

## Preventive Effects of *Moringa oleifera* on Obesity and Hyperlipidaemia: A Systematic Review

(Kesan Pencegahan *Moringa oleifera* terhadap Obesiti dan Hiperlipidaemia: Suatu Ulasan Sistematik)

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### ABSTRACT

Obesity and hyperlipidaemia are metabolic dysregulations, arising from poor lifestyle and excessive dietary intakes which may contribute to many chronic diseases if not treated. Studies have shown that plant-based supplementations can suppress this metabolic dysregulation. *Moringa oleifera* (MO) is a plant that is known to be nutritious and can alleviate obesity and hyperlipidaemia owing to its medicinal properties. A literature search on the effects of MO on obesity and hyperlipidaemia using electronic databases which included Ovid Medline and Scopus was performed. Specific descriptors were used to perform the search strategy. The articles were selected based on the principles that report on the effects of MO on obesity and hyperlipidaemia. Titles of the articles were screened for *Moringa oleifera* OR obesity OR hyperlipidaemia. Twenty-nine articles, 19 from Ovid Medline and 10 from Scopus were selected based on the inclusion and exclusion criteria. A flow chart was created to represent the study selection. Based on the chosen articles, MO was shown to suppress obesity and hyperlipidaemia directly and indirectly through the regulation of gene expression, enzyme activity and adipocytokines. Through animal trials, MO demonstrated promising results in alleviating obesity and hyperlipidaemia. More human trials should be performed to strengthen the accomplished effects seen on animals. As there were no side effects identified in animal studies, it could be recommended to patients with obesity and hyperlipidaemia.

Keywords: Adipocytokines; hyperlipidaemia; *Moringa oleifera*; obesity

### ABSTRAK

Obesiti dan hiperlipidemia adalah disregulasi metabolik yang disebabkan oleh gaya hidup yang tidak sihat dan pengambilan makanan berlebihan yang boleh menyumbang kepada banyak penyakit kronik jika tidak dirawat. Kajian menunjukkan bahawa suplemen berasaskan tumbuhan ini dapat menyekat disregulasi metabolik ini. *Moringa oleifera* (MO) adalah herba tumbuhan yang diketahui berkhasiat dan dapat mengurangkan kegemukan dan hiperlipidemia kerana kandungan perubatannya. Pencarian kepustakaan mengenai kesan MO terhadap obesiti dan hiperlipidemia dilakukan menggunakan pangkalan data elektronik yang merangkumi Ovid Medline dan Scopus. Pemerihal khusus digunakan sebagai strategi pencarian. Artikel dipilih berdasarkan prinsip yang melaporkan mengenai kesan MO terhadap obesiti dan hiperlipidemia. Judul artikel yang disaring menggunakan *Moringa oleifera* ATAU kegemukan ATAU hiperlipidemia. Dua puluh sembilan artikel, 19 daripada Ovid Medline dan 10 daripada Scopus dipilih berdasarkan kriteria kemasukan dan pengecualian. Carta aliran dibuat untuk mewakili pemilihan kajian. Berdasarkan artikel yang dipilih, MO terbukti dapat menyekat obesiti dan hiperlipidemia secara langsung dan tidak langsung melalui pengaturan ekspresi gen, aktiviti enzim dan adipositokin. Melalui kajian pada haiwan, MO menunjukkan hasil yang memberangsangkan dalam mengurangkan obesiti dan hiperlipidemia. Lebih banyak kajian manusia harus dilakukan untuk menguatkan lagi kesan MO yang dilihat pada haiwan. Oleh kerana tidak ada kesan sampingan yang ditunjukkan pada kajian haiwan maka penggunaan MO ini boleh disarankan kepada pesakit obesiti dan hiperlipidemia.

Kata-kunci: Adipositokin; hiperlipidemia; *Moringa oleifera*; obesiti

## INTRODUCTION

Obesity is a condition where abnormal or excessive fat accumulation occurs in the body which may have an adverse impact on health (WHO 2021). It develops from a wide range of contributing factors which includes dietary patterns, physical inactivity, medication use, environment, age, ethnicity as well as family history (CDC 2021). Obesity is linked to a number of metabolic diseases such as hypertension, high serum cholesterol, low HDL, hyperglycaemia, and independently associated with higher incidence of cardiovascular diseases (CVD) (International Diabetes Federation 2006). Obesity is usually assessed using the body mass index (BMI). A BMI over 25 kg/m<sup>2</sup> is defined as overweight while a 30 kg/m<sup>2</sup> and above is considered as obese. Obesity has reached epidemic proportions globally, with more than 1.9 billion adults (18 years and older) overweight and of this over 650 million being obese in 2016 (WHO 2021). In addition to that, over 340 million children and adolescent aged 5-19 were considered overweight and obese in the same year.

Obesity is the leading cause of death globally, where the rate of deaths related to a high BMI increased by 28.3%, from 41.9 to 53.7 deaths per 100,000 people (GBD Obesity Collaborators 2017). Being obese contributes to abnormalities in lipid metabolism which is described as hyperlipidaemia. This condition is not a disease but a metabolic disorder that could contribute to many diseases, particularly CVD (Singh et al. 2011). Hyperlipidaemia is characterised by elevated levels of plasma triglyceride (TG), free fatty acid (FFA), very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), apolipoprotein B (Apo B) and decreased levels of HDL (Singh et al. 2011). Approximately 60-70% of obese patients and 50-60% of overweight patients are hyperlipidaemic (Feingold & Grunfeld 2018).

A healthy lifestyle and balanced diet may not be sufficient to prevent or treat obesity and hyperlipidaemia as individuals tend to be occupied with work-life, increasing the likeliness to western-style dietary patterns. As a result, treatment of both obesity and obesity-associated hyperlipidaemia depends on pharmacological drugs such as statins, fibrates, niacin, metformin, orlistat, lorcaserin, and ezetimibe (Dias et al. 2018). Over the past years, despite promising results, several drugs have exhibited adverse side effects, with some being withdrawn due to causing severe reactions (Kang & Park 2012). Ever since ancient times, plants have been identified and consumed by humans for various medicinal purposes and even the present-day drug developments are depending on using plants to address

many modern diseases. Plants are an abundant source of chemical diversity when it comes to identifying new drug modules, mainly due to their less toxic, safe efficient and inexpensive characteristic (Oryan 2015).

MO or drumstick tree is a drought-resistant tree found at the southern foothills of the Himalayas in north-western India (Leone et al. 2015). Many parts of MO are edible and nutritious; the leaves being the most beneficial, providing a significant source of vitamin B, C, K, provitamin A as  $\beta$ -carotene, manganese, calcium, potassium, essential amino acids and protein (Leone et al. 2015). In addition to that, a comparative study between MO and other foodstuff puts this plant on top. It contains 7 times the vitamin C of oranges, 4 times the vitamin A of carrots, 4 times the calcium of milk and 2 times the protein of yoghurt. With these significant nutritive values, MO is often imported to poor countries for treating malnutrition in human, especially infants and nursing mothers (Mahmood et al. 2010). Furthermore, MO is used as a potential antioxidant, antidiabetic, anti-inflammatory, anticancer, and antimicrobial agent (Gopalakrishnan et al. 2016). As MO is nutritious with various known medicinal properties, this systematic review was conducted to evaluate the therapeutic potential of MO in the context of obesity and hyperlipidaemia.

## METHODS

### LITERATURE SEARCH STRATEGY

A literature search using Medline via Ovid Medline and Scopus was conducted to determine appropriate studies on MO in obesity and obesity-associated hyperlipidaemia. The search strategy was done using a combination of the following sets keywords: 1. *Moringa* OR *Moringa oleifera* AND 2. obesity OR obese OR hyperlipidaemia OR dyslipidaemia OR lipid OR cholesterol. All the references obtained from the selected studies were reviewed for additional relevant studies.

### SELECTION OF RESEARCH ARTICLES

Studies with the following characteristic were selected: 1. Report the effect of MO on obesity and hyperlipidaemia. Articles selection was performed by all authors with only articles conforming to the above characteristic included in the current review. The selected articles were glanced at in detail to retrieve essential information.

### INCLUSION AND EXCLUSION CRITERIA

The inclusion of articles was restricted to: 1. articles that were published in the English language with abstracts;

2. full-text articles; 3. any extracts of the plant MO used in studies; and 4. report on human and animal studies. Articles were excluded based on the following criteria: 1. report on other diseases or disorder; 2. written in other languages; and 3. case reports, review articles, letter, news, case studies.

#### DATA EXTRACTION

Data extraction was performed by two reviewers where the eligible study articles were retrieved, and any difference of opinions was resolved through further discussion between the reviewers. The articles were screened and removed in three stages. Firstly, articles that did not match the inclusion criteria based purely on the title were excluded. In the second stage, the abstract of the remaining articles was screened and excluded based on the inclusion criteria. Lastly, the remaining full-text articles were screened and removed based on the inclusion criteria. Duplicate articles were removed and was considered only once. A separate data extraction form was used to extract the following data or information from the studies: 1. title and year of publication; 2. type of extract used; 3. dosage of MO; 4. treatment period; 5.

type and sample population of the study; and 6. results or outcomes of the study.

## RESULTS

#### SEARCH RESULTS

From the literature search, 153 articles were identified from the following databases: 93 from Ovid Medline and 60 from Scopus. The title and abstract of the articles were independently assessed and screened by two reviewers for the article's selection criteria. This resulted in 30 articles, 19 from Ovid Medline and 11 from Scopus which were directly related to studies with MO on obesity and/or hyperlipidaemia. There were no duplicates materials found in both the databases search results. The 30 articles were further assessed and rejected based on the inclusion and exclusion criteria. One article from Scopus was rejected as it did not match the inclusion and exclusion criteria. Full-text articles were obtained for the selected 29 articles, 19 from Ovid Medline and 10 from Scopus. As a result, 29 full-text articles that match the inclusion and exclusion criteria were included in this review. A flow chart was created to represent the study selection (Figure 1).

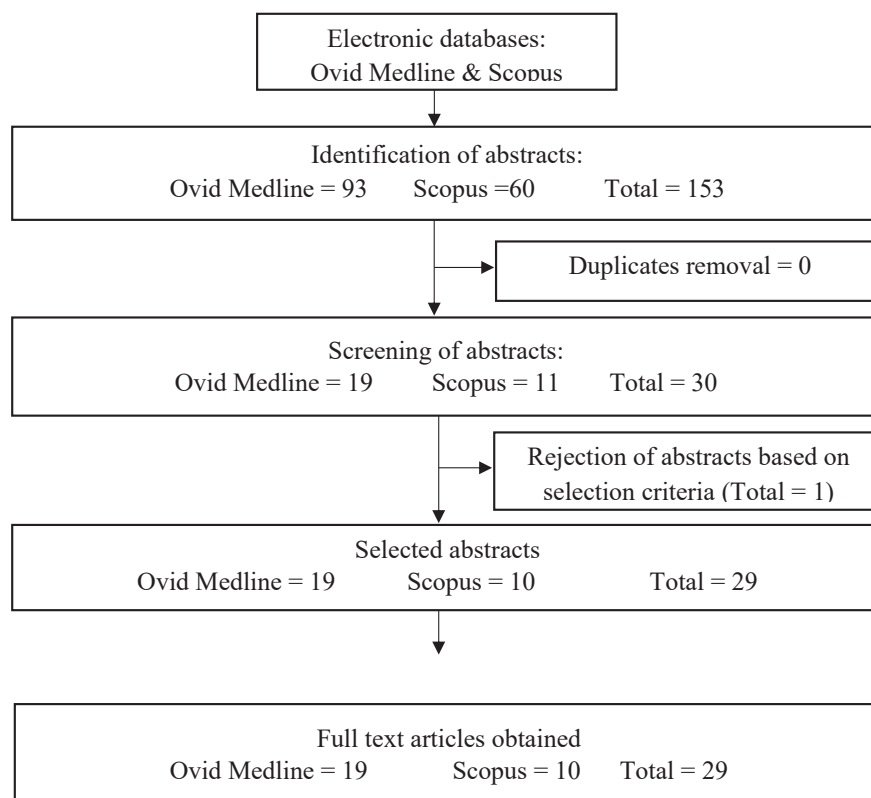


FIGURE 1. Flow chart of the study selection process

## STUDY CHARACTERISTICS

The selected 29 articles consisted of 2 *in vitro* and 27 *in vivo* studies. Within the 27 *in vivo* studies, 21 reported on rats, 3 with mice and 1 each with rabbit, dairy cow and human, respectively. All the 24 studies using rodents were given a high-fat diet (HFD) for the induction of obesity and impaired lipid levels. However, the studies using rabbit, cow and human were not administered with HFD. In addition, male and female or combination of both gender models were used in the chosen studies. Based on the type of metabolic diseases, 20 studies focused on hyperlipidaemias, showing MO's effect on lipid profiles and cytokines, six studies focused on obesity parameters while the remaining three studies focused on both the disease parameters. All the studies were conducted using experimental designs that compared the results of MO treated groups with control groups. The explants used in the chosen studies differed from one another; 23 studies reported using leaves of MO, three used the whole plant and three used seed explants as their test compound. The preparation of MO also differs from one study to another. Based on the review, 23 studies used MO extract, 4 studies used the leaf powder of MO, 2 studies used the whole plant powder and 1 study used both the powder and extract of MO for the treatment. The extract of MO plant was prepared using different solvents such as methanol, ethanol, aqueous and hexane in order to extract the highest possible nutrients in the plants. The lowest dosage of the plant extract given orally to the experimental model was 0.03 g/kg while the highest was 800 mg/kg. Furthermore, the lowest dosage of the leaf powder given was 0.737% and the highest dosage given was 30%. The least used treatment period was 14 days, with 90 days being the highest. In addition to the above, the *in vitro* study used a dosage of 5 mg/mL, 10 mg/mL, and 400 µg/mL to examine the effect of MO on the  $\alpha$ -glucosidase, pancreatic amylase, pancreatic lipase, pancreatic cholesterol esterase, adipogenesis, and cholesterol micellization.

## EFFECT OF MO ON OBESITY

Methanolic leaf extract of MO at a dosage of 500 mg/kg for 60 days exhibited a significant decrease in body, liver, kidney, and heart weights of rats when compared with a lower dosage of 250 mg/kg (Saleem et al. 2016). The same article also stated that following treatment of 90 days, methanolic leaf extract of MO at dosage of 500 mg/kg significantly decreased vascular endothelial growth factor (VEGF) as well as body weight of rats. Treatment with raw leaf powder of MO at dosage of 50 mg for 35 days elicited a significant reduction in total cholesterol

(TC), abdominal circumference (AC), body mass index (BMI), and body weight of rats (Nahar et al. 2016). Methanolic extract of MO at dosages of 150, 300, and 600 mg/kg for 30 days significantly reduced the atherogenic index in rats (Jain et al. 2010). Aqueous extract of MO at a dosage of 800 mg/kg for 3 months significantly reduced weight gain, lowered fat accumulation and reduced weight of liver in the tested mice (Waterman et al. 2015). Ethanolic extract of MO aerial parts significantly lowered body weight, atherogenic index and cardiovascular risk index in rats at a dosage of 600 mg/kg for 12 weeks (Metwally et al. 2017).

While the aqueous leaf extract of fermented and non-fermented MO at 250 mg/kg for 10 weeks did not significantly alter adiposity, quadriceps muscle in mice, however the liver weight did decrease significantly (Joung et al. 2017). Ethanolic extract of MO aerial parts at a dosage of 600 mg/kg for 12 weeks significantly decreased TC, AC, and BMI in rats (Ahmed et al. 2014). Raw grinded leaf powder of MO at dosages of 10 and 15% for 45 days caused a reduction in body weight in rats (Halaby et al. 2013). The methanolic leaf extract of MO at a dosage of 200 and 400 mg/kg for 49 days significantly decreased atherogenic index, liver weight and kidney weight in obese rats (Bais et al. 2014). Ethanolic leaf extract of MO at a dosage of 300 and 600 mg/kg for 14 days did not elicit any significant effect on body weight in rats (Atsukwei et al. 2014). Aqueous and ethanolic extract and grinded leaf powder of MO at a dosage of 400 mg/kg and 0.737% significantly reduced atherogenic index in rats (Helmy et al. 2017). Hexane seed oil extract at a dosage of 0.5 mL/kg for 8 weeks significantly reduced body weight in obese rats (Elabd et al. 2017). MO powder at a dosage of 0.03 g/kg and 0.07 g/kg significantly reduced body mass index non-academic staff of both sexes of Bingham University, Nigeria (Seriki et al. 2015).

Furthermore, Elabd et al. (2018), stated that treatment for 3 months with aqueous extract of MO as a dosage of 200 mg/kg showed a significant ( $P < 0.05$ ) decrease in total body weight compared to the obese group rats. Ethyl alcohol leaf extract of MO at a dosage of 300 mg/kg markedly reduced the percentage of weight gain after treatment for 6 weeks (Othman et al. 2019). Hydroalcoholic MO leaf extract at a dosage of 100 and 200 mg/kg for 28 days showed significant ( $P < 0.001$ ) reduction in elevated levels of body weight compared to the control group of rats (Rajanandh et al. 2012). Aqueous extract of MO powder at a dose of 200 mg/kg for 60 days completely prevented fructose induced weight gain in obese group and partially prevented

the weight loss observed in STZ induced diabetic rats (Divi et al. 2012). Petroleum ether leaf extract of MO at a dosage of 400 µg/mL for 4 weeks decreased body weight, relative epididymal, perirenal, and mesenteric fat weight, fat tissue size as well as hepatic fat accumulation in C57BL/6J mice (Xie et al. 2018).

#### EFFECT OF MO ON HYPERLIPIDAEMIA

Methanolic leaf extract at a dosage of 500 mg/kg for 60 days significantly reduced serum TC, triglyceride (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and significantly increased HDL levels compared to the dosage 250 mg/kg (Saleem et al. 2016). Methanolic extract of MO at dosage of 150, 300, and 600 mg/kg for 30 days significantly decreased the levels of TG, VLDL, LDL, and increased level of HDL in obese rats (Jain et al. 2010). Aqueous leaf extract of MO at a dosage of 800 mg/kg for 3 months significantly lowered TC and lipids in liver in obese rats (Waterman et al. 2015). Aqueous extract of fermented MO at a dosage of 250 mg/kg for 10 weeks significantly decreased lipid accumulation but only partially reduced by non-fermented MO at the same dosage in rats (Joung et al. 2017). Ethanolic extract of aerial parts of MO at a dosage of 600 mg/kg for 12 weeks significantly decreased serum TC, LDL, TG levels and significantly decreased levels of HDL in rats (Ahmed et al. 2014). Grinded leaf powder of MO at dosage of 0.5% and 1.0% for 4 weeks significantly reduced serum and liver TG, PL, TC while significantly decreasing HDL in only serum (Ndong et al. 2007). Leaf powder of MO at dosage of 10 and 15% for 45 days significantly reduced TC, TG, LDL, VLDL while significantly decreasing HDL (Halaby et al. 2013).

Methanolic leaf extract of MO at a dosage of 200 and 400 mg/kg for 49 days significantly decreased TC, TG, LDL, fatty deposition in liver and significantly decreased HDL as well as degeneration of hepatocytes (Bais et al. 2014). Ethanolic extract of MO at a dosage of 300 and 600 mg/kg for 14 days have significant effect on TC, and TG in male and female rats. However, only dosage of 600 mg/kg had significant reduction in LDL levels and increment of HDL levels in male and female rats (Atsukwei et al. 2014). Aqueous and ethanolic extract of MO (200 and 400 mg/kg) together with leaf powder (0.737% and 1.475%) significantly reduced TC level. However, only 0.737% and 400 mg/kg dosage of MO significantly reduced LDL and increased HDL levels. Apart from that, there was no significant change obtained from all the doses for the TG level (Helmy et al. 2017). Hexane seed oil extract of MO at a dosage of 0.5 mL/kg

for 8 weeks significantly reduced TC, LDL, and increased HDL levels in obese rats (Elabd et al. 2017). Grinded MO leaf powder at a dosage of 10% for 30 days significantly reduced the LDLC level in New Zealand white rabbits (Sun et al. 2018). MO silage at a dosage of 136 g/kg for 35 days significantly decreased TC, LDLC, and HDLC in Holstein cows (Zeng et al. 2018). MO powder at a dosage of 0.03 g/kg and 0.07 g/kg did not significantly reduce LDL, TC, HDL, and TG in non-academic staff of both sexes of Bingham University, Nigeria (Seriki et al. 2015). Treatment with MO for 3 months at a dosage of 200 mg/kg significantly reduced blood cholesterol, triglycerides, LDL and a significant ( $P < 0.05$ ) increase in HDL compared to the HFD (obese group) (Elabd et al. 2018). MO at a dosage of 300 mg/kg for 6 weeks significantly reduced the total lipids, cholesterol, triglycerides, LDL, atherogenic index, and increased HDL levels compared to HFD supplemented rats (Othman et al. 2019). MO treatment to obese male rats at a dosage of 600 mg/kg for 2 months caused a significant decrease in elevated serum insulin, total cholesterol, and triacylglycerol (Hussein et al. 2019). Hydroalcoholic MO leaf extract at a dosage of 100 and 200 mg/kg for 28 days elicited a significant reduction in total cholesterol, triglycerides, low density lipoprotein, very low density lipoprotein, atherogenic index and similarly significant ( $P < 0.001$ ) increase in high density lipoprotein level (Rajanandh et al. 2012). Moreover, methanolic leaf and stem bark extract of MO at a dosage of 300 and 600 mg/kg showed significant reduction in TC, TG, LDL and increase in HDL ( $P < 0.001$ ) (Onwe et al. 2015). Methanolic seed extract of MO at a dosage of 100 and 200 mg/kg significantly reduced total cholesterol, VLDL and increased HDL after treatment for 6 weeks. However, there was insignificant reduction in LDL levels found between the MO treated and control groups (Ajayi et al. 2020).

Aqueous leaf extract of MO at a dose of 200, 400, and 600 mg/kg for 6 weeks resulted in an insignificant alteration in serum total lipids, cholesterol, tri-acyl-glycerol, LDL and VLDL. However, there was a significant increment in the level of HDL of the MO treated group compared to the control (Gheith & El-Mahmoudy 2019). Methanolic leaf extract at a dosage of 400 mg/kg for 10 weeks significantly prevented the fructose induced elevation in hepatic lipid stores but did not reduce hypertriglyceridemia in high fat diet rats (Muhammad et al. 2019). Aqueous leaf extract of MO at a dose of 400 mg/kg for 4 weeks showed a significant decrease in total cholesterol and LDL by 26.8% and 40.6%, respectively (Aborhyem et al. 2016). In addition,

the level of HDL in rats fed with MO (control +ve) group increased from the baseline value (22.3 mg/dl) by 48.8% to reach 33.5 mg/dl after two weeks, and by 10.7% to reach 24.7 mg/dl after four weeks of treatment with MO (Aborhyem et al. 2016). Moreover, MO treatment for 4 weeks decreased VLDL level by 36.5% when compared to rats fed on an atherogenic diet (Aborhyem et al. 2016). Petroleum ether leaf extract of MO at a dosage of 400 µg/mL for 4 weeks suppressed adipogenesis in 3T3-L1 adipocytes in a dose-dependent manner (Xie et al. 2018). In addition, petroleum ether leaf extract of MO at a dosage of 400 µg/mL for 4 weeks markedly reduced the serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) (Xie et al. 2018).

#### EFFECT OF MO ON ADIPOCYTOKINES

Methanolic extract of leaf extract at a dosage of 500 mg/kg for 90 days elicited significant increase in serum ghrelin, with an inverse observation with regards to serum obestatin (Saleem et al. 2016). Aqueous leaf extract of MO at a dosages of 800 mg/kg for 3 months significantly reduced adipokines leptin, resistin and enhanced adiponectin levels (Waterman et al. 2015). Meanwhile, ethanolic leaf extract of MO at a dosage of 600 mg/kg for 12 weeks significantly decreased levels of serum leptin, resistin and increased serum adiponectin (Ahmed et al. 2014).

#### EFFECT OF MO ON GENE EXPRESSION

Aqueous leaf extract of MO at a dosage of 80 mg/kg significantly for 3 months reduced gene expression of pro-inflammatory markers such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6 in the liver and ileum. Apart from that, gene expression of adiponectin in adipose tissue was enhanced due treatment with MO (Waterman et al. 2015). Ethanolic leaf extract of MO at a dosage of 600 mg/kg for 12 weeks down-regulated leptin and resistin genes, reaching  $0.41 \pm 0.02$  fold and  $0.44 \pm 0.02$  fold, respectively. In addition, the adiponectin gene expression was up-regulated to

$1.91 \pm 0.07$  fold in the MO-treated group (Metwally et al. 2017). Aqueous leaf extract of fermented MO at a dosage of 250 mg/kg significantly down-regulated hepatic genes (ACC, SREBPIC) expression. In addition, the expression of genes related to lipid uptake (CD36, ACOX1, ATGL, HSL), oxidation and lipolytic activity increased.

Apart from that, non-fermented MO had significantly downregulated the expression of LPL gene. The gene expression of pro-inflammatory cytokines (TNF- $\alpha$ , IL-6, IL-12, IL-1 $\beta$ , MCP1) in the liver, quadriceps muscle and epididymal adipose tissue were down-regulated as a result of treatment with 250 mg/kg of fermented MO (Joung et al. 2017). Petroleum ether leaf extract of MO at a dosages of 400 µg/mL for 4 weeks significantly downregulated the expression of adipogenesis-associated proteins PPAR $\gamma$ , CCAAT/enhancer-binding proteins  $\alpha$  and  $\beta$  (C/EBP $\alpha$  and C/EBP $\beta$ ) as well as fatty acid synthase (FAS) while upregulating lipolysis-associated protein [hormone-sensitive lipase (HSL)] in 3T3-L1 adipocytes (Xie et al. 2018). Moreover, the same treatment regime significantly downregulated the expression of adipogenesis-associated proteins (PPAR $\gamma$  and FAS) and upregulated the expression of a lipolysis-associated protein [adipose triglyceride lipase (ATGL)] in HFD mice hepatic and epididymal fat tissue (Xie et al. 2018).

#### EFFECT ON ENZYME ACTIVITY

Methanolic leaf extract of MO at a dosage of 150, 300 and 600 mg/kg significantly reduced the enzyme activity of HMG-CoA reductase (Jain et al. 2010). Aqueous leaf extract of MO at a dosage of 5 mg/mL markedly inhibited  $\alpha$ -glucosidase and pancreatic  $\alpha$ -amylase activity while inhibiting pancreatic cholesterol esterase, pancreatic lipase and cholesterol micellization activity (Adisakwattana & Chanathong 2011).

#### SUMMARY OF RESULTS/FINDINGS

A summary of the manuscripts reviewed has been listed in Table 1.

TABLE 1. Characteristic of study extracted from articles

Title and Year	Extract/ Dosage/ treatment period / explant used	Type and sample population	Results/outcomes
Comparison study between effect of methanolic extract of <i>Moringa oleifera</i> and exogenous Ghrelin on lipid profile in atherogenic rats. (2016)	Extract: Methanolic extract of leaf Dosage: 250, 500 mg/kg Treatment: 60 days	50 male rats each weighing 200-250 g, aged between 10-17 weeks	500 mg/kg of MO elicited higher significant decrease in serum cholesterol, TG, LDL, VLDL, body weight, liver weight, kidney weight, heart weight and increased in HDL levels

Antiobesity activity of <i>Moringa oleifera</i> leaves against high fat diet-induced obesity in rats. (2016)	Extract: Raw leaves grinded into powder (no extraction) Dosage: 50 mg Treatment: 35 days	24 adult male long Evans rats weighing 150-180 g	MO significantly decreased thoracic circumference (TC), Abdominal circumference (AC), BMI, body weight
Effect of methanolic leaf extract of <i>Moringa oleifera</i> on some biochemical markers in obesity induced rats. (2016)	Extract: Methanolic extract of leaf Dosage: 250 mg/kg for 60 & 90 days, 500mg/kg for 60 & 90 days	60 male rats weighing 200-250g, aged between 10-17 weeks	500 mg/kg of MO for 3 months elicited significant increase in serum ghrelin and significant decrease in serum obestatin, vascular endothelial growth factor, (VEGF) as well as body weight
Hypolipidemic activity of <i>Moringa oleifera</i> Lam., Moringaceae, on high fat diet induced hyperlipidaemia in albino rats. (2010)	Extract: Methanolic leaf extract Dosage: 150, 300, 600 mg/kg Treatment: 30days	36 male albino Wistar rats weighing 180-200 g	All the three doses of MO significantly decreased the levels of TC, TG, VLDL, LDL, reduced atherogenic index (AI) and increased HDL as well as significant reduction of HMG-CoA reductase activity
Isothiocyanate-rich <i>Moringa oleifera</i> extract reduces weight gain, insulin resistance and hepatic gluconeogenesis in mice. (2014)	Extract: Aqueous leaf extract Dosage: 800 mg/kg Treatment: 3 months	24 male C57BL/6J mice aged between 5 weeks	MO fed mice significantly showed less gain weight, lowered fat accumulation, lowered lipids in liver, reduced weight of liver, reduced adipokines (leptin resistin), lowered cholesterol, enhanced adiponectin and lowered TNF $\alpha$ gene expression
$\alpha$ -glucosidase inhibitory activity and lipid lowering mechanism of <i>Moringa oleifera</i> leaf extract. (2011)	Extract: Aqueous leaf extract Dosage: 5 mg/mL Treatment: -	<i>In Vivo</i> study	Aqueous Leaf extract of MO inhibited $\alpha$ -glucosidase, pancreatic amylase, pancreatic cholesterol esterase and cholesterol micellization
Molecular mechanism of the anti-obesity potential effect of <i>Moringa oleifera</i> in the experimental model. (2016)	Extract: Ethanolic extract of aerial parts of MO Dosage: 600 mg/kg Treatment: 12 weeks	32 adult female rats at 90 days age weighing (130 $\pm$ 10) g	MO fed rats significantly decreased body weight, AI, cardiovascular risk index (CRI), down-regulated leptin, resistin gene and up-regulated adiponectin gene
Fermented <i>Moringa oleifera</i> decreases hepatic adiposity and ameliorates glucose intolerance in high-fat diet-induced obese mice. (2017)	Extract: Aqueous leaf extract Dosage: 250mg/kg FM & NFM Treatment: 10 weeks	C57BL/6J mice aged between 4 weeks	- Fermented MO (FM) and Non-fermented MO (NFM) extract did not significantly altered adiposity, quadriceps muscle - Liver weight, lipid accumulation, activity of hepatic genes, proinflammatory cytokines was significantly decreased
<i>Moringa oleifera</i> offers a multi-mechanistic approach for management of obesity in rats. (2014)	Extract: Ethanolic extract of aerial parts of MO Dosage: 600 mg/kg Treatment: 12 weeks	32 adult female albino rats weighing 130 $\pm$ 10 aged 90 days	Mo significantly decreased TC, AC, BMI, serum cholesterol, LDL, TG, serum leptin, serum resistin and decreased levels of HDL, serum adiponectin
Preventive effects of <i>Moringa oleifera</i> (Lam) on hyperlipidaemia and hepatocyte ultrastructural changes in iron deficient rats. (2007)	Extract: Raw grinded leaf powder (no extraction) Dosage: 0.5%, 1.0% of MO Treatment: 4 weeks	24 male Wistar rats aged at 4 weeks	0.5 and 1.0% of MO significantly decreases TG, phospholipids (PL), TC in serum and liver as well as decreases HDL in serum only
Effect of <i>Moringa oleifera</i> on serum lipids and kidney function of hyperlipidaemia rats. (2013)	Extract: Leaves powder (no extraction) Dosage: 10 and 15% Treatment: 45 days	32 male albino rats weighing 130 $\pm$ 10g	10 and 15% of MO significantly caused reduction in TC, TG, LDL, VLDL, body weight gain and increased HDL significantly
Antiobesity and hypolipidemic activity of <i>Moringa oleifera</i> leaves against high fat diet-induced obesity in rats. (2014)	Extract: Methanolic leaf extract Dosage: 200 and 400 mg/kg Treatment: 49 days	50 wistar albino rats weighing 120-150g	200 and 400 mg/kg of MO significantly decreased TC, TG, LDL, atherogenic index, liver weight, kidney weight, fatty deposition in liver and increased HDL, degeneration of hepatocytes
Hypolipidaemic effect of ethanol leaf extract of <i>Moringa oleifera</i> Lam. In experimentally induced hypercholesterolemic Wistar rats. (2014)	Extract: Ethanolic leaf extract Dosage: 300 and 600 mg/kg Treatment: 14 days	36 male and female Wistar weighing 130.53 $\pm$ 4.86g	300 and 600 mg/kg did not produce any change on body weight. 300 and 600 mg/kg significantly reduced TC, TG in male and female but only 600 mg/kg significantly increased HDL and decreased LDL levels in male and female

Hypolipidemic effect of <i>Moringa oleifera</i> Lam leaf powder and its extract in diet-induced hypercholesterolemic rats. (2017)	Extract: Aqueous and Ethanolic leaf extract and leaf powder Dosage: 200 and 400 mg/kg extract, 0.737% and 1.475% leaf powder Treatment: 60 days	36 adult male albino rats weighing 188±15.21g	200 and 400 mg/kg of MO extract and 0.737% and 1.475% of powder reduced the TC level. 0.737% and 400 mg/kg significantly reduced LDL, atherogenic index and increased HDL levels. No significant changed observed in TG level in all the doses
A Comparative study of the effects of three <i>Moringa</i> species on obesity-induced oxidative stress state in liver tissue. (2017)	Extract: Hexane seed oil extraction Dosage: 0.5 mL/kg Treatment: 8 weeks	30 male Wistar rats	All three <i>Moringa</i> seed oil significantly reduced TC, LDL, body weights and increased HDL levels
Effects of <i>Moringa oleifera</i> leaves as a substitute for alfalfa meal on nutrient digestibility, growth performance, carcass trait, meat quality, antioxidant capacity and biochemical parameters of rabbits. (2016)	Extract: Grinded leaf Dosage: 10%, 20%, 30% Treatment: 30 days	200 New Zealand white rabbits	Grinded MO leaf powder at a dosage of 10% for 30 days significantly reduced the LDLC level
Effects of <i>Moringa oleifera</i> silage on milk yield, nutrient digestibility and serum biochemical indexes of lactating dairy cows. (2016)	Extract: MO whole plant silage Dosage: 68g/kg, 136g/kg Treatment: 35days	60 Holstein cows	MO silage at a dosage of 136 g/kg for 35 days significantly decreased TC, LDLC and HDLC levels
Effect of <i>Moringa oleifera</i> on lipid profile, blood pressure and body mass index in human. (2015)	Extract: MO powder Dosage: 0.03 g/kg, 0.07 g/kg Treatment: 14 days	16 non-academic staffs of both sexes of Bingham University, Nigeria	- MO powder at a dosage of 0.03 g/kg and 0.07 g/kg significantly reduced body mass index - MO powder at a dosage of 0.03g/kg and 0.07g/kg did not significantly reduce LDL, TC, HDL and TG
Investigating of <i>Moringa oleifera</i> role on gut microbiota composition and inflammation associated with obesity following high fat diet feeding. (2018)	Extract: Aqueous leaf extract Dosage: 200 mg/kg Treatment: 3 months	Swiss Albino mice of either sexes	Aqueous extract of <i>Moringa oleifera</i> showed a significant ( $P < 0.05$ ) decrease in total body weight, Lactobacillus, blood cholesterol, triglycerides, LDLc and a significant ( $P < 0.05$ ) increase in Bifidobacteria, HDLC compared to H.F.D (obese group) - <i>Moringa</i> leaf extract (ME) treatment markedly reduced the percentage of body weight gain, total lipids, cholesterol, triglycerides, LDL, atherogenic index compared to HFD supplemented rats. - <i>Moringa</i> leaf extract (ME) treatment markedly increased HDL levels
<i>Moringa oleifera</i> leaf extract ameliorated high-fat diet-induced obesity, oxidative stress and disrupted metabolic hormones. (2019)	Extract: Ethyl alcohol leaf extract Dosage: 300 mg/kg Treatment: 6 weeks	Male Wistar rats	- <i>Moringa</i> leaf extract (ME) treatment markedly reduced the percentage of body weight gain, total lipids, cholesterol, triglycerides, LDL, atherogenic index compared to HFD supplemented rats. - <i>Moringa</i> leaf extract (ME) treatment markedly increased HDL levels
<i>Moringa oleifera</i> ameliorates lipid metabolic disorders, oxidative stress and the inflammatory status in high fat diet-induced obesity in rats. (2019)	Extract: Aqueous leaf extract Dosage: 600 mg/kg Treatment: 2 months	White male Albino rats	<i>Moringa oleifera</i> treatment to obese male rats caused a significant decrease in elevated serum insulin, total cholesterol and triacylglycerol
<i>Moringa oleifera</i> Lam. A herbal medicine for hyperlipidaemia: A pre-clinical report. (2012)	Extract: Hydroalcoholic leaf extract Dosage: 100 & 200 mg/kg Treatment: 28 days	Male Albino rats of Wistar strain	Showed significant ( $P < 0.001$ ) reduction in elevated levels of body weight, total cholesterol, triglycerides, low density lipoprotein, very low density lipoprotein, atherogenic index and similarly significant ( $P < 0.001$ ) increase in high density lipoprotein level
Extracts of <i>Moringa oleifera</i> a sure bet for Hyperlipidaemia management. (2015)	Extract: Methanolic leaf & stem bark extracts Dosage: 300 & 600 mg/kg Treatment: N.A	Wistar Albino rats	Methanolic leaf and stem bark extract showed reduction in TC, TG, LDL and increase in HDL ( $P < 0.001$ )



Evaluation of antidiabetic and antihyperlipidemic potential of aqueous extract of <i>Moringa oleifera</i> in fructose fed insulin resistant and STZ induced diabetic wistar rats: a comparative study. (2012)	Extract: Aqueous leaf extract powder Dosage: 200 mg/kg Treatment: 60 days	Male Albino Wistar rats	AEMO administration completely prevented fructose induced weight gain in F group and partially prevented the weight loss observed in STZ induced diabetic rats
Lipid altering potential of <i>Moringa oleifera</i> Lam seed extract and isolated constituents in Wistar rats. (2020)	Extract: Methanol seed extract Dosage: 100 & 200 mg/kg Treatment: 6 weeks	Wistar rats	<ul style="list-style-type: none"> <li>- The <i>Moringa</i> seed extract significantly reduced total cholesterol, VLDL and increased HDL</li> <li>- Insignificant reduction in LDL were found in the <i>Moringa</i> treated group</li> </ul>
Amelioration of hyperlipidaemia and atherosclerosis index by <i>Moringa oleifera</i> leaf extract. (2019)	Extract: Aqueous leaf extract Dosage: 200, 400 & 600 mg/kg Treatment: 6 weeks	White male rats	<ul style="list-style-type: none"> <li>- Aqueous leaf extract showed insignificant alterations in serum total lipids, cholesterol, tri-acyl-glycerols, LDL-C, VLDL-C</li> <li>- Aqueous leaf extract significantly increased HDL-C compared to the control rats</li> </ul>
<i>Moringa oleifera</i> Lam. prevents the development of high fructose diet-induced fatty liver. (2019)	Extract: Methanolic leaf extract Dosage: 400 mg/kg Treatment: 10 weeks	Female Sprague Dawley rats	<ul style="list-style-type: none"> <li>- The methanolic leaf extracts of <i>M. oleifera</i> (M + H) prevented the fructose induced elevation in hepatic lipid stores</li> <li>- <i>Moringa</i> leaf extracts did not reduce hypertriglyceridemia in high fat diet rats</li> <li>- <i>Moringa oleifera</i> showed a significant decrease in total cholesterol and LDL by 26.8% and 40.6%, respectively.</li> <li>- The level of HDL in rats fed on <i>Moringa oleifera</i> (control +ve) group increased from baseline value (22.3 mg/dl) by 48.8% to reach 33.5 mg/dl after two weeks, and by 10.7% to reach 24.7 mg/dl after four weeks</li> <li>- <i>Moringa oleifera</i> decreased VLDL level by 36.5% respectively when compared to rats fed on atherogenic diet</li> </ul>
Effect of <i>Moringa oleifera</i> on lipid profile in rats. (2016)	Extract: Aqueous leaf extract Dosage: 400 mg/kg Treatment: 4 weeks	Male Albino rats	<ul style="list-style-type: none"> <li>- <i>Moringa</i> suppressed adipogenesis in 3T3-L1 adipocytes in a dose-dependent manner</li> <li>- <i>Moringa</i> significantly downregulated the expression of adipogenesis-associated proteins PPAR<math>\gamma</math>, CCAAT/enhancer-binding proteins <math>\alpha</math> and <math>\beta</math> (C/EBP<math>\alpha</math> and C/EBP<math>\beta</math>), and fatty acid synthase (FAS)] and upregulated the expression of a lipolysis-associated protein [hormone-sensitive lipase (HSL)] in 3T3-L1 adipocytes</li> <li>- <i>Moringa</i> decreased BW; relative epididymal, perirenal, and mesenteric fat weight and fat tissue size; and hepatic fat accumulation. Furthermore, MOPEE markedly reduced the serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C).</li> <li>- <i>Moringa</i> significantly downregulated the expression of adipogenesis-associated proteins (PPAR<math>\gamma</math> and FAS) and upregulated the expression of a lipolysis-associated protein [adipose triglyceride lipase (ATGL)] in HFD mice hepatic and epididymal fat tissue.</li> <li>- <i>Moringa</i> markedly increased the degree of phosphorylation of AMPK<math>\alpha</math> and ACC in HFD mice hepatic and epididymal fat tissue.</li> </ul>
<i>Moringa oleifera</i> leaf petroleum ether extract inhibits lipogenesis by activating the AMPK signaling pathway. (2018)	Extract: Petroleum ether leaf extract Dosage: 400 ug/mL & 0.5 g/kg Treatment: 4 weeks	C57BL/6J mice & 3T3-L1 adipocytes	<ul style="list-style-type: none"> <li>- <i>Moringa</i> significantly downregulated the expression of adipogenesis-associated proteins (PPAR<math>\gamma</math> and FAS) and upregulated the expression of a lipolysis-associated protein [adipose triglyceride lipase (ATGL)] in HFD mice hepatic and epididymal fat tissue.</li> <li>- <i>Moringa</i> markedly increased the degree of phosphorylation of AMPK<math>\alpha</math> and ACC in HFD mice hepatic and epididymal fat tissue.</li> </ul>

## DISCUSSION

The trend of being obese and overweight is accelerating towards a critical level worldwide due to the popularity of unhealthy diets and lack of physical inactivity. Obesity is a condition where the amount of fat tissue in the body is elevated to a point where physical and mental health are impaired (Graves 2010). Early measures need to be taken to address this condition as prolonged visceral obesity and hyperlipidaemia could lead towards CVD and type 2 diabetes. The present systematic review was aimed at investigating the role of different extract of MO in alleviating obesity and hyperlipidaemia. Based on the review of the selected manuscripts, different doses, extracts and explants of MO significantly reduced body, liver, kidney and heart weight, TC, AC, BMI, CRI as well as fat accumulation in obese rats. In addition, a clinical trial has demonstrated that MO supplement for 14 days significantly decreased BMI in humans.

The possible mechanism that underlies these results could be through the inhibition of pancreatic lipase enzyme activity. The bioactive compounds present in MO would prevent the action of this enzyme in breaking down fat molecules into TG which would then be stored in adipose tissue (Burhans et al. 2018). As a result of this impairment, the fat molecules would then be eliminated through the faeces (Nagy et al. 2014; Zechner et al. 2012). Besides that, MO reduces obesity parameters through prevention of adipocyte differentiation by inhibiting the accumulation of fat cells in adipose tissues (Uto-Kondo et al. 2009). Another possible mechanism of MO suppressing obesity maybe through intensifying lipid metabolism via induction of norepinephrine in the fats cells (Okuda et al. 2001).

Hyperlipidaemia is a term used to describe an individual who has an imbalance of circulating lipids in the bloodstream. In the present review, elevated lipids levels (LDL, TG, VLDL, TC, PL) in hyperlipidaemic rat, rabbit and cow models were significantly reduced as a result of treatment with different extracts, doses, and explants of MO. In addition, the reduced lipid level of HDL in obese rats, rabbit and cow was significantly increased by MO treatment. MO is rich in phytosteroids (phytosterols) such as kampesterol, sitosterol and stigmasterol (Nur Zahirah et al. 2018). These compounds are almost structurally similar to cholesterol and are responsible for its action on reducing the lipid levels in the body through inhibition of intestinal cholesterol absorption (Trautwein et al. 2003). The phytosterols would also interfere and compete with cholesterol for solubilisation in dietary mixed-micelles (Mel'nikov et al. 2004). In the case of

levels of HDL, the reduction may have been due to the effect of reduction in the cholesterylester transfer protein (CETP) (Raposo et al. 2014).

Adipocytokines are inflammatory markers secreted by the adipose tissue (adipocytes) that serve to balance biological processes in the body. Enhanced accumulation of adipose tissue leads to dysregulation in the production of adipokines which then cause a malfunction in the mechanism of weight control, leading to development of obesity-related diseases (Fasshauer & Blüher 2015). Based on our review, significant results were elicited by MO in treating obesity and hyperlipidaemia by reducing the levels of leptin, resistin, and obestatin as well as increasing levels of ghrelin and adiponectin. Since MO significantly reduced fat accumulation, thus MO would suppress the dysregulation on the adipokines which in return reduces inflammation and obesity related diseases. HMG-CoA reductase is a rate limiting enzyme that plays a vital role in the regulation of cholesterol biosynthesis. This enzyme is found in all over the body cell, but mostly abundant in the liver (Roberts et al. 2004). In the present review, we found that the enzyme activity of HMG-CoA reductase was significantly suppressed by the treatment with MO. This is due to the effect of compounds in MO, such as statins, which acts as HMG-CoA inhibitor that would compete with HMG-CoA reductase's active site to suppresses the cholesterol producing pathway of in the liver (Feingold 2020). As soon as the liver stops synthesizing cholesterol, levels of circulating cholesterol in the blood would drop, thus prevent obesity and hyperlipidaemia (Roberts et al. 2004).

Lastly, MO treatment at different dosages and extract significantly down-regulated proinflammatory cytokine (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12, MCP1) and hepatic gene expression (ACC, SREBPIC) in the liver, ileum, quadricep muscle and epididymal adipose. Furthermore, different dosages and extracts of MO significantly down-regulated leptin, resistin, LPL gene while up-regulating the adiponectin gene. Apart from that, MO also significantly down-regulated genes related to lipid uptake (CD36, ACOX1, ATGL, HSL), oxidation and lipolytic activity. These data indicated that a down-regulatory mechanism of all the genes related to obesity and hyperlipidaemia occurred as a result of treatment with MO.

## CONCLUSION

The present review showed that different extract, explant, and dosages of MO are essential anti-obesity and anti-hyperlipidaemic agent that led to a reduction in weight loss and serum lipids in experimental rats, rabbits, cow

and humans. In addition, there was also an evidence from *in vitro* studies that exhibited the preventive effects of MO on the obesity parameters. As this particular plant has great medicinal value, more human intervention should be focused on as we could clearly observe the lack of clinical evidence on the effects of MO on different human population. Considering that the results from the animal studies were promising, therefore, it can be recommended to patients that having complication with high lipid levels and obesity.

#### STRENGTH AND LIMITATIONS OF THIS REVIEW

The main limitation of this review would be the inadequate information on the risk of bias assessment. As a result, the overall strength of evidence across individual studies could not be evaluated. The source of MO used in the articles were not homogenised as the extracts reported originated from different parts of the plant, including the leaf, whole plant, and extract. Furthermore, three articles included in the review reported using raw leaf powder, without outlining any extraction protocols for the study. The solvent used for the extraction of the plant was also not standardized ranging from methanol, ethanol, aqueous and hexane. These different originating sources of MO may produce different effects on obesity and hyperlipidaemia; thus analysis of results and outcomes would eventually be complicated.

This review provides a better understanding on the protective effects of MO on obesity and hyperlipidaemia. To the best of our knowledge, this is the one of few systematic reviews that focuses on the protective effects of MO against obesity and hyperlipidaemia. Our present analysis covered a wide scope and was not restricted to a specific sex, type, age, health status of the rats, plant source, dosage, treatment period or solvent. Apart from that, the present review was not limited or focused on obesity and hyperlipidaemia, exploring the effects on adipocytokines, gene expression and enzyme activities as well. We included *in vitro*, animal, and human studies in order to have the most recent and reliable evidence on the stated topic.

#### FUTURE STUDIES PROPOSED

MO has received endless attention over the past decades with its promising effects on metabolic dysregulation being demonstrated in a number of studies. The future study of naringin as a flavonoid requires an integrative approach involving human, cellular and molecular studies as there have been sufficient positive outcomes

observed on animal and *in-vitro* trials. Furthermore, the diagnostic techniques have to be enhanced to allow greater data collection on the absorption and excretion of MO. The greater advances would ensure a better analysis to give an enhanced understanding on the effects of MO on obesity and hyperlipidaemia as well as other diseases.

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