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REVIEW

Gamma-oryzanol as a potential intervention in obesity and skeletal muscle disorders: a preclinical review from rodent studies

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Abstract

Excessive consumption of the Western diet leads to obesity and skeletal muscle disorders. Natural bioactive substances found in natura or minimally processed foods contribute to the regulation of important biological processes across different organs and tissues and have been highlighted as potential agents in the management of these disorders. Gamma-oryzanol (γOz) is a non-phenolic steryl ferulate considered one of the most potent natural antioxidants, presenting anti-obesity, anti-inflammatory, antidiabetic, hypolipidemic, and anticancer properties, suggesting a promising strategy for the management of chronic diseases. The aim of this work is to review the application of γOz as a strategy to combat obesity and skeletal muscle disorders. The review focused on preclinical, peer-reviewed journal articles, particularly those involving animal models of obesity. References were selected according to their relevance to the topics discussed, without applying any date limitations. The literature search was conducted using the PubMed, Web of Science, and Lens.org databases, employing the following terms: "obesity," "adipose tissue," "obesity target organs," "skeletal muscle," "bioactive compounds," and "gamma-oryzanol." The evidence reviewed demonstrates that γOz is a potential form of prevention and treatment for obesity-induced dysfunctions across different organs and tissues in preclinical models. Specifically, in skeletal muscle, γOz was able to mitigate the redox-inflammatory imbalance, improve the antioxidant system, increase the expression of GLUT-4, and promote improved muscular energy regulation, possibly due to AMPK activation. Nevertheless, the literature reveals a gap in knowledge regarding the effect of this phytosterol on skeletal muscle dysfunction in diet-induced obesity models. Therefore, pioneering investigations are needed in this largely unexplored field.

Keywords Gamma-oryzanol · Obesity · Metabolic disease · Skeletal muscle

Introduction

According to the World Health Organization (WHO), in 2022, 2.5 billion adults were overweight, and more than 890 million adults were living with obesity, reflecting more than a twofold increase in the global prevalence of these conditions between 1990 and 2022. Additionally, it was estimated that 37 million children under the age of 5 and over 390 million children and adolescents aged 5 to 19 years were overweight [1, 2].

The excessive intake of macronutrients and energy from the chronic consumption of Western diets, rich in simple sugars and saturated fats, contributes to the development of obesity. This condition is associated with hypertrophy, hyperplasia, hypoxia, and necrosis of the adipose tissue, leading to macrophage infiltration and a pro-inflammatory environment characterized by elevated levels of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). These alterations are accompanied by an increase in reactive oxygen species (ROS) and impaired redox balance in response to endothelial and microvascular dysfunction in white adipose tissue (WAT) [3]. This chronic redox-inflammatory imbalance established in the WAT can become systemic, negatively impacting several organs and tissues, including skeletal muscle (Fig. 1) [3].

Investigation of therapeutic strategies involving natural foods has gained attention in the literature due to their potential in modulating mechanisms related to obesity and

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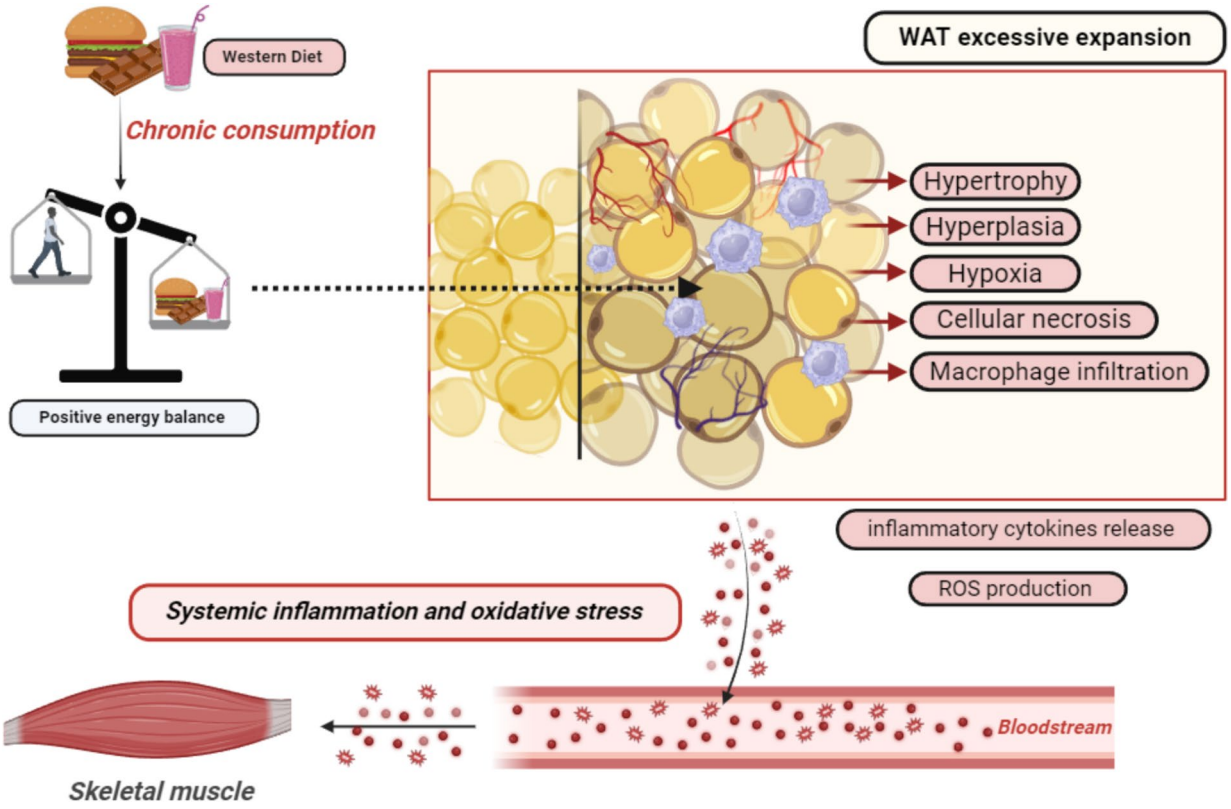

Fig. 1 Obesity development. Chronic consumption of the Western diet promotes excessive expansion of the white adipose tissue characterized by hypertrophy, hyperplasia, hypoxia, cell necrosis, and macrophage infiltration, contributing to a systemic inflammatory state and oxidative stress condition that negatively affect skeletal muscle. ROS: reactive oxygen species; WAT: white adipose tissue. Created with BioRender.com. Elaborated by the authors

its associated systemic dysfunctions, suggesting possible treatment applications. Gamma-oryzanol (γOz), a bioactive compound found in brown rice, is considered one of the most potent natural antioxidants and exhibits anti-obesogenic properties [4, 5]. The aim of this work is to review the application of γOz as a strategy to combat obesity and skeletal muscle disorders.

Materials and methods

This review selected references based on their relevance to the topics covered. The literature search was conducted using scholarly databases such as the PubMed, Web of Science, and Lens.org databases, employing the following terms: "obesity," "adipose tissue," "obesity target organs," "skeletal muscle," "bioactive compounds," and "gamma-oryzanol." The review focused on preclinical, peer-reviewed journal articles, particularly those involving animal models of obesity. Studies were included if they provided clear methodological descriptions, used validated models of diet or genetically induced obesity, and assessed metabolic, inflammatory, or oxidative parameters relevant to the review topic. Preprints, conference proceedings, reviews, in vitro-only studies, and articles lacking sufficient methodological detail were excluded to ensure the credibility of the review. No temporal restrictions were imposed on the selection of references, allowing for the inclusion of all relevant studies to support a comprehensive analysis.

Obesity and skeletal muscle disorders

Voluntary muscle is an important predictor of longevity and functional capacity, playing essential roles in locomotion, respiration, and the conversion of chemical energy into mechanical energy [6, 7]. Constituting approximately 40–50% of the total body mass in healthy, eutrophic individuals, it performs both postural and fast and powerful contractions, which are primarily associated with oxidative and glycolytic muscle fibers, respectively [6, 8].

Overweight and obesity exert multiple effects on muscle tissue, including reduced insulin uptake, impaired phosphorylation of Insulin Receptor Substrate-1 (IRS-1), and decreased translocation of Glucose Transporter Type 4 (GLUT-4) to the cell membrane. These alterations contribute

to hyperglycemia, accompanied by ectopic fat accumulation in the musculature, with intramuscular lipids stored as triacylglycerols within lipid droplets. This is associated with increased concentrations of lipotoxic intermediates, such as diacylglycerols and ceramides [9].

Obese skeletal muscles exhibit impaired fundamental functions, including cellular respiration, adenosine triphosphate (ATP) production, and β-oxidation of lipids. They also demonstrate mitochondrial fragmentation, elevated ROS levels, and increased levels of inflammatory cytokines such as IL-6, IL-8, IL-15, and TNF-α mediated by pro-inflammatory factors Toll-Like Receptor 4 (TLR4) and Nuclear Factor-Kappa-B (NFk-B). Additionally, the reduction of AMP-activated protein kinase alpha (AMPK-α), which regulates myogenesis through microRNA-206 (miR-206) and its target cyclin D1, results in decreased muscular stem cell proliferation and impaired regenerative processes (Fig. 2) [9–18].

In addition, exposure to Western diets can alter several key markers that contribute to metabolic and energy dysregulation in the skeletal muscles of obese individuals [19]. Using omics techniques, evidence suggests that the lipid and amino acid composition in the skeletal muscles of healthy and obese individuals differs significantly, affecting the anaplerotic capacity of the citric acid cycle and energy production. Moreover, disturbances in membrane phospholipids may compromise the function of endoplasmic and sarcoplasmic reticulum, exacerbating metabolic dysfunction [19, 20].

Excessive weight leads to diminished muscle function, quality, and mass; increases the risk of several metabolic comorbidities; and reduces the life expectancy of affected individuals [21]. The investigation of therapeutic strategies involving natural foods has gained attention in the literature, as bioactive compounds present in these foods are considered safer and more accepted as potential treatments for

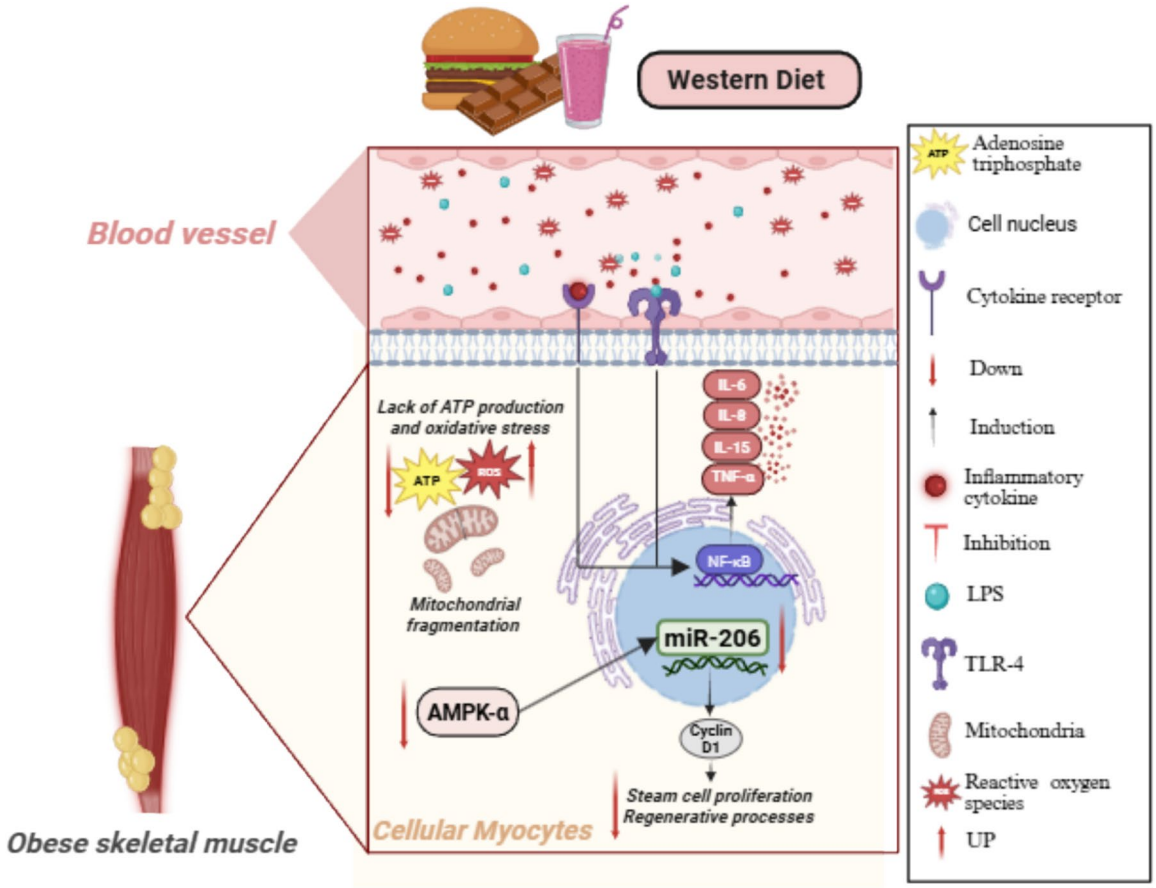

Fig. 2 Obese skeletal muscle. Obesity induces reduced ATP production and increased oxidative stress, accompanied by mitochondrial fragmentation. The release of proinflammatory cytokines is mediated by the transcription of NFκB, which is stimulated by inflammatory signals and lipopolysaccharide (LPS). The muscle tissue exhibits impaired satellite cell proliferation and regenerative capacity due to the reduction of the AMPK-α and miR-206 transcription. AMPK-α: AMP-activated alpha; IL-6: interleukin 6; IL-8: interleukin-8; IL-15: interleukin 15; TNF-α: tumor necrosis factor alpha; NFκB: nuclear factor-kappa-B; miR-206: microRNA-206; TLR-4: toll-like receptor 4. Created with BioRender.com. Elaborated by the authors

non-communicable chronic diseases, such as obesity and muscle disorders, compared to synthetic drugs [22].

Bioactive compounds as a potential form of treatment for obesity and muscular disorders

Several types of bioactive compounds can be found in both plant-based and animal-derived dietary sources [23]. In plant-based foods such as blueberries, citrus fruits, cruciferous vegetables, grapes, green teas, raspberries, seeds, and soybeans, the main bioactive compounds include phenolic compounds and flavonoids, synthesized through plant secondary metabolism, especially in in-natura or minimally processed foods. Conversely, animal-derived foods like red meat and fish provide non-phenolic compounds such as bioactive peptides (e.g., carnosine) and polyunsaturated fatty acids (e.g., docosahexaenoic acid-DHA), which contribute to health-promoting effects and the maintenance of overall health through distinct biological processes [23, 24].

In conditions of obesity, alkylresorcinols, β-sitosterol, curcumin, and rosmarinic acid have been shown to improve body weight, blood glucose levels, insulin sensitivity, cholesterol excretion, serum triglyceride levels, inflammation, and oxidative stress [25–28]. Concordantly, reduced adipogenesis, increased expression of thermogenic genes in adipose tissue, enhanced fat oxidation, improved gut microbiota composition, and better redox-inflammatory state balance have been associated with the consumption of bioactive compounds such as resveratrol, quercetin, and epigallocatechin gallate [29–32]. In addition to their metabolic effects, these compounds also exert beneficial actions across distinct organs and tissues, including skeletal muscles, contributing to disease prevention and the maintenance of muscular function [33].

These nutraceuticals have been widely investigated as a non-pharmacological therapeutic strategy for treating skeletal muscle dysfunctions associated with obesity, and they offer a practical approach to confronting muscular degeneration [34]. Muscle inflammation and oxidative stress resulting from WAT dysfunction in the obesogenic environment are reported to play an important role in the morphological and structural degeneration of the skeletal muscle. This degeneration may lead to long-term pain, sarcopenia, and frailty [34–36].

Therefore, bioactive compounds with anti-obesogenic, anti-inflammatory, and antioxidant properties become relevant. Concerning their specific effects on metabolic disorders related to obese WAT, grape proanthocyanidins reduced WAT pro-inflammatory macrophage infiltration and decreased ROS production through the inhibition of NFk-B, TNF-α, monocyte chemoattractant protein-1 (MCP-1), serine protease inhibitor (PAI-1) and IL-6, followed by higher expression of adiponectin and of nuclear factor erythroid 2–related factor 2 (NRF-2) activation [37]. Additionally, decreased cyclooxygenase-2 (COX-2) and leptin levels were observed, suggesting improved control of glucolipid metabolism [38].

In addition to its effects on WAT, β-sitosterol enhanced skeletal muscle function by promoting the phosphorylation of Acetyl-CoA Carboxylase (ACC) and AMPK activation mediated by the serine–threonine liver kinase B1 (LKB-1) pathway to improve mitochondrial function, fat oxidation, and glycolytic activity [39]. Furthermore, rosmarinic acid enhanced mitochondrial function and upregulated the genes related to mitochondrial biogenesis, such as PGC1-α, SIRT-1, and TFAM, attenuating skeletal muscle insulin resistance [40].

Accordingly, 5-heptadecylresorcinol prevented myofibrillar degeneration by modulating Sirtuin 3, Peroxisome Proliferator-Activated Receptor Alpha (SIRT3/PGC-1α), Mitochondrial Transcription Factor (TFAM), and NRF-1 [41]. Additionally, the polyphenolic fraction of bergamot leaf extract attenuated the redox-inflammatory imbalance in skeletal muscle once lower levels of lipid peroxidation, protein carbonylation, TNF-α, and IL-6 were reported [42].

Concerning muscle proteostasis, curcumin can act on muscle-specific ubiquitin E3 ligase, atrogin-1/muscle atrophy F-box gene (MAFbx) and muscle RING-finger protein-1 (MuRF1), which are responsible for proteasomal degradation [43, 44]. Also, epigallocatechin gallate modulates the phosphatidylinositol-3 kinase/protein kinase/FOXO (PI3-K/AKT/FOXO) axis and was able to suppress the catabolic action of Forkhead Box O1 (FOXO1) [45]. The therapeutic potential of natural compounds in obesity and muscular disorders is vast and should be further investigated to serve as an adjuvant approach in the prevention and treatment of these conditions.

Gamma-oryzanol as a potential intervention in obesity and muscular disorders

Rice (*Oryza sativa* L.) is a staple food for more than half of the world's population [46, 47]. Rice bran, the main by-product of polished rice, is composed mainly of the pericarp, integument, and aleurone layer, containing high nutritional value due to the presence of the essential amino acid lysine, insoluble dietary fibers, minerals, fatty acids, and approximately 94% of the phytochemical content of γOz [5, 48]. Interestingly, this by-product is often discarded or used as animal feed and is rarely intended for human consumption [49].

The γOz is a non-phenolic compound formed by the esterification of the carboxylic group of ferulic acid with the hydroxyl group of sterols (campesterol, stigmasterol, and

β-sitosterol) or triterpene alcohols (cycloartanol, cycloartenol, 2,4-methylene cycloartenol, and cyclobranol) [49]. Considered one of the most potent natural antioxidants, this steryl ferulate also exhibits anti-inflammatory, antidiabetic, hypolipidemic, and anticancer properties and has potential therapeutic applications in obesity (Table 1) [5, 47].

Sulaiman et al. reported the anti-obesity effects of γOz through the reduction of inflammatory cytokines and enhancement of antioxidant capacity [46]. Wang et al. observed that the 10-week treatment with γOz at 100 mg/kg significantly reduced the body weight, adipose tissue mass, and dyslipidemia in a high-fat-induced obesity mice model [50]. Concordantly, Sasiarini et.al. investigated the impact of 12 weeks of γOz administration (3.5 g) in a Sprague–Dawley rat model of obesity induced by a high-fat and high-fructose diet. Histological analysis revealed that γOz improved adipocyte expansion in WAT and potentially suppressed the expression of pro-inflammatory macrophages [51].

The positive metabolic impacts of this compound are evident and have already shown beneficial effects on other obesity-targeted organs, such as the liver, kidneys, heart, and cerebral amygdala (Table 1). Guo et al. fed Sprague–Dawley rats a high-fat diet with wheat flour containing γOz (0.71%/100 g) for 16 weeks. In vitro analyses of HepG2 liver cells demonstrated that dietary enrichment with γOz was able to regulate lipid and glucose metabolism by increasing the AMPK phosphorylation and the expression of AKT and PI3K, while decreasing the expressions of diacylglycerol acyltransferase 1 (DGAT1) and Stearoyl-CoA desaturase (SCD). In addition, in vivo results demonstrated that γOz was able to control body weight and improve hyperlipidemia, hepatic fat accumulation, and hyperglycemia [52].

Through innovative precision medicine techniques, Siqueira et al. evaluated the effect of a 10-week isolated treatment with 0.5% (w/w) of γOz in obese Wistar rats with nonalcoholic fatty liver disease (NAFLD) induced by a high sugar-fat diet. Their findings demonstrated that the compound prevented lipid accumulation and changes in the hepatic proteomic profile, highlighting improvements in lipid metabolism and in the redox-inflammatory state of the liver [53]. In addition to these findings, Francisqueti-Ferron et.al. (2017) demonstrated the ability of γOz to prevent multisystemic diseases, such as cardiorenal metabolic syndrome, in Wistar rats with diet induced obesity (high sugar-fat diet) supplemented with 0.5% (w/w) for 20 weeks. Its protective effects were associated with improvements in body weight, hypertriglyceridemia, glomerular filtration rate, and renal creatinine/protein ratio along with structural and functional protection of the heart [54]. Regarding the kidneys, the same authors showed that the 10-week treatment with 0.5%

Table 1 Representative table of γOz therapeutic potential

Reference	Reported model	γOz dosage	In vitro/in vivo	Organ/system	Findings
[50]	Wild type littermate male mice ($n = 20$ per group)	100 mg/Kg	In vivo	White adipose tissue	Significantly reduced body weight, WAT mass and dyslipidemia
[51]	Male Sprague–Dawley rats ($n = 7$ per group)	3.5 g	In vivo	White adipose tissue	Improved adipocyte expansion in WAT and suppressed pro-inflammatory macrophages
[52]	Male Sprague–Dawley rats ($n = 10$ per group)	0.71%/100 g	In vitro/in vivo	Liver	Increased hepatic phosphorylation of AMPK, Akt and PI3K decreased expression of DGAT1 and SCD
[53]	Male Wistar rats ($n = 6$ per group)	0.5% (w/w)	In vivo	Liver	Lower hepatic lipid accumulation, optimized lipid metabolism, improved redox/inflammatory state, and changes in the proteomic profile
[54]	Male Wistar rats ($n = 8$ per group)	0.5% (w/w)	In vivo	Cardiorenal system	Improved body weight, hypertriglyceridemia, glomerular filtration rate, and renal creatinine protein ratio along with structural and functional protection of the heart
[55]	Male Wistar rats ($n = 7$ per group)	0.5% (w/w)	In vivo	Kidney	Improvement of kidney redox-inflammatory state and modulation of the RAGE/AGEs axis
[56]	Male mice ($n = 11$ per group)	0.5% (w/w)	In vivo	Cerebral amygdala	Increased dopamine levels, along with reduced mRNA expression of TNF-α and IL-1β in the cerebral amygdala

WAT white adipose tissue, *AMPK* AMP-activated protein kinase alpha, *AKT* protein kinase, *PI3K* phosphatidylinositol-3 kinase, *DGAT1* diacylglycerol acyltransferase 1, *SCD* stearoyl-CoA desaturase, *RAGE* receptor for AGEs, *AGE* advanced glycation end products, *TNF-α* tumoral necrosis factor alpha, *IL-1β* interleukin-1 beta, *GLUT-4* glucose transporter 4

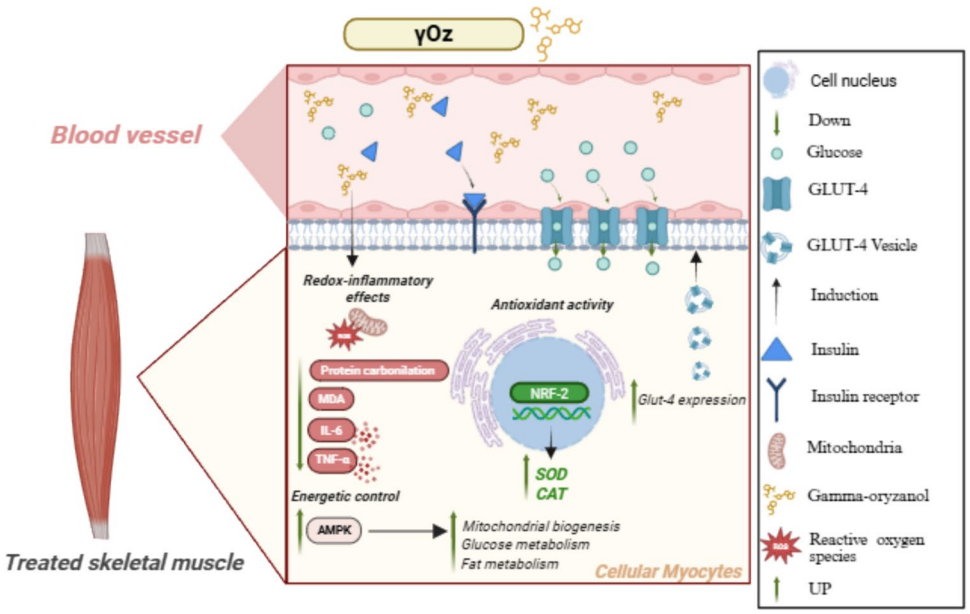

Fig. 3 Effects of γOz treatment on skeletal muscle. γOz improved the redox-inflammatory balance, enhanced antioxidant activity, GLUT-4 expression, and improved the energetic control. γOz: gamma-oryzanol; MDA: malondialdehyde; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; AMPK: AMP-activated protein kinase; NRF-2: nuclear factor erythroid 2; SOD: superoxide dismutase; CAT: catalase; GLUT-4: glucose transporter 4. Created with BioRender.com. Elaborated by the authors

(w/w) of γOz improved the renal redox-inflammatory state by modulating the receptor for advanced glycation end products (RAGE)/AGE axis [55].

Akter et al. (2020) reported that dietary supplementation with 0.5% γOz for 8 weeks alleviated high-fat diet-induced anxiety-like behaviors. Treated animals exhibited higher dopamine levels in the cerebral amygdala, along with a significant reduction in the relative mRNA expression of TNF-α and IL-1β in this same tissue [56].

Although the beneficial effects of this compound on obesity and its target organs are well documented, the literature lacks sufficient information regarding the effects of γOz on skeletal muscle. During the elaboration of this review, only one study was identified that investigated these effects on obesity-induced muscular dysfunctions. The authors reported the outcomes of the 10-week treatment with 0.5w/w γOz added to the chow of Wistar rats with obesity induced by a HSF diet. The treatment mitigated redox-inflammatory imbalance in oxidative muscle by reducing protein carbonylation, malondialdehyde levels, and inflammation through decreased TNF-α and IL-6 levels. Higher antioxidant activity of superoxide dismutase (SOD) and catalase (CAT) was also observed, along with an increase in the expression of GLUT-4. AMPK activation was proposed as a potential mechanism contributing to mitochondrial biogenesis and enhanced muscular energy control through glucose and fat metabolism (Fig. 3) [57].

Given these findings, further exploration of the effects of γOz on obesity-related muscular dysfunctions and the underlying mechanisms is both relevant and necessary.

Final considerations and conclusion

This review has highlighted the beneficial effects of natural compounds on obesity and muscle dysfunction. The evidence reviewed demonstrates that various bioactive compounds derived from natural sources, such as polyphenols, flavonoids, and other plant-derived substances, can positively influence the obesogenic state and muscle health by mitigating metabolic disturbances, inflammation, and oxidative stress. The potential of γOz intervention as a preventive and therapeutic agent in obesity-induced dysfunctions across various organs and tissues, enhancing overall metabolic balance, is remarkable. Similar benefits have been observed in skeletal muscle. Although the current findings are limited, pioneering research in this largely unexplored field is essential to elucidate how γOz can revolutionize the treatment of obesity-related muscular disorders.

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Author contribution T.L.N.P., J.S.S., C.R.C. Study conception. T.L.N.P. Data collection, Design and Wrote the main manuscript text. J.S.S. Review and editing. C.R.C. work supervision.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval Not applicable.

Competing interests The authors declare no conflict of interest.

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