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REVIEW ARTICLE

Gamma-oryzanol as a potential intervention for normalizing insulin secretion and pancreatic β-cell function

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ABSTRACT

The bioactive substance gamma-oryzanol (GO), which is mostly present in rice bran oil, has attracted a lot of interest due to its possible therapeutic application in metabolic conditions like diabetes mellitus. The effects of GO on insulin secretion and pancreatic β-cell function are examined in this study. Gamma-oryzanol improves β-cell viability, lowers oxidative stress, and modifies intracellular signaling pathways linked to glucose metabolism, all of which increase insulin secretion, according to experimental and clinical evidence. Additionally, GO's anti-inflammatory and antioxidant qualities shield β-cells from dysfunction and apoptosis brought on by hyperglycemia and lipid toxicity. Relevant studies were identified through a systematic search of PubMed, ScienceDirect, and Google Scholar for articles published between 2017 and 2026 using the keyword "gamma-oryzanol", "insulin secretion", 'pancreatic β-cell function". Additionally, the substance seems to support glucose homeostasis and pancreatic function by upregulating important genes involved in insulin synthesis and secretion. All things considered, GO shows great promise as a natural agent for maintaining β-cell integrity and increasing insulin secretion, providing a novel complementary approach to managing diabetes. Gamma-oryzanol is frequently linked to anti-inflammatory, anti-cancer, anti-diabetic, and cholesterol-lowering properties. Because Orz reduces insulin activity, cholesterol metabolism, and associated chronic inflammation, its potential to treat metabolic diseases has recently been investigated. After apoptosis and increased endoplasmic reticulum (ER) stress were decreased, oral GO administration increased glucose-stimulated insulin secretion in islets from diabetic mice fed a high-fat diet. We also examined the effects of GO on low-dose streptozotocin-induced diabetic mice, which demonstrated elevated ER stress and consequent β-cell apoptosis. Furthermore, γ-oryzanol improved glucose dysmetabolism in this model by lowering the mRNA levels of genes linked to apoptotic signaling and ER stress in islets. All things considered, GO shows encouraging potential as a natural agent for enhancing insulin secretion and maintaining the integrity of β-cells, providing a new complementary strategy for controlling and preventing diabetes.

Keywords: Rice bran oil, glucose homeostasis, pancreatic β-cells, gamma-oryzanol, insulin secretion

Abbreviations
AMPK: Activated protein kinase
CAT: Catalase
ELISA: Enzyme Linked Immune Sorbent Assay

ER: Endoplasmic Reticulum
GLUT2: Glucose Transporter 2
GO: Gamma-oryzanol
GPx: Glutathione Peroxidase
GSIS: Glucose-Stimulated Insulin Secretion
IL-1β: Interleukin-1 beta
IL-6: Interleukin
MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NF-KB: Nuclear factor-kappa B
PPAR-γ: Proliferator-activated receptor gamma
ROS: Reactive Oxygen Species
RPMI: Roswell Park Memorial Institute
SOD: Superoxide Dismutase
TNF-α: Tumor Necrosis Factor-alpha
PP: Pancreatic Polypeptide
ATP: Adenosine triphosphate

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by impaired insulin secretion, insulin resistance, and progressive pancreatic β-cell dysfunction.[1] Due to it's rising prevalence worldwide, diabetes is a serious public health concern.[2] However, inflammation, lipid toxicity, and damage and loss of function are the primary causes of β-cell oxidative stress.[3] Diabetes is brought on by either insufficient production of the hormone insulin or a decrease in the sensitivity of the cells of the body to the effects of insulin. The symptoms of diabetes comprise weight loss, blurred vision, and the three classic symptoms of polyurea (excessive urination), polyphagia (excessive hunger), and polydipsia (excessive thirst). If treatment is not received, the illness may result in a number of health problems, including kidney, nerve, eye, and cardiovascular system problems. Therefore, a key therapeutic strategy for managing diabetes is to identify naturally occurring bioactive substances that can enhance insulin secretion and preserve β-cell integrity.[4,5] Every year, endocrine diseases cause about 2 million deaths, of which 1.5 million are believed to be caused by untreated or poorly managed diabetes.[6] Gamma-oryzanol (GO), a mixture of ferulic acid esters of phytosterols and triterpene alcohols, is primarily found in rice bran oil.[7] Its pharmacological properties include anti-inflammatory, hypolipidemic, antidiabetic, and antioxidant effects.[8] Gamma-oryzanol can improve lipid profiles, control glucose metabolism, and protect cells from oxidative stress-induced cellular damage, according to numerous studies.[9] By regulating key molecular pathways, gamma-oryzanol may enhance the viability of pancreatic β-cells, boost insulin secretion, and reduce insulin resistance, according to recent research.[10] Because of its numerous biological activities and natural sources, GO is a promising nutraceutical option for the management and prevention of diabetes. To shed light on the potential mechanisms of action of GO, this study investigates its effects on insulin secretion and pancreatic β-cell function. and treatment consequences for preserving glucose homeostasis.[11] Data from both cell-line experiments and animal models show that GO significantly reduces endoplasmic reticulum (ER) stress in β-cells, a crucial factor in the onset and progression of diabetes.[12] By lowering ER stress and preserving cellular homeostasis and appropriate protein folding, GO inhibits apoptosis and preserves β-cell viability. This protective effect encourages sustained insulin biosynthesis and preserves the structural integrity of the β-cell secretory machinery.[13] Additionally, GO restores impaired insulin secretion by increasing glucose-stimulated insulin secretion (GSIS), the main physiological mechanism through which β-cells release insulin when blood glucose levels rise.[14] By stabilizing intracellular calcium signaling, reducing oxidative stress, and improving mitochondrial function, gamma-oryzanol increases β-cell responsiveness.[15] This review aims to explore and summarize the recent scientific findings on the potential intervention of GO on insulin secretion and pancreatic β-cell function. In the end this improves glucose

regulation and presents a promising therapeutic option for managing diabetes.[16]

METHODS

The following electronic databases PubMed, and Science Direct as well as Google Scholar were comprehensively and systematically searched for publications in the English language on the effects of gamma oryzanol on insulin secretion and pancreatic β-cell function. Experimental studies, relevant mechanistic reports, and English-language review articles were all considered. Studies unrelated to pancreatic function or insulin secretion were excluded. Data from the selected studies were critically analyzed to provide an overview of the physiological effects, signaling pathways, and biochemical processes associated with gamma-oryzanol treatment. The collected information was combined to provide a thorough understanding of the effects of gamma-oryzanol on β-cell viability and insulin secretion, highlighting its potential as a natural diabetes treatment. After excluding duplicate publications, and those that did not meet the inclusion criteria, 52 publications were selected. The selected articles were analyzed and reviewed.

In vitro effects of gamma-oryzanol on β-cells

Analytically pure GO was studied for its effects on pancreatic β-cell function and insulin secretion. Rat insulinoma (INS-1) cells were cultivated at 37°C with 5% CO_2 in Roswell Park Memorial Institute (RPMI-1640) medium supplemented with 10% fetal bovine serum. [17,18] For up to 48 hours, cells were exposed to varying concentrations of GO (5–50 μM), with untreated cells acting as controls. The cytoprotective effect of GO was evaluated by measuring cell viability using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (MTT).[19] Using the glucose-stimulated insulin secretion (GSIS) assay, cells were exposed to 16.7 mM glucose, and the Enzyme Linked Immune Sorbent Assay (ELISA) was used to quantify the amount of insulin released.[20] The role of GO in glucose homeostasis, insulin regulation, oxidative stress reduction, and β-cell protection has been studied in vitro, in vivo, and in clinical settings.

Mechanisms of gamma-oryzanol effects on pancreatic β-cell function

Gamma-oryzanol influences β-cell function through a range of antioxidant, anti-inflammatory, anti-apoptotic, and metabolic regulatory mechanisms that collectively enhance insulin secretion and preserve cellular integrity. [21] First, GO possesses potent antioxidant qualities. It scavenges reactive oxygen species (ROS) and boosts endogenous antioxidant enzymes such as glutathione peroxidase (GPx) and catalase (CAT) as well as superoxide dismutase (SOD). Because lipids and glucose are the primary causes of β-cell dysfunction in diabetes, this reduction in oxidative stress protects β-cells from harm. Second, GO suppresses nuclear factor-kappa B (NF-κB) activation and lowers the expression of pro-inflammatory cytokines such as TNF-α, interleukin-1 beta (IL-1β), and interleukin-6 (IL-6),[22] and through this anti-inflammatory effect GO supports the health of β-cells and insulin. To sum up, GO supports pancreatic β-cell function by increasing insulin gene transcription, improving glucose sensing, reducing oxidative and inflammatory damage, and inhibiting apoptosis. These various mechanisms highlight GO's therapeutic potential as a natural compound for preserving β-cell health and improving glycemic control in diabetes management.[23]

Gamma-oryzanol's impact on β-cell dysfunction in insulin secretion

As stated previously, gamma-oryzanol, a bioactive component found in rice bran oil, has shown great promise in boosting insulin secretion and protecting pancreatic β-cells. [24] β-cell dysfunction, which is marked by increased oxidative stress, decreased glucose responsiveness, inflammatory damage, and impaired insulin synthesis, is a characteristic of both type 1 and type 2 diabetes mellitus. Gamma-oryzanol has several beneficial effects to reverse these pathological changes and restore normal insulin secretory function. One of the primary effects of GO is its antioxidant activity, which reduces oxidative stress in β-cells and aids in neutralizing reactive oxygen species (ROS). [25] Gamma - oryzanol strengthens the defense of β-cells, whose low levels of antioxidant enzymes make them especially susceptible to oxidative damage, by boosting the activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) **(Figure 1)**.[26] This defense lessens oxidative damage, maintains mitochondrial function, and encourages sustained insulin release. Additionally, GO helps correct lipid-induced β-cell dysfunction by regulating lipid metabolism through the activation of the

peroxisome and AMP-activated protein kinase (AMPK) proliferator-activated receptor gamma (PPAR-γ) pathways.[27] These actions indirectly enhance β-cell performance by decreasing lipotoxicity and promoting energy balance. In summary, gamma-oryzanol mitigates β-cell dysfunction by reducing oxidative stress and inflammation, increasing insulin gene expression, improving glucose responsiveness, and preventing lipotoxic damage. Through these intricate processes, GO helps restore normal insulin secretion and is a promising natural therapeutic agent for the management and prevention of diabetes.[28]

Effect of antioxidant activity of gamma-oryzanol on β-cell function

Gamma-oryzanol is crucial for maintaining pancreatic β-cell function due to its potent ability to scavenge free radicals.[30] Oxidative stress is one of the primary causes of β-cell dysfunction because an excess of reactive oxygen species (ROS) damages cellular components, prevents insulin secretion, and promotes β-cell apoptosis. Because β-cells have a low capacity for antioxidant enzymes, protecting them from oxidative damage is crucial for preserving normal insulin synthesis and secretion.[31] Gamma-oryzanol produces its antioxidant effects by neutralizing ROS and increasing the activity of glutathione peroxidase (GPx), an endogenous antioxidant enzyme catalase, and superoxide dismutase (SOD). This action preserves the integrity and viability of β-cells by reducing deoxyribonucleic acid oxidative damage to proteins and cellular membranes.[32] By lowering oxidative stress, GO also helps to maintain ATP synthesis and mitochondrial membrane potential, two processes required for glucose-stimulated insulin secretion (GSIS). Furthermore, GO indirectly enhances β-cell function by preventing inflammatory responses caused by oxidative stress. By stopping oxidative activation of NF-κB, GO reduces the release of inflammatory cytokines, such as TNF-α and IL-1β, which are known to impact insulin gene transcription and secretion.[33]

Effects of gamma-oryzanol on hyperlipidemia in pancreatic β-cells

Gamma-oryzanol has demonstrated significant potential in mitigating the detrimental effects of hyperlipidemia on pancreatic β-cell function. Hyperlipidemia, characterized by elevated levels of circulating lipids such as triglycerides and free fatty acids (FFAs), contributes to β-cell dysfunction through lipotoxicity, oxidative stress, and inflammation. When combined, these factors accelerate the onset of type 2 diabetes, decrease insulin secretion, and promote apoptosis.[34] Gamma-oryzanol protects β-cells by controlling lipid metabolism and reducing lipid-induced toxicity. By activating important metabolic regulators such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma (PPAR-γ), it increases lipid oxidation, decreases lipid accumulation, and improves overall cellular energy balance. Through these channels, GO helps β-cells maintain normal lipid levels, preventing lipid overload and preserving insulin secretion capacity.

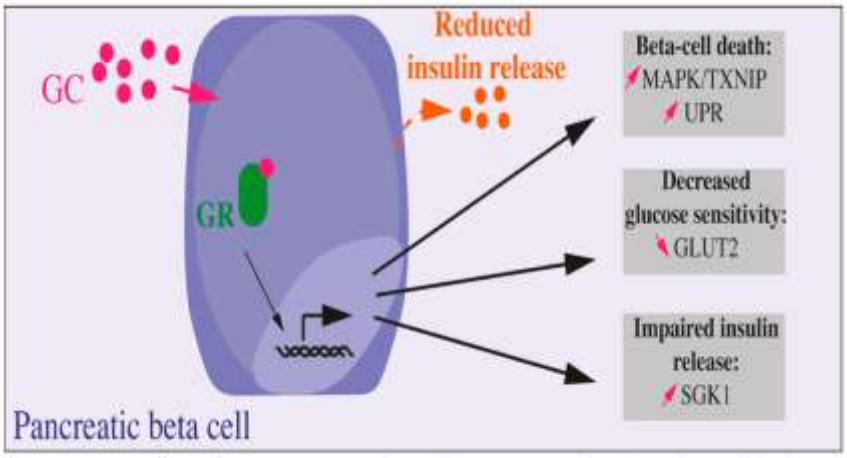

Figure 1. Molecular mechanism of glucocorticoid-induced insulin resistance [29]

In conclusion, GO prevents β-cell dysfunction caused by hyperlipidemia through the regulation of lipid metabolism, reduction of oxidative stress, and inhibition of inflammatory signaling. By maintaining glucose homeostasis, enhancing insulin secretion, and protecting β-cell integrity, these combined effects demonstrate GO's potential as a natural therapeutic agent for diabetes associated with dyslipidemia.[35]

Impact of gamma-oryzanol on pancreatic endocrine activity

Gamma-oryzanol improves insulin secretion and β-cell function by modulating endocrine pancreatic activity through a few interconnected mechanisms. Its potent antioxidant properties protect mitochondrial integrity, reduce oxidative stress in pancreatic β-cells, and increase ATP production—a critical signal for the release of insulin in response to glucose.[36] Gamma-oryzanol also reduces inflammatory pathways and IL-6 by blocking pro-inflammatory cytokines such as TNF-α, thereby stopping cytokine-induced β-cell dysfunction. Additionally, it improves lipid metabolism by reducing lipotoxicity, which often lowers β-cell viability and insulin secretory capacity.[37] Through these combined effects, GO supports β-cell survival, encourages insulin synthesis and exocytosis, and preserves optimal endocrine pancreatic function.

Regulatory role of gamma-oryzanol in glucose homeostasis and β-cell protection

Gamma-oryzanol plays a crucial regulatory role in maintaining glucose homeostasis by increasing insulin secretion, improving insulin sensitivity, and strengthening β-cell resilience **(Figure 2)**. Because oxidative stress is a major cause of β-cell damage, its antioxidant activity protects cellular integrity and functional ability. Furthermore, by modifying inflammatory mediators, GO prevents apoptosis and lessens cytokine-induced β-cell dysfunction. By reducing lipotoxic stress and improving lipid profiles, it further stabilizes glucose-responsive insulin release. Gamma-oryzanol is a promising natural substance for preserving balanced glucose regulation and safeguarding β-cells when these mechanisms are considered collectively.[38] Gamma-oryzanol enhances metabolic stability and reduces the secretory load on β-cells by raising peripheral insulin sensitivity. It lowers circulating free fatty acids and alters lipid profiles to lessen lipotoxic stress, which often compromises the viability of β-cells. Its ability to maintain calcium homeostasis and stabilize mitochondrial function strengthens β-cell resilience, supporting sustained glucose regulation and long-term endocrine pancreatic health.[39]

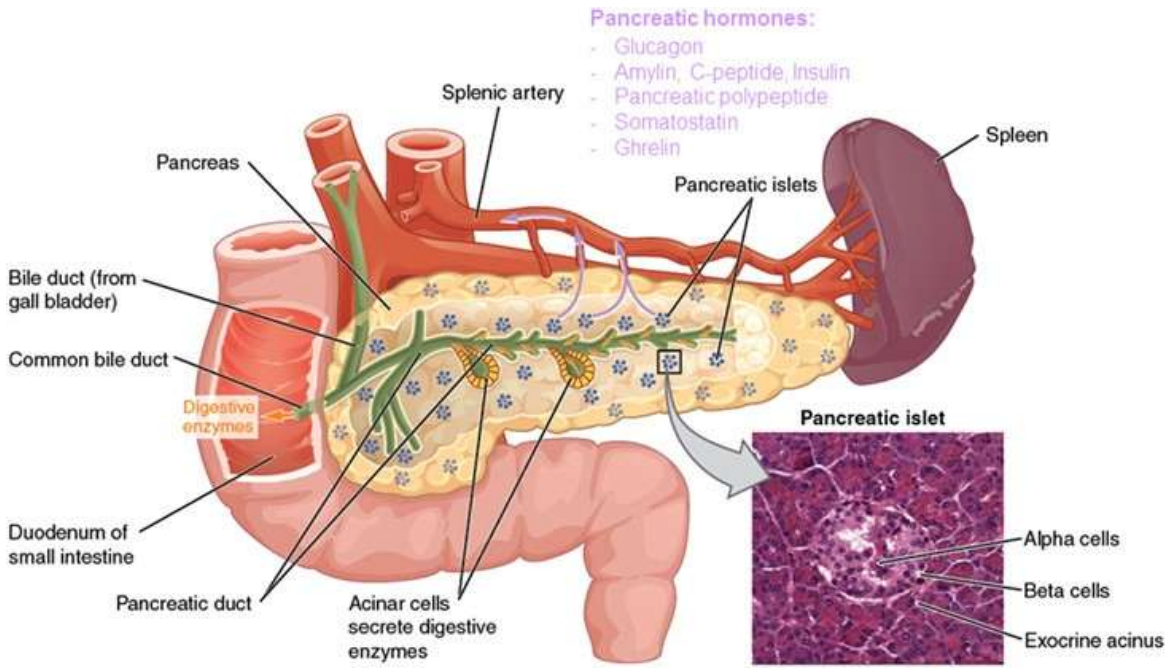

Figure 2. Pancreatic regulation of glucose homeostasis [40]

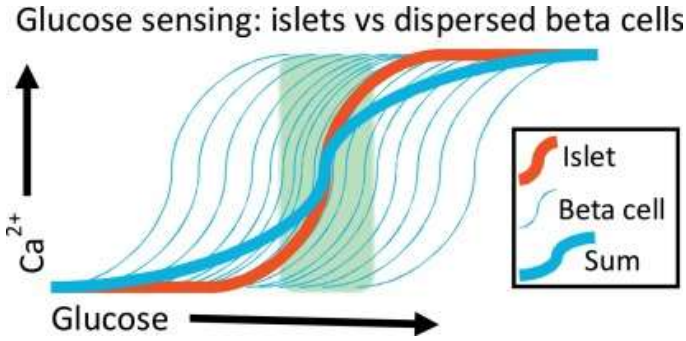

Figure 3. Intact pancreatic islets and dispersed beta-cells both generate intracellular calcium oscillations but differ in their responsiveness to glucose [48]

β-cells and pancreatic islets

Pancreatic β-cells, which produce, store, and secrete insulin, are crucial for regulating glucose homeostasis and are found in the islets of Langerhans.[41] These cells react rapidly to blood glucose levels by releasing insulin, which promotes cellular glucose uptake and preserves metabolic equilibrium. Within the pancreatic islet microenvironment, β-cells interact closely with α, (alpha) δ, (delta) PP (pancreatic polypeptide), and ε-cells to form an integrated endocrine network that controls hormone release **(Figure 3)**.[42] The loss or impairment of β-cells, which are essential for preventing hyperglycemia, is one of the primary features of diabetes mellitus.

Pancreatic β-cells are specialized endocrine cells found in the islets of Langerhans, accounting for 60–70% of the islet cell mass.[43] Their primary function is the production, storage, and glucose-stimulated secretion of insulin, the main hormone responsible for lowering blood glucose and maintaining metabolic homeostasis.[44] Glucose transporter 2 (GLUT2) allows β-cells to absorb glucose when glucose levels rise. This is followed by ATP production, K^+-ATP channel closure, depolarization of the cell membrane, and activation of voltage-dependent Ca^{2+} channels, all of which result in insulin exocytosis.[45] A variety of hormone-secreting cell types make up the endocrine pancreatic islet, including α-cells that produce glucagon, δ-cells that secrete somatostatin, PP-cells that release pancreatic polypeptide, and ε-cells that produce ghrelin.[46] Through intricate vascular networks, gap junctions, and paracrine signals, these cell populations exchange information. This structural and functional arrangement allows for coordinated regulation of nutrient metabolism, with β-cells serving as the main regulators of glucose balance.[47]

Pancreatic β-cell electrical activity

β-cell electrical activity is necessary to regulate insulin secretion and preserve glucose homeostasis. When extracellular glucose levels rise, glucose enters β-cells primarily through GLUT2 transporters.[49] It is broken down there to create ATP. When the intracellular ATP/ADP ratio rises, ATP-sensitive potassium (K^+-ATP) channels close, causing membrane depolarization. In this depolarized state, voltage-dependent calcium (Ca^{2+}) channels open, allowing Ca^{2+} to enter and causing the exocytosis of insulin-containing granules.[50]

Pulsatile insulin release, which is more physiologically effective than continuous secretion, is ensured by the rhythmicity of β-cell electrical oscillations.[51] These oscillatory patterns are synchronized throughout the islet by gap junctions between β-cells, resulting in coordinated waves of electrical activity and Ca^{2+} signaling. When these electrical processes are disrupted by oxidative stress, lipid overload, or inflammation, Ca^{2+} entry is impaired and insulin secretion is decreased, resulting in β-cell dysfunction that is frequently seen in diabetes.[52]

Recommendations

Future studies should concentrate on clarifying the molecular mechanisms by which GO enhances pancreatic β-cell function and insulin secretion. To ascertain long-term safety profiles and ideal dosing approaches, preclinical and clinical research studies are necessary. Examining its potential for synergy with conventional antidiabetic treatments could improve glucose regulation and β-cell preservation. Advanced methods such as electrophysiology and calcium imaging are recommended to better understand gamma-oryzanol's effects on β-cell electrical activity and

insulin granule exocytosis and to support its development as a therapeutic agent for diabetes management. The effects of GO on lipid metabolism, its anti-inflammatory and antioxidant qualities in vivo, and its possible role in preventing β-cell dysfunction in early-stage diabetes should also be assessed.

CONCLUSION

Gamma-oryzanol is a promising natural medicinal substance for diabetes mellitus. The lipid-modulating, anti-inflammatory, and antioxidant properties of GO hold great potential for enhancing pancreatic β-cell function and insulin secretion. By preserving β-cell integrity, stabilizing electrical activity, and encouraging glucose-stimulated insulin release, it contributes to better glucose homeostasis. Diabetes mellitus can be prevented and treated based on these intricate effects. Further preclinical and clinical research is required to confirm its efficacy, optimize dosage, and examine its long-term effects on metabolic health and β-cell preservation. Additionally, GO's modulation of β-cell electrical signaling and calcium dynamics highlights its role in maintaining pulsatile and physiologically efficient insulin secretion. Its inclusion in dietary or therapeutic strategies may provide a supplement to conventional antidiabetic treatments by promoting long-term pancreatic health and slowing the progression of β-cell dysfunction in diabetes.

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Conflict of Interest

There are no conflicts of interest.

Authors' Contributions

MAMEA and MNB are responsible for conception, writing the manuscript and acquisition and collection of data. MRA and IM are responsible for conception, critical revision of paper and analysis, and interpretation of data. IM and MNB are responsible for study design and methods used, MA and MAMEA are responsible for acquisition, collection of data, writing manuscript and analysis, and interpretation of data. All authors have read and approved the final manuscript.

Data Availability Statement

Ther were no new data generated data sharing is not applicable.

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Declaration of the AI Usage in Scientific Writing

The language, grammar, structure, and clarity of this manuscript were enhanced by AI-assisted tools, such as OpenAI's ChatGPT. The authors created and verified all scientific concepts, experimental plans, analyses, interpretations, and findings. Neither original data nor scientific judgments were produced by the AI. The writers are still solely accountable for accuracy and honesty.

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