020) findings. According to several recent research, DDP4 inhibitors can target the Nrf2 signaling pathway (Choi et al., 2015). According to Abo-Haded et al. (2017), sitagliptin has also been shown to reduce methotrexate-induced hepatotoxicity via altering the Nrf2 and NF-κB signaling pathways, which in turn has anti-inflammatory and antiapoptotic effects.

CONCLUSION: In addition to up-regulating Nrf2 and HO-1 gene expressions, sitagliptin has a beneficial protective impact against Scop-induced cognition impairments through anti-oxidant, anti-inflammatory, enhanced mitochondrial activity, prevention of apoptosis, and neurotrophic actions.

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يعمل سيتاجليبتين على تخفيف العجز الإدراكي العصبي الناتج عن السكوبولامين عن طريق تنشيط مسار Nrf2/HO-1 وتحسين نشاط الميتوكوندريا

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يتم إعاقة ذاكرة الجرذان بواسطة مضادات المستقبلات المسكارينية سكوبولامين (سكوب)، الذي يثبط النقل العصبي الكولينيز الهدف من البحث كان تقييم التأثير الوقائي للسيتاجليبتين والعمليات الأساسية له في الإعاقات المعرفية العصبية الناجمة عن سكوب. تم تقسيم ثلاثين من ذكور الجرذان البيضاء البالغة إلى ثلاث مجموعات:السليمه الضابطه ومجموعه الاسكوبولامين ومجموعه الاسكوبولامين المعالجه بالسيتاجليبتينز تم تقييم الفئران عصبيا. تم قياس ما يلي: BDNF، Nrf2، HO-1، نشاط سيترات سينسيز (CS)، أستيل كولين، MDA، SOD، TNF-α، إنترلوكين (6- (IL، IL-10، وأميلويد Aβ42) 42 β). بالإضافة إلى ذلك، تم إجراء التحليلات النسيجية والكيميائية المناعية للحصين.

النتائج إلى جانب مستويات أعلى بكثير من MDA، وTNF-α، وIL-6، والأسيتيل كولين، وAβ 42، بالإضافة إلى الاستجابة المناعية للحصين GFAP وCaspase-3، أظهرت مجموعة الاسكوبولامين أيضًا انخفاضًا في الأداء المعرفي مقارنة بالمجموعة الضابطة. بالإضافة إلى ذلك، فإنه ينظم التعبير الجيني BDNF وNrf2 وHO-1 في الحصين ويقلل بشكل ملحوظ نشاط IL-10 وSOD وCS. أظهر المجموعه المعالجه تحسنًا كبيرًا في العجز المعرفي العصبي الناجم عن الاسكوبولامين . نستنتج من ذلك بالإضافة إلى تنظيم التعبيرات الجينية Nrf2 وHO-1، فإن سيتاجليبتين له تأثير وقائي مفيد ضد ضعف الإدراك الناجم عن الاسكوبولامين من خلال نشاط الميتوكوندريا المعزز المضاد للأكسدة والمضاد للالتهابات والوقاية من موت الخلايا المبرمج والتاثيرات العصبيه