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Novel insights on anti-obesity potential of the miracle tree, *Moringa oleifera*: A systematic review

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ABSTRACT

Moringa oleifera (MO) has started to focus the attention of many researchers, especially in the last decade, due to its rich nutrient content and bioactive compounds that have numerous pharmaceutical potentials. In this systematic review, 36 research articles were included that explored the anti-obesity potential of MO through in-vitro and in-vivo studies. The research articles included 9 in-vitro studies, 27 in-vivo studies, and 3 clinical studies. The studies mainly focused on the extract of MO prepared using MO leaves and few studies particularly focused on MO isothiocyanates. The in-vitro studies were mainly based on 3T3-L1 cells, while the in-vivo studies involved a good range of male and female mice and rats. Only two research involved human studies. The major anti-obesity mechanisms of MO were through improving the lipid profile (levels of total cholesterol, triglycerides, low-density lipoprotein, very low-density lipoprotein, high-density lipoprotein, and high-density lipoprotein cholesterol) and body weight, regulating significant genes associated with adipogenesis, glucose uptake, insulin resistance, and hormones (such as leptin, vaspin, resistin, and insulin). The clinical trials studying the anti-obesity potential of MO on humans is limited and related to the impact of MO on body mass index, total cholesterol, low-density lipoprotein, and postprandial blood glucose only.

1. Introduction

Obesity is defined as a condition in which the amount of body fat is increased rapidly, obesity measured and reported in terms of body mass index (BMI) (Bahmani et al., 2016). The BMI is defined as the weight of the individual (in kilograms) divided by the square of the individual's height (in centimeters). Obesity can lead to many chronic diseases such as type 2 diabetes, cardiovascular diseases, stroke, hypertension, and contribute to certain types of cancer (Sergent, Vanderstraeten, Winand, Beguin, & Schneider, 2012). Obesity can also negatively impact the individual psychologically causing mental health disorders (such as depression), social discrimination, and physical inability (Ramezani et al., 2018).

Obesity treatment differs based on the conditions of the individual (with reference to the BMI), usually the treatment can start by altering the lifestyle of the individual, followed by body weight (bw) management programs and nutrition counselling, then pharmacotherapy (drugs such as Bupropion-naltrexone, Liraglutide, and Orlistat) can be

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introduced, and finally, in severe conditions, bariatric surgery is the last choice. Some plants and herbs (such as green tea, roselle, St. John's wort, rosemary, and dandelion) have been used in the treatment of obesity, either based on folk medicine or advanced research (Gamboa-Gómez et al., 2015). Some bioactive compounds have been reported for their anti-obesity potential such as polyphenols, gallic acid, catechins, oleuropein, capsaicin, quercetin, anthocyanins, and caffeine (Konstantinidi & Koutelidakis, 2019). Many plants and herbs have helped in improving the lipid profile by decreasing the levels of total cholesterol, triglycerides, and low-density lipoprotein, and decreasing adipose tissue by lowering adipocytes differentiation and proliferation (Gamboa-Gómez et al., 2015).

Moringa oleifera (MO) is a common highly nutritious herb that has been widely used in folk medicine, due to its numerous pharmacological potentials, it is known as "the miracle tree" (Dehghani & Alizadeh, 2016; Gopalakrishnan, Doriya, & Kumar, 2016). MO belongs to the family of Moringaceae and is native to India, it has been primarily cultivated in Asia, Africa, and other parts of the world (Singh et al., 2020). MO is a fast-growing evergreen plant that can tolerate poor soil and limited availability of water (Mirhashemi, Mohseni, Hasanzadeh, & Pishvaee, 2018). MO contains high amounts of proteins, carbohydrates, oils, vitamins, minerals (such as potassium and calcium), amino acids, and phenolic compounds (Daghaghele, Kiasat, Safieddin Ardebili, & Mirzajani, 2021; Mehwish et al., 2021; Xiong et al., 2021). Phenolic compounds such as gallic acid, chlorogenic acid, caffeic acid, rutin, kaempferol, *p*-coumaric acid, vicenin-2, and quercetin were detected in MO leaf extract (Kim, Choi, & Shin, 2020; Muhammad, Pauzi, Arulselvan, Abas, & Fakurazi, 2020). Some unique isothiocyanates were also extracted from MO leaves (Waterman et al., 2015).

MO has been reported for several pharmacological properties such as antioxidant, anticancer, anti-diabetic, anti-obesity, anti-inflammatory, anti-allergic, antiasthmatic, anti-ulcer, antiepileptic, and antipyretic effects (Bhattacharya, Tiwari, Sahu, & Kumar, 2018). Most of the pharmacological activities of MO are due to the high flavonoid, glucoside, and glucosinolate content in this plant (Abd Rani, Husain, & Kumolosasi, 2018).

An important pharmacological activity of MO is its anti-obesity potential. A combination of in-vitro, in-vivo, and clinal studies have been conducted to explore the anti-obesity potential of MO extracts or specific compounds isolated from MO. Compounds such as quercetin, isoquercetin, quercetin-3-*O*-malonylglucoside, astragalin have been identified in MO extracts showing anti-obesity activity (Balusamy, Perumalsamy, Ranjan, Park, & Ramani, 2019; Kim et al., 2020; Muni Swamy, Ramesh, Devi Prasad, & Meriga, 2020). This systematic literature review focuses on the reported in-vitro, in-vivo, and clinical studies concerning the anti-obesity potential of MO and its mechanisms.

2. Materials and methods

2.1. Data sources and search strategy

The present systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Review and Meta Analyses) statement. The research involved all the studies published from the 1st January 2010 to the 6th June 2021. English-written articles were identified by searching in PubMed and Scopus, and manual search using Google Scholar. The search strategy was based on the following items: "moringa" AND "obesity" OR "antiobesity" OR "lipid profile" OR "lipids" "BMI" OR "body mass index" OR "body weight" OR "cholesterol" OR "triglycerides".

2.2. Inclusion and exclusion criteria

For each of the relevant abstracts, full publications were retrieved for evaluation based on criteria established a priori. English research articles published between 2010 and 2020 were included. Research articles based on in-vitro and in-vivo were included, while in-silico based research articles were excluded. Research articles focusing on MO extracts only were included, however, those considering a mixture of plant extracts or a formulation that is a mixture of several constituents (including MO) were not considered. The research articles included were relevant to the theme of anti-obesity. The flow diagram of the study, Fig. 1, shows the number of records screened, included, and excluded. The relative study design and level of evidence demonstrated were as suggested by Centre for Evidence-Based Medicine.

3. Results and discussion

Several studies explored the anti-obesity potential and mechanism of MO extracts. In this section, the findings of the studies selected for qualitative synthesis are outlined and explained. A total of 36 research articles were included in the qualitative synthesis. Out of the 36 original research articles. The research articles included 8 in-vitro studies, 24 in-vivo studies, 1 study involved in-vitro and in-vivo, 2 studies involved in-vivo and clinical studies, and 1 study was based on clinical trial only. The studies proposed several anti-obesity mechanisms of MO extracts. The summary of the main and most significant mechanisms is presented in Fig. 2.

3.1. Effect of MO on body weight, lipid content and lipid profile

One of the most common anti-obesity mechanisms of herbs is through modifying the lipid profile of the individual, it is usually associated with reduction of total cholesterol (CHO), triglycerides (TG), low-density lipoprotein (LDL-C), very low-density lipoprotein (VLDL-C), and enhancement of high-density lipoprotein (HDL) (or high-density lipoprotein cholesterol (HDL-C)) levels. The effect of MO on lipid profile was the subject of several studies as summarized in Table 1.

The effect of MO on lipid content was evaluated based on the lipid profile which included measurement of CHO, TG, LDL-C, VLDL-C, and HDL/HDL-C. A study considered the administration of methanolic MO extract to 50 male Albino Wistar rats at a dose of 250 mg/kg or 500 mg/kg for 60 days, the extract was helpful in significantly decreasing the total CHO, TG, LDL-C, and VLDL-C levels, and significantly increasing the levels of HDL-C (Saleem, Al-Dujaily, & Al-Murshidi, 2016). Besides, several studies evaluated the potential of MO extract on the lipid profile of animals fed with high-fat diet (HFD). A study reported that the male C57BL/6J mice that were fed with HFD diet containing 0.1% leaf powder for 7 weeks, experienced a reduction in the increased levels of CHO, TG, and LDL-C due to HFD, and prevented hypercholesterolemia and fat deposition in the mice (Kim & Kim, 2019). In addition, another study also considered mice fed with HFD to evaluate the effect of petroleum ether MO extract on the lipid profile (Xie et al., 2018). The male C57BL/6J mice that were fed with HDF were administered with 0.125, 0.25, or 0.5 g/kg of MO extract and their lipid profile was analyzed. MO extract was successful in reducing the body weight, relative epididymal, perirenal, mesenteric fat weight and fat tissue size, hepatic fat accumulation, and levels of TC, LDL-C, and aspartate aminotransferase (AST) of the tested animals. Furthermore, it was also reported that MO extract helped significantly in decreasing the levels of CHO, TG, VLDL, and LDL, and increasing HDL levels in Albino Wistar rats that were fed with HFD and orally administrated with 200 or 400 mg/kg/day of methanolic MO extract for 3 weeks (Madkhali et al., 2019). In fact, the same study also suggested that the MO extract was efficient in decreasing the waist size, Lee index, BMI, and food intake, and reversing HFD-induced endothelium dysfunction. Moreover, a recent study also proved the capability of MO oil extract (dosage of 400 mg/kg) in reducing the body weight and the levels of CHO, TG, VLDL, and LDL, in diet-induced obesity in Albino Wistar rats fed with HFD for 12 weeks (Greish et al., 2021). In fact, MO oil extract helped in increasing the level of HDL. The study also proved that MO oil extract can improve oxidative stress and male fertility markers in the diet-induced obesity of male rats.

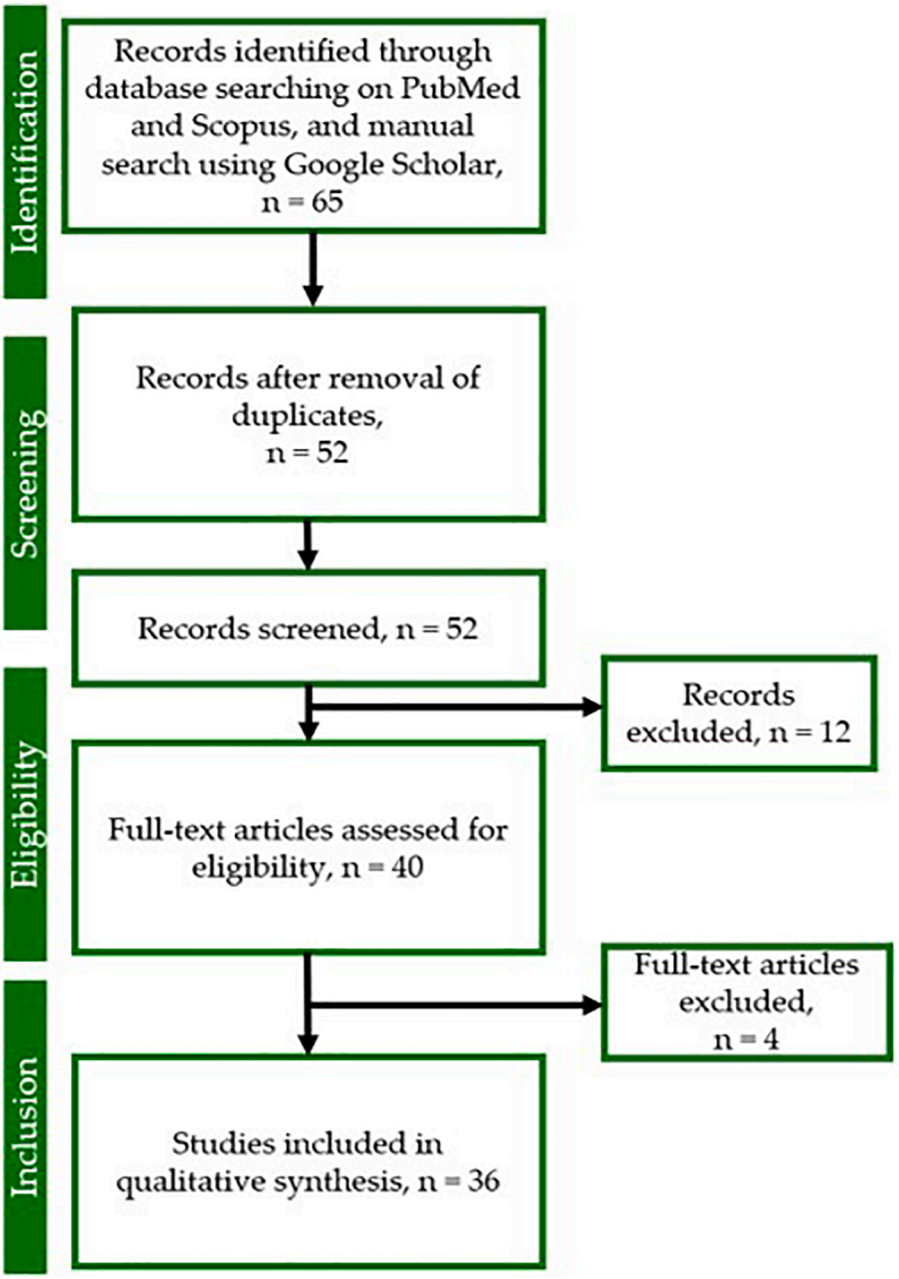

Fig. 1. Flow diagram of the study.

A study evaluated the obesity modulation efficiency of MO aqueous extract using 40 adult male Wistar albino rats (Al-Gebily, Morsy, Elzawahry, Ibrahim, & Abdel-Wahhab, 2019). The test group were administrated MO extract (20%) with HFD, after 6 weeks a significant decrement in body weight gain, BMI, and levels of CHO, TG, LDL, and glucose. In addition, MO was also capable of increasing HDL and irisin to improve lipid metabolism. In addition, the methanolic (Bais, Singh, & Sharma, 2014; Jain, Patil, Haswani, Girase, & Surana, 2010), ethyl alcohol (Othman, Amer, Basos, & El-Missiry, 2019), and aqueous (Hussein, El-Senosi, & El-Sharkawy, 2018) extracts of MO leaves also showed the same impact on those parameters in a similar study using Wistar Albino rats.

In the studies discussed earlier, MO extracts were capable of reducing the body weight and BMI of obese animals. Intake of powdered MO dried leaves has shown significant influence on anthropometric parameters on adult male long Evans rats fed with HFD (Nahar, Faisal, Iqbal, Rahman, & Yusuf, 2016). The oral intake of 50 mg of MO dried leaves per day for 35 days reduced the body weight, BMI, thoracic circumference (THC), and abdominal circumference (ABC) of HFD-induced obese rats.

The MO extract content also showed promising effects in human trials. A randomized, double-blind, placebo-controlled trial studied the effect of hard gelatinous capsules of MO leaves ethanolic extract (1 capsule per day containing 400 mg of extract for 8 weeks) on the BMI, TC, and LDL of 15 female overweight or obese (Ezzat et al., 2020). The BMI, TC, and LDL of the participants decreased significantly after 8 weeks. In a similar study, the effect of MO dried leaves powder on the LDL of 15 obese, with type II diabetes mellitus, individuals were examined (Kumar K & Mandapaka, 2013). The subjects were supplemented with the MO leaf powder formula for 20 days (50 g per day). The level of serum LDL decreased significantly after 20 days, as well as glucose levels.

The studies described earlier used MO extract in their biomedical studies, the content and composition of the extracts used were not identified and quantified. This can be considered a limitation since the

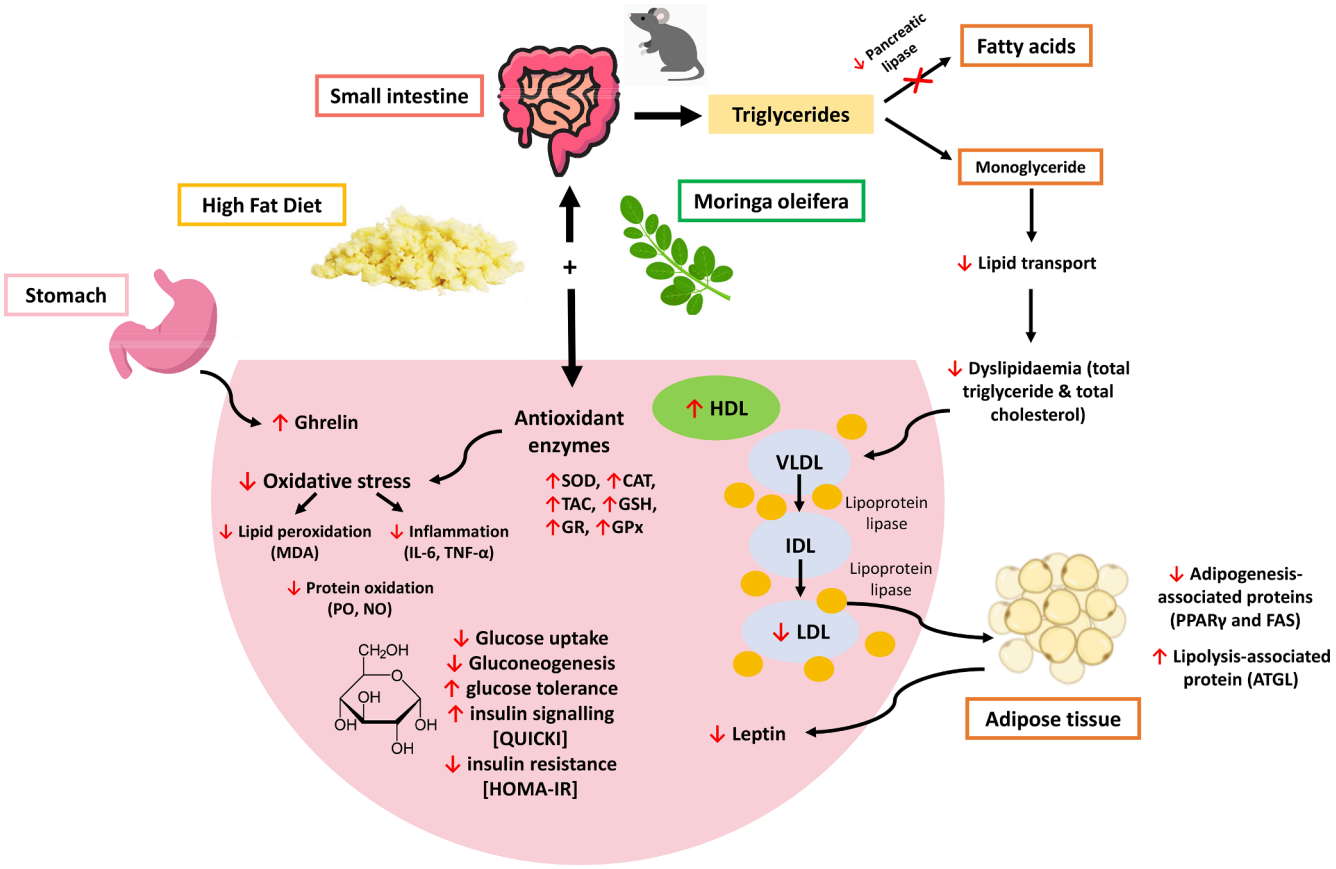

Fig. 2. Summary of significant anti-obesity mechanisms of MO extracts proposed by different in-vivo studies using animal models fed with high fat diet (Od-Ek, Deenin, Malakul, Phoungpetchara, & Tunsophon, 2020). Supplementation of MO could have caused an inhibition in the pancreatic lipase (supported by in-vitro findings) decreasing the breakdown of triglycerides into fatty acids. Strong evidence has been reported regarding the potential of MO in improving the lipid profile (decreasing total cholesterol, triglycerides, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and enhancing high-density lipoprotein (HDL) levels). MO extracts have regulated fat storage by downregulating the expression of adipogenesis-associated proteins (peroxisome proliferator-activated receptor gamma (PPARγ) and fatty acid synthase (FAS)) and upregulation of expression of lipolysis-associated protein (adipose triglyceride lipase (ATGL)). MO was also effective in improving the levels of antioxidant enzymes and thus decreasing oxidative stress, lipid peroxidation, protein oxidation, and inflammation. In addition, MO was effective in decreasing glucose uptake, gluconeogenesis, and glucose tolerance, while improving insulin signaling and resistance. Besides, MO also influenced satiety hormones in which it decreased levels of leptin, while increasing the levels of ghrelin. CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; HOMA-IR, homeostasis model assessment for insulin resistance; IDL, intermediate-density lipoprotein; IL-6, Interleukin 6; MDA, malondialdehyde; NO, nitric oxide; PO, protein carbonyl; QUICKI, quantitative insulin sensitivity check index; SOD, superoxide dismutase; TAC, total antioxidant capacity; TNF-α, tumor necrosis factor-α.

compounds involved in these mechanisms are not identified. Yet, few studies isolated specific compounds from MO and evaluated their anti-obesity activity. Such evidence can help in providing advanced evidence on the pharmacological mechanism behind the anti-obesity activity of MO. The compounds Niazinin B (Compound 1) and 2(4-[α-L-rhamnosyloxy)benzyl]isothiocynate (Compound 2) (Fig. 3) were extracted and isolated from MO seeds (Huang, Yuan, & Wang, 2020). The two compounds were studied for their inhibitory potential of intracellular lipid accumulation in 3T3-L1 adipocytes. Compound 1 showed no significant results, whereas Compound 2 inhibited the intracellular lipid accumulation significantly with a half maximal inhibitory concentration (IC_{50}) of 9.2 μg/mL (equal to 29.6 μM). Astragalin (Fig. 3) is another bioactive compound isolated from MO leaves was efficient in decreasing the TC and lipid accumulation in 3T3-L1 cells (Muni Swamy et al., 2020). In fact, benzylamine (Fig. 3), another compound found in MO, was successful in decreasing the lipid peroxidation markers in the liver of C57BI6 male mice (Iffiú-Soltész et al., 2010). Benzylamine was administrated in drinking water (3600 μmol/kg day) of mice with induced insulin resistance and HFD for 17 weeks.

Many plants, including MO, contain natural isothiocyanates (with a common functional group, —N═C═S) which are produced by the conversion of glucosinolates using enzymes into different types of isothiocyanates. Isothiocyanates have shown the ability to improve the lipid profile of diabetic individuals (Palliyaguru, Yuan, Kensler, & Fahey, 2018). The bioactive isothiocyanates extracted from MO seeds effectively decreased body weight and adiposity in C57B1/6J male mice fed with (a) standard low-fat diet containing 0.34% bioactive isothiocyanate, and (b) very high-fat diet containing 0.25% bioactive isothiocyanate for 12 weeks (Jaja-Chimedza et al., 2018). Furthermore, MO leaves extract were also able to decrease the body weight, decrease the percentage increase in weight, and decrease the adiposity index significantly in male Albino rats fed with HFD (to induce obesity) and were orally administered with 200 or 400 mg/kg bw of extract for one month (Ezzat et al., 2020).

The extract of MO has also shown questionable anti-obesity activity in the favor of the liver. A study evaluated the potential of methanolic MO leaves extract on hepatic lipid stores and hypertriglyceridemia due to a high fructose diet (HFRD) (Muhammad, Ibrahim, Ndhlala, & Erlwanger, 2020). A total of 51 female Sprague Dawley rats fed with HFRD were administered with 400 mg/kg extract for 10 weeks, however, the extract was not capable of preventing hypertriglyceridemia due to HFRD. Yet, a different study reported that MO aqueous extract decreased the liver weight and lipid accumulation in male C57BL/6

Table 1
Effect of MO on anthropometric measurements, lipid content, lipid profile, and preventing cardiovascular diseases.

Paper	Type of study and level of evidence	Compound/extract	Sample	Posology/treatment	Main results
(Saleem, Al-Dujaily, & Al-Murshidi, 2016)	Animal study (level 6)	MO leaves methanolic extract	50 male Albino Wistar rats	MO extract was administrated at a dose of 250 mg/kg or 500 mg/kg for 60 days	MO extract significantly decreased the total CHO, TG, LDL-C, and VLDL-C levels, and significantly increased the level of HDL-C.
(Kim & Kim, 2019)	Animal study (level 6)	MO leaves petroleum ether extract	20 male C57BL/6J mice (9-week-old)	Mice were fed HFD diet containing 0.1% leaf powder for 7 weeks	MO extract reduced the increased levels of CHO, TG, and LDL-C due to HFD. Extracts prevented hypercholesterolemia and fat deposition.
(Madkhali et al., 2019)	Animal study (level 6)	MO leaves methanolic extract	24 adult Wistar Albino rats	Rats were fed HFD and orally administrated 200 or 400 mg/kg/day of extract for 3 weeks	MO extract significantly helped in improving the lipid profile (decrease in CHO, TG, VLDL, and LDL, and increase in HDL), reducing waist size, Lee index, BMI, and food intake. It also reversed HFD-induced endothelium dysfunction.
(Xie et al., 2018)	Animal study (level 6)	MO leaves ethanolic extract	60 male C57BL/6J mice (6-week-old)	Mice fed with HFD and administered with 0.125, 0.25, or 0.5 g/kg of extract	MO extract resulted in decreasing the body weight, relative epididymal, perirenal, mesenteric fat weight and fat tissue size, hepatic fat accumulation, and levels of TC, LDL-C, and AST.
(Al-Gebily et al., 2019)	Animal study (level 6)	MO leaves aqueous extract	40 adult male Albino Wistar rats	Test group of obese animals were administrated with MO extract (20%) and HFD	The body weight gain, BMI, and levels of CHO, TC, and LDL decreased significantly, while levels of HLD increased significantly in the test group.
(Bais et al., 2014)	Animal study (level 6)	MO leaves methanolic extract	50 young male Albino Wistar rats with body weight of 120–150 g	Test groups were fed with HFD and 200 or 400 mg/kg MO extract for 49 days	The body weight, organ weight and levels of CHO, TC, and LDL decreased significantly, while levels of HLD increased significantly in the test group.
(Jain et al., 2010)	Animal study (level 6)	MO leaves methanolic extract	36 male Albino Wistar rats with body weight of 180–200 g	Test groups were fed with HFD and 150, 300, or 600 mg/kg MO extract for 30 days	The body weight, atherogenic index, and levels of CHO, TC, VLDL and LDL decreased significantly, while levels of HLD increased significantly in the test group.
(Hussein et al., 2018)	Animal study (level 6)	MO leaves aqueous extract	48 white male Albino rats (12–16 weeks-old) with average body weight of 160–200 g	Rats with HFD-induced obesity were orally administered with 600 mg/kg bw of extract for two months	MO extract was able to decrease the levels of CHO and TC significantly and reduce oxidative stress markers related to hyperlipidaemia.
(Othman et al., 2019)	Animal study (level 6)	MO leaves ethyl alcohol extract	36 adult male Wistar rats with average body weight of 200–230 g	Test group were fed HFD with oral administration of 200 mg/kg bw of extract for 6 weeks	MO extract was able to decrease the atherogenic index and levels of total lipids, CHO, TC, LDL significantly, while it increased the level of HDL.
(Greish et al., 2021)	Animal study (level 6)	MO oil extract	60 adult male Albino Wistar rats of 10–12 weeks age and 120–150 g body weight	Animals were subjected to HFD and MO oil extract (400 mg/kg)	The body weight and the levels of CHO, TG, VLDL, and LDL decreased significantly, while the level of HDL increased significantly in the test group. In addition, MO oil extract improved oxidative stress and male fertility markers.
(Nahar et al., 2016)	Animal study (level 6)	MO dry leaves (powdered form)	24 adult male long Evans rats with 150–189 g body weight	Animals were subjected to HFD and oral intake of MO dry leaves powder (50 mg/day) for 35 days	Intake of MO reduced anthropometric measurements (body weight, BMI, THC, and ABC) significantly.
(Ezzat et al., 2020)	Randomized, double-blind, placebo-controlled trial (level 1)	MO leaves petroleum ether extract in the form of hard gelatin capsules	15 female overweight or obese (BMI of 29–34 kg/m^2) participants of the age between 44 and 55 years old	Participant received 1 capsule per day containing 400 mg of extract for 8 weeks	The BMI, TC, and LDL of the participants significantly decreased after 8 weeks of MO intake.
(Kumar K & Mandapaka, 2013)	Randomized double-blind trial (level 1)	Dry MO leaves powder formula (with 5% table salt, 7% red chili powder and 7% coriander powder)	15 subjects (9 male and 6 female) with type II diabetes and obesity	Participants received 50 g of MO powder formula per day for 20 days	The level of LDL (and glucose) decreased significantly by MO leaves.
(Muni Swamy et al., 2020)	Laboratory study (level 6)	Astragalin (3-O-glucoside of kaempferol) isolated from MO leaves	3T3-L1 cells	Measurement of lipolytic and antiadipogenic activity	Astragalin decreased the TC content and lipid accumulation, and increased glycerol release in 3T3-L1 adipocytes.
(Huang et al., 2020)	Laboratory study (level 6)	Niazinin B (Compound 1) and 2(4-[α-L-rhamnosyloxy)benzyl] isothiocynate (Compound 2) extracted and isolated from MO seeds	3T3-L1 cells	Measurement of inhibition of lipid accumulation in 3T3-L1 adipocytes	Compound 1 showed no significant results, while compound 2 significantly inhibited the intracellular lipid accumulation with an IC_{50} of 9.2 μg/mL (equal to 29.6 μM).

(*continued on next page*)

Table 1 (*continued*)

Paper	Type of study and level of evidence	Compound/extract	Sample	Posology/treatment	Main results
(Sawmy & Meriga, 2020)	Laboratory study (level 6)	MO leaves hydroalcoholic extract	Pancreatic lipase	Measurement of inhibition activity	MO extract showed significant inhibition of pancreatic lipase activity (IC_{50} = 437.1 µg/mL).
(Adisakwattana & Chanathong, 2011)	Laboratory study (level 6)	MO leaves aqueous extract	Pancreatic lipase and cholesterol esterase	Measurement of inhibition activity	MO extract showed low inhibition activity against pancreatic cholesterol esterase, while no activity against pancreatic lipase.
(Joung et al., 2017)	Animal study (level 6)	Fermented and nonfermented MO leaves aqueous extract	Male C57BL/6 mice (4-week-old)	Mice were fed HFD diet for 10 weeks, HFD was supplemented with each type of extract at a dose of 250 mg/kg bw.	MO extracts caused a decrease in liver weight and lipid accumulation, and upregulation of liver metabolism genes. The lipotoxicity in quadriceps muscles which were induced by HDF were lowered by fermented MO extract.
(Iffiú-Soltész et al., 2010)	Animal study (level 6)	Benzylamine, as a compound found in MO	24 of C57BI6 male mice	Benzylamine was administrated in drinking water (3600 µmol/kg day) of mice with induced insulin-resistance and HFD for 17 weeks	Benzylamine was successful in decreasing the lipid peroxidation markers in the liver.
(Mabrouki et al., 2020)	Animal study (level 6)	MO leaves methanolic extract	24 three-month-old healthy male Wistar rats	Extract was orally administrated at a dose of 200 mg/kg/bw or 400 mg/kg/bw to obese rats for 12 weeks	MO extract significantly increased cardiac marker enzyme level, while it significantly decreased cardiac catalase, glutathione peroxidase, and superoxide dismutase levels.
(Jaja-Chimedza et al., 2018)	Animal study (level 6)	MO seed ethanolic extract containing bioactive isothiocyanates	48 normal and obese C57B1/6J male mice (5-week-old)	Normal mice were fed standard low-fat diet containing 0.34% bioactive isothiocyanate, while obese mice were fed a very high-fat diet containing 0.25% bioactive isothiocyanate for 12 weeks	Treatment with MO extract decreased body weight and adiposity.
(Ezzat et al., 2020)	Animal study (level 6)	MO leaves petroleum ether extract	42 male Albino rats	Rats with HFD-induced obesity were orally administered with 200 or 400 mg/kg bw of extract for one month	MO extract was able to decrease the final body weight, the percentage increase in weight, and the adiposity index significantly.
(Muhammad et al., 2020)	Animal study (level 6)	MO leaves methanolic extract	51 female Sprague Dawley rats (21-day-old)	Rats with HFRD were administered with 400 mg/kg extract for 10 weeks	MO extract did not help in preventing fructose-induced hypertriglyceridemia.

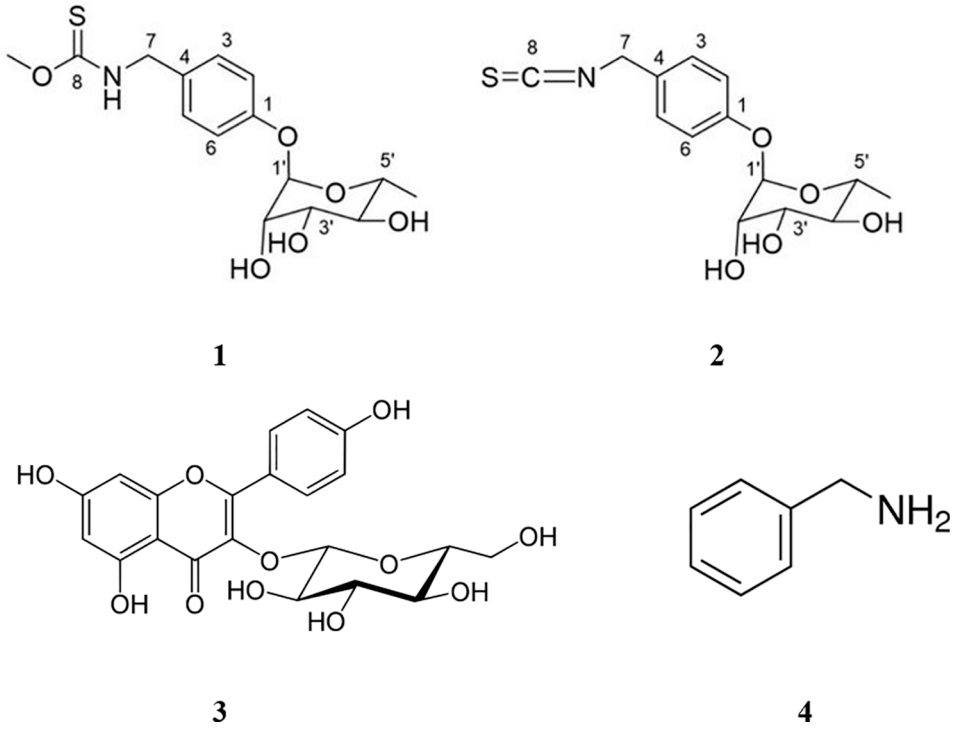

Fig. 3. Structure of Niazinin B (Compound 1), 2(4-[α-L-rhamnosyloxy)benzyl]isothiocynate (Compound 2), Astragalin (Compound 3) and Benzylamine (Compound 4).

mice fed HFD diet supplemented with each type of extract at a dose of 250 mg/kg bw for 10 weeks (Joung et al., 2017). In addition, the lipotoxicity in quadriceps muscles induced by HDF was lowered.

One of the methods through which the lipid content can be regulated is through the inhibition of pancreatic lipase. Pancreatic lipase plays a significant role in the metabolism of fat, thus the inhibition of pancreatic lipase reduces the hydrolysis of lipids, leading to a decrement in the absorption of lipid monomers and thus a reduction in fat accumulation (Liu, Liu, Chen, & Shi, 2020). Hydroalcoholic extract of MO leaves has shown promising pancreatic lipase inhibition (IC_{50} = 437.1 μg/mL) based on an in-vitro study (Sawmy & Meriga, 2020). Compounds such as hexamethanoic acid, tetradecanoic acid, stearic acid, malic acid, *cis*-vaccenic acid, *trans*-phytol, palmitoyl chloride, and flavone were identified in the hydrochloric extract of MO leaves in this study. Furthermore, a comparable study investigated the inhibition of pancreatic lipase and cholesterol esterase by MO leaves aqueous extract (Adisakwattana & Chanathong, 2011). Surprisingly, MO extract slightly inhibited pancreatic cholesterol esterase activity, while it showed no inhibition activity against pancreatic lipase. The findings of this study do not agree with the findings of the recent study conducted by Liu et al. A major difference between these two studies is the type of solvent used to prepare MO extract. The type of solvent used for extraction can significantly affect the extracted bioactive compounds and thus bioactivity (Ali Redha, Hasan, & Mandeel, 2018).

MO extract has also shown the potential of decreasing the risk of cardiovascular diseases. The administration of methanolic MO extract to three-month-old obese male Wistar rats at a dose of 200 mg/kg/bw or 400 mg/kg/bw for 12 weeks, significantly increased the cardiac marker enzyme level, while it significantly decreased cardiac catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) levels (Mabrouki, Rjeibi, Taleb, & Zourgui, 2020). The methanolic extract of MO leaves was analyzed by hyphenated chromatographic-mass spectrometry technique (LC-ESI-MS) through which the following compounds were identified: quinic acid, protocatchuic acid, epicatechin, *p*-coumaric acid, *trans*-ferrelic acid, rutin, hyperoside, naringin, quercetrin, 3,4-di-*O*-caffeoylquinic acid, salviolonic acid, quercetin, kaempferol, apigenin, luteolin, cirsiliol, cirsilineol, and acacetin. The most dominant phytochemicals in this extract were hyperoside (316.822 μg/g extract) and quercetin (204.685 μg/g extract), while the other phytochemicals were present in concentrations of less than 50 μg/g extract.

Overall, MO extracts and their components have shown a wide range of mechanisms to improve the lipid profile and lipid content. Through in-vitro studies, MO was able to inhibit intracellular lipid accumulation, and decrease the TC and lipid accumulation. Based on the in-vivo studies, MO was able to improve the lipid profile by decreasing the levels of CHO, TG, LDL-C, VLDL-C, and increasing the levels of and HDL/HDL-C. In addition, MO has also shown promising results in reducing the body weight, relative epididymal, perirenal, adiposity index, mesenteric fat weight and fat tissue size, hepatic fat accumulation, and the levels of AST, CC, GPx, and SOD. One clinical study suggested that MO can decrease BMI, TC, and LDL in overweight or obese individuals. Fig. 4 summarizes the main effects and mechanisms of MO in regulating the lipid and fat content.

3.2. Regulation of adipogenesis genes by MO

Adipogenesis is defined as the process in which preadipocytes develop into mature adipocytes, this process is regulated by several genes including peroxisome proliferator-activated receptor gamma (PPARγ) and sterol regulatory element-binding protein-1 (SREBP-1) (Ebrahimi et al., 2020). PPARγ, which is activated by coactivator-1 alpha (PGC1α), is associated with the synthesis of lipids, accumulation of fat, and insulin sensitivity. Besides, PPARγ can regulate the

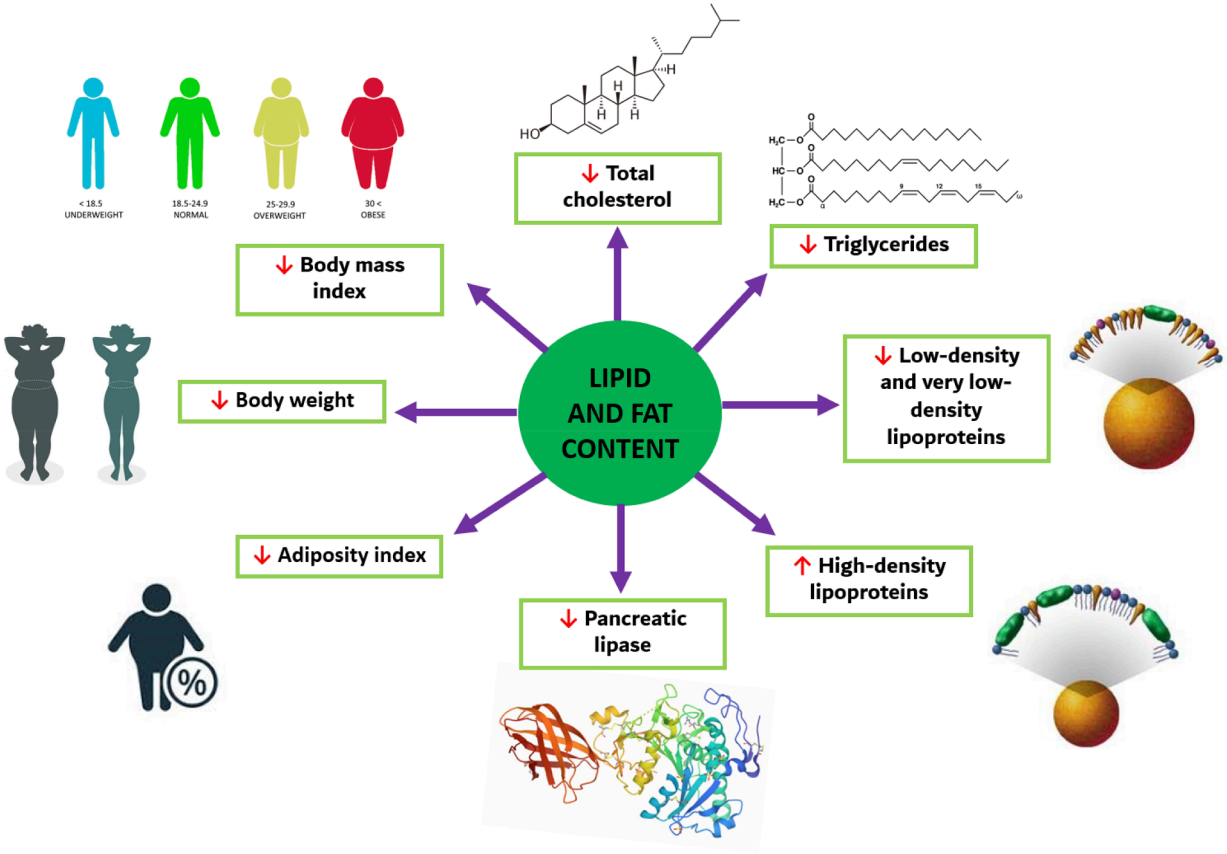

Fig. 4. Summary of the main effects and mechanisms of MO in regulating the lipid and fat content.

adipogenesis and lipogenesis by inducing the activity of enzymes (such as fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC)) involved in lipid synthesis and adipocyte differentiation (Ebrahimi et al., 2020). In addition, lipoprotein lipase (LPL), and glyceraldehyde-3-phosphate dehydrogenase (GPDH) also influence adipocyte differentiation and fat accumulation (Salehpour et al., 2020).

MO has shown significant regulation of adipogenesis genes in several studies as outlined in Table 2. With respect to the laboratory studies, a total of 4 research articles studied the regulation of adipogenesis genes using 3T3-L1 cells, and 1 research article was based on human adipose tissue mesenchymal stem cells. Ethanolic extract of MO leaves has induced apoptosis in 3T3-L1 cells by upregulating BAX and down-regulating BCL-2 expression, enhancing caspase-3 activity, and showing nuclear condensation (Balusamy et al., 2019). The extract inhibited adipogenesis by decreasing triglyceride content and suppressing CCAAT/enhancer-binding protein beta (C/EBPβ), adiponectin, FABP4, and PPARγ. Isoquercetin and quercetin-3-O-malonylglucoside were identified as the major component of the MO extract used in this study. Similarly, ethanol fractionated MO leaves extract reduced cellular lipid level, and decreased the expression of PPARγ, FAS, and ACC (in a concentration-dependent manner), and CCAAT/enhancer-binding protein alpha (C/EBPα) (in a concentration-independent manner) in 3T3-L1 cells (Kim et al., 2020). In addition, it has also been reported that petroleum ether MO leaves extract significantly downregulated expression of PPARγ, C/EBPα, C/EBPβ, and FAS, and upregulated expression of hormone-sensitive lipase (HSL), and enhanced the degree of phosphorylation of AMP-activated protein kinase α (AMPKα) and ACC significantly (Xie et al., 2018). The composition of MO leaves petroleum ether

Table 2
Regulation of adipogenesis genes by MO.

Paper	Type of study and level of evidence	Compound/extract	Sample	Posology/treatment	Main results
(Balusamy et al., 2019)	Laboratory study (level 6)	MO leaves ethanolic extract	3T3-L1 cells	Measurement of apoptosis and adipoogenesis	MO extract induced apoptosis by upregulating BAX and down-regulating BCL-2 expression, enhanced caspase-3 activity, and showed nuclear condensation. MO extract inhibited adipogenesis by decreasing triglyceride content and suppressing adipogenesis marks (C/EBPβ, adiponectin, FABP4, and PPARγ).
(Muni Swamy et al., 2020)	Laboratory study (level 6)	Astragalin (3-O-glucoside of kaempferol) isolated from MO leaves	3T3-L1 cells	Measurement of lipolytic and antiadipogenic activity	Astragalin downregulated the expression of PPARγ, C/EBPα, FAS, and leptin genes. On the other hand, it upregulated adiponectin expression.
(Kim et al., 2020)	Laboratory study (level 6)	MO leaves ethanolic extract	3T3-L1 cells	Anti-adipogenic activity	MO extract inhibited α-glucosidase, and lipase. The extract also reduced cellular lipid level, and decreased the expression of PPARγ, FAS, ACC (in a concentration-dependent manner), and C/EBPα (in a concentration-independent manner).
(Xie et al., 2018)	Laboratory study (level 6)	MO leaves petroleum ether extract	3T3-L1 cells	Anti-adipogenic activity	MO extract inhibited adipogenesis and had no effect on cell viability up to 400 μg/mL dosage. It significantly downregulated expression of adipogenesis-associated proteins (PPARγ, C/EBPα, C/EBPβ, and FAS) and upregulated expression of a lipolysis-associated protein (HSL), and significantly enhanced the degree of phosphorylation of AMPKα and ACC.
(Barbagallo et al., 2016)	Laboratory study (level 6)	MO extract (plant part and type of extract were not specified)	Human adipose tissue mesenchymal stem cells	Anti-adipogenic activity	MO extract showed the potential of reducing inflammation, lipid accumulation, and enhancing thermogenesis by the activation of UCP1, SIRT1, PPARα, and PGC1α. In addition, the extract was also helpful in inducing the activity of a protective and antioxidant enzyme known as heme oxygenase-1 (HO-1). The extract significantly reduced the expression of molecules involved in adipogenesis and upregulation of the expression of mediators participating in thermogenesis and lipid metabolism.
(Xie et al., 2018)	Animal study (level 6)	MO leaves petroleum ether extract	60 male C57BL/6J mice (6-week-old)	Mice fed with HFD and administered with 0.125, 0.25, or 0.5 g/kg of extract	MO extract significantly resulted in downregulation of expression of adipogenesis-associated proteins (PPARγ and FAS) and upregulation of expression of lipolysis-associated protein (ATGL). Besides, the degree of phosphorylation of AMPKα and ACC were also increased.
(Ezzat et al., 2020)	Animal study (level 6)	MO leaves petroleum ether extract	42 male Albino rats	Rats with HFD-induced obesity were orally administered with 200 or 400 mg/kg bw of extract for one month	MO extract was effective in significantly suppressing FAS and HMG-CoA. On the other hand, the levels of QUICKI were enhanced and the mRNA expression of MC4R and PPARα was increased, significantly.
(Waterman et al., 2015)	Laboratory study (level 6)	MO isothiocyanates extracted from leaves	H4IIE rat hepatoma cells	Gluconeogenesis assay	MO isothiocyanates downregulated the expression of G6P.
(Waterman et al., 2015)	Animal study (level 6)	MO isothiocyanates extracted from leaves	24 male C57BL/67 mice (at age of 4 or 5 weeks)	Extract was incorporated in the mice diet to deliver 800 mg of extract per kg of food, delivering 66 mg/kg/d of extract for three months	MO isothiocyanates decreased hepatic G6P expression.

extract is outlined at the end of this section. Astragalin (Fig. 3), isolated from MO leaves, downregulated the expression of PPARγ, C/EBPα, FAS, and leptin genes, but upregulated adiponectin expression in 3T3-L1 cells (Muni Swamy et al., 2020). Astragalin has previously been reported for its anti-obesity activity and activation of β-adrenergic receptor pathway; yet those findings were very limited (Riaz et al., 2018). A different in-vitro study used human adipose tissue mesenchymal stem cells reported that the MO extract activated uncoupling protein 1 (UCP1), sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor alpha (PPARα), and PGC1α causing reduction in inflammation, lipid accumulation and enhancement of thermogenesis (Barbagallo et al., 2016).

Isothiocyanates extracted from MO leaves (containing 4-[(α-L-rhamnosyloxy)benzyl]isothiocyanate (Compound 5) and 4-[4-O-acetyl-α-L-rhamnosyloxy)benzl]isothiocyanate (Compound 6)) decreased the expression of hepatic glucose-6-phosphatase (G6P) based on in-vitro (using H4IIE rat hepatoma cells) and in-vivo studies (Waterman et al., 2015). The in-vivo study used C57BL/67 male mice (at age of 4 or 5 weeks) and had the extract incorporated in their diet at a dose of 800 mg of extract per kg of food, delivering 66 mg/kg/d of extract.

Two studies used animal models in studying the regulation of adipogenesis genes by MO extract. A study reported that petroleum ether MO leaves extract were successful in downregulating the expression of adipogenesis-associated proteins (PPARγ and FAS) and upregulating the expression of lipolysis-associated protein (adipose triglyceride lipase (ATGL)) (Xie et al., 2018). Besides, the degree of phosphorylation of AMPKα and ACC was also increased in the animal models. In this study, 60 male C57BL/6J mice were fed with HFD and administered with 0.125, 0.25, or 0.5 g/kg of extract. The compounds quercitrin, isoquercitrin, and chrysin-7-glucoside were suggested as promising adipogenesis regulators present in MO. The second study used male Albino rats with HFD-induced obesity that were orally administered with 200 or 400 mg/kg bw of MO ethanolic extract for one month (Ezzat et al., 2020). The MO extract significantly suppressed FAS and β-hydroxy β-methylglutaryl-CoA (HMG-CoA). On the other hand, the levels of quantitative insulin sensitivity check index (QUICKI) were enhanced and the mRNA expression of melanocortin 4 receptor (MC4R) and PPARα were increased significantly. The ethanolic extract of MO leaves was analysed and the compounds identified in the extract were quercetin, quercetin-*O*-hexoside, quercetin-*O*-malonylhexoside, quercetin-*O*-rhamnosyl-hexosyl, kaempferol, kaempferide, kaempferol-*O*-pentoside, kaempferol-*O*-hexoside, kaempferol-*O*-malonyl hexoside, kaempferol-*O*-xylosyl-apiosyl-acetyl, feruloylquinic acid, apigenin-*O*-hexoside, and luteolin-*O*-rutinoside.

Based on the in-vitro studies, it is very clear that MO can inhibit

Table 3
Regulation of glucose uptake and insulin resistance by MO.

Paper	Type of study and level of evidence	Compound/extract	Sample	Posology/treatment	Main results
(Lahrita et al., 2015)	Laboratory study (level 6)	MO leaves methanolic extract	3T3-L1 pre-adipocytes	Measurement of glucose activity	MO extract showed insulin-induced glucose activity at a concentration of 50 μg/mL.
(Leone et al., 2018)	Clinical study – details about level of study were not mentioned clearly in the research	MO leaves powder	Saharawi people living in refugee camps: 17 Saharawi diabetic and 10 healthy people	Traditional meal supplemented with 20 g of *Moringa olifera* leaves powder were given to the participants	In diabetic participants, a lower increment of the postprandial blood glucose was determined after MO leaves intake.
(Waterman et al., 2015)	Laboratory study (level 6)	MO isothiocyanates extracted from leaves	H4IIE rat hepatoma cells	Gluconeogenesis assay	MO isothiocyanates inhibited gluconeogenesis.
(Attakpa et al., 2017)	Animal study (level 6)	MO leaves ethanolic extract	30 male C57BL/6 mice (4-week-old)	Mice received HFD for 8 weeks and then treated with 200, 400, or 600 mg/kg bw of extract by oral administration for 8 weeks	MO extract was beneficial in preventing weight gain, decreasing blood glucose, significantly restoring insulin levels to normal values, simulating the activation of insulin dependent Akt pathway, and increasing protein content of GLUT 4 in skeletal muscle, enhancement of hepatic steatosis.
(Iffiú-Soltész et al., 2010)	Animal study (level 6)	Benzylamine, as a compound found in MO	24 of C57BI6 male mice	Benzylamine was administrated in drinking water (3600 μmol/kg day) of mice with induced insulin-resistance and HFD for 17 weeks	In adipocytes, the insulin-induced activation of glucose transport and inhibition of lipolysis stayed the same. In the aorta, the nitrite levels were partially restored which decreased by HFD.
(Waterman et al., 2015)	Animal study (level 6)	MO isothiocyanates extracted from leaves	24 male C57BL/67 mice (at age of 4–5 weeks)	Extract was incorporated in the mice diet to deliver 800 mg of extract per kg of food, delivering 66 mg/kg/d of extract for three months	MO isothiocyanates increased glucose tolerance and insulin signaling.
(Ezzat et al., 2020)	Animal study (level 6)	MO leaves petroleum ether extract	42 male Albino rats	Rats with HFD-induced obesity were orally administered with 200 or 400 mg/kg bw of extract for one month	MO extract was able to decrease the levels of glucose, insulin, and HOMA-IR significantly.
(Othman et al., 2019)	Animal study (level 6)	MO leaves ethyl alcohol extract	36 adult male Wistar rats with average body weight of 200–230 g	Test group were fed HFD with oral administration of 200 mg/kg bw of extract for 6 weeks	MO extract was able to significantly decrease the levels of glucose, insulin, HOMA-IR, and QUICKI.
(Joung et al., 2017)	Animal study (level 6)	Fermented and nonfermented MO leaves aqueous extract	Male C57BL/6 mice (4-week-old)	Mice were fed HFD for 10 weeks, HFD was supplemented with each type of extract at a dose of 250 mg/kg bw	MO extracts resulted in an improved glucose intolerance test. The fermented MO extract also lowered the proinflammatory cytokine mRNA expression in the liver, the epididymal adipose tissue, and quadriceps.
(Jaja-Chimedza et al., 2018)	Animal study (level 6)	MO seed ethanolic extract containing bioactive isothiocyanates	48 normal and obese C57B1/6J male mice (5-week-old)	Normal mice were fed standard low-fat diet containing 0.34% bioactive isothiocyanate, while obese mice were fed a VHFD containing 0.25% bioactive isothiocyanate for 12 weeks	Treatment with MO extract decreased inflammatory gene expression, and showed an enhancement of glucose tolerance, and antioxidant gene expression.

adipogenesis, this can be by several associated mechanisms which include suppressing C/EBPα, C/EBPβ, FABP4, PPARγ, FAS, G6P, and HMG-CoA, yet the suppression of ACC and adiponectin is questionable. The in-vivo studies also supported the findings of the in-vitro studies through downregulating the expression of adipogenesis-associated proteins and upregulating the expression of lipolysis-associated protein. Nevertheless, no clinical studies have been conducted to explore the regulation of adipogenesis genes in humans.

3.3. Regulation of glucose uptake and insulin tolerance by MO

The glucose uptake into fat and muscle cells is controlled by insulin through regulation of vesicles that contain glucose transporter type 4 (GLUT4) (Leto & Saltiel, 2012). The PI3K/Akt pathway is involved in the apoptosis and glucose transport within cells and is significantly linked to insulin resistance-related T2DM (Yang et al., 2020). Compounds that can upregulate PI3K/Akt signaling and improve insulin sensitivity.

The mechanism of regulation of glucose uptake and insulin tolerance by MO was investigative with different perspectives as outlined in Table 3. It was reported MO leaves ethanol extract helped in preventing weight gain, decreasing blood glucose, significantly restoring insulin levels to normal values, simulating the activation of insulin-dependent Akt pathway, increasing protein content of GLUT4 in skeletal muscle, and enhancing hepatic steatosis. These effects were observed in 30 male C57BL/6 mice that received HFD for 8 weeks and then treated with 200, 400, or 600 mg/kg bw of the extract by oral administration for 8 weeks (Attakpa et al., 2017).

Benzylamine, as a compound found in MO, was administrated in drinking water (3600 μmol/kg day) to insulin-resistance C57BI6 male mice induced by HFD for 17 weeks (Iffiú-Soltész et al., 2010). In adipocytes, the insulin-induced activation of glucose transport and inhibition of lipolysis stayed the same. In aorta, the nitrite levels were partially restored which initially decreased due to HFD. MO isothiocyanates extracted from leaves (containing 4-[(α-L-rhamnosyloxy)benzyl]isothiocyanate (Compound 5) and 4-[4-O-acetyl-α-L-rhamnosyloxy)benzl] isothiocyanate (Compound 6)) increased glucose tolerance and insulin signaling in male C57BL/67 mice (Waterman et al., 2015). The extract was incorporated in the mice diet to deliver 800 mg of extract per kg of food, delivering 66 mg/kg/d of extract (Waterman et al., 2015). The same research group reported that MO isothiocyanates extract from leaves inhibited gluconeogenesis in H4IIE rat hepatoma cells. MO leaves extract showed insulin-induced glucose activity at a concentration of 50 μg/mL in 3T3-L1 pre-adipocytes (Lahrita, Kato, & Kawabata, 2015).

As mentioned earlier, MO contains unique bioactive isothiocyanates. It has been reported that the MO seed ethanol extract containing bioactive isothiocyanates decreased inflammatory gene expression, and showed an enhancement of glucose tolerance, and antioxidant gene expression in C57B1/6J male mice (Jaja-Chimedza et al., 2018). In this research, normal mice were fed a standard low-fat diet containing 0.34% bioactive isothiocyanate, while obese mice were fed a very high-fat diet (VHFD) containing 0.25% bioactive isothiocyanate for 12 weeks.

The levels of glucose, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) were decreased significantly in male Albino rats with HFD-induced obesity that were orally administered with 200 or 400 mg/kg bw of MO leaves petroleum ether extract for one month (Ezzat et al., 2020). The content of the MO ethanolic extract used in this study has been described earlier in Section 3.2. Another study also reported that MO leaves ethyl alcohol extract significantly decreased the levels of glucose, insulin, HOMA-IR, and QUICKI of adult male Wistar rats of HFD-induced obesity (Othman et al., 2019).

In a different study that compared fermented and nonfermented MO leaves aqueous extract's anti-obesity potential, suggested that MO extracts showed an improved glucose intolerance test (Joung et al., 2017). In addition, the fermented MO extract lowered the proinflammatory cytokine mRNA expression in the liver, the epididymal adipose tissue, and quadriceps. This research used C57BL/6 male mice fed with HFD for 10 weeks, HFD was supplemented with each type of extract at a dose of 250 mg/kg bw.

A clinical study suggested that MO leaves powder lowered the increment of the postprandial blood glucose in diabetic participates (Leone et al., 2018). The participants of this study were Saharawi people living in refugee camps who were given traditional meal supplemented with 20 g of MO leaves powder.

To summarize, MO extracts have improved the regulation of glucose uptake and insulin tolerance. This was achieved through the activation of insulin dependent Akt pathway, increasing the protein content of GLUT4, lowering postprandial blood glucose, enhancement of glucose tolerance and antioxidant gene expression. Nevertheless, only one clinical study suggested the regulation of glucose uptake by MO. Again, further evidence through clinical studies is required to provide a better understanding of glucose uptake and insulin tolerance regulation by MO.

3.4. Effect of MO on hormones and satiety hormones

The regulation of several hormones can influence obesity. Ghrelin and leptin are two appetite-regulating hormones that can significantly affect the energy balance and thus cause changes in appetite, food intake and weight gain (Rasaei, Abdul Karim, Abd Talib, Mohd Noor, & Karandish, 2019). Ghrelin is an orexigenic hormone that can regulate food intake and stimulate appetite, it is inversely correlated with body fat mass and is responsive to diet-induced alteration of body weight (Haghshenas et al., 2014). Leptin can regulate energy balance which is transmitted to the central nervous system (CNS) to lower appetite, acting as an energy-saving signal to the CNS (Koshki, Mollanovruzi, & Lamir, 2018).

A total of 1 laboratory study and 8 animal studies focused on the anti-obesity mechanism of MO in terms of the effect on hormone regulation or satiety hormones (Table 4). A study focusing on astragalin isolated from MO leaves reported that, at a concentration of 20 μg/mL, astragalin significantly increased secretion of adiponectin and decreased the secretion of leptin in 3T3-L1 cells (Muni Swamy et al., 2020). The level of adiponectin is negatively correlated with the percentage of body fat (Payab, Amoli, Qorbani, & Hasani-Ranjbar, 2017).

Aqueous extract of MO leaves was efficient in restoring the elevated level of leptin in male Albino rats with HFD-induced obesity (Hussein et al., 2018). HFD-induced obese rats received 600 mg/kg bw of MO extract every day for 2 months after induction of obesity. In another study, the effect of MO leaves petroleum ether extract on hormone regulation of male Albino rats that were subjected to HFD-induced obesity and were orally administered with 200 or 400 mg/kg/bw of extract for one month was evaluated (Ezzat et al., 2020). MO leaves petroleum ether extract was able to decrease the levels leptin, and vaspin, significantly. In a similar study, focusing on methanolic MO leaves extract, findings showed that the extract caused a significant decrease in serum obestatin (anorectic peptide), and VEGF levels, while it caused a significant increase in the serum ghrelin level in Albino Wistar male rats which were administered with extract at a dose of 250 mg/kg or 500 mg/kg for 2 or 3 months (Saleem, Al-Dujaily, & Al-Murshidi, 2016) . Another study also reported that MO leaves ethyl alcohol extract significantly decreased the level of leptin, while increasing the level of ghrelin of adult male Wistar rats of HFD-induced obesity (Othman et al., 2019).

The ethanolic MO extract (of aerial parts of the plant) was helpful in lowering the levels of leptin, resistin, malondialdehyde (MDA) and nitric acid (NO), and increasing the levels of adiponectin, significantly (Ahmed et al., 2014). These findings were based on an animal studying involving adult female Albino rats that received high cholesterol diet (HCD) for 12 weeks and were then treated with 600 mg/kg bw of the extract by oral administration for 12 weeks. Another study also used ethanolic MO extract (of aerial parts of the plant) and reported that the extract down-regulated mRNA expression of leptin and resistin, while it up-regulated adiponectin genes expression which was parallel to

Table 4
Regulation of hormones and satiety hormones.

Paper	Type of study and level of evidence	Compound/extract	Sample	Posology/treatment	Main results
(Kilany et al., 2020)	Animal study (level 6)	MO seed oil extract	48 Male Sprauge Dawely rats	Rats were fed with HFD for 20 weeks and 800 mg/kg bw *Moringa oleifera* seed oil extract	MO extract significantly improved HFS induced haematological and metabolic perturbations, reduced leptin and resistin. These effects were a result of promotion of antioxidant enzymes and reduction in lipid peroxidation, decreases in inflammatory cytokines, and iNOS protein expression.
(Muni Swamy et al., 2020)	Laboratory study (level 6)	Astragalin (3-O-glucoside of kaempferol) isolated from MO leaves	3T3-L1 cells	Measurement of lipolytic and antiadipogenic activity	At a concentration of 20 μg/mL, astragalin significantly increased secretion of adiponectin and decreased the secretion of leptin.
(Metwally et al., 2017)	Animal study (level 6)	MO ethanolic extract (aerial parts of plant)	32 adult female Wistar rats (90-days-old)	Rats were fed with HCD and extract of 600 mg/kg bw for 12 weeks	MO extract down-regulated mRNA expression of leptin and resistin, while it up-regulated adiponectin genes expression which was parallel to decrease in body weight and enhanced atherogenic index, coronary artery index, glucose level, and insulin level.
(Ahmed et al., 2014)	Animal study (level 6)	MO ethanolic extract (aerial parts of plant)	32 adult female Albino rats	Rats received HCD for 12 weeks and then treated with 600 mg/kg bw of extract by oral administration for 12 weeks	MO extract was helpful in lowering food intake, decreasing BMI, and the levels of leptin, resistin, MDA and NO. It also significantly increased the levels of adiponectin.
(Ezzat et al., 2020)	Animal study (level 6)	MO leaves petroleum ether extract	42 male Albino rats	Rats with HFD-induced obesity were orally administered with 200 or 400 mg/kg bw of extract for one month	MO extract was able to significantly decrease the levels of leptin, and vaspin.
(Hussein et al., 2018)	Animal study (level 6)	MO leaves aqueous extract	48 white male Albino rats (12–16 weeks-old) with average body weight of 160–200 g	Rats with HFD-induced obesity were orally administered with 600 mg/kg bw of extract for two months	MO extract was able to restore the elevated levels of leptin, and nuclear factor kappa B (NF-κB).
(Saleem, Al-Dujaily, & Al-Murshidi, 2016)	Animal study (level 6)	MO leaves methanolic extract	40 Albino Wistar male rats	Extract was administrated at a dose of 250 mg/kg or 500 mg/kg for 2 or 3 months	MO extract caused a significant decrease in body weight, serum obestatin, and VEGF levels, while it caused a significant increase in serum ghrelin level.
(Othman et al., 2019)	Animal study (level 6)	MO leaves ethyl alcohol extract	36 adult male Wistar rats with average body weight of 200–230 g	Test group were fed HFD with oral administration of 200 mg/kg bw of extract for 6 weeks	MO extract was able to decrease leptin level, while increasing the level of ghrelin.
(Waterman et al., 2015)	Animal study (level 6)	MO isothiocyanates extracted from leaves	24 male C57BL/67 mice (at age of 4 or 5 weeks)	Extract was incorporated in the mice diet to deliver 800 mg of extract per kg of food, delivering 66 mg/kg/d of extract for three months	MO isothiocyanates decreased plasma insulin, leptin, resistin, IL-1β, and TNFα.

decrease in body weight and enhanced atherogenic index, coronary artery index, glucose level, and insulin level (Metwally et al., 2017). This study was used adult female Wistar rats which were fed with HCD and extract of 600 mg/kg bw for 12 weeks.

One study considering the seed oil extract of MO reported that the seed oil extract was helpful in significantly improving HFS induced hematological and metabolic perturbations, and reducing leptin and resistin concentration (Kilany, Abdelrazek, Aldayel, Abdo, & Mahmoud, 2020). This study used male Sprague Dawely rats that were fed with HFD for 20 weeks and 800 mg/kg bw MO seed oil extract. Another study explored the effect of MO isothiocyanates extracted from its leaves on levels of plasma insulin, leptin, resistin, IL-1β, and TNFα (Waterman et al., 2015). The extract was incorporated in the diet of C57BL/67 male mice to deliver 800 mg of extract per kg of food, delivering 66 mg/kg/day of extract. The results suggested that MO extract was effective in decreasing the levels of plasma insulin, leptin, resistin, IL-1β, and TNFα.

To summarize, MO extracts were effective in ameliorating the levels of important hormones affected by obesity conditions. The findings suggested that MO is effective in reducing the levels of leptin, resistin, vaspin, QUICKI, HOMA-IR, obestatin, and increasing the levels of ghrelin and GLUT 4. Nevertheless, no clinical findings have been published to support these results which are based on in-vitro and in-vivo studies.

3.5. Other anti-obesity effects and mechanisms of MO

Several cellular mechanisms can be influenced by obesity. Four studies focused on different mechanisms related to the anti-obesity potential of MO (Table 5). A study evaluated the effect of aqueous MO extract on the gut microbiota of young Swiss albino mice (Elabd, Morsy, & Elmalt, 2018). The mice were administered with the extract at a dose of 200 mg/kg orally for 3 months to mice with HFD, as a result, the intestinal levels of Bifidobacteria decreased significantly, while body weight, interlukin 6, and Lactobacilli levels increased significantly. The extract was able to significantly restore the body weight, interleukin 6, and bacterial levels.

A different study analyzed the effect of ethanolic MO extract on the activity of Serum paraoxonase and arylesterase 1 (PON1) in obese adult rats who received 600 mg/kg bw for 12 weeks (Sarhat, Wadi, & Mahmood, 2018). PON1, the lipophilic antioxidant component of HDL-C, can inhibit the oxidative modification of LDL protecting lipoproteins against oxidation (Unal et al., 2012). The MO extract caused a significant decrease in serum PON1, TAS, CAT, and SOD levels, while the serum MDA (oxidative stress marker) level increased significantly. A different study evaluated the obesity modulation efficiency of MO aqueous extract using 40 adult male Wistar albino rats metabolism (Al-Gebily et al., 2019). The test group were administrated MO extract

Table 5
Other anti-obesity activities of MO.

Paper	Area of study, type of study and level of evidence	Compound/ extract	Sample	Posology/treatment	Main results
(Elabd et al., 2018)	Effect of MO extract on gut microbiota: Animal study (level 6)	MO leaves aqueous extract	45 young Swiss Albino mice	Extract was administrated at a dose of 200 mg/kg orally for 3 months to mice with HFD	Upon feeding mice with HFD, the intestinal levels of Bifidobacteria decreased significantly, while body weight, interlukin 6, and Lactobacilli levels increased significantly. MO extract was able to significantly restore the body weight, interleukin 6, and the bacterial levels.
(Sarhat et al., 2018)	Enzyme activity of paraoxonase and arylesterase: Animal study (level 6)	MO ethanolic extract (aerial parts of plant)	40 obese adult rats	Obese rats received 600 mg/ kg bw for 12 weeks	MO extract caused a significant decrease in serum PON1, TAS, CAT, and SOD levels, while the serum MDA level increased significantly.
(Al-Gebily et al., 2019)	Enzymatic activity and oxidative stress markers: Animal study (level 6)	MO leaves aqueous extract	40 adult male Wistar albino rats	Test group of obese animals were administrated with MO extract (20%) and HFD	Upon the treatment with MO extract, the levels of alanine aminotransferase, aspartate aminotransferase, LDH, CL, PON1, TNF-α, MDA, and NO decreased significantly with the help of MO, while the levels of GSH, SOD, and CAT increased significantly.
(Othman et al., 2019)	Oxidative stress markers and liver function enzymes: Animal study (level 6)	MO leaves ethyl alcohol extract	36 adult male Wistar rats with average body weight of 200–230 g	Test group were fed HFD with oral administration of 200 mg/kg bw of extract for 6 weeks	MO extract was able to significantly decrease the levels of MDA, PC, and NO, while it increased the levels of SOD, CAT, TAC, GSH, GR, and Gpx.
(Alia et al., 2019)	Haematological profile: Animal study (level 6)	MO leaves ethanolic extract	40 male DDY mice	Extract was fed to HFD mice with a dose of 5.6 mg/20 g bw/day or 11.2 mg/20 g bw/ day	MO extract helped in prevention of worsening the conditions of HFD mice, by increasing haemoglobin, slightly decreasing white blood cells, granulocytes, and mean platelet volume.

(20%) with HFD, after 6 weeks a significant decrease in lactate dehydrogenase (LDH), creatine kinase (CK), tumor necrosis factor alpha (TNF-α), cardio-hepatic MDA, and NO. On the other hand, the levels of cardio-hepatic glutathione, SOD, and CAT. The impact of MO on SOD and CAT is not clear as different studies have reported different findings, this can be associated with the dosage of extract and duration of the test. Another study also reported that MO leaves ethyl alcohol extract can regulate lipid peroxidation caused by obesity by significantly decreased the levels of MDA, NO, and protein carbonyl (PO) of adult male Wistar rats of HFD-induced obesity (Othman et al., 2019). In fact, the same study also reported that MO was effective in reducing the increase of alanine amino transferase (ALT), AST, alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) levels in the HFD-induced obese rats, ameliorating the levels of tissue liver function enzymes. Moreover, MO was also efficient in protecting the liver tissue by significantly increasing the levels of SOD, CAT, total antioxidant capacity (TAC), GSH, glutathione reductase (GR), and glutathione peroxide (Gpx).

The hematological profile of male DDY mice fed with HFD and ethanolic MO leaves extract at a dose of 5.6 mg/20 g bw/day or 11.2 mg/20 g bw/day showed that the extract contributed to preventing worsening the conditions of HFD mice, by increasing hemoglobin, slightly decreasing white blood cells, granulocytes, and mean platelet volume (Alia et al., 2019).

In addition to the main anti-obesity mechanisms of MO, MO also ameliorates the gut microbiota, oxidative stress markers, tissue liver function enzymes, and hematological profile of obese species.

4. Future perspectives

4.1. Novel anti-obesity bioactive compounds from MO

Most of the studies have focused on evaluating the anti-obesity of MO extracts rather than specific compounds isolated from MO. Based on the current evidence, it is clear that MO extracts contain bioactive compounds with anti-obesity activity. However, the studies focusing on the anti-obesity activity of specific compounds isolated from MO extracts are limited. Thus, this could potentially be the next milestone in anti-obesity research focusing on MO. This will provide a better understanding of the components of MO with an anti-obesity activity which can ultimately be incorporated in pharmaceutical products targeting weight loss. In fact, the solvents used to prepare MO extracts in the reported studies were typical organic solvents including petroleum ether, methanol, ethanol, and water. It is recommended to explore new solvents such as natural deep eutectic solvents to prepare extracts, due to their unique chemical properties that can enhance the extraction efficiency and being environmentally friendly with low or eliminated toxicity (Ali Redha, 2021).

4.2. MO in functional food products

Dried MO leaves and seeds have been used in a wide range of function food products including wheat bread, cookies, and snacks (Mehwish et al., 2020). With the current knowledge of anti-obesity potential of MO plant, this can be commercialized and incorporated to formulate new functional foods with fitness and weight-loss effectiveness. MO leaves are completely edible and are a rich source of protein (equivalent to the protein content of soybeans and kidney beans) containing 22–24% protein (Sahay, Yadav, & Srinivasamurthy, 2017). In fact, the genus *Moringa* has been reported to have a higher vitamin A content in comparison with carrots, higher vitamin C content than oranges, greater calcium content than milk, more potassium content in comparison with bananas, and higher levels of iron than spinach (Minaiyan, Asghari, Taheri, Saeidi, & Nasr-Esfahani, 2014). Since MO leaves can be eaten fresh or cooked and its seeds can be eaten fresh, roasted, or powdered; this can significantly increase the options of incorporating MO leaves and seeds in different functional foods with health promoting benefits (Palizban, Bakhshaei, & Asghari, 2015).

5. Conclusions

MO showed anti-obesity activity through different in-vitro and in-vivo studies. The anti-obesity activity mechanisms associated with this potential included decreasing body weight and improving the lipid profile by decreasing the levels of total cholesterol, triglycerides, low-density lipoprotein, very low-density lipoprotein, and increasing the levels of high-density lipoprotein, and high-density lipoprotein cholesterol. In addition, MO regulated genes associated with adipogenesis, such as downregulating the expression of adipogenesis-associated

proteins (PPARγ, C/EBPα, C/EBPβ, and FAS) and upregulating the expression of a lipolysis-associated protein (HSL) and improving phosphorylation of AMPKα and ACC. MO also showed its potential in increasing glucose tolerance and insulin signaling. Besides, MO also decreased the levels of the hormones: leptin, vaspin, and resistin. MO has shown clear anti-obesity potential through laboratory studies and animal studies, however, the evidence available which are based on clinical trials involving humans are very limited which were related to the effect of MO on body mass index, total cholesterol, low density lipoprotein, and postprandial blood glucose only. Thus, future studies could focus on clinical trials exploring the different mechanisms of the anti-obesity potential of MO on humans.

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Ethical statement

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CRediT authorship contribution statement

Ali Ali Redha: Conceptualization, Methodology, Validation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **Simone Perna:** Conceptualization, Methodology, Data curation, Supervision, Project administration. **Antonella Riva:** Data curation, Funding acquisition. **Giovanna Petrangolini:** Data curation, Funding acquisition. **Gabriella Peroni:** Data curation, Funding acquisition. **Mara Nichetti:** Data curation, Funding acquisition. **Giancarlo Iannello:** Data curation, Funding acquisition. **Maurizio Naso:** Data curation, Funding acquisition. **Milena Faliva:** Data curation, Funding acquisition. **Mariangela Rondanelli:** Conceptualization, Validation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abd Rani, N. Z., Husain, K., & Kumolosasi, E. (2018). Moringa genus: A review of phytochemistry and pharmacology. *Frontiers in Pharmacology, 9*, 108. https://doi.org/10.3389/fphar.2018.00108.

Adisakwattana, S., & Chanathong, B. (2011). α-glucosidase inhibitory activity and lipid-lowering mechanisms of Moringa oleifera leaf extract. *European Review for Medical and Pharmacological Sciences, 15*, 803–808.

Ahmed, H. H., Metwally, F. M., Rashad, H., Zaazaa, A. M., Ezzat, S. M., & Salama, M. M. (2014). Moringa oleifera offers a multi-mechanistic approach for management of obesity in rats. *International Journal of Pharmaceutical Sciences Review and Research, 29*(2), 98–106.

Al-Gebily, M., Morsy, F., Elzawahry, E., Ibrahim, D., & Abdel-Wahhab, K. (2019). Obesity modulating efficiency of moringa oleifera extract on obese modeled rats. *Egyptian Academic Journal of Biological Sciences. C, Physiology and Molecular Biology, 11*(1), 75–91. https://doi.org/10.21608/eajbsc.2019.28305.

Ali Redha, A. (2021). Review on extraction of phenolic compounds from natural sources using green deep eutectic solvents. *Journal of Agricultural and Food Chemistry, 69*(3), 878–912. https://doi.org/10.1021/acs.jafc.0c06641.

Ali Redha, A. A., Hasan, A. M., & Mandeel, Q. (2018). Phytochemical determinations of pomegranate (punica granatum) rind and aril extracts and their antioxidant, antidiabetic and antibacterial activity. *Natural Products Chemistry & Research, 06*(04). https://doi.org/10.4172/2329-6836.1000332.

Alia, F., Rizky, A. A., Syamsunarno, M., Ayu Sumirat, V., Ghozali, M., & Atik, N. (2019). The haematological profiles of high fat diet mice model with moringa oleifera leaves ethanol extract treatment. *Biomedical and Pharmacology Journal, 12*(04), 2143–2149. https://doi.org/10.13005/bpj/1849.

Attakpa, E. S., Sangare, M. M., Behanzin, G. J., Ategbo, J.-M., Seri, B., & Khan, N. A. (2017). Moringa olifeira lam. Stimulates activation of the insulin-dependent akt pathway. Antidiabetic effect in a diet-induced obesity (DIO) mouse model. *Folia Biologica (Praha), 63*(2), 42–51.

Bahmani, M., Eftekhari, Z., Saki, K., Fazeli-Moghadam, E., Jelodari, M., & Rafieian-Kopaei, M. (2016). Obesity phytotherapy: Review of native herbs used in traditional medicine for obesity. *Journal of Evidence-Based Complementary & Alternative Medicine, 21*(3), 228–234. https://doi.org/10.1177/2156587215599105.

Bais, S., Singh, G. S., & Sharma, R. (2014). Antiobesity and hypolipidemic activity of *Moringa oleifera* leaves against high fat diet-induced obesity in rats. *Advances in Biology, 2014*. https://doi.org/10.1155/2014/162914.

Balusamy, S. R., Perumalsamy, H., Ranjan, A., Park, S., & Ramani, S. (2019). A dietary vegetable, Moringa oleifera leaves (drumstick tree) induced fat cell apoptosis by inhibiting adipogenesis in 3T3-L1 adipocytes. *Journal of Functional Foods, 59*, 251–260.

Barbagallo, I., Vanella, L., Distefano, A., Nicolosi, D., Maravigna, A., Lazzarino, G., … Li Volti, G. (2016). M. oleifera Lam. Improves lipid metabolism during adipogenic differentiation of human stem cells. *European Review for Medical and Pharmacological Sciences, 20*, 5223–5232.

Bhattacharya, A., Tiwari, P., Sahu, P., & Kumar, S. (2018). A review of the phytochemical and pharmacological characteristics of Moringa oleifera. *Journal of Pharmacy and Bioallied Sciences, 10*(4), 181. https://doi.org/10.4103/JPBS.JPBS_126_18.

Daghaghele, S., Kiasat, A. R., Safieddin Ardebili, S. M., & Mirzajani, R. (2021). Intensification of extraction of antioxidant compounds from *Moringa Oleifera* leaves using ultrasound-assisted approach: BBD-RSM design. *International Journal of Fruit Science, 21*(1), 693–705. https://doi.org/10.1080/15538362.2021.1926396.

Dehghani, M., & Alizadeh, M. H. (2016). The effects of the natural coagulant Moringa oleifera and alum in wastewater treatment at the Bandar Abbas Oil Refinery. *Environmental Health Engineering and Management, 3*(4), 225–230. https://doi.org/10.15171/EHEM.2016.24.

Ebrahimi, R., Toolabi, K., Jannat Ali Pour, N., Mohassel Azadi, S., Bahiraee, A., Zamani-Garmsiri, F., & Emamgholipour, S. (2020). Adipose tissue gene expression of long non-coding RNAs; MALAT1, TUG1 in obesity: Is it associated with metabolic profile and lipid homeostasis-related genes expression? *Diabetology & Metabolic Syndrome, 12*(36). https://doi.org/10.1186/s13098-020-00544-0.

Elabd, E. M. Y., Morsy, S. M., & Elmalt, H. A. (2018). Investigating of moringa oleifera role on gut microbiota composition and inflammation associated with obesity following high fat diet feeding. *Open Acess Macedonian Journal of Medical Sciences, 6*(8), 1359–1364.

Ezzat, S. M., El Bishbishy, M. H., Aborehab, N. M., Salama, M. M., Hasheesh, A., Abdel Motaal, A., … Metwally, F. M. (2020). Upregulation of MC4R and PPAR-α expression mediates the anti-obesity activity of Moringa oleifera Lam. In high-fat diet-induced obesity in rats. *Journal of Ethnopharmacology, 251*(112541).

Gamboa-Gómez, C. I., Rocha-Guzmán, N. E., Gallegos-Infante, J. A., Moreno-Jiménez, M. R., Vázquez-Cabral, B. D., & González-Laredo, R. F. (2015). Plants with potential use on obesity and its complications. *EXCLI Journal, 14*, 809–831. https://doi.org/10.17179/EXCLI2015-186.

Gopalakrishnan, L., Doriya, K., & Kumar, D. S. (2016). Moringa oleifera: A review on nutritive importance and its medicinal application. *Food Science and Human Wellness, 5*(2), 49–56. https://doi.org/10.1016/j.fshw.2016.04.001.

Greish, S. M., Abdel Kader, G. S., Abdelaziz, E. Z., Eltamany, D. A., Sallam, H. S., & Abogresha, N. M. (2021). Lycopene is superior to moringa in improving fertility markers in diet-induced obesity male rats. *Saudi Journal of Biological Sciences, 28*(5), 2956–2963. https://doi.org/10.1016/j.sjbs.2021.02.034.

Haghshenas, R., Jafari, M., Ravasi, A., Kordi, M., Shariatzadeh, M., Hedayati, M., & Rahimi, M. (2014). The effect of eight weeks endurance training and high-fat diet on appetite-regulating hormones in rat plasma. *Iranian Journal of Basic Medical Sciences, 17*(4), 237–243.

Huang, L., Yuan, C., & Wang, Y. (2020). Bioactivity-guided identification of anti-adipogenic isothiocyanates in the moringa (moringa oleifera) seed and investigation of the structure-activity relationship. *Molecules, 25*(11). https://doi.org/10.3390/molecules25112504.

Hussein, S. A., El-Senosi, Y. A., & El-Sharkawy, G. H. (2018). Moringa Oleifera improve lipid metabolic disorders in obesity induced oxidative stress in rats. *Benha Veterinary Medical Journal, 35*(2), 380–395. https://doi.org/10.21608/bvmj.2018.96443.

Iffiú-Soltész, Z., Wanecq, E., Lomba, A., Portillo, M. P., Pellati, F., Szoko, E., … Carpene, C. (2010). Chronic benzylamine administration in the drinking water improves glucose tolerance, reduces body weight gain and circulating cholesterol in high-fat diet-fed mice. *Pharmacological Research, 61*(2010), 355–363.

Jain, P. G., Patil, S. D., Haswani, N. G., Girase, M. V., & Surana, S. J. (2010). Hypolipidemic activity of Moringa oleifera Lam., Moringaceae, on high fat diet induced hyperlipidemia in albino rats. *Revista Brasileira de Farmacognosia, 20*(6), 969–973. https://doi.org/10.1590/S0102-695X2010005000038.

Jaja-Chimedza, A., Zhang, L., Wolff, K., Garf, B. L., Kuhn, P., Moskal, K., … Raskin, I. (2018). A dietary isothiocyanate-enriched moringa (Moringa oleifera) seed extract improves glucose tolerance in a high-fat-diet mouse model and modulates the gut microbiome. *Journal of Functional Foods, 47*, 376–385.

Joung, H., Kim, B., Park, H., Lee, K., Kim, H.-H., Sim, H.-C., … Do, M.-S. (2017). Fermented *Moringa oleifera* decreases hepatic adiposity and ameliorates glucose intolerance in high-fat diet-induced obese mice. *Journal of Medicinal Food, 20*(5), 439–447. https://doi.org/10.1089/jmf.2016.3860.

Kilany, O. E., Abdelrazek, H. M. A., Aldayel, T. S., Abdo, S., & Mahmoud, M. M. A. (2020). Anti-obesity potential of Moringa olifera seed extract and lycopene on high fat diet induced obesity in male Sprauge Dawely rats. *Saudi Journal of Biological Sciences, 27*(10), 2733–2746. https://doi.org/10.1016/j.sjbs.2020.06.026.

Kim, D.-S., Choi, M.-H., & Shin, H.-J. (2020). Extracts of Moringa oleifera leaves from different cultivation regions show both antioxidant and antiobesity activities. *Journal of Food Biochemistry, 44*.

Kim, Y.-J., & Kim, H. S. (2019). Screening *Moringa* species focused on development of locally available sustainable nutritional supplements. *Nutrition Research and Practice, 13*(6), 529–534. https://doi.org/10.4162/nrp.2019.13.6.529.

Konstantinidi, M., & Koutelidakis, A. E. (2019). Functional foods and bioactive compounds: A review of its possible role on weight management and obesity's metabolic consequences. *Medicines, 6*(94). https://doi.org/10.3390/medicines6030094.

Koshki, M. H., Mollanovruzi, A., & Lamir, A. R. (2018). Effect of chronic high-intensity exercise on hunger and satiation and levels of acylated ghrelin and leptin in women. *Biomedical Human Kinetics, 10*(1), 67–75. https://doi.org/10.1515/bhk-2018-0011.

Kumar K, P., & Mandapaka, R. T. (2013). Effect of Moringa oleifera on blood glucose, LDL levels in type II diabetic obese people. *Innovative Journal of Medical and Health Science, 3*(1), 23–25.

Lahrita, L., Kato, E., & Kawabata, J. (2015). Uncovering potential of Indonesian medicinal plants on glucose uptake enhancement and lipid suppression in 3T3-L1 adipocytes. *Journal of Ethnopharmacology, 168*, 229–236.

Leone, A., Bertoli, S., Lello, S. D., Bassoli, A., Ravasenghi, S., Borgonovo, G., … Battezzati, A. (2018). Effect of moringa oleifera leaf powder on postprandial blood glucose response. In vivo study on saharawi people living in refugee camps. *Nutrients, 10*(1494).

Leto, D., & Saltiel, A. R. (2012). Regulation of glucose transport by insulin: Traffic control of GLUT4. *Nature Reviews Molecular Cell Biology, 13*, 383–396.

Liu, T.-T., Liu, X.-T., Chen, Q.-X., & Shi, Y. (2020). Lipase inhibitors for obesity: A review. *Biomedicine & Pharmacotherapy, 128*(110314). https://doi.org/10.1016/j.biopha.2020.110314.

Mabrouki, L., Rjeibi, I., Taleb, J., & Zourgui, L. (2020). Cardiac ameliorative effect of moringa oleifera leaf extract in high-fat diet-induced obesity in rat model. *BioMed Research International, 2020*.

Madkhali, H. A., Alharthy, K. M., Asiri, M. A., Ansari, M. N., Rehman, N. U., & Hamad, A. M. (2019). Moringa oleifera Lam. (Family Moringaceae) leaf extract attenuates high-fat diet-induced dyslipidemia and vascular endothelium dysfunction in Wistar albino rats. *Tropical Journal of Pharmaceutical Research, 18*(12), 2597–2604.

Mehwish, H. M., Rajoka, M. S. R., Xiong, Y., Cai, H., Aadil, R. M., Mahmood, Q., … Zhu, Q. (2021). Green synthesis of a silver nanoparticle using Moringa oleifera seed and its applications for antimicrobial and sun-light mediated photocatalytic water detoxification. *Journal of Environmental Chemical Engineering, 9*. https://doi.org/10.1016/j.jece.2021.105290.

Mehwish, H. M., Riaz Rajoka, M. S., Xiong, Y., Zheng, K., Xiao, H., Anjin, T., … He, Z. (2020). Moringa oleifera – A functional food and its potential immunomodulatory effects. *Food Reviews International*. https://doi.org/10.1080/87559129.2020.1825479.

Metwally, F. M., Rashad, H. M., Ahmed, H. H., Mahmoud, A. A., Abdol Raouf, E. R., & Abdalla, A. M. (2017). Molecular mechanisms of the anti-obesity potential effect of Moringa oleifera in the experimental model. *Asian Pacific Journal of Tropical Biomedicine, 7*(3), 214–221.

Minaiyan, M., Asghari, G., Taheri, D., Saeidi, M., & Nasr-Esfahani, S. (2014). Anti-inflammatory effect of Moringa oleifera Lam. Seeds on acetic acid-induced acute colitis in rats. *Avicenna Journal of Phytomedicine, 4*(2), 127–136.

Mirhashemi, M. S., Mohseni, S., Hasanzadeh, M., & Pishvaee, M. S. (2018). Moringa oleifera biomass-to-biodiesel supply chain design: An opportunity to combat desertification in Iran. *Journal of Cleaner Production, 203*, 313–327. https://doi.org/10.1016/j.jclepro.2018.08.257.

Muhammad, A. A., Pauzi, N. A. S., Arulselvan, P., Abas, F., & Fakurazi, S. (2020). *In vitro* wound healing potential and identification of bioactive compounds from *Moringa oleifera* lam. *BioMed Research International, 2020*. https://doi.org/10.1155/2013/974580.

Muhammad, N., Ibrahim, K. G., Ndhlala, A. R., & Erlwanger, K. H. (2020). Moringa oleifera Lam. Prevents the development of high fructose diet-induced fatty liver. *South African Journal of Botany, 129*, 32–39. https://doi.org/10.1016/j.sajb.2018.12.003.

Muni Swamy, G., Ramesh, G., Devi Prasad, R., & Meriga, B. (2020). Astragalin, (3-O-glucoside of kaempferol), isolated from *Moringa oleifera* leaves modulates leptin, adiponectin secretion and inhibits adipogenesis in 3T3-L1 adipocytes. *Archives of Physiology and Biochemistry*. https://doi.org/10.1080/13813455.2020.1740742.

Nahar, S., Faisal, F., Iqbal, J., Rahman, Md., & Yusuf, Md. (2016). Antiobesity activity of Moringa oleifera leaves against high fat diet-induced obesity in rats. *International Journal of Basic and Clinical Pharmacology, 1263–1268*. https://doi.org/10.18203/2319-2003.ijbcp20162427.

Od-Ek, P., Deenin, W., Malakul, W., Phoungpetchara, I., & Tunsophon, S. (2020). Anti-obesity effect of Carica papaya in high-fat diet fed rats. *Biomedical Reports, 13*(30). https://doi.org/10.3892/br.2020.1337.

Othman, A. I., Amer, M. A., Basos, A. S., & El-Missiry, M. A. (2019). Moringa oleifera leaf extract ameliorated high-fat diet-induced obesity, oxidative stress and disrupted metabolic hormones. *Clinical Phytoscience, 5*(48). https://doi.org/10.1186/s40816-019-0140-0.

Palizban, A., Bakhshaei, B., & Asghari, G. (2015). Quantitative analysis of the nutritional components in leaves and seeds of the Persian Moringa peregrina (Forssk.) Fiori. *Pharmacognosy Research, 7*(3), 242–248. https://doi.org/10.4103/0974-8490.157968.

Palliyaguru, D. L., Yuan, J.-M., Kensler, T. W., & Fahey, J. W. (2018). Isothiocyanates: Translating the power of plants to people. *Molecular Nutrition & Food Research, 62*(18), 1700965. https://doi.org/10.1002/mnfr.201700965.

Payab, M., Amoli, M. M., Qorbani, M., & Hasani-Ranjbar, S. (2017). Adiponectin gene variants and abdominal obesity in an Iranian population. *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity, 22*, 85–90.

Ramezani, M., Changizi-Ashtiyani, S., Sadeghzadeh, F., Hosseini, S.-S., Zarei, A., & Hosseini, N. (2018). Effect of hydroalcoholic extract of some medicinal plants on obesity. *European Journal of Medicinal Plants, 24*(1), 1–10. https://doi.org/10.9734/EJMP/2018/41111.

Rasaei, B., Abdul Karim, N., Abd Talib, R., Mohd Noor, I., & Karandish, M. (2019). The effect of simultaneous consumption of coffee caffeine and sleep deprivation on plasma ghrelin and leptin levels. *International Journal of Nutrition Sciences, 4*(2), 88–96. https://doi.org/10.30476/ijns.2019.82136.1017.

Riaz, A., Rasul, A., Hussain, G., Zahoor, M. K., Jabeen, F., Subhani, Z., … Selamoglu, Z. (2018). Astragalin: A bioactive phytochemical with potential therapeutic activities. *Advances in Pharmacological Sciences, 2018*. https://doi.org/10.1155/2018/9794625.

Sahay, S., Yadav, U., & Srinivasamurthy, S. (2017). Potential of Moringa oleifera as a functional food ingredient: A review. *International Journal of Food Science and Nutrition, 2*(5), 31–37.

Saleem, H., Al-Dujaily, A. N. G., & Al-Murshidi, M. H. H. (2016). Comparison study between effect of methanolic extract of moringa oleifera and exogenous ghrelin on lipid profile in atherogenic rats. *Research Journal of Pharmaceutical Biological and Chemical Sciences, 7*(3), 2210–2221.

Saleem, H., Al-Dujaily, A. N. G., & Al-Murshidi, M. H. H. (2016). Effect of Methanolic Leaf Extract of Moringa oleifera on Biochemical Markers in obesity induced rats. *Research Journal of Pharmaceutical, Biological and Chemical Sciences, 7*(3), 2222–2232.

Salehpour, A., Shidfar, F., Hedayati, M., Neshatbini Tehrani, A., Farshad, A. A., & Mohammadi, S. (2020). Bisphenol A enhances adipogenic signaling pathways in human mesenchymal stem cells. *Genes and Environment, 42*(13). https://doi.org/10.1186/s41021-020-00150-6.

Sarhat, E. R., Wadi, S. A., & Mahmood, A. R. (2018). Effect of ethanolic extraction of moringa oleifera on paraoxonase and arylesterase enzyme activity in high fat diet-induced obesity in rats. *Research Journal of Pharmacy and Technology, 11*(10), 4601–4604.

Sawmy, G. M., & Meriga, B. (2020). Therapeutic effect of Moringa oleifera leaf extracts on oxidative stress and key metabolic enzymes related to obesity. *International Journal of Pharmaceutical Sciences and Research, 11*(4), 1949–1957.

Sergent, T., Vanderstraeten, J., Winand, J., Beguin, P., & Schneider, Y.-J. (2012). Phenolic compounds and plant extracts as potential natural anti-obesity substances. *Food Chemistry, 135*(1), 68–73. https://doi.org/10.1016/j.foodchem.2012.04.074.

Singh, A. K., Rana, H. K., Tshabalala, T., Kumar, R., Gupta, A., Ndhlala, A. R., & Pandey, A. K. (2020). Phytochemical, nutraceutical and pharmacological attributes of a functional crop Moringa oleifera Lam: An overview. *South African Journal of Botany, 129*, 209–220. https://doi.org/10.1016/j.sajb.2019.06.017.

Unal, E., Eris, C., Kaya, B., Uzun, H., Cavdar, F., Yildar, M., … Titiz, I. (2012). Paraoxonase and arylesterase activities, lipid profile, and oxidative damage in experimental ischemic colitis model. *Gastroenterology Research and Practice, 2012*, 1–5. https://doi.org/10.1155/2012/979506.

Waterman, C., Rojas-Silva, P., Tumer, T. B., Kuhn, P., Richard, A. J., Wicks, S., … Raskin, I. (2015). Isothiocyanate-rich *Moringa oleifera* extract reduces weight gain, insulin resistance, and hepatic gluconeogenesis in mice. *Molecular Nutrition & Food Research, 59*(6), 1013–1024. https://doi.org/10.1002/mnfr.201400679.

Xie, J., Wang, Y., Jiang, W.-W., Luo, X.-F., Dai, T.-Y., Peng, L., … Sheng, J. (2018). Moringa oleifera leaf petroleum ether extract inhibits lipogenesis by activating the AMPK signaling pathway. *Frontiers in Pharmacology, 9*. https://doi.org/10.3389/fphar.2018.01447.

Xiong, Y., Rajoka, M. S. R., Mehwish, H. M., Zhang, M., Liang, N., Li, C., & He, Z. (2021). Virucidal activity of Moringa A from Moringa oleifera seeds against Influenza A Viruses by regulating TFEB. *International Immunopharmacology, 95*. https://doi.org/10.1016/j.intimp.2021.107561.

Yang, Q., Wen, Y., Shen, J., Chen, M., Wen, J., Li, Z., … Xia, N. (2020). Guava leaf extract attenuates insulin resistance via the PI3K/Akt signaling pathway in a Type 2 diabetic mouse model. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 2020*(3), 713–718.