

Research Article

Anti-Obesity Effects of *Melastoma malabathricum* var Alba Linn in Rats Fed with a High-Fat Diet

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Abstract. Obesity is one of the major public health problems worldwide and it is generally associated with many diseases. Although synthetic drugs are available for the treatment of obesity, herbal remedies may provide safe, natural, and cost-effective alternative to synthetic drugs. One example of such drugs is *Melastoma malabathricum* var Alba Linn (MM). Although several studies have been reported for the pharmacological activities of MM, there is no report on the anti-obesity effect of MM. The aim of the present study is to evaluate the anti-obesity potential of methanolic extract of MM. The anti-obesity effect of MM on rats fed with a high-fat diet was investigated through determination of the changes in body weight, fat weight, organ weights, and blood biochemicals. The animals in this study were divided into three groups: a normal group with a standard diet (N), a control group fed with high-fat diet (C), and a MM treatment group fed with high-fat (HFD + MM) diet for 8 weeks. There was no significant difference in the amount of food intake between control and HFD + MM treatments. These results also suggest that MM does not induce a dislike for the diet due to its smell or taste. The study shows that MM significantly prevented increases in body weight, cholesterol, LDL, HDL, and total lipids that resulted from the high-fat diet. MM also decreased the epididymal fat (E-fat) and retroperitoneal fat (R-fat) weights and phospholipid concentrations induced by the high-fat diet. On the basis of these findings, it was concluded that MM had anti-obesity effects by suppressing body weight gain and abdominal fat formation.

KEY WORDS: Anti-obesity; High-fat diet; *Melastoma malabathricum* var Alba Linn.

INTRODUCTION

Obesity is a condition or a state of excess adipose tissue mass and it may result from increased in energy intake and decreased on energy expenditure, or a combination of the two. Obesity is no more limited to developed countries but spreading globally, and in USA and some European countries, it is an epidemic condition (1). According to the WHO, more than 1.4 billion adults were overweight, and half a billion were obese; at least 2.8 million people are dying each year as a result of being overweight or obese. Globally, over 42 million preschool children were overweight in 2010 (2). Several factors such as lack of exercise and consumption of energy-rich diets due to behavioral and societal changes, etc. are the main contributors to the etiology of obesity (3).

Obesity has an important impact on lifestyle-related diseases such as coronary heart disease, dyslipidemia, glucose intolerance, type II diabetes mellitus, hypertension, cardio-metabolic syndrome, osteoarthritis, stroke, gall bladder disease, obstructive sleep apnea, gastroesophageal reflux disease

(GERD), and some cancers namely endometrial, breast, and colon cancers (4–6). People are aware of the adverse effect posed by obesity and often use many methods for weight loss including herbs, vitamins, nutritional supplements, and meal replacement preparations. Many vitamins and nutritional supplements are available in the market claiming to be effective in reducing the body weight. However, full-scale scientific studies and research have not been carried out on these products, and in many cases, safety and efficacy of these products are questionable. Synthetic drugs are available for the treatment of obesity. The common options include sibutramine, orlistat, phentermine, diethylpropion, and fluoxetine or bupropion. Phentermine and diethylpropion are only approved for short-term use due to the potential for abuse. Sibutramine and orlistat are the medications approved for long-term use in the treatment of obesity. However, these agents should be used with caution in patients with a history of cardiovascular disorders (7).

Pharmacological treatment and surgical interventions used in some circumstances are not always appropriate (8). Unfortunately, drug treatment of obesity, despite short-term benefits, is often associated with rebound weight gain after the cessation of drug use, side effects from the medication, and the potential for drug abuse (9). Due to the increasing frequency of anti-obesity drug use and their common side effects, there is an urgent need to identify natural products with minimal or no side effects. *Melastoma malabathricum* var Alba Linn (MM),

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Table I. Changes in Food Intake Between High-Fat Diet and High-Fat Diet with MM

| Days | High-fat diet | High-fat diet + MM |
|-------|---------------|--------------------|
| Day 1 | 46.1±1.94 | 46.4±1.27 |
| Day 2 | 45.1±1.20 | 45.9±0.79 |
| Day 3 | 47.1±1.55 | 46.5±2.08 |
| Day 4 | 45.9±1.87 | 47.3±0.83 |
| Day 5 | 46.4±2.17 | 46.8±1.32 |

locally known as senduduk putih, is a medicinal herb used to treat various ailments including diarrhea, dysentery, leucorrhoea, hemorrhoids, and infection during confinement (10,11). Although the plant is widely used in Malay culture, not much scientific data are reported on the activities of MM (12). The aim of the present investigation is to study the anti-obesity potential of MM using high-fat-induced animal model.

MATERIALS AND METHODS

Animals and Diet

Male Sprague–Dawley rats (5 weeks old; weighing from 125 to 150 g) were maintained under a 12/12 h light/dark cycle, in a temperature- and humidity-controlled room. The animals were given laboratory pellet chow and water *ad libitum*. Following 1 week of acclimatization with a pelletized commercial diet, 30 rats were randomly divided into 3 groups ($n=10$) with the groups matched for body weight for a period of 8 weeks. The normal group rats were fed with laboratory pellet chow. The control group rats received the high-fat diet (beef tallow 40%, casein 36%, corn starch 10%, sugar 9%, vitamin mixture 1%, bean oil 0.5%, and mineral mixture 4% *w/w* per 100 g diet) and water for 8 weeks. The rats of the experimental group received the high-fat diet containing 5% methanolic extract of MM for 8 weeks. The body weight of each rat was estimated once a week. The animal experiment was performed according to the university's ethical committee approval (AUHAEC 47/FOP/2010).

Table II. Inhibitory Effect of MM on Body Weight Gain (Grams) Induced by High-Fat Diet

| Weeks | Normal diet | High-fat diet | High-fat diet + MM |
|-------|-------------|---------------|--------------------|
| 0 | 151.3±2.12 | 152.0±1.86 | 152.2±2.00 |
| 1 | 169.0±2.66 | 178.8±2.41 | 163.0±2.65 |
| 2 | 179.0±2.89 | 218.7±1.80 | 192.2±2.78 |
| 3 | 212.0±3.34 | 238.5±2.95 | 221.7±2.84 |
| 4 | 230.0±3.09 | 267.7±4.85 | 237.9±2.21 |
| 5 | 245.0±4.85 | 289.0±2.15 | 252.8±3.46 |
| 6 | 267.0±2.32 | 318.9±2.35 | 273.0±3.06 |
| 7 | 293.0±4.70 | 348.6±2.22 | 304.7±3.73 |
| 8 | 301.0±2.57 | 374.1±1.51 | 315.2±3.45 |

Experimental Procedure

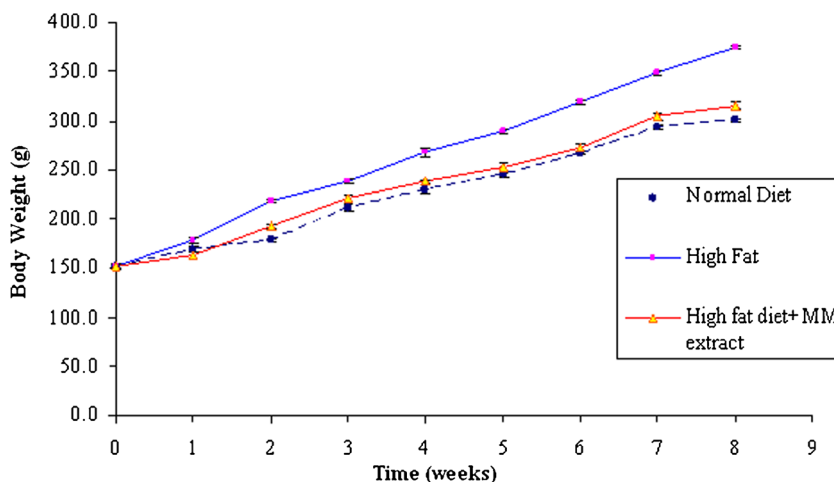
Following overnight starvation, the rats were deeply anesthetized with diethyl ether prior to sacrifice. The blood was drawn from the heart. The liver, kidney, spleen, epididymal fat (E-fat), and retroperitoneal fat (R-fat) were immediately removed and weighed. The blood samples were stored at -78°C until analysis was performed.

Estimation of Food Consumed

Animals receiving high-fat diet alone and high-fat diet containing MM groups were individually housed in cages to assess whether MM treatment influenced the food intake. Food intake was determined by measuring the difference between the pre-weighed chows and weight of the food that remained every 24 h, during the last five consecutive days of the experiment.

Lipid Analysis

The serum concentrations of total cholesterol (TC) and phospholipids (PL) were measured enzymatically with cholesterol C-test and phospholipid B-test kits obtained from Wako (Osaka, Japan). The total lipids were extracted from the liver by the method reported earlier (13). The liver triglyceride content was estimated as follows: a portion (0.5 g) of the liver

**Fig. 1.** Effect of MM extract on body weight of rats

tissue was homogenized in Krebs Ringer phosphate buffer (pH 7.4, 4.5 mL), and the homogenate (0.2 mL) was extracted with chloroform/methanol (2:1, v/v, 4 mL). The extract was concentrated under a nitrogen stream, and the residue was analyzed using triglyceride E-test kit obtained from Wako (Osaka, Japan).

Statistical Analysis

Results are expressed as mean±standard deviation (SD) for each experiment. The data obtained were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test using GraphPad Prism version 6 for windows. A *p* value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Various animal models of obesity have been used to emulate an obesity-like condition in humans in order to develop effective anti-obesity treatments. Among the tested animal models of obesity, rats that are fed with high-fat diet are considered useful where a high percentage of fat in their diet is considered to be an important factor in the development of obesity, leading to accumulation of body fat even in the absence of an increase in caloric intake (14). The diet generally will consist of high amount of fat which will induce the obesity in the animals tested by increasing the accumulation of body fat weight. The obesity condition will be compared with the animals which receive normal laboratory food. Based on this model, the anti-obesity effect of MM in rats fed a high-fat diet was investigated by analyzing the changes in total body weight, body fat weight, and blood biochemicals.

Changes in Food Intake in High-Fat Diet and High-Fat Diet + MM

The addition of MM to a high-fat diet may cause decreased food intake, possibly induced by its smell or taste. As such, an experiment was carried out to investigate whether or not MM in the high-fat diet influenced food intake in rats compared to control group which received the high-fat diet alone. This was done by measuring the food intake per rat body weight per day, following assessment of that for last five consecutive days. Based on the results, it is found that there was no significant difference in food intake between the control group and animals fed with high-fat diet with MM treatment (Table I). This result suggests that the anti-weight gain effect of MM in the high-fat diet was not caused by a refusal to ingest the feed.

Body, E-Fat, R-Fat, and Organ Weights

The changes in body weights of the animal groups during the experiment are shown in Fig. 1. Feeding a high-fat diet containing 40% beef tallow for 8 weeks produced significant increases in body weight as compared to normal group which was fed with laboratory pellet chow. Feeding a high-fat diet containing 5% MM powder significantly (*p*<0.05) reduced the increment of body weight by 26.58% (Table II). The epididymal fat (E-fat) of rats treated with high-fat diet was increased

Table III. Effect of MM on Adipose Tissue Weights

| Diet | E-fat | R-fat |
|------------------|--------------------------|--------------------------|
| Normal | 4.47±0.43 | 4.12±0.51 |
| High-fat diet | 8.05±0.89 ^a | 10.55±0.63 ^b |
| High-fat diet+MM | 6.18±0.57 ^{a,b} | 6.56±0.91 ^{a,b} |

Data are presented as mean±S.D (*n*=8). Data were statistically analyzed using one-way ANOVA and followed by Tukey's comparison tests. Letters within the column indicates significant at ^a *p*<0.05 vs normal diet, ^b *p*<0.05 vs high-fat diet

by 44.47% as compared to normal diet group. The E-fat of animals receiving high-fat diet plus MM shows an increase of 40.29% compared to that of normal diet group. However, there is a decrease of 23.23% in E-fat noted for animals receiving high-fat diet plus MM as compared to high-fat diet animals. As for the retroperitoneal fat (R-fat) analysis, animals treated with high-fat diet, the amount of R-fat was found to be increased by almost threefold (increase of 60.94%) as compared to normal diet group. Again, there is a 37.82% decrease in R-fat noted for animals receiving high-fat diet plus MM as compared to high-fat diet alone animals (Table III).

As expected, the weight of kidney, liver, and spleen of the control group rats receiving high-fat diet was increased by 44.10, 18.13, and 5.26%, respectively, as compared to animals which received normal diet (Table IV). However, substantial decreases in the weight of the organs of kidney (17.33%), liver (22.81%), and spleen (18.33%) were noted for the experimental animals receiving high-fat diet with MM as compared to the control group. The results show that MM inhibits the weight increment of the internal organs of the animals receiving high-fat diet.

Inhibitory Effect of MM on the Increase of Serum Lipids Induced by High-Fat Diet

Generally, obese people often show an increase in serum lipid concentrations. The concentration of total cholesterol, LDL-cholesterol, free-fatty acid, triglycerides, phospholipids, and total lipids in obese people will be higher when compared to normal people. As such, the data of these lipid profiles can be used as an index of obesity. Based on these facts, the concentrations of serum lipids, such as total cholesterol, LDL-cholesterol, HDL-cholesterol, phospholipids, triglycerides, and total lipids, were measured in normal, control, and MM-treated animals (Fig. 2). Through this experiment, it is

Table IV. Effects of MM on Weights of Organs in Rats

| Organs | Liver (g) | Kidneys (mg) | Spleen (mg) |
|--------------------|-------------------------|------------------------|--------------------------|
| Normal diet | 8.73±0.62 | 1.71±0.09 | 0.57±0.03 |
| High-fat diet | 12.58±0.66 ^a | 2.02±0.13 ^a | 0.60±0.03 |
| High-fat diet + MM | 9.71±0.90 ^b | 1.67±0.12 ^a | 0.49±0.05 ^{a,b} |

Data are presented as mean±S.D (*n*=8). Data were statistically analyzed using one-way ANOVA and followed by Tukey's comparison tests. Letters within the column indicates significant at ^a *p*<0.05 vs normal diet, ^b *p*<0.05 vs high-fat diet

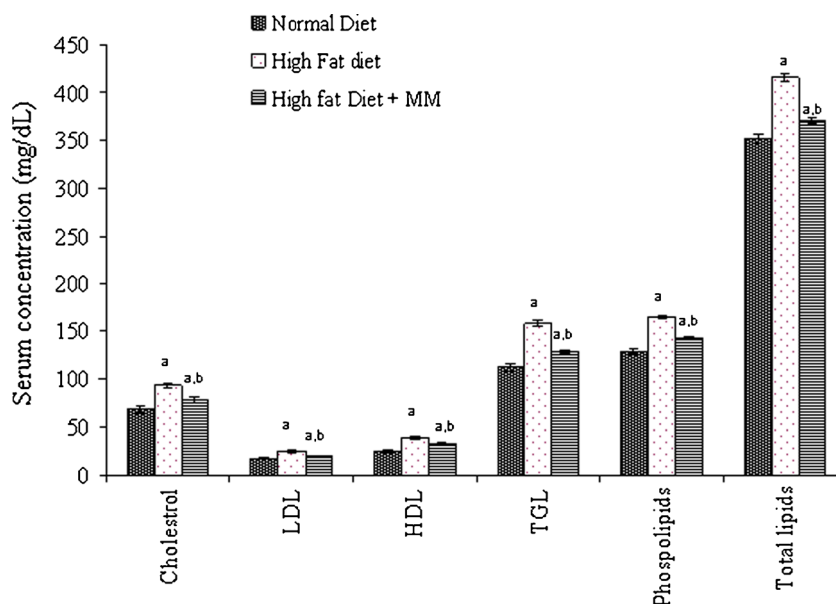


Fig. 2. Inhibitory effect of MM on the increase of serum lipid induced by high-fat diet. Data are presented as mean±S.D ($n=8$). Letters indicates significant at a $p<0.05$ vs normal diet and b $p<0.05$ vs high-fat diet

observed that high-fat diets substantially increased the concentrations of total cholesterol (26.84%), LDL-cholesterol (30.83%), and HDL-cholesterol (36.73%) compared with the normal group (Table V). In contrast, MM treatment significantly ($p<0.05$) reduced the concentrations of total cholesterol (15.94%), HDL-cholesterol (14.80%), and LDL-cholesterol (21.74%), which were induced by high-fat diets. Similarly, in the lipid profiles, high-fat feeding increased the concentrations of triglycerides (29.10%), phospholipids (21.985), and total lipids (15.46%) compared with the normal group, and MM-treated groups has lower values of 18.81, 13.36, and 10.94%, respectively, as compared with high-fat-treated group (Table IV).

A possible explanation for the substantial reduction of total cholesterol in serum by MM could be due to the reduction in the activities of the liver enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is a rate-limiting enzyme in cholesterol biosynthesis (15). Thus, feeding rats with MM may involve suppressing endogenous cholesterol biosynthesis by inhibiting HMG-CoA reductase activity. The reduction in triglycerides, phospholipids, and total lipids level in serum could be due to the inhibition of lipid absorption in gastrointestinal tract (16,17).

Table V. Percentage Decrease of Serum Lipids Induced by a High-Fat Diet with MM

| Serum lipid profile (%) | High-fat diet | High-fat diet + MM |
|-------------------------|---------------|--------------------|
| Cholesterol | 26.84 | 15.94 |
| LDL | 30.83 | 21.74 |
| HDL | 36.73 | 14.80 |
| TGL | 29.10 | 18.81 |
| Phospholipids | 21.98 | 13.36 |
| Total lipids | 15.46 | 10.94 |

As reported earlier, MM contains many flavonoid compounds and among the phytochemicals reported are ellagic acid, cyanidin-3-glucoside, cyanidin-3,5-diglucoside, β -sitosterol, ursolic acid, 2-hydroxyursolic acid, gallic acid, kaempferol, kaempferol-3- O - α -L-rhamnopyranoside, malabathrin B, malabathrin C, malabathrin D, strictinin, (-)-epicatechin, α -amyrin, quercetin, quercitrin, and rutin (18–30). Many studies that have been reported earlier show that flavonoids are having potential anti-obesity effects. In one related study, it was reported that epigallocatechin gallate (EGCG) treatment significantly reduced total body fat percentage, subcutaneous fat weight, and epididymal fat weight in high-fat-fed mice (31). It is also reported that EGCG is an *in vitro* and *in vivo* inhibitor of fatty acid synthesis and acetyl-CoA carboxylase 1 (ACC1) (32,33). ACC1 is localized in the cytosol and inhibits the β -oxidation of fatty acids through malonyl-CoA formation, which results in the inhibition of fatty acid transport, mediated by carnitine palmitoyltransferase (CPT1), into the mitochondria. Based on these reports, we strongly believe that the presence of epicatechin and other flavonoids in MM could play a major role in inhibiting the fatty acid synthesis.

A number of studies has been carried out to investigate the *in vitro* and *in vivo* anti-obesity effects of kaempferol, another flavonoid present in MM. The anti-obesity features of the compound 3- O - β -D-glucosyl-(1 \rightarrow 6)- β -D-glucosyl-kaempferol isolated from *Sauropus androgynus* are found to significantly decrease the body weight gain and blood lipid levels in rats fed with high-fat diet (34). Quercetin exhibits the anti-obesity effects by inhibiting the differentiation of preadipocytes and inducing the apoptosis of mature adipocytes (35). Rutin shows anti-obesity effects by inhibiting glycerol-3-phosphate dehydrogenase (GPDH), the cytosolic enzyme that plays an important role in the conversion of glycerol into triglyceride, in 3T3-L1 preadipocytes and in the fat and liver tissues of rats with high-fat diet-induced obesity (36,37). All this data suggests the role of flavonoids and

phenolics acids in anti-obesity activity. In summary, the presence of all these flavonoids in MM and the findings from the study suggest the potential anti-obesity action of MM and the possible mechanism and pathway of how these flavonoids exhibit anti-obesity action. Although different mechanisms for anti-obesity action have been demonstrated by different flavonoid compounds through various studies, we suggest that there could be possible synergism of all the flavonoids with other phytochemicals present in MM. Further detailed research is needed to confirm this possible synergetic effect and to draw a clear mechanism of action of flavonoid compounds from MM in anti-obesity action. Nevertheless, it is evident from our findings that MM could be developed into an effective anti-obesity agent.

CONCLUSION

In this study, we have shown that MM in a high-fat diet tends to reduce body weight, blood lipids, and body fat weight. In the blood lipid profile, MM significantly reduce the total cholesterol, LDL-cholesterol, and total lipids. As such, the findings through this study provide a basis for developing novel anti-obesity agents using MM that may have no significant adverse effects. This result suggests that MM has a potential role in therapy for obesity-related disorders.

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