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REVIEW ARTICLE

Gamma-oryzanol: a novel promising supplement for diabetes mellitus

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ABSTRACT

The global prevalence of diabetes is rising at an alarming rate, with nearly 11% of adults currently affected. Projections estimate that by 2045, approximately 800 million individuals—1 in every 8 people—will have diabetes, representing a 46% increase in cases. Effective dietary management, however, offers the potential to delay or reduce diabetes-related complications. Gamma-oryzanol (γ-ORZ), a bioactive compound in brown rice (BR), has shown promising effects on type 2 diabetes mellitus (T2DM) and its complications, as evidenced by various scientific studies. Despite its potential, γ-ORZ's mechanisms of action remain underexplored, and BR consumption is less prevalent compared to white rice (WR). This review aimed to examine the effects of γ-ORZ on diabetes, promoting further research and encouraging the adoption of BR in dietary practices. Relevant studies were identified through a systematic search of PubMed, ScienceDirect, and Google Scholar for articles published between January 2013 and December 2023 using the keywords "(Gamma-oryzanol OR γ-oryzanol OR γ-ORZ) AND (Diabetes Mellitus OR Type-2 diabetes mellitus OR T2DM OR Hyperglycemia OR Insulin Resistance)." From an initial pool of 1,912 articles, 15 studies meeting the inclusion criteria were reviewed. Findings revealed that γ-ORZ exhibits antihyperglycemic, antidyslipidemic, anti-inflammatory, and antioxidant properties. It mitigates β-cell dysfunction, improves adipocyte function, enhances insulin secretion and sensitivity, and alleviates diabetic cardiomyopathy. This review underscores γ-ORZ's therapeutic potential in managing diabetes and its complications, while highlighting the need for more robust studies to validate its efficacy and compare it with standard treatments.

Keywords: Diabetes, diabetic complications, gamma-oryzanol, insulin secretion, insulin resistance

INTRODUCTION

Approximately 10.5% of adults worldwide are affected by diabetes, with nearly half remaining unaware of their condition. Projections estimate that by 2045, 783 million adults—equivalent to 1 in 8 individuals—will have diabetes, reflecting a 46% increase. However, preventative measures, early diagnosis, and appropriate management can help mitigate or delay the onset of complications associated with the disease.[1] According to the World Health Organization, diabetes is defined as a metabolic disorder characterized by chronic hyperglycemia resulting from impairments in insulin secretion, insulin action, or both, leading to disturbances in the metabolism of carbohydrates, lipids, and proteins.[2] There are three types of diabetes: type 1, type 2, and gestational diabetes; other rare categories of diabetes include monogenic DM and secondary (Type 3) DM.[3] In type 1 diabetes mellitus (T1DM), there is total absence of insulin production by the pancreas,[4] and it is believed to be an autoimmune disease characterized by T-cell-mediated destruction of pancreatic β-cells, which results in insulin deficiency and ultimately hyperglycemia.[5,6] The pathogenesis of this autoimmunity, though not yet fully understood, has been found to be influenced by both genetic and environmental factors such as viral infection.[7] Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance of the target cells coupled with glucose intolerance and obstinately raised blood glucose level.[4] The pathophysiology of T2DM is characterized by a disruption in the balance between insulin action and secretion, which is caused by either deficient insulin secretion (DIS) or insulin resistance (IR) of the target cells. [7,8] The body's ability to maintain glucose homeostasis becomes compromised by defective insulin secretion, primarily resulting from β-cell dysfunction, which leads to reduced insulin production. Concurrently, insulin resistance (IR) in metabolically active tissues impairs glucose uptake, triggering increased hepatic glucose production. While both β-cell dysfunction and IR are early events in the pathophysiology of diabetes, β-cell dysfunction is often more pronounced and plays a critical role in the progression and severity of the disease.[7,9] On the other hand, hyperglycemia is exacerbated and T2DM advances when both β-cell dysfunction and IR are present.[10,11] Conversely, overindulgence in free fatty acids and high blood sugar causes β-cell failure by triggering endoplasmic reticulum stress (ER stress) and activating the apoptotic unfolded protein response (UPR) pathways.[12] Indeed, β-cell damage is caused by metabolic and oxidative stress resulting from lipotoxicity, glucotoxicity, and glucolipotoxicity that are present in obesity.[13]

Insulin resistance (IR) is defined as a reduction in the metabolic response of insulin-responsive cells to insulin or, on a systemic level, as a reduced or impaired response of blood glucose levels to circulating insulin.[14] Insulin-deficient conditions or IR fall into three main categories: (i) reduced insulin release from β-cells; (ii) insulin antagonists in the bloodstream, resulting from counter-regulatory hormones such as cortisol and glucagon, or from non-hormonal substances that damage insulin receptors or insulin signaling; and (iii) reduced insulin response in target organs.[15] In the fed state, the interactions between growth hormone and insulin-like growth factor 1 (IGF-1) affect how well insulin functions. To avoid insulin-induced hypoglycemia during fasting, glucagon, glucocorticoids, and catecholamines reduce the insulin response. Since it establishes the relative level of phosphorylation of downstream enzymes in the regulatory signaling pathways, the insulin/glucagon ratio is crucial to this control. Systemic IR is frequently preceded by impaired insulin function in skeletal muscle, adipose tissue, and the liver, which progressively results in type 2 diabetes. Additionally, T2DM has been connected to the emergence of cardiovascular disease.[16] This is explained by the role of IR in inflammation, oxidative stress, hypertension, vascular function, atherosclerosis, and macrophage accumulation.[17-19]

The symptoms of diabetes mellitus commonly include polyuria, polydipsia, and polyphagia, and may also present with obesity and dyslipidemia in some cases. Given the critical role of insulin in the metabolism of carbohydrates, lipids, and proteins, persistent hyperglycemia and insulin dysfunction or resistance contribute to the progressive malfunction of multiple organ systems.[20] In the long run, diabetes can have a significant negative impact on the body's numerous organ systems and eventually cause major consequences. Diabetes-related complications fall into one of two categories: microvascular or macrovascular. Microvascular complications include neuropathy, nephropathy, and retinopathy, which affect the nervous system,

kidney, and eye, respectively.[20] Peripheral vascular disease, stroke, and cardiovascular disease are examples of macrovascular complications. Peripheral vascular dysfunction can result in gangrene, amputation, and non-healing wounds or traumas.[21]

Gamma oryzanol (γ-oryzanol/Oryzanol) is a compound found in rice bran oil that has been shown to have potential benefits for individuals with diabetes, especially type 2 diabetes. Studies have shown that Oryzanol can lower blood sugar levels, reduce the risk of diabetic complications, and increase insulin secretion. Gamma oryzanol also has antioxidative properties that could help mitigate oxidative stress, a condition often exacerbated in diabetes. It has been discovered that gamma oryzanol can improve insulin sensitivity and reduce insulin resistance, which are key factors in diabetes. However, longer-term studies are needed to evaluate these effects further. Replacing white rice that has high glycemic index (HGI) with unpolished brown rice that possesses low glycemic index (LGI) in the daily diet can significantly reduce the risk of diabetes and its complications.[22-26] Further exploring of these effects could provide an avenue for developing novel therapy for diabetes.

This review aimed to explore and summarize the recent scientific findings on the beneficial effects of γ-oryzanol on diabetes mellitus and its complications. Both in vitro and in vivo research articles that assessed the effects of γ-oryzanol on diabetes mellitus, published in English in the last 10 years (from January 2013 to December 2023) were retrieved from Science Direct, PubMed, Nature, International Journal of Medicine and Pharmaceutical Sciences, Preventive Nutrition and Food Science, Plos One and Biomedicine using the relevant search terms. The findings revealed antidiabetic effects of γ-oryzanol that include minimizing β-cell dysfunction through mitigation of endoplasmic reticulum stress (ER stress), antihyperglycemic effects through increased transporter type 4 (GLUT4) translocation, and reduced oxidative stress and insulin resistance via upregulation of antioxidants and upsurge of GLUT4 translocation, respectively. Other beneficial effects of gamma oryzanol on diabetes reported here are to boost insulin sensitivity as well as to reduce inflammation by raised adiponectin secretion and consequently amelioration of dyslipidemia by raising HDL cholesterol and lessening LDL cholesterol.

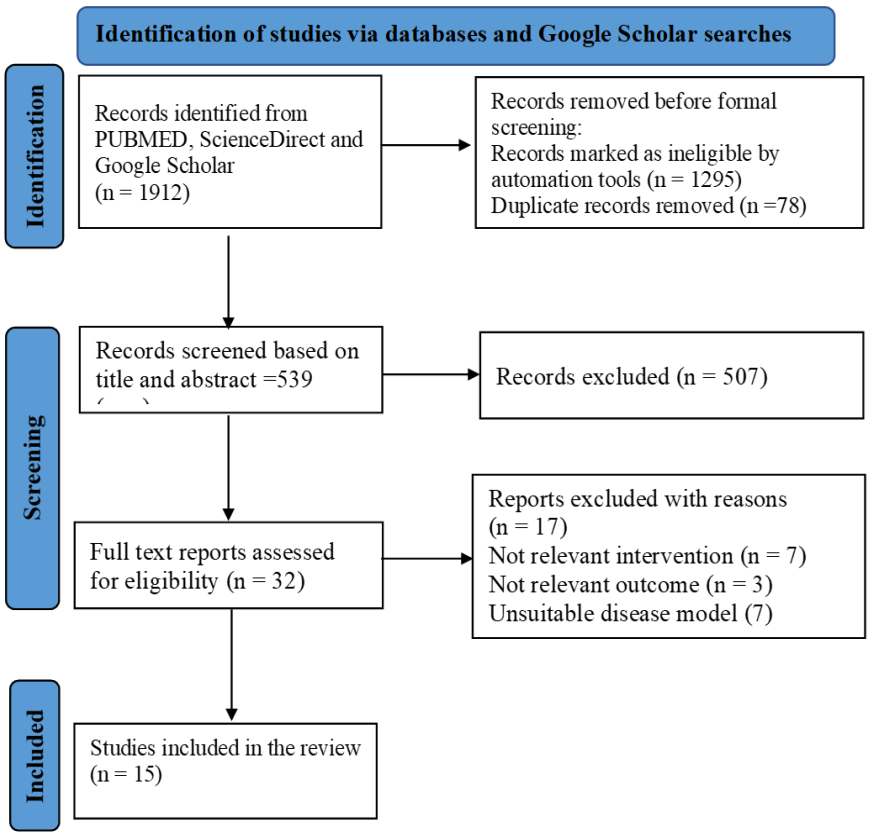

Figure 1. Process of study selection

Research 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 in diabetic states while limiting the dates of publication to the last 10 years onwards, using the following search "(Gamma-oryzanol OR γ-oryzanol OR γ-ORZ) AND (Diabetes Mellitus OR Type-2 diabetes mellitus OR T2DM OR Hyperglycemia OR Insulin Resistance)." Publications older than 10 years and those published in languages other than English were excluded from the study. Other publications were identified and traced from references in published articles/reviews found from the search of the databases. *In vivo* (preclinical and clinical) and *in vitro* studies were all considered. After excluding duplicate publications, and those that did not meet the inclusion criteria, 15 publications were selected: three clinical, ten *in vivo*, and two *in vitro* studies (Figure 1). The selected articles were analyzed and reviewed accordingly.

Mechanisms underlying the anti-diabetic effects of γ-oryzanol

Gamma-oryzanol has been reported to improve mechanisms that lead to defective insulin secretion or failed insulin action with consequent development of diabetes mellitus (DM) and diabetic-related complications (see Figure 2). These antidiabetic effects are categorically discussed below and further summarized in Table 1.

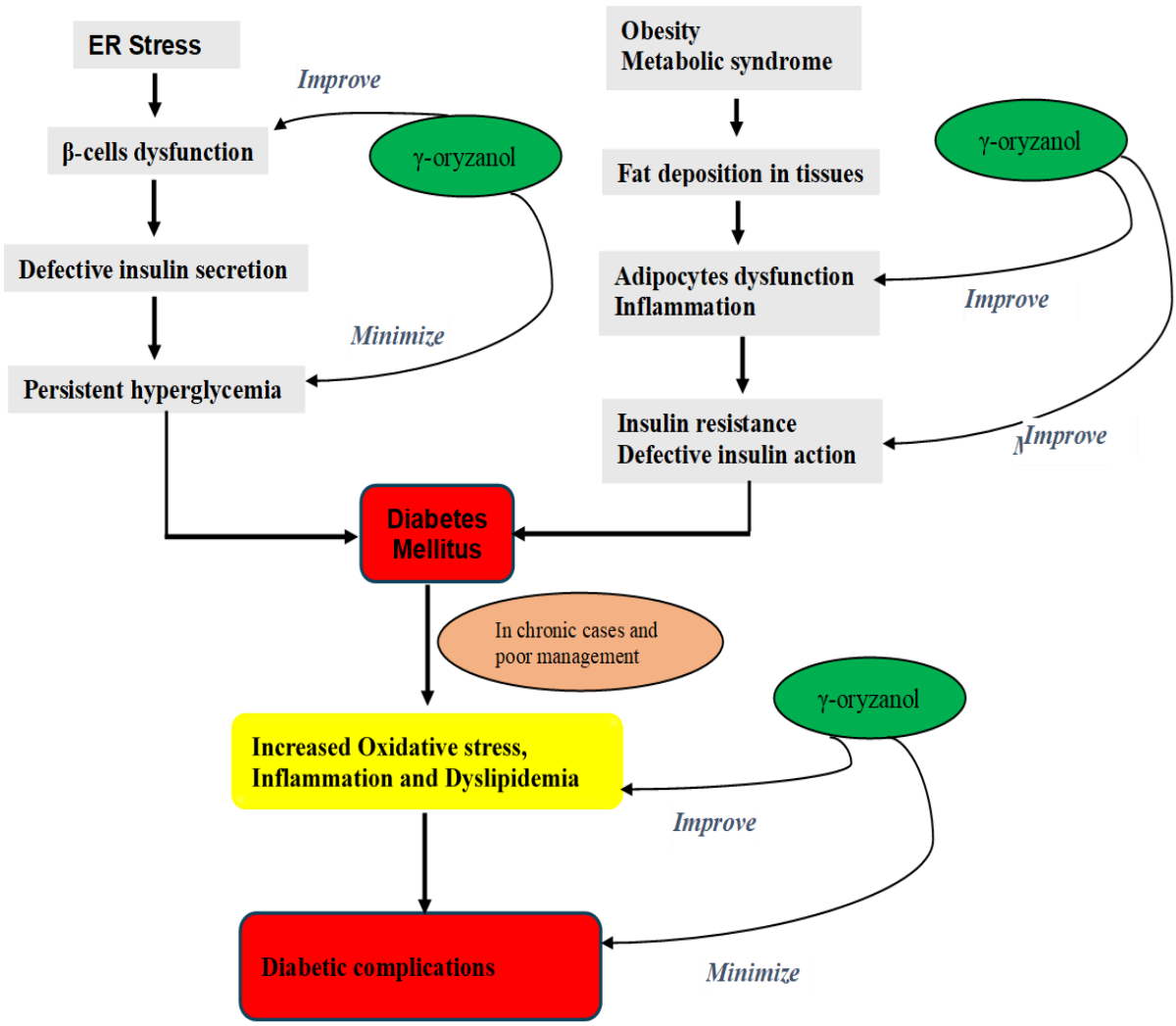

Figure 2. Pathogenesis of diabetes mellitus and related complications; note the beneficial effects of γ-oryzanol shown on different pathophysiological stages as reported in many scientific studies

Table. 1 Summary of anti-diabetic effects of γ-Oryzanol in both *in vivo* and *in vitro* studies

***In vivo* studies (Human)**			
References	**Subject/Model**	**Treatment/Intervention**	**Results/Findings**
Nakayama et al.[39]	Adult patients with type 2 diabetes in randomized, open-label, crossover study	One group consumed GBR containing 31mg γ-ORZ per pack twice a day for 8 weeks as staple food, followed with WR for the next 8 weeks, whereas the other group consumed WR first and then GBR.	Improved glycemic control in patients with type 2 diabetes: hemoglobin A1c, glycoalbumin, and plasma glucose level
Bumrungpert et al.[41]	Hyperlipidemic adults aged 20-60 years in randomized, double-blind, placebo-controlled clinical trial	Three different doses of γ-ORZ in rice bran oil (RBO) three times a day for 4 weeks	Decreased hyperlipidemia and oxidative stress
Nikooyeh et al.[23]	Adult subjects with type-2 diabetes in randomized controlled clinical trial	Gamma-oryzanol (γ-ORZ-fortified canola oil for 12 weeks	Significant decrease in blood pressure (BP), waist circumference (WC), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and triglycerides (TG) in γ-oryzanol-fortified canola oil group
Chauhan, et al.[34]	Hyperlipidemic rats fed atherogenic diet	Animals were supplied with rice bran oil (RBO) 15% and γ-ORZ (100mg/Kg body weight) for a period of 42 days	Both possess significant, antihyperlipidemic and antioxidative properties
Wang et al.[27]	Sprague-Dawley rats (weighing 350–360 g) fed HFFD	0.16% γ-ORZ-containing diet for 13 weeks	Increased adiponectin secretion, decreased blood glucose level, decreased insulin resistance, glucose AUC, and HOMA-IR in both groups
Kozuka et al.[28]	High-fat-diet-fed C57BL/6J mice model	20, 80, 320 mg/kg BW of γ-ORZ for 13 weeks	Decreased ER stress in pancreatic β-cells and brain hypothalamus Decreased pancreatic islet dysfunction Protection of β-cells against apoptosis
Kozuka et al.[30]	Eight-week-old male C57BL/6J mice	γ-Oryzanol (20, 80 or 320 $\mu g \cdot g^{-1}$ body weight dissolved in 0.5% methyl cellulose solution) was delivered into the stomach by gavage needle every day for 13 weeks	γ-oryzanol inhibits the dopamine type 2 receptor (D2R) signaling in pancreatic islets, augments glucose-stimulated insulin secretion (GSIS) and decreases glucagon secretion from murine islets
Kozuka et al.[35]	Genetically obese-diabetic (ob/ob) mice	Encapsulated nanoparticles of γ-ORZ in form of nano vehicle (Nano-Orz), was administered once every 2 weeks for 4 weeks and Gamma-oryzanol (320 mg/g body weight) everyday for 4 weeks	Nano-Orz markedly ameliorated fuel metabolism 1000-fold more than regular gamma-oryzanol through the following effects: i. decreased blood glucose levels ii. reduced plasma insulin levels iii. protection and improvement in function of pancreatic islets iv. improved insulin sensitivity. v. downregulated some plasma and hepatic lipid parameters.

Table 1. Continued

Francisqueti et al.[47]	Male Wistar rats weighing approximately 187g	Animals were fed a high-sugar and high-fat (HSF) diet and γ-ORZ for 20 weeks	γ-ORZ lowers triglyceride levels, and inhibits weight gain, adipocyte differentiation, and adipogenesis
Guo et al.[36]	Male Sprague-Dawley rats (weighing 180–200 g) fed HFFD	0.71% γ-ORZ containing diet for 16 weeks	Decreased fasting blood glucose by improving glucose metabolism, hyperlipidemia, and hepatic lipid accumulation.
Bhaskaragoud et al.[37]	High-fat-fed and low streptozotocin-induced diabetic animals	Rice bran oil concentrate (γ-ORZ), 0.1% and 0.3% for 8 weeks	Decreased hyperlipidemia, hyperglycemia, liver lipid profile, lipid peroxidation, and glucose tolerance test.
Lin et al.[38]	Male C57BL/6 mice fed a high sugar-fat diet (HSF) for 18 weeks to induce obesity and insulin resistance	Doses 0.5, 5, or 10 mg kg^{-1} day^{-1} of γ-oryzanol were given via oral gavage	Significant improvement in glycemic status, dyslipidemia, inflammation, and oxidative stress
Mattei et al.[24]	Male Wistar rats (±187 g) fed a high sugar-fat diet (HSF), for 20 weeks to induce obesity and insulin resistance	γ-ORZ (0.5w/w) for 10 weeks	Reduced insulin resistance, decreased inflammation, increased antioxidant response and GLUT4 expression.
Jung et al.[26]	In vitro study	γ-ORZ	γ-ORZ stimulates glucose uptake and improves glucose transporter type 4 (GLUT4) translocation. γ-ORZ enhances cell differentiation by the up-regulation of adipogenesis.
Sansenya et al.[33]	*in vitro* and *in silico* studies	Cycloartenyl ferulate, the principal component of γ-ORZ	Cycloartenyl ferulate possesses a potential inhibitory effect against α-glucosidase and α-amylase

Effects of oryzanol on β-cell dysfunction in DM

One of the mechanisms of action of oryzanol is on beta cell dysfunction. Beta cell (β-cell) dysfunction with consequent defective insulin secretion and persistent hyperglycemia has been directly linked with development of diabetes. These effects have been associated with endoplasmic reticulum (ER) stress in pancreatic islets of Langerhans cells.[27,28] Gamma oryzanol has been proven to mitigate ER stress in several scientific studies. Kozuka et al.[28] administered three different doses, 20, 80, and 320 mg/kg BW of γ-ORZ for 13 weeks to eight-week-old male C57BL/6J mice fed a high-fat-diet and observed that γ-oryzanol decreased pancreatic islet dysfunction and ER stress in pancreatic β-cells. Moreover, γ-oryzanol provided protection against β-cell apoptosis.

Müller [29] reported that exaggerated secretion of glucagon from pancreatic α-cells contributes to the vicious cycle of glucose dyshomeostasis that plays a role in the pathophysiology of diabetes mellitus. Kozuka et al.[30] delivered γ-Oryzanol (20, 80 or 320 $\mu g \cdot g^{-1}$ body weight dissolved in 0.5% methyl cellulose solution) using a gavage needle to eight-week-old male C57BL/6J mice every day for 13 weeks and found that γ-oryzanol significantly inhibits the dopamine type 2 receptor (D2R) signaling in pancreatic islets, and augments glucose-stimulated insulin secretion (GSIS). Moreover, γ-Oryzanol affects α-cell activities via mitigating the exaggerated secretion of glucagon in both HFD-fed mice and isolated murine islets. All these effects could help in delaying the development of diabetes and associated complications.

Effects of oryzanol on persistent hyperglycemia in DM

Hyperglycemia is known to produce oxidative stress that leads to enhanced production of mitochondrial reactive oxygen species (ROS). Reactive oxygen species, which create cellular damage by their glucose oxidation ability, have

been associated with the pathogenesis of diabetes mellitus.[31,32] In an *in vitro* study by Jung et al.,[26] γ-ORZ produced blood glucose lowering effects by stimulating glucose uptake and improving glucose transporter type 4 (GLUT4) translocation. Recently, Sansenya et al.[33] carried out *in vitro* and *in silico* studies using cycloartenyl ferulate, the principal component of γ-ORZ, and discovered that it possesses antihyperglycemic ability by means of potential inhibitory effects against α-glucosidase and α-amylase.

Gamma-oryzanol has been proved to mitigate hyperglycemia and resultant effects in both human and animal *in vivo* studies. Hypoglycemic effects of ORZ were reported by Wang et al.[27] who administered a diet containing 0.16% γ-ORZ to high-fat-high-fructose-diet (HFFD) fed Sprague-Dawley rats for 13 weeks. Kozuka et al.,[35] in their effort to counteract the extremely low absorption efficiency of γ-ORZ from the lumen performed an experiment and compared the hypoglycemic effects of encapsulated nanoparticles of γ-ORZ (nano-ORZ) delivered once every 14 days for 4 weeks and regular γ-oryzanol (320 mg/g body weight) administered daily for 4 weeks. Surprisingly, nano-ORZ ameliorated fuel metabolism a thousand-fold more than regular γ-ORZ via several mechanisms, including decreased plasma glucose levels. Some *in vitro* studies also reported blood glucose lowering effects of γ-ORZ. In another study by Guo et al.,[36] where HFFD-fed male Sprague-Dawley rats (weighing 180–200 g) were treated with 0.71% γ-ORZ containing diet for 16 weeks, the findings were decreased fasting blood glucose by improving glucose metabolism, hyperlipidemia, and hepatic lipid accumulation. Bhaskaragoud et al.[37] evaluated the antioxidant and hypolipidemic effects of γ-ORZ by treating high fat fed and low Streptozotocin-induced diabetic animals with rice bran oil concentrate (γ-ORZ) at 0.1% and 0.3% for 8 weeks. Treatment with the concentrate resulted in decreased hyperlipidemia, hyperglycemia, liver lipid profile, lipid peroxidation, and glucose tolerance test. Recently, Mattei et al.[24] fed male Wistar rats (±187 g) a high sugar-fat diet (HSF), for 20 weeks to induce obesity and insulin resistance followed by 10 weeks treatment with γ-ORZ (0.5w/w). Post-treatment γ-ORZ showed improved glycemic control by increasing GLUT4 expression. Similar findings were observed in an earlier study by Lin et al.[38]

In the randomized, open-label, crossover study using adult patients with type 2 diabetes in which the subjects were fed glutinous brown rice (GBR) twice a day for 8 weeks followed by white rice (WR) for another 8 weeks and vice versa, the outcomes were improvements in glycemic control, glycated hemoglobin A1c, glycoalbumin, and plasma glucose level in the GBR-consuming group compared with the WR fed group.[39] The observed changes were attributed to high γ-oryzanol content present in the GBR which was reported to improve glycometabolic parameters in patients with type 2 diabetes in other studies.[28,40] These previous findings were recently confirmed by Nikooyeh et al.,[23] who conducted a randomized controlled clinical trial using adult subjects with type-2 diabetes. Findings revealed that γ-oryzanol administration resulted in a statistically significant decrease in fasting blood glucose (FBG) and HbA1c among the treated group.

Effects of oryzanol on oxidative stress and insulin resistance in DM

Insulin resistance, otherwise known as impaired insulin sensitivity, is a state when body cells, tissues, or organs fail to respond to insulin, which is another feature that contributes to the pathogenesis of type-2 diabetes. Gamma-Oryzanol has been proven to improve insulin sensitivity in several scientific studies. Wang et al.[27] and Kozuka et al.[35] in their respective studies using laboratory animals observed decreased inflammation, increased antioxidant response, and GLUT4 expression in addition to reduced insulin resistance. Many studies discovered anti-oxidant effects of γ-ORZ in experimental studies. For instance, Chauhan et al.[34] reported antioxidant effects of ORZ. Similar findings were reported in the study by Bumrungpert et al.,[41] who observed decreased hyperlipidemia and oxidative stress after administering three different doses of γ-ORZ in rice bran oil (RBO) three times a day for 4 weeks to hyperlipidemic adults. Analogous observations through increased antioxidant activities were recounted in animal studies by Mattei et al.,[24] who did a 30-week study using male Wistar rats (±187 g) fed a high sugar-fat diet (HSF) for 20 weeks to induce obesity and insulin resistance, followed by therapy with γ-ORZ (0.5 w/w) for 10 weeks. Lin et al.[38] reported identical findings of managing oxidative stress by administering γ-ORZ to mice with metabolic disorder for 18 weeks.

Effects of oryzanol on insulin sensitivity and inflammation in DM

In addition to their role in energy regulation and glucose homeostasis,[42] adipose tissue also serves as an endocrine organ by secreting adipokines, notably adiponectin mainly secreted by adipocytes, cardiomyocytes, endothelial cells, and skeletal muscle cells. Adiponectin is metabolically active in muscle, liver, pancreas, and brain,[43-45] and in the latter it controls insulin sensitivity and curtails inflammation.[45] Furthermore, adiponectin can protect against heart disease by improving fat metabolism, vascular endothelial cell defense, and hindering foam cell formation as well as cellular proliferation of vascular smooth muscle.[46]

Wang et al.[27] used Sprague-Dawley rats (weighing 350–360 g) that were fed a HFFD and a 0.16% γ-ORZ containing diet for 13 weeks, showing that the treated animals displayed increased adiponectin secretion. This finding was later confirmed by Francisqueti et al.,[47] who fed male Wistar rats a high-sugar and high-fat diet plus γ-ORZ for 20 weeks. The γ-ORZ treated group exhibited improved adipocyte differentiation and adipogenesis. Recently, Lin et al.[38] discovered γ-ORZ to have reduced inflammation in mice exposed to metabolic disorder.

Effects of oryzanol on dyslipidemia in DM

Diabetes is associated with complications of dyslipidemia, notably hypertriglyceridemia, reduced HDL cholesterol levels, and raised levels of LDL cholesterol.[48-51] Gamma-oryzanol has been proven to counteract these harmful effects in numerous scientific studies. For instance, in a study conducted by Bumrungpert et al.[41] among hyperlipidemic adults treated with three different doses of γ-ORZ for 4 weeks, the treated group exhibited decreased hyperlipidemia. Also, in another study by Bhaskaragoud et al.[37] using high fat fed and low streptozotocin-induced diabetic animals treated with 0.1% and 0.3% γ-ORZ for 8 weeks, the treated animal shows reduced hyperlipidemia. Similar findings of managing dyslipidemia in animal experiments were documented in several other scientific studies.[27, 34-36, 38]

CONCLUSION

In conclusion, this review highlights the promising antidiabetic properties of gamma-oryzanol (γ-ORZ), a bioactive phytochemical derived from rice bran, as evidenced by its multifaceted therapeutic effects, including enhanced insulin secretion and sensitivity, improved glycemic control, optimized lipid profiles, and bolstering of antioxidant defenses. Furthermore, γ-ORZ has shown potential in reducing diabetes-related complications, such as cardiomyopathy and renal damage. Despite these encouraging findings, further robust investigations, particularly well-structured clinical trials, are imperative to validate its efficacy and establish its comparative therapeutic potential alongside existing standard treatments for diabetes.

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Conflicts of Interest

The authors declare no financial or any other conflicts of interest in this work.

Author Contributions

MIR and NO conducted review of the literature and drafted the manuscript. RA, RAJ, WRNI, AAMZ and ACR were involved in the design and critical review of this manuscript. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Data Availability Statement

The data supporting the findings of this study are available upon request from the corresponding author.

Declaration of Use of AI in Scientific Writing

The authors hereby declare that no generative AI was used in drafting this manuscript as well as in designing figures and tables.

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