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Research Article

Antihyperlipidemic Effect of Bitter Melon Extract (*Momordica Charantia* L.) in Wistar Rats

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Abstract

The use of alternative medicine, especially medicinal plants to treat various diseases including hyperlipidemia has increased over the last few decades in most countries around the world. Bitter melon (*Momordica charantia*) contains active ingredients such as flavonoids, tannins, saponins and polyphenols which have antihyperlipidemic effects. The study aims to determine the antihyperlipidemic effect of bitter melon aqueous extract and compare it with simvastatin in reducing total cholesterol and low-density lipoprotein (LDL), and increasing high-density lipoprotein (HDL) in male Wistar strain rats. The research is an experimental study with pre and post-test design, carried out in October-December 2021 at the Faculty of Medicine, Universitas Jenderal Achmad Yani, Cimahi Indonesia. Subjects consisted of 25 Wistar rats which were divided into five groups. The negative control group (standard diet), the positive control group (induced by a high-fat diet and propylthiouracil), and the three groups that were induced by a high-fat diet and propylthiouracil then given bitter melon extracts of 300 and 600 mg/kg BW and simvastatin 10 mg/kg BW. The method of measuring cholesterol using the Cholesterol Oxidase-Perioxidase Aminoantipyrine (CHOD-PAP) enzymatic method principle with a Semi-automatic Chemistry Analyzer. Analysis using paired t-test. The results showed a significant difference (P<0.005) in HDL and total cholesterol levels in the 600 mg/kg BW dose group, and a significant difference in LDL level in the 300 mg/kg BW dose group. The Simvastatin group showed significant differences in HDL, LDL, and total cholesterol. This is presumably because the active substances in bitter melon can inhibit the HMG-CoA reductase enzyme so that it can reduce LDL and total cholesterol levels. It can be concluded that bitter melon aqueous extract at doses 300 and 600 mg/Kg BW can reduce total and LDL cholesterol levels, and increase HDL.

Keywords: antihyperlipidemic, HDL, LDL, *Momordica charantia*, total cholesterol

Efek Antihiperlipidemik Ekstrak Buah Pare (Momordica Charantia L.) pada Tikus Wistar

Abstract

Penggunaan pengobatan alternatif, terutama tanaman obat untuk mengobati berbagai penyakit termasuk hiperlipidemia telah meningkat selama beberapa dekade terakhir di sebagian besar negara di seluruh dunia. Pare (*Momordica charantia* L.) mengandung bahan aktif flavonoid, tanin, saponin dan polifenol yang memiliki efek antihiperlipidemia. Tujuan penelitian untuk mengetahui efek antihiperlipidemia ekstrak air buah pare dan membandingkannya dengan simvastatin dalam menurunkan kolesterol total dan *low density lipoprotein* (LDL), serta meningkatkan *high density lipoprotein* (HDL) pada tikus jantan galur Wistar. Penelitian ini merupakan penelitian eksperimental dengan desain *pre and posttest*, dilaksanakan bulan Oktober-Desember 2021 di Fakultas Kedokteran Universitas Jenderal Achmad Yani Cimahi Indonesia. Subjek penelitian adalah 25 ekor tikus Wistar yang dibagi menjadi lima kelompok. Kelompok kontrol negatif (diet standar), kelompok kontrol positif (diinduksi diet tinggi lemak dan propiltiourasil), dan tiga kelompok yang diinduksi diet tinggi lemak dan propiltiourasil kemudian diberikan ekstrak pare 300 dan 600 mg/kgbb dan simvastatin 10 mg/kgbb. Analisis menggunakan uji t berpasangan. Hasil penelitian menunjukkan perbedaan bermakna (P<0,005) kadar HDL dan kadar kolesterol total pada kelompok dosis 600 mg/kgbb, dan perbedaan kadar LDL bermakna pada kelompok dosis 300 mg/kgbb. Kelompok simvastatin menunjukkan perbedaan bermakna untuk HDL, LDL, dan kolesterol total. Hal ini diduga karena buah pare mengandung zat aktif yang dapat menghambat enzim HMG-CoA reduktase sehingga dapat menurunkan kadar LDL dan kolesterol total. Dapat disimpulkan bahwa ekstrak air buah pare dengan dosis 300 dan 600 mg/kgbb dapat menurunkan kadar kolesterol total dan LDL, serta meningkatkan HDL.

Kata kunci: antihiperlipidemi, HDL, LDL, kolesterol total, *Momordica charantia*

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Introduction

Statins are currently the first-line lipid-lowering medications, but when used in high doses, they can cause side effects include myalgia, liver damage, and diabetes. Similar as treatment for dyslipidemia proceeds, adverse effects such myopathy, elevated liver enzymes, and cholelithiasis are also observed in the individual's receiving fibrates.[1] Additionally, several individuals also exhibited unfavorable therapeutic outcomes and medication resistance.[2] Hence, the development of additional and alternative therapies is still importance for the treatment of hyperlipidemia.

Indonesia is a country that is rich in medicinal plants, the people are familiar with many plants that can be used as natural medicines, one of them is bitter melon (Momordica charantia L.) which is believed can reduce cholesterol levels.[3,4] Bitter melon vines plants that is easily found in countries with tropical and subtropical climates. This plant belongs to the Cucurbitaceae, the parts of the plants that can be used are fruit, seeds, and leaves. Although bitter melon has a bitter taste, many people still consume this fruit because it is known that this fruit has various substances that are rich in benefits such as terpenoids, saponins, phenolics, and sterols.[4] The active compound in bitter melon has shown to reduce cholesterol through increasing cholesterol catabolism into bile acids in the liver.[5,6,7]

Bitter melon is usually used as an antidiabetic empirically.[8] A previous study found that bitter melon has antihyperglycemic and antihyperlipidemic effects on streptozotocin-induced Wistar rats. The study used bitter melon extract at a dose of 250, 500 and 750 mg/kg BW.[9] Other studies have revealed that the rind and flesh of the fruit, and whole parts of the bitter melon have antihyperglycemic and antihyperlipidemic effects.[10,11,12] However the effect of bitter melon on hyperlipidemia animal high-fat diet induced models still limited. Hence, the aim of this study is to determine the effect of administration bitter melon fruit aqueous extract (*Momordica charantia* L.) at a dose of 300 and 600 mg/kg BW on LDL, HDL and total cholesterol levels in hyperlipidemia Wistar strain rats. The development of bitter melon as a standardized herbal medicine and an antihyperlipidemic agent requires this research. The need for current, objective standards for assessing the safety, quality, and efficacy of these medicines has resulted from the standardization of herbal medicine. Additionally, people are becoming more aware of the potency and possible side effects. Researchers, producers, and regulatory organizations must employ rigorous scientific procedures to guarantee the quality of traditional herbal products in order to gain the public's trust and integrate them into the modern healthcare system.[13,14]

Methods

This research is an experimental study with pre and post-test design. Experimental animals were induced by a high-fat diet and propylthiouracil to obtain a hyperlipidemic state.

Bitter melon fruit extract is made from fresh bitter melon fruit from the plantation in Lembang, West Java, Indonesia. A total of two kg of bitter melon without peeling the rind was made into an extract using 1500 ml of distilled water as a solvent. The extraction method is maceration; the formed macerate was evaporated to obtain a thick extract.

The subjects in this study were 25 Wistar rats with criteria for a body weight of 200-250 grams, 2-3 months of age, and in good health (clean hair, no wounds, able to move, good appetite and drinking). This study used a high-fat diet and propylthiouracil (PTU) as an inducer of hyperlipidemia in experimental animals. Provision of a high-fat diet in

experimental rats was carried out by giving a mixture of 10 grams of duck egg yolk, 5 grams of goat fat, 5 grams of quail eggs, 5 ml of lard, 7500 mg of coconut oil and 100 ml of aquadest.[15]

Each treatment group consisted of 5 rats. All experimental animals were adapted for 7 days and given standard diet each 20-25 g/day and drinking water ad libitum. After completing the adaptation period, body weight was weighed to ensure that the rats are in accordance with the inclusion criteria. Blood was taken after the rats were fasted for 12 hours to measure the baseline HDL, LDL, and total cholesterol levels. The next stage is induction for 15 days (8-21 days). After completion of the induction period, measurements of HDL, LDL, and total cholesterol levels were carried out to reach the condition of hyperlipidemia. The final stage is giving the extract to the treatment group. After 15 days of treatment (day 37), the experimental animals were re-measured for their HDL, LDL, and total cholesterol levels. Experimental animal were fasted for 12 hours before blood sample drawn.[16,17]

To prevent pain that might arise in rats, researchers provided an anesthetic technique with CO^2 gas inhalation prior to blood sampling based on the Formulary for Laboratory Animals. Animals experiment that have been tested will be sacrificed by inhalation of CO^2 gas according to the guidelines of the American Veterinary Medical.[18] The treatment of experimental animals can be seen in Table 1.

The research was carried out from October to December 2021 at the Faculty of Medicine, Universitas Jenderal Achmad Yani. This research has received ethical approval from the Health Research Ethics Commission, Faculty of Medicine, Padjadjaran University with Number: 872/UN6.KEP/EC/2021.

Examination of lipid parameters using serum

Table 1. The treatment of experimental animals

Group	Adaptation Period	Induction Period	Treatment Period
Negative control	Standard diet and water	Standard diet and water	Standard diet and water
Positive control	Standard diet and water	- High fat diet 20-25gr/ rat/day - PTU 10,8mg/200grBW /day peroral - Water	Standard diet and water
Extract 300 mg/kgBW	Standard diet and water	- High fat diet 20-25gr/ rat/day - PTU 10,8mg/200grBW /day peroral - Water	- Standard diet and water - Aquoeus extract of bitter melon fruit 300 mg/ kgBW dose
Extract 600 mg/kgBW	Standard diet and water	- High fat diet 20-25gr/ rat/day - PTU 10,8mg/200grBW /day peroral - Water	- Standard diet and water - Aquoeus extract of bitter melon fruit dose 600 mg/kgBW
Simvastatin 10mg/kgBW	Standard diet and water	- High fat diet 20-25gr/ rat/day - PTU 10,8mg/200grBW /day peroral - Water	- Standard diet and water - Simvastatin 10 mg/ kgBW23

Table 2. HDL, LDL, dan total cholesterol (TC) level at baseline, after induction, and after extract treatment

Group	Parameter	Baseline (Mean±SD) mg/dL	After induction (Mean±SD) mg/dL	P Value	After extract treatment (Mean±SD) mg/dL	P value
Negative	TC	58.50±2.23	60.66 ± 1.53	0.077	58.00±1.00	0.057
control	HDL	64.82±9.83	52.57±10.51	0.172	54.85±9.88	0.063
	LDL	26.52±3.20	27.00±3.72	0.51	27.45±3.78	0.042
Positive	TC	52.00±7.97	85.33±2.51	0.003*	82.67±3.51	0.057
control	HDL	52.34 ±21.72	27.55± 5.92	0.040*	27.77±6.07	0.532
	LDL	22.08±5.64	48.65±9.13	0.001*	49.17±9.21	0.171
Bitter melon	TC	53.80±9.65	64.00±11.69	0.026*	59.00±10.10	0.055
300mg/kgBW	HDL	44.60 ±10.88	26.80 ± 3.81	0.011*	32.85± 6.29	0.179
	LDL	21.58±2.08	57.30±16.97	0.022*	48.85±17.18	0.010*
Bitter melon	TC	61.60 ±11.63	78.25±7.22	0.002*	70.25±6.80	0.026*
600mg/kgBW	HDL	67.16±20.72	43.80±5.58	0.039*	54.00±2.18	0.05*
	LDL	24.48±3.20	50.90±9.47	0.002*	44.35±8.55	0.063
Simvastatin	T TC	50.00±7.10	69.80±9.25	0.009*	56.20±4.96	0.016*
10mg/kgBW	HDL	69.86±5.61	38.3±6.11	0.003*	49.94±7.22	0.005*
	LDL	23.10±3.36	50.98±15.36	0.019*	43.92±13.33	0.007*

Note: Provided standard diet during the study; Induced by high-fat diet (HFD) and PTU for 15 days; HFD and PTU were induced for 15 days and then given bitter melon aquoeus extract at a dose of 300 mg/kgbw for 15 days; HFD and PTU were induced for 15 days then given bitter melon water extract at a dose of 600 mg/kgBW for 15 days; Induction of HFD and PTU for 15 days then given simvastatin at a dose of 10 mg/kgBW for 15 days; *significance <0.05.

specimen. Three ml of rat blood was taken and put into an Eppendorf tube, then centrifuged at 3000 rpm for 15 minutes then the serum was separated. The principle of examination using the Cholesterol Oxidase-Perioxidase Aminoantipyrine (CHOD-PAP) enzymatic method with a Semi-automatic Chemistry Analyzer.[16,17]

Analysis for normality test used Shapiro-Wilk, then continued with paired t-test to determine whether there was a significant difference between the groups before and after administration of the bitter melon aqueous extract.

Results

Hyperlipidemia in this experiment refers to significant increase in LDL and total cholesterol levels, and decrease in HDL after induction. The results of the induction of experimental animals showed that all rats that received a high-fat diet and propylthiouracil had an increase in LDL and total cholesterol levels, as well as a decrease in HDL compared to baseline, and none of the experimental animals dropped out. The baseline LDL, HDL, and total cholesterol levels, after the induction period, and after administration of the extract can be seen in Table 2.

Bitter melon extract affect lipid profiles, this is indicated by changes in LDL, HDL, and total cholesterol levels in the treatment groups extract at doses of 300 and 600 mg/kg BW. Although the two doses of bitter melon extract can affect the lipid profile, the dose of 300 mg/kg BW only showed a significant difference in decreasing LDL

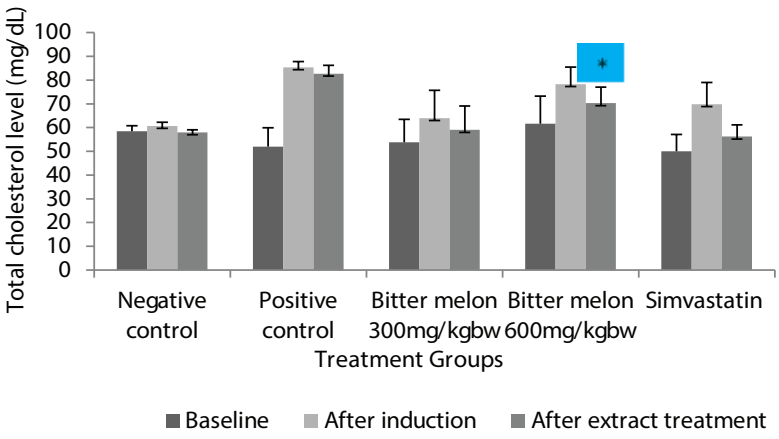

Figure 1. Effect of bitter melon extract on total cholesterol level in high fat diet induced hyperlipidemic rats

levels (p=0.01). Meanwhile, at a dose 600 mg/kg BW a significant difference was found in the reduction in total cholesterol (p=0.026) and an increase in HDL (p=0.05).

Figure 1 demonstrates the level of total cholesterol in the serum of normal and experimental groups of rats. A significant elevation of total cholesterol levels was observed in groups that induced by high fat diet and PTU when compared with the baseline. Treatment with bitter melon fruits extract dose 600mg/kg BW and simvastatin decreased total cholesterol levels. The same results were seen in LDL levels at a dose of 300 mg/kg BW bitter melon and simvastatin treatment (Figure 3).

HDL levels showed a significant decrease after high fat diet and PTU induced. In the hyperlipidemic rats treated with bitter melon extract (600 mg/ kg), the HDL level increased significantly to 54.00±2.18 mg/dL the same as the normal group (54.85±9.88mg/dL). (Figure 2)

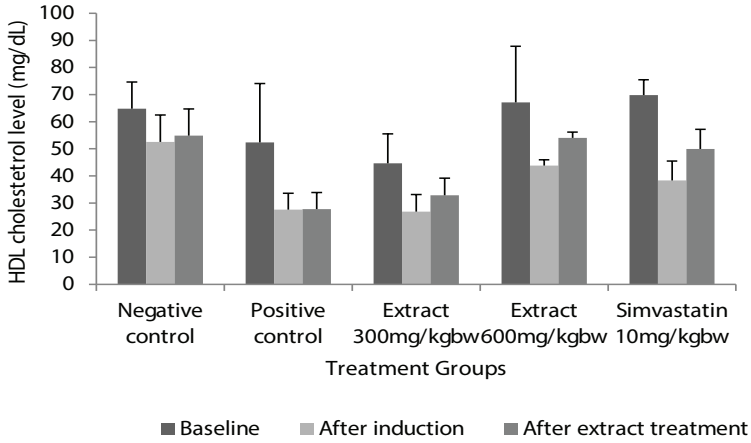

Figure 2. Effect of bitter melon extract on HDL cholesterol level in high fat diet induced hyperlipidemic rats

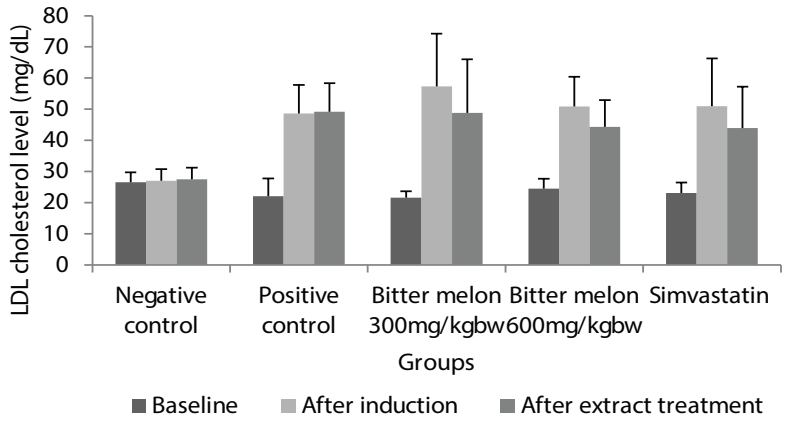

Figure 3. Effect of bitter melon extract on LDL cholesterol level in high fat diet induced hyperlipidemic rats

Discussion

The results of LDL, HDL and total cholesterol levels during the adaptation period (baseline) showed significant differences compared with after receiving a high-fat diet and propylthiouracil, except in the negative control group. This shows that induction with a high fat diet and propylthiouracil for two weeks can cause an increase in LDL and total cholesterol levels, as well as a decrease in HDL. A high fat diet can increase acetyl CoA, while propylthiouracil can decrease thyroid hormone which will result in an increase in ATP production from glucose and fatty acids, resulting in a decrease in lipolysis.[19] Administration of propylthiouracil causes hypothyroidism which can cause an increase in cholesterol levels, especially LDL cholesterol due to suppression of LDL receptors.[20]

Bitter melon contains various active compounds, including saponins and triterpenoids. Both substances have hypoglycemic and hypolipidemic effects.[4] The active compounds in bitter melon can increase the conversion of cholesterol into bile acids by downregulating of HMG-CoA reductase in the liver and adipose.[6] Bitter melon can reduce apolipoprotein C-III and apolipoprotein B. Apolipoprotein C-III and apolipoprotein B are lipoproteins involved in LDL synthesis. In addition, bitter melon can also increase apolipoprotein A-1 which plays a role in HDL synthesis, so that HDL levels can increase. To avoid atherosclerotic disease, someone must increase HDL and avoid increase LDL.[5]

The result of this study supported the previous study that stated administration of bitter melon extract in doses of 250, 500 and 750 mg/kg BW for 90 days in diabetic rats can reduce total cholesterol by different doses, the most reduction is 17.21% at a dose of 750 mg/kg BW. This shows that there is influence of dose on the antihyperlipidemic effect of bitter melon.[9] Our study showed that at a dose of 300 mg/kg BW there was no significant change in HDL and total cholesterol, while at a dose of 600 mg/kg BW there was a significant decrease in total cholesterol and a significant increase in HDL ($P<0.05$). This illustrates the effect of dose on the antyhiperlipidemic effect of bitter melon aqueous extract.

Our study showed LDL levels in a significant

difference when experimental rats treated with dose of 300 mg/kg BW (P=0.01), but when the dose was increased to 600 mg/kg BW there was no significant change. There is a phenomenon that the dose increase is not linear to enhance the therapeutic effect. Therapeutic effect that is not in line with improvement of the dose of the drug given is known as nonmonotomic dose-response relationship (NMDR).[21] The mechanism of action of the compound to produce NMDR is caused by various theories, such as, cytotoxicity, receptor specific and cofactor on cells and tissues, receptor selectivity, receptor down regulation and desensitization and competitive receptors and feedback negative.[22]

The results of this study provide scientific evidence about the efficacy of bitter melon extract in decresing total and LDL cholesterol and increasing HDL cholesterol. It gives hope that the aqueous extract of bitter melon can be used as herbal medicine for complementary therapy in hyperlipidemia. However this study did not determine the mechanism of action of bitter melon extract as antihyperlipidemia. Further investigation suggested to investigate its mechanism of action especially the role in inhibiting HMG-CoA reductase in the liver and adipose.

Conclusions

From our experimental findings it is possible to conclude that bitter melon extract exhibited promising antihyperlipidemic activity in hyperlipidemic rats. Hence, it may be pursued for its clinical usefulness in the management of hyperlipidemia.

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Conflict of Interest

The author(s) declare that they have no conflict of interest.

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