IMPACTO CIENTÍFICO EDITORA

# NEUROPROTECTIVE EFFECTS OF SEMAGLUTIDE AND TIRZEPATIDE DURING THE TREATMENT OF OBESITY AND TYPE 2 DIABETES MELLITUS

# EFEITOS NEUROPROTETORES DA SEMAGLUTIDA E TIRZEPATIDA DURANTE TRATAMENTO DE OBESIDADE E DIABETES MELLITUS TIPO 2

# EFECTOS NEUROPROTECTORES DE LA SEMAGLUTIDA Y LA TIRZEPATIDA DURANTE EL TRATAMIENTO DE LA OBESIDAD Y LA DIABETES MELLITUS TIPO 2

https://doi.org/10.56238/edimpacto2025.087-010

**Alyson Oliveira Mergulhão[1], Natália Duarte Ribeiro[2], Philype Lopes Paiva[3], Ruan Venancio Maciel[4], Claudio Quintino de Lima Junior[5], Marília Cordeiro de Sousa[6], Joede Alvarenga de Souza Luniere[7], Fábio Marques de Almeida[8], Alfredo Julio Gonzaga Horbylon[9], Poliana Peres Ghazale[10], Murillo de Sousa Pinto[11]**

## ABSTRACT

Semaglutide, an analog of glucagon-like peptide-1 (GLP-1), and tirzepatide, a dual agonist of GLP-1 and Gastric Inhibitory Peptide (GIP), are effective drugs for the treatment of type 2 diabetes mellitus and weight loss. Studies have demonstrated the presence of receptors for these drugs in the Central Nervous System. Thus, the objective of this article is to conduct an integrative literature review regarding the potential neuroprotective effects of these medications. For this purpose, the PubMed database was used to search for articles published between 2020 and 2025, focusing on the use of semaglutide and tirzepatide in

[1] Medical Student. Centro Universitário Alfredo Nasser (UNIFAN). E-mail: atymergulhao@gmail.com
Lattes: http://lattes.cnpq.br/7977818949111587
[2] Medical Student. Centro Universitário Alfredo Nasser (UNIFAN). E-mail: nataliadr2907@gmail.com
Lattes: http://Lattes.cnpq.br/2923721776263937
[3] Medical Student. Centro Universitário Alfredo Nasser (UNIFAN). E-mail: philypepaiva@gmail.com
Lattes: https://Lattes.cnpq.br/8885944143965545
[4] Medical Student. Centro Universitário Alfredo Nasser (UNIFAN). E-mail: rvenancio216@gmail.com
Orcid: 0009-0004-0329-1488
[5] Dr. in Physiological Sciences. Centro Universitário Alfredo Nasser (UNIFAN). E-mail: claudio.qlj@gmail.com
Lattes: http://Lattes.cnpq.br/1335883311437983
[6] Dr. in Nursing. Centro Universitário Alfredo Nasser (UNIFAN). E-mail: joedeluniere@unifan.edu.br
LATTES: http://Lattes.cnpq.br/0132494362508867
[7] Specialist in Mental Health and Chemical Dependency. Centro Universitário Alfredo Nasser (UNIFAN).
E-mail: joedeluniere@unifan.edu.br Lattes: http://Lattes.cnpq.br/0132494362508867
[8] Dr. in Health Sciences. Centro Universitário Alfredo Nasser (UNIFAN). E-mail: fabiomarques@unifan.edu.br
LATTES: http://Lattes.cnpq.br/9184054265912992
[9] Specialist in Internal Medicine and Rheumatology. Centro Universitário Alfredo Nasser (UNIFAN).
E-mail: alfredogonzaga@unifan.edu.br Lattes: http://Lattes.cnpq.br/3735010442170216
[10] Dr. in Neurology and Neurosciences. Centro Universitário Alfredo Nasser (UNIFAN). Universidade de Rio Verde (UniRV). E-mail: poliana.pghazale@gmail.com Lattes: http://Lattes.cnpq.br/3030441151014287
[11] Master's degree in Health Care and Evaluation. Centro Universitário Alfredo Nasser (UNIFAN).
Universidade Federal de Goiás (UFG). E-mail: murillopinto@unifan.edu.br
Lattes: http://Lattes.cnpq.br/9799290954699973

nervous system disorders. Recent studies have shown possible neuroprotective and therapeutic effects of these drugs against neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, as well as improvements in cognition and a reduced risk of dementia, with these effects being more prominent in tirzepatide due to its dual-agonist activity. Therefore, these findings highlight the ability of these substances to protect nerve cells, underscoring their potential as therapeutic approaches and the importance of further investigations to confirm their long-term safety and effectiveness.

**Keywords:** GLP-1. GIP. Neuroinflammation. Neurodegeneration.

**RESUMO**

A semaglutida, análogo do peptídeo semelhante ao glucagon tipo 1 (GLP-1), e a tirzepatida, dual agonista de GLP-1 e do Peptídeo Inibidor Gástrico (GIP), são fármacos eficazes no tratamento da diabetes mellitus tipo 2 e na perda de peso. Estudos demonstram a presença de receptores destes fármacos no Sistema Nervoso Central. Dessa forma, o objetivo deste artigo é realizar uma revisão integrativa da literatura a respeito da provável atuação neuroprotetora destes fármacos. Para isso, utilizou-se a base de dados PubMed para a busca de artigos publicados entre 2020 e 2025, com foco no uso da semaglutida e tirzepatida nos distúrbios do sistema nervoso. Estudos recentes demonstraram possíveis efeitos neuroprotetores e terapêuticos desses medicamentos contra doenças neurodegenerativas como a doença de Alzheimer e a doença de Parkinson, além de uma melhora na cognição e diminuição do risco de demência, sendo esses efeitos mais proeminentes na tirzepatida por ser um agonista de dupla ação. Portanto, evidencia-se a capacidade dessas substâncias de proteção das células nervosas, destacando seu potencial como abordagem terapêutica e a importância de novas investigações para comprovar sua segurança e eficácia a longo prazo.

**Palavras-chave:** GLP-1. GIP. Neuroinflamação. Neurodegeneração.

**RESUMEN**

La semaglutida, un análogo del péptido similar al glucagón tipo 1 (GLP-1), y la tirzepatida, un agonista dual de GLP-1 y del Péptido Inhibidor Gástrico (GIP), son fármacos eficaces para el tratamiento de la diabetes mellitus tipo 2 y para la pérdida de peso. Estudios han demostrado la presencia de receptores de estos fármacos en el Sistema Nervioso Central. De este modo, el objetivo de este artículo es realizar una revisión integradora de la literatura sobre la posible acción neuroprotectora de estos medicamentos. Para ello, se utilizó la base de datos PubMed para la búsqueda de artículos publicados entre 2020 y 2025, con énfasis en el uso de la semaglutida y la tirzepatida en trastornos del sistema nervioso. Estudios recientes han demostrado posibles efectos neuroprotectores y terapéuticos de estos medicamentos frente a enfermedades neurodegenerativas como la enfermedad de Alzheimer y la enfermedad de Parkinson, además de mejoras en la cognición y una disminución del riesgo de demencia, siendo estos efectos más prominentes en la tirzepatida por su acción agonista dual. Por lo tanto, se evidencia la capacidad de estas sustancias para proteger las células nerviosas, destacando su potencial como enfoque terapéutico y la importancia de nuevas investigaciones para confirmar su seguridad y eficacia a largo plazo.

**Palabras clave:** GLP-1. GIP. Neuroinflamación. Neurodegeneración.

## 1 INTRODUCTION

Type 2 diabetes mellitus (T2D) is a complex chronic disease that affects millions of people worldwide (Tonaco *et al.,* 2023). In recent years, Semaglutide (Ozempic®; SMG) and Tirzepatida (Mounjaro®; TRZ), have demonstrated remarkable efficacy in improving glycemic control and promoting weight loss (Ferraresi, 2025).

SMG is a peptide-like analogue of glucagon type 1 (GLP-1). This active ingredient acts as a GLP-1 receptor agonist, stimulating insulin release, reducing glucagon production, and improving glucose assimilation in peripheral tissues (GOMES; TREVISAN, 2021). In addition, SMG delays gastric emptying, which leads to weight reduction, decreased appetite, and less inclination for high-fat foods (MOURA *et al.,* 2024).

TRZ, on the other hand, is a dual agonist of GLP-1 and GIP, which combines the beneficial effects of both incretin hormones, which stimulates insulin release, reduces glucose production by the liver, and improves insulin sensitivity (Jastreboff *et al*., 2022). In addition, TRZ delays gastric emptying and increases satiety, contributing to weight loss and improved glycemic control (GUIMARÃES, 2022).

According to Huan-Tang *et al.* (2025), in addition to the effects on diabetes treatment and weight loss, evidence is growing that TRZ and SMG have neuroprotective properties against neurodegenerative diseases, such as Alzheimer's disease.

Tipa *et al.* (2024), evaluated that antidiabetic drugs have potential in preventing neurological complications, as some studies consider a connection between these compounds and DM. Although there are studies that are conclusive, it is important to be investigated to prove the safety and effectiveness of these substances. Based on this, this study aims to evaluate the effects of SMG and TRZ on neuroprotection against neurodegenerative diseases.

## 2 METHODOLOGY

This work consists of a literature review based on the analysis of previous publications. The guiding question for this work, based on the acronym PICO, was: Do SMG and TRZ have neuroprotective effects in patients who use them compared to patients who do not? The main objective is to understand the current knowledge about SMG and TRZ and their role in nervous system disorders.

The search was carried out following the sequence: definition of the descriptors used, definition of the database to be searched, initial search using Boolean operators, filtering of the articles found and evaluating those that are of interest to the search.

To define the descriptors to be used in the research, the DeCS platform was used, and the following terms were searched: "Tirzepatide", "neuroprotection" and "Semaglutide". The term "Semaglutide" was not recognized by the platform, however, as it is a compound already well established in the scientific environment, we chose to use it.

The database used for the research was PubMed and was carried out in September 2025. The first search was carried out using the terms "semaglutide" and "neuroprotection", using the Boolean operator AND and the term "psychiatry" separated by the NOT operator. A total of 42 results were obtained, in which the following filters were applied: publication date after 2020, free full text, and human search only. After applying the filters, 5 results were found.

Of these articles found, 3 were deleted for declaring a conflict of interest and one was deleted for not sufficiently addressing SMG. After that, the analysis of 2 specific articles for the SMG was carried out.

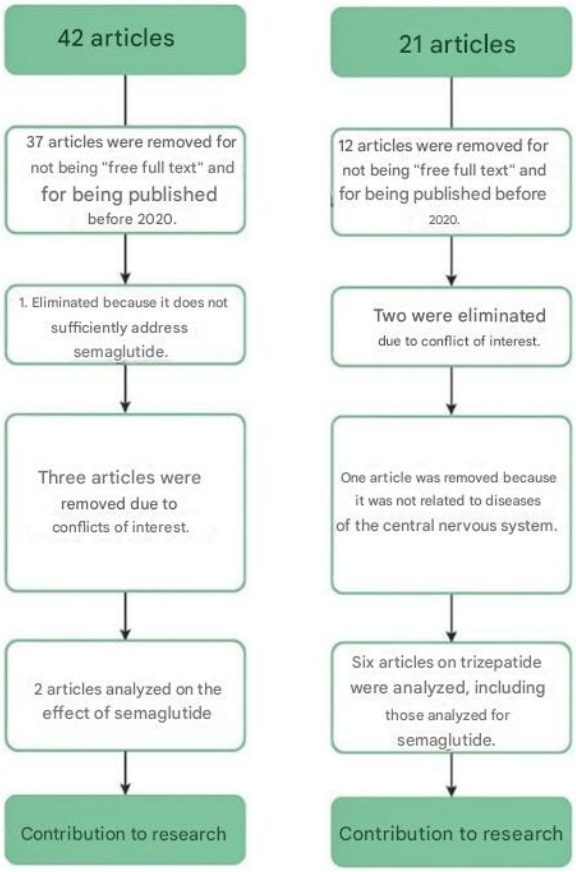
In a second combination, the terms "tirzepatide" and "neuroprotection" were used, separated by the Boolean operator AND. 21 results were obtained, in which the following filters were applied: publication date after 2020, free full text, and articles using only human searches, leaving 9 articles.

Of these 9 articles, 1 was eliminated because it was not related to diseases of the central nervous system and 2 were eliminated because it had a conflict of interest, leaving 6 articles for analysis of the TRZ, one of which was already included in those analyzed for the SMG. The selection process is summarized in Figure 1.

After selecting the articles, they were analyzed regarding the effects of drugs on neurodegenerative diseases and how they can contribute to research. The data that were repeated were discarded and the different forms of contribution of the drugs were separated for analysis and discussion.

**Figure 1**

*Flowchart for selecting articles*




Article selection process. On the right are the data found with the descriptor "semaglutide". On the right are the data found with the descriptor "tirzepatide". Source: author himself, 2025

## 3 RESULTS AND DISCUSSION

The first, conducted by Siddeeque *et al.* (2024), evaluated the neuroprotective effects of GLP-1RAs on the outcome of neurodegenerative diseases, including Alzheimer's Disease, Parkinson's Disease, Lewy Body Dementia, and Vascular Dementia, in addition to analyzing the survival of GLP-1 RA users and the control group. A significant decrease in the incidence of these diseases was observed in the group of GLP-1RAs users compared to the control group. This protective effect was even more pronounced in SMG users.

The second cohort study, by Lin *et al.* (2025), analyzed SMG and TRZ users to assess neuroprotection against neurodegenerative and cerebrovascular diseases. Similarly to the study by Siddeeque *et al*., this study also recorded a lower incidence of the outcomes researched in the GLP-1RA user group compared to the control group. Specifically, a lower incidence of dementia development was observed in the GLP-1RAs user group (SMG and TRZ). In addition, there was a lower risk of ischemic stroke and a reduction in the risk of overall mortality among GLP-1RA users. However, analysis of semaglutide alone did not reveal a significant decrease in the risk of ischemic stroke.

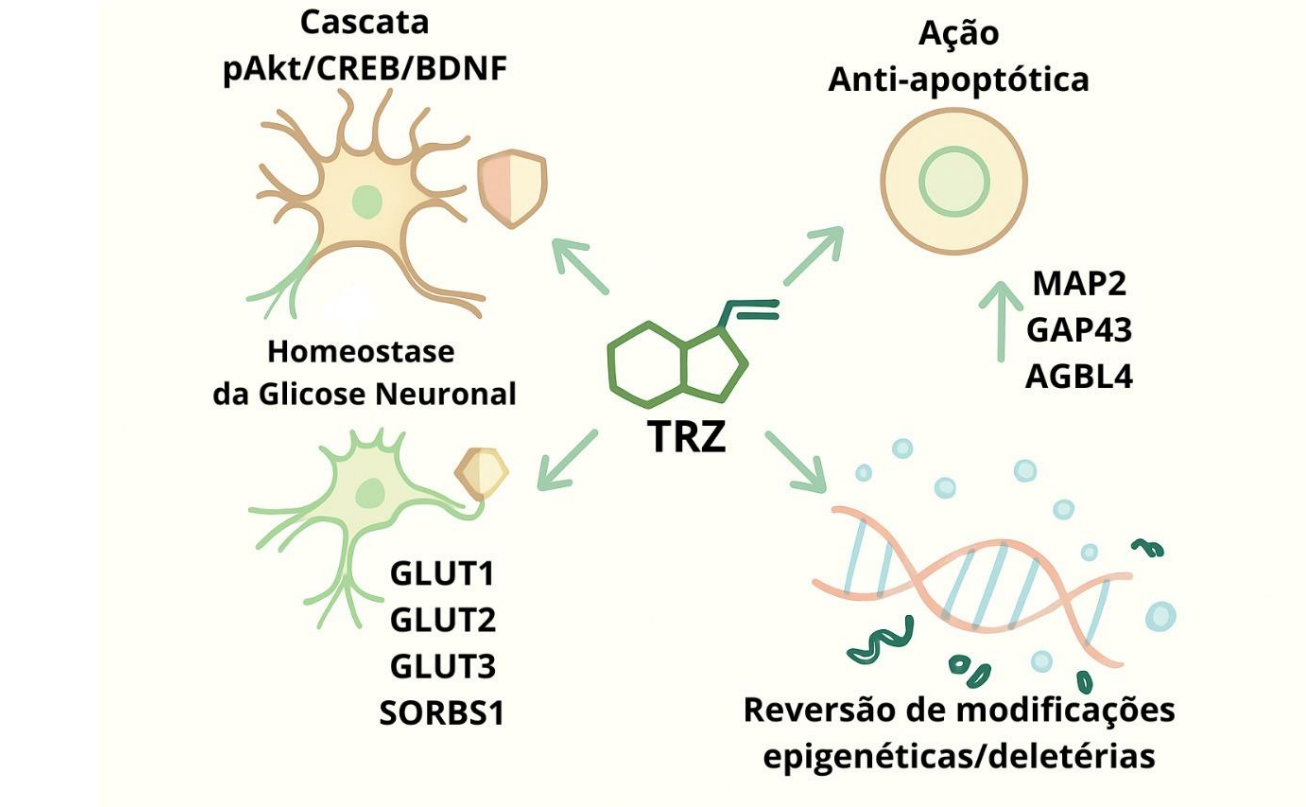
In an experimental research paper, Wang *et al.* (2025) investigated the impact of TRZ on ischemic stroke (ICVA). Treatment with TRZ in MCAO mice resulted in significant improvement in neurological scores and mitigated neuronal damage. This has been achieved by reducing infarct volume and, crucially, improving BBB dysfunction (Wang *et al.,* 2025). The permeability of the BBB, which increases markedly after stroke, was reduced by TRZ. This effect is mediated by the restoration of Claudin-1 protein expression at occlusive junctions (TJs), a process regulated by the activation of transcription factor C/EBP-α signaling (Wang *et al.,* 2025). In addition to protecting barrier integrity, TRZ exhibited a significantly higher brain-to-plasma ratio (Kp, brain) (0.12–0.14) compared to liraglutide, indicating enhanced access to the central nervous system (CNS) that is not limited by P-glycoprotein efflux (Wang *et al.,* 2025).

In parallel, an in vitro study by Fontanella *et al.* (2024) demonstrated the potential of TRZ in preventing high-glucose-induced neurodegeneration, a risk factor for cognitive disorders. Research has shown that TRZ was effective in overcoming neuronal insulin resistance and in improving high glucose-induced neurodegeneration in neuroblastoma cells (SHSY5Y) (Fontanella *et al.,* 2024).

The neuroprotective mechanism of TRZ is linked to the activation of the pAkt/CREB/BDNF signaling cascade, which promotes neuronal growth and synaptic plasticity, and to the prevention of high glucose-induced downregulation in these markers (Fontanella *et al.,* 2024). Additionally, TRZ demonstrated anti-apoptotic action, reducing the BAX/Bcl-2 ratio, a marker of cell death, and increased the expression of neurodifferentiation markers (such as MAP2, GAP43 and AGBL4) as shown in Figure 1. Regarding neuronal glucose homeostasis, TRZ prevented high glucose-induced reduction in the levels of glucose transporters (GLUT1, GLUT3, and GLUT4) and the regulator SORBS1, which are essential for insulin sensitivity (Fontanella *et al.,* 2024). Finally, TRZ reversed deleterious epigenetic modifications caused by hyperglycemia, preventing increased DNA methylation in CREB and BDNF gene promoters and regulating microRNAs involved in neuroprotection and apoptosis (Fontanella *et al.,* 2024) (Figure 2).

**Figure 2**

*Tirzepatide regulation mechanism*




TRZ activates the pAkt/CREB/BDNF signaling pathway, promoting neuronal growth and synaptic plasticity, as well as preventing hyperglycemia-induced downregulation. It also exerts anti-apoptotic action (reduction of BAX/Bcl-2 ratio) and increases the expression of neurodifferentiation markers (MAP2, GAP43 and AGBL4). TRZ also preserves neuronal glucose homeostasis by maintaining GLUT1, GLUT3, GLUT4, and SORBS1 levels. Source: Author himself, 2025.

The systematic review conducted by Alshehri *et al.* (2025) brings preclinical studies that analyze how the use of TRZ in cases of obesity and DM2, in addition to increasing insulin sensitivity and lowering fat percentage, can also have a neuroprotective effect. Initially, obesity and T2DM induce low-grade peripheral inflammation and oxidative stress, aggravating the development of central neuroinflammation and cerebral oxidative stress, are verified. Obesity and T2DM are also linked with brain leptin resistance, which is another possible link between AD and obesity. The Association between the development and progression of AD with obesity and DM2, by dysregulation of neural glucose metabolism.

The use of TRZ in these preclinical studies has shown that by inhibiting oxidative stress, inflammation, advanced glycation end products, and activating cellular autophagy, it can reduce the detrimental effect of T2DM on the pathogenesis of AD. TRZ also induces adiponectin expression and regulates brain leptin sensitivity in obese and T2DM patients. TRZ is still able, like other GLP-1 and GIP agonists, to act centrally in the development and progression of AD neuropathology by inhibiting neuroinflammation and cerebral oxidative

stress. TRZ also regulates and restores different signaling pathways, such as PIA3 K/AKT, GSK3ÿ, BDNF, CREB signaling, miR-212-3p, and miR-43a-5p, which are involved in the regulation of brain survival, growth, and neural differentiation in AD (Alshehri *et al.,* 2025).

The other systematic review, also conducted by Alshehri *et al*., also brought studies in which the neuroprotective effect of TRZ is analyzed, especially in obese people or people with DM2. Like the previous study, this review brings with it the fact that AD, the most common neurodegenerative disease, is associated with brain IRS-1 dysregulations, neuroinflammation, oxidative stress, defective cellular apoptosis, and dysregulated GLP-1/GIP neural signaling axis, inducing neurotoxicity. The creation of a link between low leptin sensitivity in the brain in obesity and T2DM, with the development of AD, is also scored due to the high presence of evidence in studies (Alshehri *et al.,* 2025).

Because TRZ has a double action and is an agonist of both GIP and GLP-1, it is one of the main possible therapeutic measures that can mitigate AD in obese people and people with DM2. Decreased peripheral inflammation, oxidative stress, and normalization of leptin sensitivity and neuronal autophagy are neuroprotective effects of TRZ, which reduces the harmful effects of obesity and T2DM on AD pathogenesis. In addition, TRZ has the direct neuroprotective effect of regulating the GIP/GLP-1 signaling axis, which reduces the development of AD (Alshehri *et al.,* 2025).

## 4 CONCLUSION

It is concluded that the GIP-1 receptor agonists, SMG and TRZ, have relevant neuroprotective potential against neurodegenerative diseases. Only one study evidenced the use of these medications and the reduction of dementia, Alzheimer's Disease and Parkinson's Disease, in addition, it has effects on reducing the risk of ischemic stroke by MGS. However, these neuroprotective effects were more evident in the use of TRZ, as it is a dual-acting agonist, unlike SMG. Preclinical studies with TRZ show that GLP-1/GIP is able to regulate neuroinflammatory processes, oxidative stress and cell signaling aggravated in obesity and Alzheimer's disease, reinforcing its neuroprotective effect. Thus, both SMG and TRZ have demonstrated efficacy as therapeutic strategies, but more long-term studies are needed for neuroprotective efficacy to be consolidated, and this class of drugs to be applied for the prevention and treatment of neurodegenerative diseases.

## ACKNOWLEDGEMENTS

We thank the support of the Alfredo Nasser University Center and our fellow collaborators.

## REFERENCES


Alshehri, G. H., et al. (2025). A novel therapeutic prospect: A dual-acting tirzepatide for Alzheimer's disease. European Journal of Pharmacology, 1003, Article 177979.

Alshehri, G. H., et al. (2025). Tirzepatide: A novel therapeutic approach for Alzheimer's disease. Metabolic Brain Disease, 40(5). Advance online publication. https://doi.org/10.1007/s11011-025-01527-3

De Sousa Guimarães, B. C., et al. (2022). Evidências científicas sobre o uso de Tirzepatida como tratamento da obesidade: Scientific evidence on the use of tirzepatide as the treatment of obesity. Brazilian Journal of Health Review, 5(4), 13632–13643.

Ferraresi, É. L. (2025). Potencial terapêutico da Tirzepatida: Uma análise do estudo SURPASS-1 para o controle da obesidade e saúde metabólica. Brazilian Journal of Health Review, 8(1), Article e76790.

Fontanella, R. A., et al. (2024). Tirzepatide prevents neurodegeneration through multiple molecular pathways. Journal of Translational Medicine, 22(1).

Gomes, H. K. B. C., & Trevisan, M. (2021). O uso do ozempic (Semaglutida) como medicamento off label no tratamento da obesidade e como auxiliar na perda de peso. Revista Artigos.Com, 29, Article e7498.

Jastreboff, A. M., et al. (2022). Tirzepatide once weekly for the treatment of obesity. New England Journal of Medicine, 387(3), 205–216.

Lin, H.-T., et al. (2025). Neurodegeneration and stroke after semaglutide and tirzepatide in patients with diabetes and obesity. JAMA Network Open, 8(7), Article e2521016.

Moura, J. P., et al. (2024). Avaliação do reposicionamento farmacológico da Semaglutida no processo de emagrecimento: Uma revisão da literatura. Research, Society and Development, 13(11), Article e118131147305.

Siddeeque, N., et al. (2024). Neuroprotective effects of GLP-1 receptor agonists in neurodegenerative disorders: A large-scale propensity-matched cohort study. International Immunopharmacology, 143, Article 113537.

Tipa, R. O., et al. (2024). Uma revisão sistemática da influência da Semaglutida na função cognitiva em modelos animais pré-clínicos e estudos de linhagens celulares. International Journal of Molecular Sciences, 25(9), Article 4972.

Tonaco, L. A. B., et al. (2023). Conhecimento do diagnóstico, tratamento e controle do diabetes mellitus no Brasil. Revista de Saúde Pública, 57, Article 75.

Wang, D., et al. (2025). Tirzepatide mitigates stroke-induced blood-brain barrier disruption by modulating Claudin-1 and C/EBP-α pathways. Molecular Medicine (Cambridge, Mass.), 31(1), Article 263.