Archives of Pharmaceutical Sciences Ain Shams University 2024; Vol. 8(2): 386-395

OPEN ACCESS

Pharmaceutical Chemistry

Review Article

Saxagliptin beyond glycemic control: a comprehensive review

Maha M. Abdrabou[a*], Enas Elmowafy[b], Haidy E. Michel[c], Samar S. Azab[c]

[a]*Health Affairs Directorate, Cairo, Egypt*
[b]*Department of Pharmaceutics and Pharmaceutical Industry, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt*
[c]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt*

ABSTRACT

This review will provide insight into Saxagliptin, a potential neuroprotective rather than a well-established anti-diabetic drug. Both glycemic and neuronal effects of Saxagliptin are mainly mediated through glucagon-like peptide-1 (GLP-1) and to a lesser extent dipeptidyl peptidase-4 (DPP-4) so, we will discuss the function of GLP-1 in the human body with a focus on its central role in the brain. Additionally, we will explore Saxagliptin's potential as a disease-modifying agent in neurodegenerative disorders, with a particular focus on Parkinson's disease (PD) and Alzheimer's disease (AD), where Saxagliptin's neuroprotective potential has been most studied. Treatment options for these disorders don't alter the underlying pathology. They are mainly palliative and marginally effective, making the premise of repurposing other drugs, such as Saxagliptin as disease-modifying agents intriguing. The pathway through which neuroprotection could be achieved will also be discussed. Our review is based on evidence from epidemiological studies and preclinical research utilizing review articles, books, and original articles obtained from PubMed, Google Scholar, and Elsevier.

Keywords: *GLP-1; DPP-4; Parkinson's disease; Alzheimer's disease; neuroprotection.*

***Correspondence** | Maha M. Abdrabou; Health Affairs Directorate, Cairo, Egypt. Email: maha.mohamed20@pharma.asu.edu.eg
Citation | Abdrabou MM, Elmowafy E, Michel HE, Azab SS, 2024. Saxagliptin beyond glycemic control: a comprehensive review. Arch Pharm Sci ASU 8(2): 386-395
DOI: 10.21608/aps.2024.304569.1182
Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.
Received 01 August 2024. **Accepted** 07 September 2024.

Published by: Ain Shams University, Faculty of Pharmacy

1. Introduction

The brain is often regarded as the most complex of all biological systems, with the mature brain composed of more than 100 billion information-processing cells called neurons. It is the core center for movement, sensory perception, emotions, language, communication, thinking, and memory. It is the origin of all the traits that define our humanity. Thus, it is anticipated that neuroprotection in the form of preserving neuronal structure and function, preventing neurodegeneration, and promoting neural repair will remain a crucial area of scientific research **[1]**.

Saxagliptin is a remarkable drug. While originally indicated for the management of type 2 diabetes mellitus (T2DM), promising new data has shown its potential for broader therapeutic applications **[2, 3]**. Indeed, Saxagliptin works to elevate GLP-1 (Glucagon-like Peptide-1) levels in the body and because GLP-1 is itself so versatile in its peripheral and central biological functions in addition to having receptors all over the body; it is not surprising that Saxagliptin has been shown to possess anti-inflammatory, anti-oxidant, anti-apoptotic and neuroprotective

capabilities in addition to its established anti-diabetic efficacy **[4]**. Saxagliptin is a selective inhibitor of dipeptidyl peptidase-4 (DPP-4), an enzyme that plays a key role in glucose metabolism and catalyzes the breakdown of GLP-1. GLP-1, a member of the incretin family, is secreted by the nutrient-sensing L cells of the intestine. When food passes through the intestinal lumen, L cells detect sugars, amino acids, and fatty acids and secrete GLP-1. This peptide possesses critical functions. **1- Local effect on the Intestinal Walls:** GLP-1 slows the gastric emptying rate, which leads to better nutrient absorption and regulates glucose entry into the bloodstream **2- Activation of Vagal Sensory Nerves:** GLP-1 activates vagal sensory nerves, which play a role in regulating appetite and satiety signaling to the brain. **3- Pancreatic Effects:** As a hormone, GLP-1 stimulates insulin secretion from the pancreatic β-cells and inhibits glucagon release from the α-cells. These effects collectively contribute to the regulation of blood glucose levels by GLP-1 and Saxagliptin **[5-7]**.

A key advantage of Saxagliptin is its ability to lower blood glucose levels without producing hypoglycemia. As its action relies on GLP-1 secretion and the peptide is only released postprandial in a glucose-dependant manner, rendering the drug's blood glucose lowering effect also glucose-dependent and eliminating the risk of hypoglycemia **[6]**. By inhibiting DPP-4, Saxagliptin increases postprandial GLP-1 by 1.8-3 folds within minutes of oral administration, and so it is conventionally used in the management of T2DM either alone or in combination with other antidiabetics to obtain optimal glycemic control **[5]**.

Beyond glycemic control, GLP-1 plays a critical neuroprotective role in the human brain. Its G-protein coupled receptors, GLP-1Rs (glucagon-like peptide-1 receptors) are widely distributed throughout the brain, with the hypothalamus, cerebral cortex, and thalamus being their richest locations **[8]**. These receptors are involved in various CNS functions including, learning and neuroprotection in the hippocampus, potentiation of cellular differentiation, modulation of neurite outgrowth, synaptic plasticity, regulation of food and water intake, regulation of insulin sensitivity, and modulation of markers of oxidative stress. Moreover, they contribute to the upregulation of tyrosine hydroxylase (TH) the rate-limiting enzyme for dopamine synthesis. These versatile roles highlight the therapeutic potential of GLP-1 and its analogs in neuronal disorders **[5]**.

Our objective with this review is to explore Saxagliptin's potential neuroprotective effects mediated through GLP-1 and DPP-4 signaling pathways with a focus on neurodegenerative disorders.

2. GLP-1 signaling pathway in the brain mediating neuroprotection

2.1. Anti-apoptotic pathway: GLP-1 decreased the number of apoptotic cells in hippocampal neurons subjected to glutamate-induced cell death and reversed neurodegeneration of cholinergic neurons in the basal forebrain. This is mediated through its action on GLP-1R, activating adenyl cyclase and increasing cyclic adenosine monophosphate (cAMP) **[9]**. In a rat model of traumatic brain injury, GLP-1 was also found to down-regulate apoptosis-related genes, namely, Bcl-2-associated X protein (Bax), and Cleaved Caspase-3 (CC-3) **[10]**. Bax, a pro-apoptotic protein, promotes apoptosis by inducing mitochondrial outer membrane permeabilization (MOMP), leading to the release of cytochrome c into the cytosol and subsequent activation of caspase cascade [11]. Additionally, GLP-1 activates the ERK (Extracellular Signal-Regulated Kinase)-CREB (cAMP response element-binding protein) signaling pathway. This pathway supports cell survival through two key

mechanisms: ERK-dependent phosphorylation of prosurvival proteins and CREB-dependent transcription of prosurvival genes **[10]**. So, GLP-1 exerts neuroprotective effects through the modulation of apoptosis-related pathways and the activation of survival signaling mechanisms.

2.2. Neuronal plasticity pathway

The link between enhancing synaptic plasticity and neuroprotection is well documented in the literature.

GLP-1 was shown to regulate calcium homeostasis, a process closely associated with synaptic plasticity and neuroprotection. Gilman et al., 2003 found that GLP-1 reduces calcium influx and membrane depolarization in response to glutamate, protecting neurons against glutamate-induced death **[12]**. These suppressive effects of GLP-1 on calcium influx and excitotoxicity are thought to be mediated by cAMP and activation of downstream kinases and transcription factors. GLP-1 not only induces cAMP production **[9]** but also triggers rapid and transient elevation of calcium (a temporary rise in calcium peaking within 1 minute of glutamate exposure before subsequent suppression) in hippocampal neurons **[12]**. In pancreatic cells, a similar mechanism takes place where GLP-1 activates the protein kinase MAPKs (mitogen-activated protein kinases) and the transcription factor CREB (cAMP response element-binding protein) in a calcium and cAMP-dependent manner **[13]**. MAPK and CREB are both engaged in synaptic plasticity. Since the regulation of calcium influx is crucial for short- and long-term changes in synaptic plasticity **[12]**, GLP-1 can potentially protect neurons from excitotoxicity and enhance plasticity.

A study published in *Nature Medicine* reported that GLP-1 enhances associative and spatial learning, synaptic plasticity, and memory through GLP-1R signaling. The study found that mice deficient in GLP-1Rs exhibited learning deficits, which were restored only after hippocampal gene transfer of the receptor **[14]**. Another study also found GLP-1 to possess a neuromodulatory effect on the process driving synaptic plasticity (long-term potentiation) in the CA1 region of the hippocampus, an effect that was inhibited by GLP-1R antagonist exendin(9-39)amide **[14, 15]**.

2.3. Neurotrophic pathway

GLP-1 has been found to induce neurite outgrowth in PC12 cells, replicating the effect of nerve growth factor (NGF). This effect of GLP-1 includes signaling mechanisms through pathways such as phosphoinositide 3-kinase (PI3-kinase) and extracellular signal-regulated kinase mitogen-activated protein kinase (ERK MAP kinase), demonstrating its neurotrophic properties. These findings indicate a potential role for GLP-1 in promoting neuronal differentiation and emphasize its therapeutic potential for neurodegenerative disorders **[16]**.

3. DPP-4 signaling pathway involved in neurodegeneration

Inflammatory pathway: The sDPP4 (the soluble form of the enzyme found in the blood, as opposed to the membrane-bound form) acts as an agonist for PAR2 (protease-activated receptor 2) thereby promoting the NF-κB (nuclear factor-kappa B) mediated release of pro-inflammatory mediators **[17]**.

4. Protective effect of Saxagliptin in neurodegenerative disorders

Epidemiological studies have linked many neurodegenerative disorders in one way or another to diabetes, Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and Huntington's disease are just a few. In a large 2008 prospective cohort study (an observational study designed to follow a set number of people over a specific period) that

followed 21,841 persons for 23 years, a positive association between T2DM and PD was found. In the study, men with diabetes were found to have higher rates of PD **[18]**. However, it is critical to realize two points. First, most of the data linking T2DM to neurodegeneration come from either epidemiological or preclinical studies, and there exists a lack of randomized controlled studies to support this evidence. Second, these epidemiological studies have yet to establish T2DM as a causative for neurodegeneration **[19]**. For instance, the 2008 study that found a positive association between diabetes and PD stated that it is a matter of correlation rather than causation. "If diabetes causes Parkinson's disease, one would expect increased duration and severity to increase Parkinson's disease risk. However, we found the highest risk for Parkinson's disease among individuals with uncomplicated or short-duration diabetes, regardless of baseline age" **[18]**.

While the evidence for insulin resistance being a causative factor in these disorders or a secondary consequence of neurodegeneration is not yet conclusive, the association is increasingly recognized, and their co-existence is unlikely to be by chance. In light of that, it is not surprising to see much research work directed towards repurposing T2DM drugs as potential treatments for neurodegenerative disorders **[20]**. Moreover, it is noteworthy that the treatment of many neurodegenerative diseases is symptomatic only; making repurposing efforts of novel disease-modifying drugs a very critical area of research.

5. Effect of Saxagliptin on Parkinson's disease (PD)

PD is a progressive neurodegenerative disorder in which loss of dopaminergic neurons in the nigrostriatal area causes its characteristic motor symptoms of tremor, bradykinesia, and rigidity. In addition to these motor symptoms, apoptosis, oxidative stress, and neuroinflammation are also present affecting cognition and memory **[21, 22]**. The disorder arises from an imbalance between direct and indirect pathways that link the striatum to the basal ganglia. Dopamine, the neurotransmitter responsible for the transmission of motor signals between the striatum and the substantia nigra of the basal ganglia, plays a critical role in this process **[23]**.

Many studies have linked diabetes to PD. Both diseases have been proven to share similar dysregulated pathways and common pathological mechanisms. Insulin signaling appears to have a significant role in this connection. Insulin is crucial for maintaining neuronal health, including the regulation of dopamine (a neurotransmitter essential for movement and coordination) release in the substantia nigra **[24]**. In a 2011 study, insulin resistance was induced through a high-fat diet in rats. It profoundly impacted substantia nigra by reducing dopamine release and attenuating its function, suggesting a direct link between dysregulated insulin signaling and PD pathogenesis **[24]**. While the loss of neurons in the substantia nigra pars and other brain stem nuclei is a characteristic pathology in PD, a 1993 study by Moroo et al. showed that the surviving dopaminergic neurons in this region exhibited an almost total loss of insulin receptors. This finding suggests a significant down-regulation of the insulin receptor system in these neurons **[25]**.

Additionally, Insulin degrading enzyme (IDE), a protease involved in regulating insulin levels, has been implicated in PD pathogenesis, especially as its activity is reduced in diabetes. IDE was found to inhibit alpha-synuclein (α-syn) a protein whose buildup is associated with PD. In PD, the aggregation of α-syn into amyloid fibers is thought to play a key role in the neurotoxic processes leading to the degeneration of dopaminergic neurons **[26]**. Moreover, diabetes and prediabetes in PD patients are correlated with

poorer clinical and pathological outcomes, manifesting as accelerated disease progression, a more severe phenotype, and an increased risk of dementia **[20]**.

On another level, GLP-1 signaling is emerging as a promising target for PD treatment. Activation of the GLP-1 receptor can lead to multiple benefits, including the reduction of neuroinflammation and oxidative stress, the enhancement of blood-brain barrier (BBB) integrity, and the restoration of insulin signaling. These effects could potentially compensate for the dysfunctional dopaminergic neurotransmission and motor deficits in PD **[27]**.

6. Evidence for neuroprotection

A study by Nassar et.al. found Saxagliptin to be neuroprotective in a rat model of rotenone (ROT)-induced PD. Saxagliptin reduced akinesia and improved motor performance and muscle coordination. It also induced neurogenesis through a 2.5-fold increase in brain-derived neurotrophic factor (BDNF) levels. Saxagliptin also exerted an anti-inflammatory effect by decreasing NF-κB, tumor necrosis factor-α (TNF-α), inducible Nitric Oxide Synthase (INOS), and Myeloperoxidase (MPO) **[28]**. Saxagliptin was also found along with other DPP-4 inhibitors to have a neuroprotective effect in diabetic patients with PD by affecting both baseline dopamine levels and motor outcomes. It produced a higher baseline dopamine transporter in the anterior, posterior, and ventral putamina, reducing the rate of levodopa-induced dyskinesia and wearing of phenomena in those patients **[29]**.

Topical administration of Saxagliptin was found to reduce glutamate levels and prevent retinal neurodegeneration in mice. Glutamate-induced neurotoxicity is a key factor in the neurodegeneration of dopaminergic neurons of the basal ganglia, a hallmark of PD **[23]**. This suggests that Saxagliptin could show potential for producing similar neuroprotective effects in PD by attenuating glutamate toxicity and protecting dopaminergic neurons.

7. Effect of Saxagliptin in Alzahimer's (AD)

AD is a progressive neurodegenerative disorder characterized by dementia and cognitive decline. The prominent pathological feature of AD is the extraneuronal accumulation of abnormally folded β-amyloid protein, forming amyloid plaques and intraneuronal neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein, which leads to loss of cholinergic neurons **[30]**.

Despite being two distinct disorders, PD and AD share many mechanistic similarities. Both neurodegenerative disorders exhibit abnormal protein aggregation, impaired protein clearance, mitochondrial dysfunction, programmed cell death, reduced glucose utilization, impaired energy metabolism, and inflammation. In light of these, it is not surprising to see multiple epidemiological studies also linking AD to T2DM **[31]**.

Insulin is known to enhance cognitive processes and exert neuroprotective effects against apoptosis, ischemia, and oxidative stress. Insulin signaling disturbance is detrimental in T2DM and cognitive disorders. Indeed, it is well documented that impaired glucose tolerance seen in T2DM impacts cognitive functions **[32]**. This effect could also be attributed to the crucial role of glucose in acetylcholine synthesis and the fact that acetylcholine deficit is associated with cognitive alterations in animals and humans **[33]**.

Cognitive functions in the context of AD are also worth exploring. A study on transgenic mice found that amyloid precursor protein (APP) (the protein involved in the formation of the neurotoxic amyloid plaques in AD) knockout mice suffered hyperinsulinemia and hypoglycemia, leading to postnatal mortality,

implicating a role for APP in glucose homeostasis **[34]**. Tau protein has also been proven to be involved in insulin dysregulation in the early stage of AD, while insulin itself once dysregulated, contributes to hyperphosphorylation and accumulation of tau. Accordingly, in rodent models of AD, long-term intranasal insulin (6 weeks) elicited a stimulatory effect on insulin signaling in the brain through down-regulation of tau kinases, attenuation of neuroinflammation (microglial activation), and prevention of the impairment in spatial learning and memory as assessed by the Morris water maze test **[5]**.

Epidemiologically, The Rotterdam prospective cohort study found that individuals with T2DM had almost doubled the risk of developing AD **[35]**. Another cohort study that followed 1,173 for 9 years found that pre-diabetes is associated with an elevated risk of AD and dementia **[36]**. Ferrari et al. stated that "a meta-analysis of 28 studies found that diabetic patients had a higher risk of dementia of all types compared to non-diabetics"**[5]**. The data collectively confirm the strong association between diabetes and AD, to the extent that AD is often referred to as type 3 diabetes **[19]**. This robust connection highlights the potential of DPP-4 inhibitors, particularly Saxagliptin, as promising disease-modifying agents for AD. Given the intricate interplay between metabolic dysfunction and neurodegenerative processes, Saxagliptin's neuroprotective properties could offer significant therapeutic benefits in managing and potentially altering the course of AD.

8. Evidence for neuroprotection

One mechanism by which Saxagliptin may induce neuroprotection is through its insulinotropic effect. Insulin has long been recognized for its impact on learning and memory. It improves memory formation, information processing, and cognitive functions through complex mechanisms of hippocampal synaptic plasticity. These mechanisms include long-term potentiation (LTP) and the regulation of NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) glutamatergic receptors **[5]**.

Saxagliptin was found neuroprotective in a rat model of streptozotocin (STZ) induced Alzheimer's disease. In this study, intracerebral administration of STZ induced the accumulation of hyperphosphorylated tau protein and plaque formation similar to AD **[37]**. Treatment with Saxagliptin produced a significant decrease in β-amyloid level, elevation in hippocampal GLP-1, and reduction in total and phosphorylated tau in the hippocampus completely reversing the cognitive deficits. Saxagliptin also successfully attenuated brain inflammation apparent in AD by reducing the levels of inflammatory markers like TNF-α and IL-1b. These results demonstrate that Saxagliptin, a drug that is effective in the treatment of T2DM also has neuroprotective properties **[37]**. DPP-4 inhibitors are thought to be involved also in clearing the pathological aggregations in AD β-amyloid plaques and neurofibrillary tangles. In a study by Chen et al. sitagliptin and Saxagliptin were found to decrease tau and neurofilament aggregation and enhance β-amyloid degradation. This was confirmed through anatomopathological evidence from AD brain patient specimens analyzed using immunohistochemistry: "While in normal aged brain, DPP-4 was low, a marked up-regulation of DPP-4 was observed in cortical neurons and immunoreactivity was found to localize around many amyloid plaques"**[5]**.

9. Neuroprotective effect of Saxagliptin in other neurological disorders

In a preclinical study on chronic unpredictable mild stress (CUMS) model of depression, Saxagliptin exhibited a notable antidepressant effect. The drug reversed the

CUMS-induced alterations across behavioral, biochemical, and pathological parameters. It produced a significant increase in brain levels of serotonin, norepinephrine, and dopamine in rats. Saxagliptin also reduced brain TNF-α, NF-κB, and iNOS in the hippocampus and cortex, thereby attenuating inflammation caused by CUMS in these brain areas. It also showed an anti-oxidant effect, decreasing malondialdehyde (MDA) while up-regulating glutathione (GSH). Furthermore, the drug caused a decrease in brain caspase-3 levels in both the cortex and hippocampus, effectively halting apoptosis. Saxagliptin also enhanced BDNF levels, contributing to its neuroprotective effects **[38]**.

10. Future Prospects for Saxagliptin

Many models of disorders involving neuronal damage have not been tested with Saxagliptin, though similar antidiabetics have been explored. This leads us to the speculation that in the future, Saxagliptin could play a role in treating a variety of other neuronal disorders.

One such disorder is multiple sclerosis (MS). A potential protective role for Saxagliptin in MS may be mediated through DPP-4 rather than GLP-1. DPP-4 also known as the cell surface antigen CD26, has a co-stimulatory immune function. It is expressed in resting B cells and natural killer cells. This expression is up-regulated upon antigen stimulation. DPP-4 inhibition in experimental allergic encephalomyelitis, an animal model of MS, was found to induce a reduction in pro-inflammatory cytokines and T-cell proliferation while increasing levels of protective transforming growth factor (TGF)-β) **[39]**. The expression of DPP-4 in immune cells along with preclinical studies in various peripheral inflammatory disorders like arthritis, and irritable bowel disease, highlights DPP-4 inhibitors as novel candidates for treating inflammatory neurological disorders **[39]**.

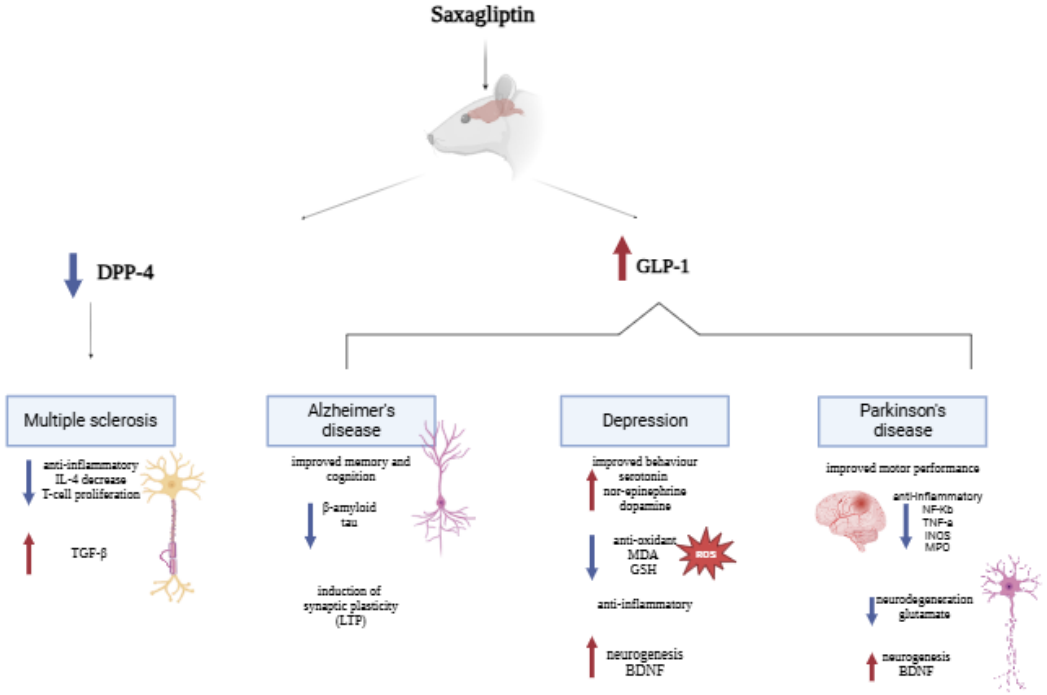

Fig. 1. The potential protective role of Saxagliptin in multiple neurological disorders

Conclusion

This review aims to provide an in-depth exploration of the potential protective role of Saxagliptin in multiple neurological disorders **(Fig. 1)**. Various studies have focused on establishing the connection between diabetes and neurodegeneration, to explain their shared pathological features and discover effective disease-modifying therapies. As a result, Saxagliptin has demonstrated promising neuroprotective effects in AD, PD, and depression. Saxagliptin is also orally active with a good safety profile and tolerability, making it an attractive candidate for drug repurposing **[40]**. These findings highlight Saxagliptin's potential as a versatile and promising therapeutic agent for a wide range of neurological disorders. However, a need for continued investigation and clinical validation should not be ignored.

List of abbreviations

PD, Parkinson's disease; AD, Alzheimer's disease; T2DM, type 2 diabetes mellitus; JNK, c-Jun NH2-terminal kinase pathway; ER, Endoplasmic reticulum; PKCα, Protein kinase C α.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Publish

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing Interests

The authors declare that no competing interests exist.

Funding statement

The author(s) received no specific funding for this work.

Authors' Contributions

The manuscript was drafted and written by Maha M. Abdrabou. All authors have read and approved the final manuscript.

Acknowledgment

The authors would like to acknowledge all faculty members in the pharmacology and toxicology department at the faculty of pharmacy, at Ain Shams University for their support.

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