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The effect of *Moringa oleifera* L. extract on total cholesterol levels and cardiac hypertrophy in cigarette smoke-exposed mice: An experimental study

Efek Moringa oleifera L. terhadap kadar kolesterol total dan hipertrofi jantung pada mencit yang terpapar asap rokok: Sebuah studi experimental

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Abstract

Cigarette smoke contains harmful chemicals that induce oxidative stress by increasing the levels of reactive oxygen species (ROS), thereby complicating cardiovascular disease treatment. *Moringa oleifera* L., rich in secondary metabolites and antioxidants, has shown medicinal potential. This study aimed to investigate the phytochemical composition of *M. oleifera* and its potential effects on cardiac hypertrophy and total cholesterol levels in mice exposed to cigarette smoke. Thirty male white mice (*Mus musculus*) were divided into five groups (n = 6). The negative control group received only food and water, whereas the positive control group was exposed to cigarette smoke without *M. oleifera* extract. Groups 1, 2, and 3 were exposed to cigarette smoke, and *M. oleifera* extract was administered at doses of 125, 250, and 500 mg/kg body weight (BW) for 14 days. On the fifteenth day, the mice were sacrificed to obtain heart samples and total cholesterol levels were measured. One-way ANOVA followed by a post-hoc test showed that *M. oleifera* extract significantly affected cardiac hypertrophy and total cholesterol levels in mice exposed to cigarette smoke ($p < 0,05$). *M. oleifera* extract significantly affected cardiac hypertrophy and total cholesterol levels in rats exposed to cigarette smoke with $p = 0,001$ and $p = 0,000$, respectively.

Keywords: Moringa oleifera L, total cholesterol, cardiac hypertrophy, cigarette smoke.

Abstrak

Asap rokok, mengandung bahan kimia berbahaya, yang menyebabkan stres oksidatif dengan meningkatkan kadar spesies oksigen reaktif, yang mempersulit pengobatan penyakit kardiovaskular. *Moringa oleifera* L., banyak mengandung metabolit sekunder dan antioksidan yang kuat, memiliki potensi sebagai tanaman obat. Penelitian experimental ini bertujuan untuk menganalisis komposisi fitokimia dan efek potensial *M. oleifera* pada hipertrofi jantung dan kadar kolesterol total pada mencit yang terpapar asap rokok. Sebanyak tiga puluh ekor mencit putih jantan (*Mus musculus*) dibagi menjadi lima kelompok (n = 6). Kelompok kontrol negatif hanya menerima pakan dan air; kelompok kontrol positif dipapar asap rokok tanpa ekstrak *M. oleifera*; kelompok 1, 2, dan 3 terpapar asap rokok diberi perlakuan ekstrak *M. oleifera* dengan dosis 125, 250, dan 500 mg/kgbb, masing-masing selama 14 hari. Pada hari ke-15, hewan coba dikorbankan untuk diambil sampel jantung dan diperiksa kadar kolesterol darah. One-way ANOVA dilanjutkan dengan uji post hoc menunjukkan bahwa ekstrak *M. oleifera* secara signifikan mempengaruhi hipertrofi jantung dan kadar kolesterol total pada mencit yang terpapar asap rokok ($p < 0,05$). Ekstrak *M. oleifera* secara signifikan mempengaruhi hipertrofi jantung ($p = 0,001$) dan kadar kolesterol total ($p = 0,000$) pada tikus yang terpapar asap rokok.

Kata Kunci: Moringa oleifera L, kolesterol total, hipertrofi jantung, asap rokok

Introduction

The World Health Organization (WHO) has identified cardiovascular disease (CVDs) as the primary contributor to global morbidity and mortality. Each year, an estimated 17.5 million fatalities occur due to CVDs, representing 31% of all global deaths. Myocardial infarction and stroke significantly contributed to these findings. Tobacco use is a key factor that influences CVD risk. Individuals who smoke regularly have a two–four times higher likelihood of developing coronary heart disease (CHD) than nonsmokers. Active and passive cigarette smokers are responsible for a significant number of fatalities annually. Approximately five million deaths can be attributed to active smoking, while over six hundred thousand deaths are caused by passive smoking. Smoking elicits oxidative processes, negatively affects platelet function, fibrinolysis, inflammation and vasomotor function; all these proatherogenic effects double the 10-year risk of fatal events in smokers compared to non-smokers (Gallucci et al., 2020).

Cigarette smoke (CS) contains over 4,720 hazardous compounds, including polycyclic aromatic hydrocarbons, free radicals, and oxidative gases. The harmful effects of smoking on cardiovascular health include vascular dysfunction, impaired endothelial and platelet functions, and alterations in lipid profiles. Inflammation is a critical factor in the development and progression of atherosclerosis (DiGiacomo et al., 2019).

Cigarette smoke inhalation can induce profound alterations in cardiovascular structure and function, particularly through cardiac or ventricular remodeling. This process includes abnormalities at the molecular, cellular, and interstitial levels, leading to modifications in heart dimensions, mass, configuration, and functional capacity. Specifically, CS exposure to cigarette smoke has been linked to the development of left ventricular enlargement, myocardial hypertrophy, and ventricular dysfunction. The mechanisms involved include alterations in hemodynamic and neurohormonal processes, oxidative stress, inflammation, decreased availability of nitric oxide (NO), and activation of matrix metalloproteinases and mitogen-activated protein kinases (Kaplan et al., 2017). Mice exposed to cigarette smoke for one month demonstrated various cardiovascular effects, including enlarged heart muscle, inflammatory responses, increased fibrosis-promoting factors, increased markers associated with atherosclerosis, and calcium deposits in the aorta. The efficacy of antioxidants in mitigating cardiac hypertrophy and reducing atherosclerosis markers associated with smoke exposure has been reported previously (Al Hariri et al., 2016; Permana et al., 2021).

Moringa oleifera L., a species of the Moringaceae family, is extensively cultivated in Indonesia and has long been used by local populations for nutritional and therapeutic applications. *M. oleifera* leaves are abundant in bioactive components with antioxidant characteristics, along with flavonoids, alkaloids, saponins, tannins, and terpenoids. These naturally derived water-soluble antioxidants exhibit antibiotic, anti-inflammatory, detoxifying, and antibacterial activities (Saputra et al., 2020). Diverse plant components, including leaves, blossoms, seedpods, seeds, roots, bark, and gum, are used in conventional medicine to address a broad range of health conditions and to enhance overall well-being (Gopalakrishnan et al., 2016). The pharmaceutical potential, along with nutritional and medicinal advantages, is particularly evident in the leaves and seeds. Specifically, leaves contain high levels of proteins, minerals, and compounds with antioxidant properties (Leone et al., 2015).

However, few in vivo studies have investigated the potential of M. oleifera as an antihypoglycemic agent against oxidative stress and apoptosis (Soliman et al., 2020; Zeng et al., 2019). The potential of *M. oleifera* leaves as an alternative antioxidant food source to mitigate free radical activity in the cardiovascular system after short-term (acute) exposure to cigarette smoke has not been explored extensively. This study aimed to assess the effects of *M. oleifera* leaf extract on the total cholesterol levels and cardiac hypertrophy in mice exposed to cigarette smoke.

Methods

Thirty male white mice (*Mus musculus*), aged 8-12 weeks old and weighing 16-20 grams, were used in this study. The mice were acclimatized for seven days before the start of the experimental procedures. All animals were provided a standard pellet diet and had access to water *ad libitum*. The mice were housed in groups of six per cage, with each cage composed of plastic tubs measuring 30 cm × 22

cm × 19 cm. The animal cages were equipped with husk bedding to absorb waste and covered with wire-woven lids. The cages were placed in a spacious room that allowed for natural ventilation.

To expose the animals to cigarette smoke, they were transferred to a designated smoking chamber, where a cigarette was connected to an air pump through a pipe, enabling controlled delivery of smoke. Clove cigarettes (Brand Surya) containing 2,2 mg nicotine and 31 mg tar were used for the exposure. Once the cigarette was lit, an air pump was activated to simultaneously introduce oxygen into the smoking chamber, at a flow rate of 0,5 ppm. The exposure regimen involved burning four cigarettes for 15 min, administered twice a day at 09:00 and 14:00 for 14 days. *M. oleifera* leaf extract was administered orally to mice using a 3 cc syringe each day at 11:00 a.m. On the fifteenth day, the mice were weighed, and their total cholesterol levels were measured. Subsequently, the animals were euthanized and heart tissue samples were obtained. Cardiac hypertrophy was assessed by determining the heart weight to body weight ratio (mg/g).

M. oleifera leaves were purchased from a local market in Medan, North Sumatra, Indonesia. *M. oleifera* leaves were thoroughly washed and dried for 2–4 d, after which they were finely powdered. Subsequently, a kilogram of powdered leaves was macerated with 70% ethanol for 24 h, after which the mixture was filtered. The residue was re-macerated until the filtrate was clear. The concentrated solution was subsequently filtered and evaporated using a vacuum evaporator at temperatures ranging from 30 °C to 40 °C and a pressure of 75 mmHg.

Adult male white mice (n = 30) were divided into five groups (n = 6). The animals in the negative control group received a standard diet without exposure to cigarette smoke, whereas those in the positive control group received a standard diet and were exposed to cigarette smoke. The treatment groups received standard food, cigarette smoke, and *M. oleifera extract* at doses of 125 mg/kg (group 1), 250 mg/kg (group 2), or 500 mg/kg body weight (group 3) for 14 days (Days 1-14) (Aliyu et al., 2021) (Moodley, 2017). The extract was suspended in a 0,5% sodium carboxymethylcellulose (Na-CMC) solution and administered orally to the treatment groups using a gastric sonde.

Cholesterol levels were measured using a cholesterol test kit (Easy Touch GCU) by pressing a button, followed by calibration and placement of the strip on the kit. Blood was extracted from the tail vein of the mice, and the sample was applied to a cholesterol-measuring strip, thereby enabling the rapid and automatic determination of blood cholesterol levels. The results are expressed in mg/dl.

Data were analyzed using the Shapiro-Wilk test for normality. One-way analysis of variance (ANOVA), followed by the LSD test for post hoc analysis, was used to compare the differences in body weight, heart weight, and cardiac hypertrophy among and between groups. Statistical significance was set at $p<0,05$. Data analysis was conducted using SPSS version 25.0.

This experimental laboratory study with a post-test control group design was approved by the Health Research Ethics Commission (KEPK) of the Faculty of Medicine of Muhammadiyah University of North Sumatra, Indonesia (No. 780/KEPK/FKUMSU/2022).

Result and Discussion

The ethanolic extract of phytochemical composition of the ethanolic extract of *M. oleifera* is shown in Table 1. This analysis identified multiple compounds including alkaloids, saponins, tannins, flavonoids, steroids, and terpenoids. A significant increase in body weight was observed in the groups treated with *M. oleifera* extract compared to that in the positive control group ($p < 0,05$).

After the 14-day treatment period, the lowest body weight was recorded for the positive control group. This weight loss was likely due to oxidative stress resulting from the exposure to cigarette smoke. Exposure to cigarette smoke causes mitochondrial damage, which impairs the body's ability to produce energy. Consequently, the body may experience weight loss due to its inability to generate energy. Body weight was used as a growth parameter to reflect the physical condition and nutrient absorption capacity of the experimental animals (Ariestiningsih et al., 2018). However, no significant difference in body weight was observed between the treatment groups.

Table 1. Qualitative determination of the phytochemical composition of *Moringa oleifera* extract.

Secondary metabolites	Reagent	Result
Alkaloid	Bouchardart	+
	Maeyer	+
Saponin	Aquadest + Alkohol 96% +HCl 2N	-
Tannin	$FeCl_3$ 5%	+
Flavonoid	$FeCl_3$ 5%	+
Steroid	Salkowsky	+
	Liebermann-Bouchard	+
Terpenoid	Salkowsky	+
	Liebermann-Bouchard	+

+ = present; − = absent.

Phytochemical screening of *the M. oleifera* extract indicated the presence of several compounds, including alkaloids, tannins, flavonoids, terpenoids, and steroids. *M. oleifera* leaves are widely acknowledged as a substantial natural antioxidant source because of the presence of various compounds such as ascorbic acid, flavonoids, phenolics, and carotenoids (Bais et al., 2014). This plant species is known for its high nutritional value and contains components such as flavonoids that exhibit antioxidant properties (Tiloke et al., 2018). The predominant phytochemical compounds present in various parts of *M. oleifera* are flavonoids, phenolic acids, tannins, saponins, alkaloids, glucosinolates, and glycosides (Paikra & Gidwani, 2017; Saleem et al., 2020). The synergistic action of these bioactive compounds leads to therapeutic outcomes, such as a decrease in blood glucose levels and anticancer, antibacterial, antifungal, neuroprotective, cardioprotective, and anti-inflammatory properties, as well as on influences the immune system (Paikra & Gidwani, 2017; Saleem et al., 2020; Tiloke et al., 2018).

One-way ANOVA revealed that *the M. oleifera* leaf extract exerted a significant influence on total cholesterol levels and cardiac hypertrophy in mice exposed to cigarette smoke ($p < 0,05$). Additional post-hoc analysis demonstrated significant differences in total cholesterol levels and cardiac hypertrophy between the positive control and all treatment groups. Table 2 presents data on body weight, heart weight, and cardiac hypertrophy parameters. Notably, no substantial differences were observed between the treatment groups.

Table 2. The body weight, heart weight, and cardiac hypertrophy were measured in the control and treatment groups.

Parameters	Body weight (g)	p-value	Heart weight (mg)	p-value	Cardiac hypertrophy (mg/g)	p-value
Negative Control	29,40±7,26	0,001*	225,70±34,97	0,026*	8,21±2,95	0,001*
Positive Control	21,80±1,30^{ab}		292,94±29,94^{ab}		13,43±0,96^{ab}	
Group 1	33,16± 5,19^{c}		265,38 ± 53,63^{c}		8,35±2,85^{c}	
Group 2	31,00 ±3,34^{c}		231,96 ± 17,14^{c}		7,55±1,04^{c}	
Group 3	33,50 ± 3,93^{c}		268,63 ± 40,61^{c}		8,13±1,73^{c}	

Values are expressed as the mean ± standard deviation (n = 6), *One-way ANOVA test. Superscript a: Significant difference compared to the negative control group. Within columns, means followed by different letters (b and c) are significantly different between the treatment groups according to the post hoc test (LSD test) ($p < 0,05$). Group 1:125 mg/kg bw, Group 2:250 mg/kg bw, and Group 3:500 mg/kg bw.

The mean total cholesterol level in the positive control group was significantly higher than those in the other treatment groups. This increase in total cholesterol levels may be attributable to oxidative stress resulting from exposure to cigarette smoke. According to Ma et al. (2020), exposure to cigarette smoke leads to lipid metabolism disorders characterized by a substantial increase in serum cholesterol levels. This alteration correlates with decreased low-density lipoprotein receptor (LDLR) expression (Ma et al., 2020). *In vivo* exposure to cigarette smoke has been found to significantly affects plasma lipid profiles, high-density lipoprotein (HDL) functionality, and the reverse cholesterol transport pathway (RCT) in cholesterol ester

transfer protein (CETP) transgenic mice. CETP plays a crucial role in facilitating the transfer of cholesterol esters from HDL in the plasma to low-density lipoproteins (LDL) or very-low-density lipoproteins (VLDL) in exchange for triglycerides. Reverse cholesterol transport (RCT) is typically characterized as the process by which cholesterol is exported from peripheral cells to plasma HDL, which is then taken up by hepatocytes for bile secretion or directly excreted into the bile and feces (Zong et al., 2015).

A previous study demonstrated that rats that were fed an atherogenic diet and received *M. oleifera* leaf extract, administered orally at a dose of 400 mg/kg body weight, exhibited a considerable decrease in total cholesterol and LDL compared to their baseline values after 28 days (Aborhyem et al., 2016). Further studies have demonstrated that the lipid-lowering effects of *M. oleifera* leaf extract are likely due to its alkaloid, tannin, cardiac glycoside, β-sitosterol, polyphenol, and flavonoid contents, which are consistent with those reported in our study (Helmy et al., 2017).

The ethanolic extract of *M. oleifera* leaves exhibited potent antioxidant and radical scavenging activities. Polyphenols, which are present at high concentrations in this extract, have been shown to exhibit potent in vitro antioxidant effects by inhibiting lipid peroxidation as chain-breaking peroxyl radical scavengers and by protecting low-density lipoproteins from oxidation. Plant sterols, including β-sitosterol, which are present in *M. oleifera* extract, inhibit the absorption of dietary cholesterol. β-Sitosterol lowers cholesterol levels by reducing plasma LDL concentrations and inhibiting the re-absorption of cholesterol from endogenous sources, while simultaneously increasing its excretion as neutral steroids in feces. Thus, β-sitosterol is a significant bioactive phytoconstituent in the leaves of *M. oleifera* (Helmy et al., 2017; Rudrapal et al., 2022).

Table 3 shows the total cholesterol levels of the control and treatment groups. The administration of *M. oleifera* leaf extract at a dose of 250 mg/kg body weight demonstrated the most significant potential to decrease total cholesterol levels and cardiac hypertrophy (125,00 ± 21,19; 7,55 ± 1,04). These findings indicate that *the M. oleifera* leaf extract is effective in reducing total cholesterol levels and cardiac hypertrophy in a dose-dependent manner. The optimal result was observed in the group that received 250 mg/kg of body weight.

Table 3. Total cholesterol levels in control and treatment groups

Parameters	Total cholesterol (mg/dl)	p-value
Negative Control	150,20±18,01	
Positive Control	189,20±18,71^{ab}	
Group 1	130,67±17,16^{c}	0,000*
Group 2	125,00 ± 21,19^{ac}	
Group 3	126,16 ± 14,12^{c}	

Values are expressed as the mean ± standard deviation (n = 6). *One-way ANOVA test. Superscript a: Significant difference compared to the negative control group. Within columns, means followed by different letters (b and c) are significantly different between treatments according to the post-hoc test (LSD test) ($p < 0,05$). Group 1:125 mg/kg bw, Group 2:250 mg/kg bw, and Group 3:500 mg/kg bw.

The results of this study are consistent with those of previous studies that have demonstrated that exposure to cigarette smoke can result in cardiac hypertrophy, inflammation, and vascular injury in (Al Hariri et al., 2016). Nicotine has been demonstrated to increase the size of cardiomyocytes in Wistar rats by activating the calcium/NFAT signaling pathway through TRPC3 (Li et al., 2016). In the present study, *M. oleifera* leaf extract at a dose of 250 mg/kg body weight reduced cardiac hypertrophy. However, the precise mechanism by which *the M. oleifera* extract prevents cardiac hypertrophy remains unclear. Al Hariri et al. (2016) provided relevant information regarding the role of antioxidants in preventing cardiac hypertrophy. Their findings indicated that CS exposure to cigarette smoke causes cardiac hypertrophy in rats. However, pre-treatment with pomegranate antioxidants for one week before and throughout the four weeks of exposure to cigarette smoke prevented cardiac hypertrophy in the treated group (Al Hariri et al., 2016; Konmy et al., 2016).

The combination of antioxidant content found in moringa leaves proved to be more effective than a single antioxidant. This is caused by synergistic and antioxidant cascade mechanisms. The flavonoids in moringa leaves prevent LDL oxidation by donating H+ and inhibiting the activity of 3-hydroxy-3methylglutaryl coenzyme-A reductase (HMG-CoA Reductase). Tannins in Moringa leaves act as antioxidants, and astringent tannins react

with mucosal proteins and small intestinal epithelial cells to inhibit fat absorption in the body. Saponins bind to cholesterol and bile acids, thereby lowering the cholesterol levels. Vitamin C aids in hydroxylation of bile acid clots and increases cholesterol excretion. Vitamin B3 reduces the production of VLDL (Low-Density Lipoprotein) and stimulates blood circulation. Thereby reducing the occurrence of fat deposition in the blood vessels (Sari & Suwondo, 2022).

M. oleifera leaf extract inhibits inflammation by deactivating NF-κB, which involves preventing the degradation of IκB-α and blocking nuclear translocation of the p65 subunit. Consequently, this inhibition interferes with the binding of NF-κB to its target DNA, leading to the downregulation of proinflammatory mediators, including IL-6, TNF-α, and COX-2 (Luetragoon et al., 2020). A similar mechanism may also play a role in the administration of *M. oleifera* extract in reducing cardiac hypertrophy in mice. Furthermore, *M. oleifera* extract inhibited cell growth and DNA synthesis (Cirmi et al., 2019). These results highlight the potential of *M. oleifera* as a natural remedy for diseases associated with inflammation, and provide insights into its antioxidant properties and capacity to alleviate lipid metabolic disorders in smokers.

This study had some limitations, including the fact that the long-term effects of *M. oleifera* leaf extract as an antihyperlipidemic and anti-cardiac hypertropy treatment were not determined.

Conclusion

Administration of 250 mg/kg body weight *M. oleifera* leaf extract demonstrated the highest efficacy in reducing total cholesterol levels and mitigating cardiac hypertrophy in mice exposed to cigarette smoke. The ethanolic extract of *M. oleifera* leaves shows promise as a therapeutic intervention to prevent lipid metabolic disorders in smokers.

Furthermore, our study underscores the significant radical-scavenging activity of *M. oleifera*, indicating its potential as a natural antioxidant and candidate for addressing inflammation-related conditions such as cardiac hypertrophy. Future research should prioritize quantitative phytochemical analysis of the metabolic compounds present in *M. oleifera* leaf extract, investigate the molecular mechanisms underlying cardiac hypertrophy, and conduct clinical trials to evaluate its effectiveness in reducing the risk of atherosclerosis in smokers.

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