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Therapeutic potential of *Moringa oleifera* Lam. in metabolic disorders: A molecular overview

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ABSTRACT

Moringa oleifera (*M. oleifera*) Lam. (family Moringaceae) possesses anti-inflammatory, anticancer, anti-diabetic, neuroprotective, and cardioprotective properties. The present review aimed to explore the protective effects of *M. oleifera* Lam. against metabolic disorders and to serve as a guide for future research on this medicinal plant. Research data on the anti-diabetic and anti-obesity properties of *M. oleifera* Lam. were collected from Science Direct, PubMed, Springer, Google Scholar, Web of Science, *etc*. *M. oleifera* has a protective effect against metabolic disorders through the modulation of various signaling pathways involved in glucose and lipid metabolism. Specifically, *M. oleifera* enhances insulin sensitivity by activating insulin receptor phosphorylation and the PI3K/Akt pathway, which promotes glucose uptake by facilitating GLUT-4 translocation to the cell membrane. In addition, it improves energy homeostasis and lipid metabolism by modulating the AMPK pathway. Inhibition of inflammatory biomarkers (nuclear factor kappa B, tumor necrosis factor-α, interleukin-1β, monocyte chemoattractant protein-1) and lipid peroxidation markers (malondialdehyde, F2-isoprostanes), along with enhanced activity of antioxidant enzymes (glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase), contributes to its anti-diabetic and anti-obesity effects. This review suggests that *M. oleifera* Lam. modulates key signaling pathways involved in glucose and lipid metabolism and holds promise as a potential therapeutic agent for managing metabolic diseases.

KEYWORDS: *Moringa oleifera*; Metabolic disease; Anti-diabetic; Antioxidant; Anti-inflammatory; Anti-obesity

1. Introduction

The incidence of chronic diseases such as obesity and diabetes mellitus is increasing worldwide[1]. The development of innovative strategies for managing and preventing diabetes in individuals with obesity is essential. The latest projections from the International Diabetes Federation estimate that 643 million people will have

Summary

Question: Can *Moringa oleifera* Lam. be an effective natural therapy for ameliorating diabetes and obesity due to its antioxidant and anti-inflammatory properties?

Findings: This review highlights preclinical and clinical findings on *Moringa oleifera*, which demonstrate its potential to reduce blood glucose, improve insulin sensitivity, and modulate various signaling pathways associated with diabetes and obesity. In addition, we present its pharmacokinetic and toxicological profiles. However, clinical studies in humans remain limited.

Meaning: *Moringa oleifera* Lam. has shown promising potential as a natural supplement for the management of diabetes and obesity; however, further clinical studies are needed to validate its efficacy and safety in humans.

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diabetes by 2030, increasing to 783 million by 2045. Interestingly, it is predicted that by 2030, 20% of women and 14% of men worldwide will have clinical obesity. The World Obesity Federation states that nations with high income and socioeconomic status are more likely to experience an increase in the prevalence of obesity[2]. Current treatments for diabetes and obesity include medications such as metformin, sulfonylureas, thiazolidinediones, glucagon-like peptide-1 agonists, and SGLT-2 inhibitors. Each of these drugs acts through distinct mechanisms to regulate blood glucose levels. Medications approved to treat obesity include orlistat, liraglutide, phentermine-topiramate, bupropion-naltrexone, semaglutide, and setmelanotide. These medications help regulate appetite, reduce fat absorption, and improve metabolic function. However, their effectiveness is often limited by adverse side effects, high costs, and suboptimal long-term outcomes. Despite their proven efficacy, conventional drugs often cause adverse side effects and may lose effectiveness over time, prompting growing global interest in alternative therapies, particularly plant-based treatments[3,4].

Moringa oleifera (*M. oleifera*) Lam., a member of the Moringaceae family, has attracted much interest because of its strong pharmacological characteristics, which include anti-obesity and anti-diabetic effects. The bioactive substances flavonoids, alkaloids, tannins, saponins, and terpenoids are abundant in *M. oleifera*, a plant native to tropical and subtropical areas, which targets important molecular pathways linked to oxidative stress, glucose metabolism, and lipid control. The ability of *M. oleifera* to improve insulin sensitivity and modulate glucose metabolism through several key signaling pathways is primarily responsible for its anti-diabetic benefits at the molecular level. It has been demonstrated that the bioactive substances of *M. oleifera*, such as flavonoids and saponins, activate AMP-activated protein kinase (AMPK), thereby lowering blood glucose levels and increasing insulin sensitivity[5]. Furthermore, it reduces oxidative stress by regulating reactive oxygen species (ROS) and activating antioxidant enzymes. These effects lead to significant changes in biomarkers such as glycated hemoglobin (HbA1c), fasting blood glucose (FBG), and glucose transporter type 4 (GLUT4). *M. oleifera* inhibits fat storage and regulates lipid metabolism through multiple pathways, thereby showing the potential to combat obesity. It promotes fat oxidation and suppresses lipid synthesis by modulating the AMPK pathway. By activating AMPK, *M. oleifera* decreases the levels of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, which are often high in obese individuals and prevents adipogenesis, *i.e.*, the production of new fat cells. Additionally, *M. oleifera* regulates the expression of key enzymes involved in lipid metabolism-related enzymes such as lipoprotein lipase, improving lipid profiles and reducing fat accumulation in the coronary arteries[6]. The low pharmacokinetics and bioavailability of *M. oleifera* phytoconstituents limit their clinical effectiveness. Recent advancements in nanotechnology have addressed these issues, enhancing the stability, bioavailability, and effectiveness of *M. oleifera* extract nanoformulations[7,8]. The primary objective of this review was to summarize the anti-diabetic and anti-obesity potential of *M. oleifera* Lam. This review highlights how a deeper understanding of the molecular aspects of *M. oleifera* can advance the development of more effective, versatile alternative therapies for metabolic diseases. This review also discusses the toxicological and pharmacokinetic aspects of *M. oleifera* Lam.

2. Insights into the pharmacokinetics of *M. oleifera*

Patel *et al*. reported that *M. oleifera* pods significantly increased plasma rifampicin levels in mice. The active portion of *M. oleifera* pods inhibits the cytochrome P-450 enzyme and improves intestinal blood flow *via* niazirine, a compound from *M. oleifera*. The area under the curve (AUC), maximum concentration (C_{max}), and half-life ($t_{1/2}$) of rifampicin increased, indicating improved systemic availability and reduced metabolism of the drug[9]. Thirteen secondary metabolites were isolated from methanol extracts of *M. oleifera* leaves. While they showed no cytotoxicity at the tested concentrations, they significantly inhibited the CYP3A4 enzyme, a key regulator of drug metabolism. These findings suggest that *M. oleifera* may not only have strong anticancer potential but could also affect drug interactions due to its impact on CYP3A4 activity[10]. The pharmacokinetics and tissue distribution of gastrodigenin-rhamnopyranoside, a hepatoprotective compound isolated from *M. oleifera* seeds, demonstrated excellent specificity and stability, along with remarkable hepatoprotective effects both *in vitro* and *in vivo*[11]. Twelve bioactive compounds were identified from naturally ripened, dry methanolic pod extracts of *M. oleifera* using GC-MS, supported by *in silico* ADMET analysis. Among them, 7-octadecyl (M1) and γ-tocopherol (M8) showed favorable gastrointestinal absorption, improved pharmacokinetic properties, limited blood-brain barrier permeability, and inhibition of various CYP enzymes[12]. Mishra and Talapatra conducted molecular docking studies with anthraquinone, serpentine, and niazirine isolated from *M. oleifera* and reported a strong binding affinity of anthraquinone with receptor B (PDB ID: 3EKN). Serpentine and niazirine showed favorable binding energies with receptor A (PDB ID: 3EKK) and competitive affinities with synthetic drugs such as metformin and glibenclamide. ADME predictions revealed that all compounds, except glibenclamide and serpentine, exhibited significant gastrointestinal absorption. Niazirine exhibits high bioavailability, reflecting favorable pharmacokinetic properties. However, unlike other drugs that can cross the blood-brain barrier, niazirine and its derivatives are unable to do so. The study revealed variations in solubility and lipophilicity among the compounds, with serpentine exhibiting optimal values

for enhanced bioavailability[13]. Aqueous extracts of *M. oleifera* leaves were studied in rats using an HPLC-MS method to analyze specific plasma compounds. The results showed that peak levels of each biomarker were reached within 30 minutes, indicating rapid absorption into the bloodstream. Among the compounds, vicenin-2 and cryptochlorogenic acid achieved higher plasma concentrations compared to the others. The short elimination half-lives observed for most compounds suggest rapid clearance from the body. Additionally, the biphasic peak phenomenon observed with compounds such as vitexin and vicenin-2 suggests possible interactions, underscoring the complexity and therapeutic potential of these extracts[14]. *M. oleifera* supplementation was shown to be safe and well tolerated in adult HIV patients when co-administered with nevirapine. Pharmacokinetic analysis revealed no significant changes in nevirapine's AUC, C_{max}, or 12-hour concentrations. However, a notable interaction between *M. oleifera* and amodiaquine (AQ) was observed, leading to altered pharmacokinetics and increased plasma levels of its active metabolite, desethyl amodiaquine (DEAQ) [15]. Supplementation with *M. oleifera* alongside AQ resulted in an increased T_{max} for both AQ and its active metabolite, DEAQ. Additionally, there was a significant decrease in AQ's C_{max} (P=0.04) and a slight reduction in its AUC. Pretreatment with *M. oleifera* also delayed the T_{max} for both DEAQ and AQ, suggesting that moringa may enhance CYP2C8 activation, potentially accelerating AQ metabolism to DEAQ. This could lead to slower elimination and an increased risk of toxicity. This interaction with CYP isoenzymes, particularly CYP2C8, may impact the efficacy and safety of AQ treatment[16].

3. Toxicological studies of *M. oleifera*

Acute toxicity assessments demonstrated that *M. oleifera* extract is safe at doses of up to 2 000 mg/kg. However, subacute toxicity studies suggest that prolonged or higher doses (1 600 mg/kg) may lead to hematological and biochemical alterations, potentially impacting liver and kidney function. Risks include anemia and changes in immunological markers, body weight, and other health indicators[17]. While *M. oleifera* offers various health benefits, determining the appropriate dosage and duration of use is crucial to avoid potential adverse effects. The liver stress may be indicated by elevated liver enzymes such as aspartate transaminase (AST) and alanine aminotransferase (ALT), while total protein, albumin, and globulin levels typically remain constant. Low doses of methanolic extract from *M. oleifera* seeds show no immediate side effects. However, a lethal dose (LD_{50}) of approximately 3 873 mg/kg in rats leads to signs of toxicity at higher concentrations, with notable effects occurring at 1 600 mg/kg[18]. Prolonged use may result in kidney and liver damage, as indicated by significant changes in liver and kidney function markers (P<0.05). Therefore, caution is recommended during extended use[19]. According to a previous acute toxicity study, high doses of aqueous extracts of *M. oleifera* leaves up to 1 000 mg/kg in mice do not produce major toxic effects or organ damage, indicating that they are safe for long-term use. No significant differences in growth, food intake, or general health status were observed between the treated animals and the control groups, and the hematological measurements remained stable in both groups[20]. *M. oleifera* root extracts have been shown to exhibit dose- and time-dependent toxicity in guinea pigs, causing irreversible kidney damage and reversible liver damage at elevated doses (7 000 mg/kg)[21]. Ouédraogo *et al*. reported that *M. oleifera* protects against gentamycin-induced nephrotoxicity by normalizing elevated creatinine and blood urea levels. These findings reveal that the ethanolic extract of *M. oleifera* leaves promotes kidney function and regeneration while exhibiting minimal or no toxicity in rabbits at doses up to 5 000 mg/kg. The combined histological and biochemical investigations suggest that the co-administration of *M. oleifera* and gentamicin may mitigate tissue damage by reducing lipid peroxidation. Research has shown that the oral toxicity (LD_{50}) of *M. oleifera* dry leaf powder is up to 2 000 mg/kg, without causing significant pathological changes or clinical symptoms at this dose[22]. The cytotoxic and anti-inflammatory properties of both aqueous seed extracts (50 μg/mL) and the coagulant *M. oleifera* lectin indicate potential cytotoxicity toward peripheral blood mononuclear cells; however, this effect was not observed with diluted extracts[23]. The ethanolic extract of *M. oleifera* leaves (250-2 000 mg/kg) exhibited significant central nervous system depressant effects in addition to sedative, anxiogenic, and mild anticonvulsant effects. Sedation was evidenced by prolonged pentobarbitone-induced sleep, while the anxiogenic effects suggest a potential exacerbation of anxiety symptoms. These changes may be related to the modulation of neurotransmitter systems such as dopamine, gamma-aminobutyric acid, and serotonin (5-HT), potentially leading to seizures and behavioral changes[24]. The oral administration of the methanolic extract of *M. oleifera* bark did not produce significant acute or subacute toxicity in mice. No abnormalities were observed in behavior, body weight, organ weight, or hematological or biochemical parameters, even at doses up to 2 000 mg/kg body weight over 14 days. This highlights the relative safety of the extract at the dosage evaluated[25]. However, the 80% methanolic extract of *M. oleifera* (2 000-3 000 mg/L) leaves may induce toxicity in HepG2 cells by reducing cell viability through potential oxidative stress pathways. This finding reinforces the need for careful dosing when *M. oleifera* is used for health benefits, as lower concentrations may increase antioxidant effects, and higher doses could be harmful[26]. Ibrahim *et al*. investigated the lethal dose and toxicological implications of *M. oleifera* in rabbits and rats. The results revealed that better tolerance was observed in rabbits than in rats when a high

lethal dose of 6616.67 mg/kg body weight was given to the rats and 26043.67 mg/kg body weight was given to the rabbits. *M. oleifera* at high doses is associated with severe toxicity and organ damage, although lower doses of 1000 mg/kg appear to be typically harmless. The observed symptoms and histological changes highlight the importance of precise dosing to avoid adverse consequences. Following acute administration of lethal doses, subjects experienced symptoms including reduced body temperature, diminished activity and consciousness, and blurred vision, all of which progressively worsened over time. Both rats and rabbits showed similar response patterns, including significant reductions in various health parameters[27]. *M. oleifera* leaf extract (MLE) and seed extracts (MSEs) were tested for toxicity in rats in a study conducted by Ilyas *et al*. Acute dosages of up to 2200 mg/kg were safe and did not cause any mortality. Hematological and metabolic indicators remained largely unchanged following subacute dosing (600-1800 mg/kg) for 21 days; however, a reduction in food intake and body weight was observed. There was a modest reduction in mean corpuscular hemoglobin, red blood cell count, and hemoglobin levels, possibly due to mild hemolysis. Although prolonged high dosages may cause a risk of nephrotoxicity, no definitive liver or kidney damage has been observed. Because of its higher protein content, MSE results in greater weight reduction compared to MLE; however, both are deemed safe for medical use[28]. Methanolic MLE (2000 mg/kg) is considered safe and does not cause significant adverse effects. Although a marked increase in AST levels indicates potential cellular damage, no discernible rise in ALT indicates that liver damage is likely minimal. Elevated AST levels may also reflect injury to other tissues, such as the heart or muscles. Furthermore, the absence of significant differences in bilirubin levels between the treatment and control groups suggests that the extract does not induce notable hemolysis[29]. Gao *et al*. examined the effect of MLE on metabolic adaptation and gut microbiota in mice. After eight weeks of supplementation at a dose of 750 mg/kg body weight, mild abnormalities in intestinal and liver function were observed, leading to increased inflammation and compromised integrity of the intestinal barrier[30]. The safety of hydroalcoholic MSE enriched with moringa isothiocyanate-1 was evaluated in a 14-day oral toxicity study in rats. Mortality in the highest dose group (2571 mg/kg body weight/day) was associated with reduced body weight and decreased food intake. The medium- and high-dose groups exhibited the most clinical symptoms, including piloerection and irregular breathing. Non-surviving animals in the high-dose group showed signs of stomach discoloration, gastrointestinal distension, and testicular/epididymal cell degeneration. Additionally, females in the medium- and high-dose groups displayed increased liver weight. No adverse effects were observed in the low-dose (78 mg/kg body weight/day) or medium-dose (772 mg/kg body weight/day) groups. No adverse effects were observed with hydroalcoholic MSE extract at 257 mg/kg body weight/day, corresponding to a moringa isothiocyanate-1 dose of 100 mg/kg body weight/day[31]. *M. oleifera* does not cause cytotoxicity at lower concentrations (12.5, 25, 50, and 100 μg/mL); however, it becomes toxic at higher concentrations, such as 200 μg/mL[32]. In addition, 1-*O*-(4-hydroxymethylphenyl)-α-*L*-rhamnopyranoside, a phenolic glycoside isolated from MSE, demonstrated safety and biocompatibility in acute oral toxicity tests. According to research conducted *in vitro* (10, 50, and 100 mg/mL) and *in vivo* (50, 100, and 150 mg/kg), 1-*O*-(4-hydroxymethylphenyl)-α-*L*-rhamnopyranoside effectively protects against liver damage caused by CCl_4 by lowering oxidative stress, enhancing antioxidant systems, and modifying inflammatory mediators and apoptosis[33]. Chin *et al*. evaluated the safety of a film containing 0.1%, 0.5%, and 1% MLE through toxicity testing. They discovered that the 0.5% formulation considerably accelerated wound healing in streptozocin (STZ)-induced diabetic rat models without causing cutaneous toxicity. The extract demonstrated strong potential for treating diabetic wounds, as evidenced by improved wound closure, collagen deposition, and re-epithelialization. According to the study, the LD_{50} for hydroalcoholic *M. oleifera* exceeded 2000 mg/kg, with no signs of mortality or morbidity observed during the 14-day monitoring period. No adverse effects were reported at this dose. Repeated oral dosages of 250, 500, and 1000 mg/kg hydroalcoholic *M. oleifera* extract over 28 days showed no signs of toxicity or mortality. Additionally, no significant differences were observed in food and water intake or organ weights between the treated and control groups[34]. No signs of toxicity or mortality were observed in rats after 12 weeks of treatment, indicating that the LD_{50} of the aqueous extract of *M. oleifera* leaves exceeds 5000 mg/kg body weight[35]. Aliyu *et al*. investigated the acute and sub-acute hepato-nephrotoxicity of hydroalcoholic MLE administered orally at doses of 125, 250, 500, 1000, and 2000 mg/kg in ICR mice. Chemical profiling of the extract confirmed the presence of major phytoconstituents, including glucomoringin, niaziminin, quercetin, and kaempferol. In the acute toxicity study, treated mice exhibited mild anemia. Additionally, slight elevations in biochemical markers such as creatinine, AST, and creatine kinase were observed, along with histopathological evidence of mild to moderate hepato-nephrotoxicity, including hepatic degeneration, renal tubular necrosis, interstitial nephritis, and edema. Based on these findings, the LD_{50} of MLE is estimated to be greater than 2 g/kg[36]. Both the protein concentrate fraction and the extract from *M. oleifera* leaves-rich in flavonoids, lectins, and trypsin inhibitors-exhibited no evidence of cytotoxicity, hemolysis, or genotoxicity when administered at a dose of 2000 mg/kg[37]. Kilany *et al*. investigated the cardioprotective effects of *M. oleifera* against cisplatin-induced cardiac damage in rats. Their findings showed that pretreatment with ethanolic extracts of *M. oleifera* at a dose of 250 mg/kg and 500 mg/kg improved cardiac function and oxidative stress indicators. Additionally, the extract exerted a dose-dependent effect in

normalizing the altered lipid profile and restoring histological features[38]. Silva *et al*. evaluated the toxicity of an aqueous MLE following repeated oral administration at doses of 250, 500, and 1 000 mg/kg over 13 weeks. The treatment did not initially affect body weight or food and water consumption. However, from the 7th week onward, higher doses were associated with reduced food intake and body weight, as well as elevated transaminase levels. Additionally, a significant reduction in lipid parameters was observed across all treatment groups, while hematological and histological parameters remained unchanged. These findings suggest that caution is warranted when administering doses above 500 mg/kg of the optimized extract[39]. Kim *et al*. investigated the protective effects of *M. oleifera* on ethanol-induced hepatic steatosis. *M. oleifera* extracts, administered at doses of 100, 200, and 400 mg/kg, significantly reduced serum levels of AST, ALT, and triglycerides (TGs). Histological and immunohistochemical analyses revealed a marked reduction in hepatic steatosis, evidenced by decreased lipid droplet accumulation and TNF-α expression. Additionally, *M. oleifera* mitigated ethanol-induced oxidative stress, as assessed through H_2DCFDA and JC-1 staining, while enhancing antioxidant defenses, including increased levels of glutathione (GSH) and nuclear factor erythroid 2-related factor 2 (Nrf2). Furthermore, SPECT imaging showed improved liver function, with higher liver uptake values in the treated groups. These findings suggest that *M. oleifera* extract holds promise in preventing ethanol-induced liver damage[40].

4. Insights into the metabolic effects of *M. oleifera*

4.1. *M. oleifera* in diabetes mellitus: Evidence from preclinical studies

M. oleifera and its leaf extracts have shown anti-diabetic activity by decreasing oxidative and inflammatory markers such as malondialdehyde (MDA), peroxisome proliferators-activated receptors γ (PPAR γ), TNF-α, IL-6, and IL-1β, and by increasing the levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in STZ/alloxan-induced diabetic animal models[41–43]. In addition, they modulate the enzymes involved in carbohydrate and lipid metabolism, as well as kidney functional parameters[44–47]. Furthermore, they exhibit anti-diabetic potential by enhancing serum lipoprotein lipase activity and regulating metabolic biomarkers such as glucose transporter type (GLUT)-1, GLUT-4, G6PD, and AMP-kinase[48]. *In silico* analysis revealed that *M. oleifera*-derived phytochemicals, piceatannol, and vanillic acid, exhibit strong binding affinities to the DPP-4 enzyme (–7.9 and –5.7 kcal/mol), suggesting their potential as natural inhibitors for the management of type 2 diabetes mellitus (T2DM)[49]. In alloxan-induced type 1 diabetic mice, both unfermented and fermented ethanolic extracts of *M. oleifera* leaves significantly reduced FBG levels and restored 26%-50% of pancreatic β-cell populations. This effect was associated with a decrease in oxidative and inflammatory markers, such as MDA, NO, protein carbonyl, TNF-α, IL-1α, IL-12, IL-18, and an increase in antioxidant defenses, such as CAT, SOD, GPx, GSH, total antioxidant capacity, with comparable effects observed between the two extracts[50,51]. Additionally, in a pregnant diabetic model, *M. oleifera* leaf powder significantly reduced blood glucose and blood pressure, indicating its potential in managing type 1 diabetes mellitus-associated hypertension[52].

Dietary powders derived from *M. oleifera* leaves and seeds significantly restored erectile function markers in STZ-induced diabetic models by downregulating key enzymes such as PDE-5, arginase, acetylcholinesterase, monoamine oxidase, angiotensin converting enzyme, and adenosine deaminase and arginase, while also reducing NO and thiobarbituric acid reactive substances (TBARS) levels. Furthermore, *M. oleifera* leaf supplementation was shown to reduce DNA damage in parotid gland cells[53,54]. *In vitro* assays revealed that *M. oleifera* flowers exhibit antioxidant and enzyme-inhibitory activities, suggesting their therapeutic potential in mitigating oxidative stress and hyperglycemia[55]. Both ethanolic and aqueous extracts of *M. oleifera* leaves ameliorated STZ-induced diabetic nephropathy by suppressing inflammatory markers (inducible nitric-oxide synthase, nuclear factor kappa, IL-1β, IL-6), fibrotic markers (transforming growth factor-β1, collagen Ⅳ), and oxidative stress indicators (MDA, advanced glycation end-products). The extracts also enhanced antioxidant defenses (SOD, CAT), improved glucose tolerance and body weight, and reduced renal dysfunction parameters, including proteinuria, albuminuria, blood urea nitrogen, creatinine, and urea nitrogen[56,57].

Topical application of methanolic MLE showed potent antioxidant and wound-healing effects in STZ-induced diabetes. These effects were mediated through the upregulation of vascular endothelial growth factor and transforming growth factor-β1 signaling pathways, along with enhanced activity of antioxidant enzymes such as SOD and CAT, helping to combat oxidative damage[58]. In STZ-induced T2DM rats, MLE enhanced endogenous antioxidant enzyme activity and significantly reduced TBARS levels, indicating decreased oxidative stress[59]. In type 1 diabetes mellitus models, the extract also exhibited protective and regenerative effects by increasing cellular height and reducing proliferating cell nuclear antigen expression and tissue degeneration[60]. *M. oleifera* leaf powder exhibited strong antihyperglycemic and antioxidant activity in *Drosophila melanogaster* models of T2DM. It significantly reduced levels of glucose, low density lipoprotein (LDL), TG, MDA, ROS, TBARS, monoamine oxidase, acetylcholinesterase, α-amylase, and α-glucosidase. Additionally, it elevated high density lipoprotein (HDL), GSH, SOD, CAT, and glutathione-S-transferase (GST) levels, indicating improved metabolic regulation, oxidative balance,

and enzymatic homeostasis[61,62]. In STZ-induced diabetic rats, *M. oleifera* leaf supplementation attenuated cognitive decline by lowering blood glucose and pro-inflammatory cytokines (TNF-α, IL-6), reducing neuronal apoptosis markers (Bax, Caspase-3), and enhancing insulin and Bcl-2 levels[63]. Meanwhile, seed extract rich in moringa isothiocyanate-1 and moringin promoted oxidative resilience in *Caenorhabditis elegans* by extending lifespan, upregulating GSTs and GPx-3, and activating the SKN-1/Nrf2 pathway, underscoring *M. oleifera*'s systemic therapeutic potential in diabetes and its complications[64].

Aqueous MLE lowered blood glucose, hepatic and renal injury markers [ALT, AST, alkaline phosphatase (ALP), urea], and tissue oxidative-stress markers (H_2O_2, MDA, protein carbonyl) while enhancing antioxidant defenses and GLUT-4 expression, thereby alleviating pancreatic- and hepatic-lesions in STZ-induced diabetes[65]. Extracts from various parts of *M. oleifera* have demonstrated anti-diabetic activity by reducing blood glucose, TG, LDL, and MDA levels while increasing HDL, SOD, CAT, and GSH levels in alloxan-induced diabetic models[66–68]. Additionally, *M. oleifera* protects kidney function in rats with diabetic nephropathy by enhancing GSK-3β activity and activating the Nrf2/HO-1 pathway[69]. A meta-analysis by Watanabe *et al*. reported a significant reduction in blood sugar, total cholesterol (TC), and TG levels in diabetic mice treated with *M. oleifera* extracts. These results suggest that *M. oleifera* may be a promising candidate for the treatment and prevention of diabetes and dyslipidemia in humans[70]. The combined effects of various *M. oleifera* extracts in alloxan-induced diabetic mice showed that the combination of methanolic extracts from *Moringa* leaves and seeds significantly lowered TC and TG levels, improved kidney and liver function markers, and normalized blood glucose levels more effectively than either extract alone[71]. Zhao *et al*. investigated the combined effects of rosiglitazone and aqueous MLE on lipid and glucose metabolism in a rat model of T2DM. Their findings showed that the combination significantly reduced serum leptin levels and improved glucose and lipid profiles more effectively than rosiglitazone alone. These effects were associated with the activation of the Akt/GSK3β/β-catenin signaling cascade, indicating the therapeutic potential of this combination[72].

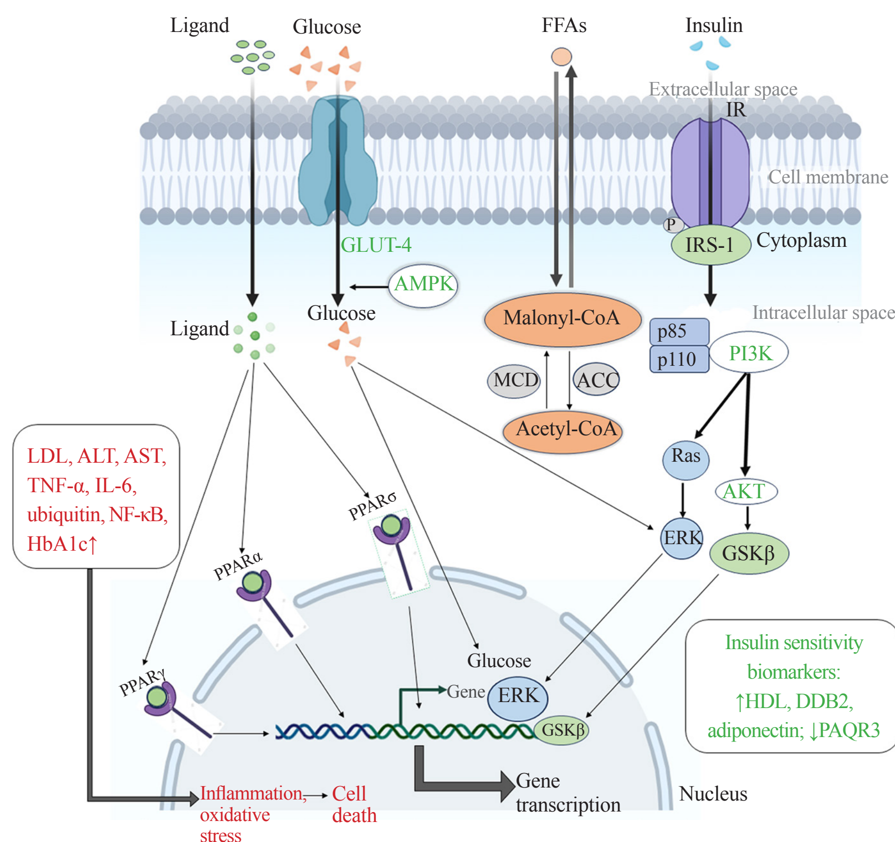

Figure 1. The molecular aspects of *Moringa oleifera* (*M. oleifera*) in diabetes. The molecular mechanisms of *M. oleifera* in diabetes mellitus involve the modulation of key biomarkers. Green-colored biomarkers indicate an increase in the expression or activity of factors that help reduce hyperglycemia, while red-colored biomarkers represent diabetogenic factors whose levels are suppressed by *M. oleifera* to alleviate the condition. FFA: Free fatty acid; IR: Insulin resistance; IRS-1: Insulin receptor substrate-1; GLUT: Glucose transporter type; AMPK: AMP-activated protein kinase; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B (also known as Akt); LDL: Low-density lipoprotein; ALT: Alanine transaminase; IL-6: Interleukin-6; AST: Aspartate transaminase; TNF-α: Tumor necrosis factor-α; NF-κB: Nuclear factor kappa B; HDL: High-density lipoprotein; GSK3β: Glycogen synthase kinase 3 beta; PPAR: Peroxisome proliferator-activated receptor; ERK: Extracellular signal-regulated kinase; CoA: Coenzyme A; MCD: Malonyl coenzyme A decarboxylase; ACC: Acetyl coenzyme A carboxylase; DDB2: Damage specific DNA binding protein 2; PAQR3: Progestin and adipoQ receptor family member 3.

Table 1. Molecular aspects of *Moringa oleifera* (*M. oleifera*) in preclinical studies of diabetes, obesity, and metabolic syndrome.

Parts used	Disease	Animal model / Assay method	Extract type	Cell line/animal	Dose and duration	Molecular aspects	Ref
Leaves	T1DM	Alloxan-induced diabetes	Aqueous extract	Wistar rats	200, 400, and 800 mg/kg for 28 days	↓ FBG, urea, and creatinine level ↔ BW and histopathology of liver, kidney, and pancreas ↑ SOD, GPx, CAT ↓ AST, ALP, ALT, TB	[41]
Leaves	T2DM	STZ-induced diabetes	Ethanolic extract	Wistar rats	200-400 mg/kg for 21 days	↓ Insulin levels ↓ Blood glucose level, DPP-Ⅳ ↓ PPARγ, IL-6, IL-1β, and TNF-α	[42]
Leaves	T2DM	STZ-induced diabetes	Aqueous extract	Wistar rats	800 mg/kg for 4 weeks	↓ FBG	[43]
Leaves	T2DM	STZ-induced diabetes	Ethanolic extract	Albino rats	250 and 500 mg/kg for 4 weeks	↓ Fasting serum glucose, TG, TC, LDL-C ↑ SOD, GSH, CAT, HDL-C ↓ MDA ↑ BW, serum insulin The architecture of the liver and pancreas is maintained	[45]
Leaves	T2DM	STZ-induced diabetes	Dietary leaf powder with oral zinc sulfate	Wistar rats	3% *M. oleifera* leaf supplemented in diet and 100 mg/kg oral zinc sulfate for 6 weeks	↓ FBG, TG, LDL-C ↔ TC ↑ HDL-C	[46]
Leaves	T2DM	STZ-induced diabetes	Aqueous extract	Wistar rats	500 mg/kg/day for 4 weeks	↓ Serum glucose, LDL, TG, MDA, and BW ↑ HDL, insulin level, β-cell function, GSH	[47]
Leaves	T2DM	STZ-induced diabetes	Methanolic extract (fraction 1-5)	Albino rats	500 mg/kg for 28 days	↓ FBG, α-amylase ↑ Serum lipo-protein lipase, GLUT-1 and GLUT-4 ↑ G6PD and AMPK	[48]
Leaves	T1DM	Alloxan-induced diabetes	Unfermented ethanolic and fermented crude extracts	*In vitro* and mice	200 mg/kg body weight for 2 weeks	↓ FBG and ↔ between unfermented *vs.* fermented extract; 26%-50% regeneration of β-cells ↓ MDA, NO, PC, IL-1α, IL-12, IL-18 ↑ CAT, SOD, GPx, GSH, TAC	[50]
Leaves	T1DM & Hypertension	Alloxan-induced pregnant diabetes	Powder	Wistar rats	200 mg/kg and 400 mg/kg	↓ Blood glucose and blood pressure	[52]
Leaves	T2DM	STZ-induced diabetes	Extract	Male albino rats	200 mg/kg for 3 weeks	↓ Blood glucose ↔ BW ↓DNA damage in parotid gland cells	[54]
Leaves	Diabetic nephropathy	STZ-induced diabetes	Ethanolic extract	Wistar rats	100 mg/kg for 8 weeks	↓ iNOS, NF-κB, IL-1β, IL-6, AGEs ↓ Total protein, creatinine, uric acid, and urea nitrogen ↑ Glucose tolerance, BW	[56]
Leaves	Diabetic nephropathy	STZ-induced diabetes	Aqueous extract	Sprague-Dawley rats	100 and 200 mg/kg for 8 weeks	↓ TGF-β1 and collagen type Ⅳ ↓ MDA ↑ SOD, CAT ↓ Proteinuria, and albuminuria, BUN, CCr	[57]
Leaves	Diabetic wound healing & antioxidant activity	STZ-induced diabetes	Methanolic extract	Wistar rats	10% *w/w* and 20% *w/w* ointment for 20 days	↑ VEGF and TGF-β1 proliferative activity, SOD & CAT	[58]
Leaves	T2DM	STZ-induced diabetes	Hydroalcoholic extract	Wistar rats	500 mg kg for 45 days	↑ CAT, SOD and GST ↓ TBARS	[59]
Leaves	T1DM	STZ-induced diabetes	Aqueous extract	Albino rats	250 mg/kg for 4 weeks	↑ Cellular height ↓ PCNA, degeneration	[60]

Table 1. Molecular aspects of *Moringa oleifera* (*M. oleifera*) in preclinical studies of diabetes, obesity, and metabolic syndrome (continued).

Parts used	Disease	Animal model/ Assay method	Extract type	Cell line/animal	Dose and duration	Molecular aspects	Ref
Leaves	T2DM	Hetero allelic mutant of insulin receptor gene of *Drosophila melanogaster*	Leaf powder	*Drosophila melanogaster* (Fruit fly)	0.5%, 1.5%, 2.5%, 4.0%, and 5.5% for 5 days	↓ Serum glucose, LDL, TG, MDA ↑ HDL, GSH	[61]
Leaves	T2DM	15% and 30% sucrose induced diabetes	Powder	*Drosophila melanogaster* (Fruit fly)	1% *w/v* for 14 days	↓ α-amylase and α-glucosidase, ROS, TBARS ↓ Glucose, TG, MAO, acetylcholin esterase activity ↑ SOD, CAT, GST	[62]
Leaves	Diabetes-induced cognitive impairment	STZ-induced diabetes	Moringa leaves	Sprague-Dawley rats	2.0, 4.0, and 8.0 g for 8 weeks	↓ Blood glucose ↑ Blood insulin, BCl-2 ↓ Neuronal apoptosis (Bax, Caspase 3, Bax/BCl-2), TNF-α, IL-6 ↔ FBG, fasting insulin	[63]
Leaves	T2DM	STZ-induced diabetes	Lyophilized aqueous extract	Albino rats	100 mg/kg BW for 14 days	↓Blood glucose, MDA, PC levels ↓ ALT, AST, ALP, urea, albumin ↑ SOD, GSH, GST, GLUT4	[65]
Leaves	T1DM	Alloxan-induced diabetes	Aqueous extract	Albino rats	200 mg/kg for 15 days	↓ Blood glucose level	[67]
Leaves	T2DM	STZ-induced diabetes	Aqueous extract	Male Sprague-Dawley rats	200 mg/kg for 8 weeks	↓ FBG, FINS, FFA, TNF-α ↓ Serum leptin level ↑ Akt, GSK3β, β-catenin level	[72]
Leaves	T2DM, nonalcoholic fatty liver	High-lipid diet model	Infusion and ethanolic extract	BALB/c mice	500 mg/kg/day for 2 months	↓ SGPT, SGOT, lipid profiles, urea and glucose levels	[73]
Leaves	T2DM	Polysaccharide fermentation model (STC-1 cells)	Isolated polysaccharide from *M. oleifera* (MOP-3) rich in arabinose, rhamnose, and galactose	STC-1 cells	MOP-1: 0.2 mol/L MOP-2: 0.4 mol/L MOP-3: 0.8 mol/L	↑ SCFA production, GLP-1 secretion in STC-1 cells	[104]
Leaves	T2DM	Alpha-amylase inhibition assay	Silver nanoparticles	*In vitro*	20-100 µL	Inhibit α-amylase	[108]
Leaves & seeds	T2DM & erectile dysfunction	STZ-induced diabetes	Powder	Wistar rats	2% and 4% with or without acarbose for 14 days	↓ PDE-5, arginase, AChE, MAO, ACE, ADA ↓ NO, TBARS	[53]
Leaves & seeds	T1DM	Alloxan-induced diabetes	Methanolic extract	Swiss albino mice	500 mg/kg BW/ day for 1-3 months	↓ Blood glucose, TC, TG, creatinine ↑ GSH, CAT ↓ MDA, NO, PC	[71]
Seeds	Diabetic nephropathy	High-fat feed with STZ-induced diabetes	Ethanolic extract	Wistar rats	50, 100 &200 mg/kg for 4 weeks	↑ Nrf2/HO-1, SOD, and p-GSK-3β levels ↓ Oxidative stress, blood glucose, BUN, proteinuria, serum creatinine ↑ Serum insulin	[69]
Seeds	Diabetic nephropathy	High-glucose induced human renal mesangial cells	Ethanolic extract	Human renal mesangial cells	80 µg/mL; 100 µg/mL; 200 µg/mL	↓ Proliferation of human renal mesangial cells	[69]
Seeds	T2DM	C2C12/IR and high-fat diet with STZ-induced diabetes	Peptide MoHpP-2	*In vitro* and *in vivo*	50 mg/kg body weight for 10 weeks	↓ Blood glucose, bile acid formation, and IR ↑ CAT, SOD, GPx, GSH, unsaturated fatty acid synthesis; ↑ Glucose consumption and TAC	[105]
Seeds & Cassava	T1DM	Alloxan-induced diabetes	Fermented moringa seed-cassava inclusion	Albino rats	80%:20% for 3 weeks	↓ FBG, MDA, TC, TG, LDL-C; ↑ GSH, SOD, CAT	[66]

Table 1. Molecular aspects of *Moringa oleifera* (*M. oleifera*) in preclinical studies of diabetes, obesity, and metabolic syndrome (continued).

Parts used	Disease	Animal model/ Assay method	Extract type	Cell line/animal	Dose and duration	Molecular aspects	Ref
Flower	Antioxidants and enzymes in carbohydrate metabolism	DPPH, hydroxyl (OH˙), and hydrogen peroxide (H_2O_2) free radicals, as well as FRAP, α-amylase and α-glucosidase inhibition assay	Ethanolic extract	*In vitro*	DPPH (10-50 mg/mL) FRAP and ˙OH (100 mg/g sample) α-amylase (1-5 mg/mL) α-glucosidase (1-5 mg/mL)	↓ DPPH ↓ OH˙ activity ↓ H_2O_2 activity ↓ α-amylase and α-glucosidase	[55]
Leaves and albumin	T1DM	STZ-induced diabetes	*M. oleifera* leaves extract- albumin	BALB/c mice	800 mg/kg *M. oleifera*+615 mg/kg albumin for 14 days	↓ TNF-α and IFN-γ	[51]
Leaves, seeds & pods	T1DM	Alloxan-induced diabetes	30% ethanolic extracts	Wistar rats	200, 300 mg/kg for 4 weeks	↓ FBG	[44]
Leaves, flowering buds, and stem bark	T1DM	Alloxan-induced diabetes	Methanolic extract	Albino mice	500 mg/kg for 15 days	↓ Blood glucose, α-glucosidase	[68]
Whole plant	Obesity and T2DM	High-fat diet with STZ-induced diabetes	Methanolic extract	Wistar albino rats	500 mg/kg for 12 weeks	↓ Body and liver weights ↓ Plasma glucose level, IL-1β, TNF-α, COX-2 ↑ IL-10, IL-6	[75]
Leaves	Obesity	High-fat diet-induced obesity	Ethanolic extract	Male albino rats	200 mg/kg and 400 mg/kg for 1 month	↑ *MC4R* and *PPAR–α* mRNA expression ↓ *FAS* and *HMG–CoA reductase* mRNA	[76]
Leaves	Obesity	Pancreatic lipase inhibition assay	Ethanolic extract	3T3-L1	400 µg/mL	↓ PPARγ, C/EPB-α, PI3K, p-Akt, and FAS enzyme ↓ Adiponectin ↓ Lipase, TG accumulation in 3T3-L1 cells	[82]
Leaves	Obesity	Diet-induced obesity	*M. oleifera* oil extract	Albino Wistar rats	400 mg/kg for 4 weeks	↓ BW, TC, TG, LDL-C, VLDL ↔ Testosterone levels ↑ HDL, FSH, LH ↓ iNOS, sperm abnormality ↑ CAT, SOD and GSH ↓ MDA	[83]
Leaves	Obesity	High-fat diet-induced obesity	Aqueous extract	Wistar rats	1 mg/g for 30 days	↓ Serum, kidney, and liver cholesterol ↔ serum total protein ↑ Serum albumin	[84]
Leaves	Obesity	High-fat diet-induced obesity	Ethanolic extract	Albino rats	300 mg/kg for 8 weeks	↓ MDA, degenerative alterations in the kidney sections ↑ GSH, TAC, SOD, CAT, GSH-Px, GSH-reductase	[85]
Leaves	Obesity	C57BL/6J mutant model	Petroleum ether extract	3T3-L1 adipocytes; High-fat diet mice	400 µg/mL for 24 h and 0.5 g/kg body weight for 14 weeks	↑ AMPK ↓ TG, TC, AST, LDL-C ↑ HSL, ATGL	[97]
Seeds	Obesity	High-fat and high-fructose diet	Seed extract	Wistar rats	150, 200 mg/kg for 28 days	↓ Glomerular volume ↑ SOD in the kidney tubules and glomeruli ↔ Body weight, TG ↓ Blood glucose, serum creatinine	[87]

Table 1. Molecular aspects of *Moringa oleifera* (*M. oleifera*) in preclinical studies of diabetes, obesity, and metabolic syndrome (continued).

Parts used	Disease	Animal model/ Assay method	Extract type	Cell line/animal	Dose and duration	Molecular aspects	Ref
Fruit	Obesity	2-Nitropropane induced model	Ethanolic extract	Swiss obese male mice	BW once a day for 10 weeks	↓ MDA, 8-OHdG, SGPT, SGOT ↑ GSH, CAT, MnSOD activity	[74]

8-OHdG: 8-hydroxy-2'-deoxyguanosine; Akt: Protein kinase B (also known as Akt); ALP: Alkaline phosphatase; ALT: Alanine transaminase; AMPK: AMP-activated protein kinase; AST: Aspartate transaminase; ATGL: Adipose triglyceride lipase; BCl-2: B-cell lymphoma-2; BW: Body weight; BUN: Blood urea nitrogen; CAT: Catalase; COX-2: Cyclooxygenase-2; DPPH: 2,2-diphenyl-1-picrylhydrazyl; FAS: Fatty acid synthase; FBG: Fasting blood glucose; FFA: Free fatty acid; FINS: Fasting insulin; FRAP: Ferric reducing antioxidant power assay; G6PD: Glucose-6-phosphate dehydrogenase; GLUT: Glucose transporter type; GPx: Glutathione peroxidase; GSH: glutathione; GSK3β: Glycogen synthase kinase 3 beta; GST: Glutathione-S-transferase; ·OH: hydroxyl radical; H_2O_2: Hydrogen peroxide; HDL-C: High-density lipoprotein cholesterol; HMG: CoA reductase-3-hydroxy-3-methylglutaryl-coenzyme A reductase; HSL: Hormone-sensitive lipase; LDL-C: Low-density lipoprotein cholesterol; IL-1: Interleukin-1; IL-6: Interleukin-6; IR: Insulin resistance; iNOS: Inducible nitric oxide synthase; IRS-1: Insulin receptor substrate-1; MDA: Malondialdehyde; MC4R: Melanocortin receptor 4; Nrf2: Nuclear factor erythroid 2-related factor 2; NF-κB: Nuclear factor kappa B; PC: Protein carbonyl; PDE5: Phosphodiesterase 5; PI3K: Phosphoinositide 3-kinase; SOD: Superoxide dismutase; MnSOD: Manganese superoxide dismutase; STZ: Streptozotocin; TC: Total cholesterol; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TG: Triglyceride; TNF-α: Tumor necrosis factor-α; TAC: Total antioxidant capacity; TGF-β1: Transforming growth factor-beta1; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; PCNA: Proliferating cell nuclear antigen; SCFA: Short-chain fatty acid; STC-1 cells: Intestinal L-cells; TB: Total bilirubin; MoHpP2: *M. oleifera* hypoglycemic peptide 2; AChE: Acetylcholinesterase; MAO: Monoamine oxidase; ACE: Angiotensin converting enzyme; ADA: Adenosine deaminase and arginase; TBARS: Thiobarbituric acid reactive substances; CCr: Creatinine clearance; PPAR: Peroxisome proliferator-activated receptor; VEGF: Vascular endothelial growth factor; DPP-Ⅳ: Dipeptidyl peptidase-Ⅳ; AGEs: Advanced glycation end-products; ROS: Reactive oxygen species; MOP: Isolated polysaccharide from *M. oleifera*; GLP-1: Glucagon-like peptide-1; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; ↓: Decrease; ↑: Increase; ↔ : No change.

The *in vitro* and preclinical studies demonstrating the molecular potential of *M. oleifera* against diabetes are summarized in Figure 1 and Table 1.

4.2. *M. oleifera* in obesity: Evidence from preclinical studies

The study demonstrated that the methanolic extract of *M. oleifera* leaves reduced cholesterol levels and modulated the expression of genes involved in lipid metabolism, including β-hydroxy-methylglutaryl-CoA (HMG-CoA) reductase, PPARα1, and PPARγ[26]. The therapeutic potential of *M. oleifera* in managing hyperlipidemia, hyperglycemia, and nonalcoholic fatty liver disease has been evaluated. Studies on *Moringa* infusion and ethanolic extract revealed a significant reduction in key metabolic parameters, including serum glutamic pyruvic transaminase, serum glutamic-oxaloacetic transaminase, lipid profiles, urea, and glucose levels compared to those in the nonalcoholic fatty liver disease placebo group. The ethanolic extract showed greater efficacy in controlling blood sugar levels, whereas the infusion offered enhanced therapeutic benefits in reducing hepatic steatosis and inflammation[73]. The antioxidant effect of the ethanolic extract of *M. oleifera* fruits was evaluated in a model of 2-nitropropane-induced liver injury in obese subjects. The treatment significantly reduced levels of MDA, 8-hydroxy-2'-deoxyguanosine, serum glutamic pyruvic transaminase, and serum glutamic-oxaloacetic transaminase, while increasing GSH levels. These findings highlight the potential of *M. oleifera* fruit extract as a promising antioxidant agent for protecting against oxidative stress-induced liver damage[74]. The methanolic extract of the whole *M. oleifera* plant significantly reduced key parameters such as body weight, liver weight, and plasma glucose levels, with the most pronounced effects observed at a dose of 500 mg/kg. Additionally, the extract modulated inflammatory response by decreasing proinflammatory cytokines TNF-α and IL-1β, while increasing the levels of anti-inflammatory cytokines, including cyclooxygenase-2, IL-10, and IL-6[75].

The therapeutic potential of *M. oleifera* in metabolic syndrome has been demonstrated through its ability to target visceral fat and modulate key metabolic pathways. This modulation leads to increased expression of melanocortin-4-receptor and peroxisome proliferator-activated receptor alpha mRNAs, along with a significant reduction in fatty acid synthase and HMG-CoA-reductase expression (P<0.01). Further, research has highlighted the therapeutic potential of *M. oleifera* aqueous leaf extract, which exhibits anti-hepatic lipid deposition effects comparable to those of certain pharmacological agents. At higher doses, *M. oleifera* demonstrates significant anti-obesity activity, surpassing some standard medications[76]. The ethanolic extract of *M. oleifera* (300 mg per kg) significantly reduced glucose, insulin, leptin levels, and visceral fat while increasing adiponectin levels in obese rats. Additionally, it mitigated high-fat diet (HFD)-induced oxidative stress by decreasing MDA levels and enhancing the activities of SOD and CAT. Notably, no significant changes were observed in non-obese rats treated with the extract alone[77]. Co-fermentation of *M. oleifera* leaves with Fuzhuan brick tea positively influenced lipid metabolism and inflammation by downregulating key adipogenic markers, including sterol regulatory protein-1c, CD36, PPARγ, and fatty acid binding protein-2. These effects were associated with the activation of the AMPK, mitogen-activated protein kinase, and phosphoinositide 3-kinase (PI3K)

pathways, leading to improved insulin sensitivity[78]. In mice fed an HFD for 7 weeks, oral administration of *M. oleifera* leaf ethanolic extract (280 mg kg/day and 560 mg/kg/day) enhanced brown adipose tissue function by upregulating bone morphogenetic protein 7 expression, leading to improved metabolic regulation and anti-obesity effects[79]. In another study, *M. oleifera* ethanolic extract delayed glucose and fat absorption by inhibiting α-amylase and α-lipase, indicating its potential utility in obesity management[80]. Matsuoka *et al*. employed the zebrafish obesogenic test to identify anti-adipogenic compounds in MLE. The dichloromethane extract and its active fraction significantly reduced visceral adipose tissue accumulation by downregulating key adipogenic markers, including CCAAT/enhancer-binding protein beta and delta. These findings suggest that *M. oleifera* may exert anti-obesity effects by modulating adipogenesis at the molecular level[81]. MLE have also been demonstrated to have anti-obesity activity by reducing body weight, TC, TGs, LDL, VLDL, MDA, inducible nitric-oxide synthase, FBG, PPARγ, CCAAT/enhancer-binding protein alpha, PI3K, p-Akt, and fatty acid synthase levels. Additionally, they increased levels of HDL, hormones such as follicle-stimulating hormone and luteinizing hormone, and antioxidant enzymes including CAT, SOD, and GSH in various obesity-induced animal models[82–85]. The effects of an aqueous extract of *M. oleifera* seeds and purified *M. oleifera* microRNAs (miRNAs) were evaluated in human hepatoma (HepG2) cells and a pre-obese mouse model. Both the seed extract and miRNAs significantly reduced intracellular lipid accumulation and apoptosis in HepG2 cells. In obese mice, purified *M. oleifera* miRNAs regulated lipid metabolism by downregulating the expression of PPARγ and sterol regulatory protein-1c, suggesting potential for treating metabolic disorders. Additionally, fatty acid binding protein-2 and CD36—key proteins involved in fatty acid transport and lipid uptake, respectively — were modulated, leading to decreased lipid storage[86]. MSE demonstrated renoprotective effects in a high-fat, high-fructose diet model. Administration of 150-200 mg/kg for 28 days significantly reduced serum creatinine, improved glomerular structure, and increased SOD expression in both kidney tubules and glomeruli ($P<0.01$). Additionally, it led to a reduction in blood glucose levels[87]. The *in vitro* and preclinical studies demonstrating the molecular potential of *M. oleifera* against obesity are summarized in Figure 2 and Table 1.

4.3. M. oleifera in diabetes mellitus and obesity: Evidence from clinical studies

Numerous clinical studies have explored the effects of *M. oleifera* on various health conditions, such as T2DM, obesity, and hypercholesterolemia, as well as its safety in healthy individuals. A summary of these findings is presented in Table 2. A major limitation of these studies is their relatively small sample size, which limits the generalizability of the results. For example, in a preliminary safety study, single oral doses of *M. oleifera* leaf powder up to 4 g were found to be safe in healthy volunteers. The highest dose (4 g) enhanced insulin secretion without adversely affecting kidney or liver function, as indicated by blood urea nitrogen, creatinine, AST, and ALT levels. Furthermore, no adverse events were reported in a dose escalation study administering 0, 1, 2, or 4 g of *M. oleifera* once daily for two weeks, supporting its safety even at higher doses. Across all seven clinical studies reviewed, no significant side effects were observed, suggesting that *M. oleifera* is well tolerated, even with long-term use or at elevated dosing, underscoring its potential as a safe therapeutic agent[88]. A study evaluating the effects of *M. oleifera* at a dosage of 4 g/day for four weeks in naïve T2DM patients found no significant improvements in glycemic control. These findings suggest that the efficacy of *M. oleifera* may be influenced by factors such as dosage, treatment duration, and individual patient characteristics[89]. In a clinical study, administration of *M. oleifera* hard gelatin capsules (400 mg/day) for eight weeks in overweight and obese female individuals resulted in significant reductions in body mass index (BMI), TC, and low-density lipoprotein cholesterol (LDL-C), with no reported side effects. These benefits were associated with decreased leptin levels, increased adiponectin, and inhibition of HMG-CoA reductase—findings consistent with earlier preclinical studies in HFD-induced obese rats[76]. A single-dose study in T2DM patients consuming 20 g of *M. oleifera* leaf powder with a meal showed a significant reduction in postprandial blood glucose levels compared to the control group. However, the effects in nondiabetic populations remain unclear and require further investigation[90]. *M. oleifera* leaf powder supplementation (2 400 mg/day for 12 weeks) significantly improved FBG and HbA1c levels in prediabetic subjects, without affecting appetite hormones, microbiota, or hepatic and renal markers, supporting its role as a natural antihyperglycemic agent[91]. In a clinical study, administration of MLE for 10 weeks in obese patients with T2DM resulted in significant improvements in BMI, insulin levels, blood pressure, and high-density lipoprotein cholesterol (HDL-C). Although individual responses varied, the overall outcomes in T2DM patients were predominantly positive[92]. Conversely, Afiaenyi investigated the effectiveness of steaming *M. oleifera* leaves over 14 days, administering doses ranging from 0 to 60 g/day to 32 healthy participants. Although the study revealed no significant changes in waist circumference, waist-to-hip ratio, or fasting plasma glucose, a reduction in systolic blood pressure was observed at higher doses (40-60 g/day). However, this was accompanied by increases in TG and HDL-C levels. Despite these findings, overall assessing the effectiveness of *M. oleifera* remains challenging due to variability in dosage regimens, preparation methods, and treatment durations across the seven studies reviewed. Notably, only five of these studies disclosed their preparation methods, with four utilizing capsules made from dried, powdered *M. oleifera* leaves[93]. A randomized placebo-controlled trial in patients with T2DM and

hypertension found that *M. oleifera* leaf capsules at a dose of 6 g/day significantly improved blood glucose and blood pressure, while a lower dose of 3 g/day showed minimal effect. These findings indicate a dose-dependent efficacy and favorable safety profile[94]. Supplementation with 1 g/day of *M. oleifera* leaf powder for 12 weeks in hyperlipidemic patients significantly reduced TG, LDL, blood pressure, body weight, BMI, and waist circumference, while increasing HDL levels, suggesting beneficial modulation of lipid profiles and cardiovascular risk markers[95].

Overall, Figures 1&2, and the data in Tables 1 & 2 suggest that *M. oleifera* may be particularly effective in improving key metabolic markers, including blood glucose, cholesterol levels, BMI, and blood pressure. Future research should aim to establish optimal dosing, develop standardized preparation methods, and validate its therapeutic efficacy across diverse populations. Notably, the absence of significant side effects reported in existing studies supports the safety of *M. oleifera* as a dietary supplement with promising potential for managing cardiometabolic diseases.

4.4. Anti-obesity and anti-diabetic activity of isolated compounds from *M. oleifera*

Certain phytochemicals from *M. oleifera*, particularly serpentine, and niazirine, have demonstrated a high affinity for mutated insulin receptor tyrosine kinases. The strongest interactions were observed between these compounds and receptor A, while anthraquinone exhibited significant binding affinity for receptor B. These interactions may help regulate insulin receptor function, contributing to the anti-diabetic effects of these compounds[13]. Several compounds isolated from *M. oleifera* seeds were found to significantly reduce HepG2 cell viability and lower blood glucose levels in STZ-induced diabetic mice, indicating their potential

Figure 2. The molecular aspects of *M. oleifera* in obesity. *M. oleifera* exerts its anti-obesity effects by modulating various molecular pathways. Green-colored biomarkers represent factors whose expression or activity is increased by *M. oleifera*, promoting lipid metabolism and inhibiting adipogenesis both of which contribute to weight loss. In contrast, red-colored biomarkers denote obesity-related factors whose level or activity is suppressed by *M. oleifera*. Through these targeted molecular changes, *M. oleifera* helps mitigate the development and progression of obesity. MAPK: Mitogen-activated protein kinases; MAPKK: Mitogen-activated protein kinase kinase; MAPKKK: Mitogen-activated protein kinase kinase kinase; JNK: c-Jun *N*-terminal kinase; TNF-α: Tumor necrosis factor-α; IGF: Insulin growth factor; C/EBPβ: CCAAT-enhancer-binding protein β; AgRP: Agouti-related protein; NPY: Neuropeptide Y; INF: Interferon; TGF: Transforming growth factor; BMP: Bone morphogenetic protein; GSK3: Glycogen synthase kinase-3; POMC: Pro-opiomelanocortin; NUCB2: Nucleobindin2; mTORC: Mechanistic target of rapamycin complex; STAT: signal transducer and activator of transcription; PI3K: Phosphatidylinositol 3-kinase; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; JAKs: Janus kinases.

Table 2. Molecular aspects of *M. oleifera* in clinical studies of diabetes, obesity, and metabolic syndrome.

Type of extract and part of the plant used	Extract preparation	Patient population and disease	Treatments and duration	Clinical outcome	Adverse effects	Ref
Leaves hard gelatin capsules	Powdered *M. oleifera* leaves were macerated using 70% ethanol and evaporated to yield dried ethanol extract	Disease: Obesity (*n*=15)	400 mg/capsule for 8 weeks	↓ BMI, TC, and LDL *vs*. baseline. Normalization of AST and ALT	Not reported	[76]
Powdered leaf capsules	Dried leaves were powdered and filled into a gelatin capsule	10 healthy subjects	Baseline: 0 g Week 2: 1 g Week 4: 2 g Week 6: 4 g 8-week duration	↔ BUN, creatinine, AST, ALT, and plasma glucose ↑ Plasma insulin	No adverse events up to high dose (4 g) administration	[88]
Powdered leaf capsules	Dried leaves of *M. oleifera* were ground and sieved to form powder. The powder was filled into capsule shells	Disease: T2DM (*n*= 32) Placebo: 16 patients Treatment group: 16 patients	Placebo: 8 placebo capsules Treatment group: 4 g/day (8 capsules), 4 capsules each before breakfast and dinner time (500 mg *M. oleifera* powder) for 4 weeks	↔ Glycemic control	No adverse effects	[89]
Leaf powder	The leaves were dried in the shade and ground to a fine powder with an electric grinder	*n*=27, nondiabetic patients: 10, diabetic patients: 17, each received both control and *M. oleifera* leaf powder	20 g added to a meal as a single administration	Lower increment of postprandial blood glucose in diabetic subjects	Not reported	[90]
Dried powdered leaves	Powdered *M. oleifera* leaves capsule	Disease: T2DM (*n*=65) Placebo: 34 patients; Treatment group: 31 patients	2 400 mg/day for 12 weeks	↓ Fasting glucose ↓ HbA1c ↓ Insulin resistance (HOMA-IR) ↑ GLP-1 levels ↔ Weight or lipid profile	Not reported	[91]
Leaves extract	Not reported	Cross-over study (*n*=48) Placebo: 24 patients; Treatment: 24 patients Disease: Obesity and T2DM	Treatment: NA; Duration: Period 1-10 weeks; Washout: 2 weeks; Period 2: 10 weeks	↓ BMI, Trends to LDL and HbA1c ↓ Blood pressure ↑ HDL	Not reported	[92]
Steamed leaves	Not reported	Disease: T2DM (*n*=24) Placebo: 6 patients; Treatment: 3 groups, with each group consisting of 6 patients	Group 1: control; Group 2: 20 g; Group 3: 40 g; Group 4: 60 g; 14 days	↔ Waist circumference, waist-hip ratio, and FBG in all groups. ↓ SBP, ↔ DBP and TC in Groups 3 and 4 ↓ LDL in Group 2 ↑ TG and ↓LDL in Group 3 ↑ HDL in Groups 1, 2, and 4 ↓ Hb, packed cell volume, and WBC in Group 4 Significant changes observed in the parameters assessed were not dose-dependent	Not reported	[93]
Dried leaves	Powdered moringa capsule	T2DM patients (*n*= 24)	3 g and 6 g twice a day for three months	↓ Blood glucose and blood pressure	Not reported	[94]
Powdered moringa capsule	Not reported	Overweight hyperlipidemic patients (*n*=40)	1 g for 12 weeks; *Moringa* group-0.5 g/capsule containing *Moringa* leaf, twice a day Control group-0.5 g/capsule containing corn starch, twice a day	↓ Body weight, BMI, and waist circumference ↓ FBG, TG, LDL ↓ SBP, DBP ↑ HDL-C ↔ TC	Not reported	[95]

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WBC: White blood cells; HOMA-IR: Homeostatic model assessment for insulin resistance; Hb: Hemoglobin; HbA1c: Glycated hemoglobin A1c.

as effective hypoglycemic agents[14]. A notable study examined the antilipidemic and antiadipogenic effects of rutin, a bioactive compound extracted from *M. oleifera* leaves. Rutin effectively inhibited two key digestive enzymes-pancreatic lipase and α-glucosidase, with IC_{50} values of 35 and 40 μg/mL, respectively. This enzymatic inhibition significantly reduced fat accumulation by 79.9% in 3T3-L1 adipocytes, without inducing toxicity at concentrations up to 160 μg/mL. Additionally, rutin enhanced glucose uptake by modulating leptin and adiponectin levels through activation of the AMPK pathway. This was accompanied by the upregulation of GLUT-4 and uncoupling protein 1, along with the downregulation of PPAR-γ, supporting its potential role in metabolic regulation[96]. Quercetin, a major bioactive compound extracted from *M. oleifera* using petroleum ether, has been identified as a key contributor to its metabolic effects. These findings highlight the therapeutic potential of *M. oleifera* petroleum ether extract in managing obesity and related metabolic disorders. Additionally, treatment with an aqueous extract of *M. oleifera* has been shown to significantly reduce body weight, TC, TG, and LDL while increasing HDL-C (P<0.05)[97]. Waterman *et al*. reported that the primary bioactive compounds in *M. oleifera* responsible for alleviating obesity and T2DM are moringa isothiocyanates. These compounds primarily exert their effect by inhibiting gluconeogenesis, enhancing insulin signaling, and promoting lipid metabolism. These findings support the potential of *M. oleifera* as a dietary intervention for the prevention and management of T2DM and obesity[98].

The antiadipogenic activities of two sulfur-containing compounds from *M. oleifera* seeds niazinin B and 4-(α-*L*-rhamnosyloxy)benzyl isothiocyanate have been demonstrated, with the latter exhibiting significant activity at an IC_{50} of 9.2 μg/mL (29.6 μM). This potent effect is primarily attributed to the isothiocyanate constituents of *M. oleifera*[99]. Additionally, the bioactive compound niazirin, isolated from *M. oleifera* leaves, has shown anti-diabetic activity by reducing ROS production and MDA levels, while enhancing SOD and GPx activity. These effects help attenuate high glucose-induced oxidative stress *via* the PKCζ/Nox4 pathway. In STZ-induced T2DM animal models, niazirin also decreased levels of LDL, TNF-α, IL-10, phosphoenolpyruvate carboxykinase, and homeostatic model assessment for insulin resistance levels, while stimulating AMPK phosphorylation and increasing PFKFB3 expression and HDL-C levels, supporting its therapeutic potential in diabetes management[100,101]. Isolated compounds from *M. oleifera* leaves, such as quercetin and kaempferol exhibited strong inhibitory activity against α-glucosidase and pancreatic lipase in 3T3-L1 cells. This was associated with reduced α-amylase activity, TC, TG, and LDL-C, along with an increase in HDL-C, highlighting their potential role in managing metabolic disorders[102]. Dietary fibers derived from *M. oleifera* leaves exhibited anti-diabetic activity in STZ-induced T2DM animal models. These effects were mediated through enhanced glucagon-like peptide-1 secretion, increased expression of G protein-coupled receptor 43, elevated short-chain fatty acids levels, and activation of key signaling pathways, including AMPK, PI3K/Akt, and extracellular signal-regulated kinase phosphorylation[103,104]. *M. oleifera* hypoglycemic peptide-2 isolated from *M. oleifera* seeds has demonstrated notable anti-diabetic effects. In STZ-induced T2DM mice and insulin-resistant C2C12/IR cells, *M. oleifera* hypoglycemic peptide-2 significantly reduced blood glucose, MDA, AST, and ALT levels. Concurrently, it increased the levels of antioxidant enzymes including SOD, CAT, GSH, as well as GLUT-4. Additionally, it inhibited α-glucosidase activity, further supporting its potential as a therapeutic agent for diabetes management[105]. Treatment with a water-soluble lectin extracted from *M. oleifera* seeds significantly reduced the glycemic index and FBG levels, while improving insulin levels in STZ-induced T2DM mouse models[106]. These findings highlight its potential role in glycemic regulation and diabetes management. All studies involving isolated compounds from *M. olefera* that demonstrate anti-diabetic and anti-obesity effects are summarized in Table 3.

4.5 Anti–diabetic activity of M. oleifera nanoparticles

Table 4 represents all studies on various *M. oleifera* nanoformulations that exhibit anti-diabetic activity. Selenium nanoparticles synthesized from *M. oleifera* bark and leaves exhibited anti-diabetic activity *in vitro* by inhibiting α-amylase and α-glucosidase[107]. Biosynthesized silver nanoparticles using aqueous MLE demonstrated anti-diabetic activity by inhibiting α-amylase activity by up to 65%[108]. *M. oleifera*-based gold, selenium, and biocompatible zirconium-doped WO_3 nanoparticles showed significant antioxidant activity by scavenging free radicals[109,110]. Both selenium and silver nanoparticles derived from *M. oleifera* showed anti-diabetic effects by reducing MDA, FBG, HbA1c, TC, TG, and LDL-C levels while increasing GSH, SOD, CAT, and HDL levels in STZ-induced T2DM animal models[111,112]. The combination of ZnO nanoparticles and MLE has been reported to normalize body weight loss and glycemic levels, while enhancing serum insulin and male reproductive hormone levels, including testosterone, luteinizing hormone, and follicle-stimulating hormone, in rats with alloxan-induced diabetes. Additionally, the formulation was shown to restore diabetes-induced histopathological alterations in the testes. These findings suggest that the ZnO-*M. oleifera* combination may help reverse diabetes-associated reproductive dysfunction in males[113]. *M. oleifera* nanoparticles improved insulin levels and reduced fasting blood sugar, TG, homeostatic model assessment for insulin resistance, and inflammatory markers (TNF-α and IL-6) in high-fat diet-induced prediabetic rats[114]. Non-metallic *M. oleifera* nanoparticles also exhibited significant *in vitro* inhibitory activity against α-glucosidase and α-amylase, along with enhanced free radical scavenging capacity[115]. Both nano-encapsulated *M. oleifera* seeds and functional soft cheese fortified with their

Table 3. Molecular aspects of isolated compounds from *M. oleifera* in diabetes, obesity and metabolic syndrome.

Parts used	Disease	Animal model/ Assay method	Extract type	Cell line/animal	Dose and duration	Molecular aspects	Ref
Leaves	T2DM	*In silico*	Serpentine, niazirin, anthraquinone	Mutated insulin receptor tyrosine kinase proteins A and B	-	Inhibition of insulin receptor tyrosine kinases, α-amylase and α-glucosidase activities	[13]
Leaves	T2DM	Molecular docking	*M. oleifera*-derived phytochemicals *vs.* alogliptin	*In silico*	-	Piceatannol and vanillic acid inhibit the DPP-Ⅳ enzyme (–7.9 kcal/mol and –5.7 kcal/ mol, respectively)	[49]
Leaves	T2DM and obesity	3T3-L1 adipocytes	Hydroalcoholic extract, rutin (Quercetin-3-*O*-rutinoside)	3T3-L1 adipocytes	10, 20, 40 μg/ mL; Lipase and glucosidase IC_{50}: 35, 40 μg/mL	Inhibited lipogenesis ↓ PPAR-γ ↑ AMPK, GLUT-4, UCP-1 expression	[96]
Leaves	T2DM and obesity	C57BL/6J mutant model	Aqueous extractisothiocyanates	Mice	66 mg/kg/day of isothiocyanates (MICs) for 12 weeks	↑ IRS-1 and IRS-2 ↓ IL-1β, TNF-α, and IL-6 ↑ Adiponectin, ATGL ↓ FAS, SREBP1c, and FSP27 ↓ Weight gain	[98]
Leaves	Hypoglycemic and hypolipidemic effects	α-glucosidase and pancreatic lipase inhibitory activity	Quercetin and kaempferol	3T3-L1 cell	(123.34 ± 3.89) μg/ mL and (181.30 ± 4.42) μg/mL	↓ α-amylase ↓ TC, TG, LDL-C ↑ HDL-C	[102]
Leaves	T2DM	A high-fat diet with a low dose of STZ-induced diabetes	*M. oleifera* dietary fiber extract	*In vitro* & mice	1-5 mg/mL and MDF 40, 80, 200, 800 mg/kg for 4 weeks	↓ FBG, α-amylase, α-glucosidase, insulin resistance ↓ MDA, TC, TG, LDL-C ↑ Serum insulin ↑ SOD, GSH, HDL-C, SCFAs, GLP-1, GPR43, AMPK, ERK, PI3K/Akt	[103]
Seeds	Oxidative stress	*Caenorhabditis elegans* model	Hydroalcoholic extract contains MIC-1, moringin	*In vitro* (N2 nematodes and L1 stage nematodes)	0.1 and 0.5 mg/mL for 2 days Survival assay: MSE 0.1-1 mg/mL, MIC-1: 50-200 μM for 3 days	↑ GST4, 7, 31, 33, 37, 39 and GPx-3, SKN-1/Nrf2 pathway activation ↑ Life span of *Caenorhabditis elegans*	[64]
Seeds	Obesity	Oil red O staining assay	Niazinin B and 4-(α-*L*-rhamnosyloxy)benzyl isothiocyanate	3T3-L1 preadipocytes	10 μg/mL	↑ Intracellular lipid accumulation	[99]
Seeds	T2DM	Obesity-induced diabetes	Niazirin	*db/db* mice	10, 20 mg/kg for 4 weeks	↓ BW, water, and food intake ↓ FBG ↑ Hepatic carbohydrate metabolism and fatty acid oxidation through AMPK activation and ↓ fatty acid synthesis *via* AMPK ↓TNF-α, LDL, TC, TG, NEFA ↑ IL-10, HDL	[101]
Seeds	T2DM& cardiac function	High-fat diet with a low dose of STZ-induced diabetes	Water-soluble lectin (WSMoL)	C57BL/6 Mice	5 mg/kg for 21 days	↓ FBG, Insulin resistance ↔ BW ↑ Left ventricular ejection fraction	[106]
Leaves and seed	Oxidative stress and T2DM	High glucose induced oxidative stress and STZ-induced diabetes	Niazirin	*In vitro* and mice	5 μM-80 μM 40 mg/kg for 2 weeks	↑ TAC, GPx, SOD ↓ Proliferation of VSMCs ↑ Free radical scavenging activity (ABTS, DPPH, FRAP assay) ↓ ROS, MDA, PKCζ/Nox4	[100]

IRS-1/IRS-2: Insulin receptor substrate-1 and -2; SREBP1c: Sterol regulatory element-binding protein 1c; FSP27: Fat-specific protein 27; PKCζ : Protein kinase C zeta; Nox4: NADPH oxidase 4; UCP-1: Uncoupling protein 1; SCFAs: Short chain fatty acids; GPR43: G protein-coupled receptor 43; ERK: Extracellular signal-regulated kinase; PI3K/Akt: Phosphoinositide 3-kinase/Protein kinase B signaling pathway; NEFA: Non-esterified fatty acids; MICs: Moringa isothiocyanates; MIC-1: Moringa isothiocyanate-1; SKN-1/Nrf2: Transcription factor SKN-1/Nuclear factor erythroid 2-related factor 2 in humans; GST4, 7, 31, 33, 37, 39: Various isoforms of glutathione S-transferase; GPx-3: Glutathione peroxidase-3; VSMCs: Vascular smooth muscle cells; ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); FRAP: Ferric reducing antioxidant power assay; DPPH: 2,2-diphenyl-1-picrylhydrazyl; MSE: *M. oleifera* L. seed extract; MDF: *M. oleifera* dietary fiber.

Table 4. Molecular aspects of nanoparticles of *M. oleifera* in diabetes, obesity and metabolic syndrome.

Parts used	Disease	Animal model/ Assay method	Extract type	Cell line/animal	Dose and duration	Molecular aspects	Ref
Whole plant	Antioxidant and antidiabetic potential	DPPH radical scavenging, α-amylase and α-glucosidase inhibition assay	*M. oleifera*-SeNPs	*In vitro*	1 000 µg/mL	↑ 84% DPPH scavenging activity ↓ α-amylase (44.53%), α-glucosidase (19.3%)	[110]
Leaves	T2DM	Alpha-amylase inhibition assay	Silver nanoparticles	*In vitro*	20-100 µL	Inhibit α-amylase enzyme	[108]
Leaves	Enzymatic assay in carbohydrate metabolism and antioxidant assay	Alpha-amylase and α-glucosidase inhibition assay	*M. oleifera*- AuNPs	*In vitro*	Antioxidant activity (20, 40, 60, 80, and 100 µg/mL); Antidiabetic activity (50, 100, 150 & 200 µg/mL); 130 µg/mL	Dose-dependent increase in radical scavenging activity and maximum effect (55.9%) at 100 µg/mL) (IC_{50}=60 µg/mL) A dose-dependent increase in inhibition of α-amylase activity (IC_{50}=130 µg/mL)	[109]
Leaves	T2DM	STZ-induced diabetes	Aqueous extract of Ag NPs	Albino rats	0.2 mg/kg BW for 6 weeks	↓ FBG, HbA1c, TC, TG, LDL-C, MDA ↑ HDL-C, restoring insulin levels ↑ GSH, SOD, CAT	[111]
Leaves	T2DM	High-fat diet with STZ-induced diabetes	Aqueous extract of SeNPs	Sprague-Dawley rats	0.25, 0.5 mg/kg body weight for 28 days	↓ FBG, LDL, HOMA-IR, insulin ↔ TC and TG ↑ HDL-C ↑ Hepatic antioxidant enzyme activity (SOD, GSH-Px, CAT) ↓ MDA ↓ ALT, AST, ALP ↓ TNF-α, IL-6, IL-1β, iNOS, and AGEs	[112]
Leaves	T1DM and compromised reproductive function	Alloxan induced diabetes	ZnO NP + *M. oleifera* leaf extract	Albino Wistar rats	ZnO NPs (7.5 mg/kg BW), *M. oleifera* leaf extract (250 mg/kg of BW)	↓ Serum glucose and glucagon levels ↑ BW, serum insulin, testosterone, FSH, and LH levels Restored spermatogenic activity	[113]
Leaves	T2DM	High-fat diet for 4 weeks (Prediabetic model)	*Moringa* nanoparticles	*Rattus norvegicus*	75, 125, and 225 mg/kg for 4 weeks	↑Insulin ↓ Fasting blood sugar, TNF-α, IL-6, TG, and HOMA-IR levels	[114]
Leaves	Diabetes	α-glucosidase and amylase inhibitory activity, ABTS, DPPH and FRAP assay	*Moringa* nanoparticles	*In vitro* (MCF-7 and HepG2 cell line)	7.81-1 000 µg (α-glucosidase and α-amylase) 2-1 000 µg/mL (MCF-7 and HepG2)	↓ α-glucosidase and amylase ↑ Free radical scavenging activity	[115]
Leaves	Diabetes	α-amylase inhibition assay, DPPH assay	WO_3 *vs.* Zr-doped WO_3 NPs (3%, 5%, 7%)	*In vitro*	Enzymatic activity 125 -500 µg/mL and antioxidant dose 10-50 µg/mL	↓ α-amylase ↑ 85% Free radical scavenging activity for Zr-doped WO_3 NPs	[117]
Leaves & bark	Diabetes	α-amylase & α-glucosidase inhibition assay	SeNPs	*In vitro*	20, 40, 60, 80, and 100 µg/mL	↓ α-amylase and α-glucosidase are higher at 100 µg/mL. However, activity is higher for SeNPs from the bark	[107]
MSE and OLE	T2DM	STZ-induced diabetes	MSE and OLE loaded Whey protein isolate nanoparticles	Sprague-Dawley rats	200 mg/kg BW for 8 weeks	↑ SOD, CAT ↑ Insulin, HDL ↓ Glucose, TC, LDL, TG, AST, ALP, ALT, TNF-α, IL-6	[116]

AGEs: Advanced glycation end-products; MCF-7: Human breast cancer cell line; HepG2: Human liver cancer cell line; MSE: *M. oleifera* L. seed extract; OLE: *Ocimum tenuiflorum* L. leaves extract; SeNPs: Selenium nanoparticles; AuNPs: Gold nanoparticles; Ag NPs: Silver nanoparticles; ZnO NP: Zinc oxide nanoparticles; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

nanoform exhibited significant antihyperglycemic effects in STZ-induced diabetic rats. These formulations enhanced insulin levels, reduced inflammatory markers (TNF-α and IL-6), and improved antioxidant enzyme activity (SOD and CAT). They also increased HDL-C levels while decreasing TC, TGs, and LDL-C. Additionally, both formulations improved kidney and liver function by lowering creatinine, urea, uric acid, AST, ALT, and ALP[116]. Zr-doped WO_3 nanoparticles (3%-7%) demonstrated enhanced *in vitro* anti-diabetic and antioxidant activity, exhibiting dose-dependent α-amylase inhibition at concentrations of 125-500 μg/mL and up to 85% free radical scavenging activity at 10-50 μg/mL compared to undoped WO_3, highlighting their superior efficacy in modulating carbohydrate metabolism and reducing oxidative stress[117]. Altogether, these findings suggest their potential application in pharmaceutical and dairy products for diabetes management.

5. Conclusion, future perspectives, and research gaps

As exemplified in this paper, *M. oleifera* Lam. has shown beneficial effects in various models of metabolic diseases, including diabetes, obesity, and metabolic syndrome. Its anti-diabetic and anti-obesity effects are attributed to multiple mechanisms, such as reductions in blood glucose, TC, TG, and LDL levels, along with increases in HDL levels. *M. oleifera* enhances insulin sensitivity by modulating key signaling pathways, including insulin receptor phosphorylation, PI3K, and Akt pathways, which facilitate glucose uptake by promoting GLUT-4 translocation to the cell membrane.

Additionally, *M. oleifera* reduces oxidative stress and elevates antioxidant defense through the upregulation of enzymes such as SOD, CAT, and GSH. It also modulates inflammatory responses by downregulating proinflammatory cytokines such as NF-κB, TNF-α, IL-1β, and IL-6, while upregulating anti-inflammatory cytokines such as IL-4 and IL-10. Moreover, *M. oleifera* regulates lipid metabolism by inhibiting adipogenesis and fatty acid synthesis, contributing to improved lipid profiles and reduced fat accumulation. The plant's bioactive compounds-including flavonoids, phenolic acids, and saponins-target critical molecular pathways associated with glucose and lipid metabolism, making *M. oleifera* a promising candidate for managing diabetes and obesity. Despite these promising results, there are still research gaps in understanding the molecular mechanisms underlying the anti-diabetic and anti-obesity effects of *M. oleifera*. The specific molecular mechanisms involved, especially those mediated by different plant parts (seeds, stems, flowers, roots), are still not fully understood. In particular, its interactions with key metabolic pathways such as the AMPK, PI3K/Akt, mTOR, and GSK-3, which play vital roles in energy homeostasis, insulin signaling, and lipid metabolism, require further investigation.

Another major challenge is the low bioavailability of *M. oleifera*'s bioactive compounds. Advanced nanoformulations that optimize particle size, surface charge, and release profiles could significantly improve their bioavailability and therapeutic efficacy. However, long-term safety and toxicity studies are essential to ensure their safe use.

Future research should focus on large-scale, multicenter randomized controlled trials to validate preclinical findings and evaluate the long-term efficacy and safety of *M. oleifera* in human populations. Addressing these critical research gaps will help unlock the full potential of *M. oleifera* as an alternative or adjunctive therapy for diabetes, obesity, and metabolic syndrome, contributing to the development of effective, natural treatments for these prevalent conditions.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data availability statement

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

Authors' contributions

Conception or design of the work and supervision of the project was done by PVT. VVD was responsible for data collection. KR and MIH performed data analysis and interpretation, as well as drafted the article. MD and PVT made critical revision of the article. All authors contributed to the final approval of the version to be published.

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