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Recent Updates on the Potential of Medicinal Plants from Indonesia as Anti-Atherosclerotic Agents

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ABSTRACT

Introduction*: Atherosclerosis is one of the causes of problems in the cardiovascular system. This condition can be prevented by using natural products, one of which is medicinal plants.* ***Aims****: This review collects data on medicinal plants that are easily found in Indonesia that can reduce or improve atherosclerosis conditions.* ***Result****: There are 10 plants reviewed that have a high level of safety and potential to be developed as medicine. The plant parts used are fruit and leaves. Some are commonly used as cooking spices such as turmeric and garlic which are found to be useful for improving atherosclerosis conditions. In the context of modern drug development, Indonesia holds significant potential for exploring these plants as sources of active compounds for pharmaceutical applications. Scientific studies of these natural materials are crucial for identifying bioactive components and understanding their mechanisms of action. With the right approach, Indonesia's natural resources could form the basis for developing new, safer, and more effective drugs.* ***Conclusion****: Additionally, Indonesia has a considerable opportunity in the global market for natural health products, including nutraceuticals and dietary supplements, as global interest in natural health solutions continues to grow.*

KEYWORDS*: Instant powder drink, yield, water absorption, viscosity, shelf life*

INTRODUCTION

Cardiovascular diseases (CVDs) have been reported as the leading cause of death globally, with a mortality rate of 17.9 million deaths per year. Heart attack condition may be caused in part by atherosclerosis. Atherosclerosis is the most common cause of CVD (Frostegård, 2013). Atherosclerosis occurs when plaques are formed due to the accumulation of lipids in the arteries. These plaques consist of a mixture of cholesterol, fats, blood cells, and other components, which can disrupt the flow of oxygen-rich blood to vital tissues in the body (NHLBI, n.d.). In Indonesia, the prevalence of

CVD based on physician diagnosis of 1.5%, with the highest prevalence observed in North Kalimantan, Yogyakarta, and Gorontalo. The 2014 Indonesian Sample Registration System (SRS) reported that Coronary Heart Disease (CHD) was the second leading cause of death after stroke, accounting for 12.9% of all major causes of mortality in Indonesia (P2PTM Kemenkes RI, 2019). Data from BPJS shows an increasing trend in healthcare expenditures for CHD over the years. In 2014, CHD-related expenses amounted to 4.4 trillion Rupiah, rising to 7.4 trillion Rupiah in 2016, and further increasing to 9.3 trillion Rupiah by 2018. This highlights the significant burden on the state in managing CHD, which could be controlled (P2PTM Kemenkes RI, 2019) by addressing risk factors and minimizing the incidence of CHD, including through the utilization of alternative therapies based on natural resources. While there are many medications available to treat this illness, using medicinal plants can also prevent or minimize atherosclerosis. The discovery of safe and effective drugs remains a prominent topic in the cardiovascular field (Atanasov et al., 2021; Ooi et al., 2018). High safety profiles are a significant advantage for drug development from natural sources. Consequently, the development of antiatherosclerosis candidates derived from natural products presents substantial research opportunities, especially considering the abundant natural resources available in Indonesia. Phytomedicine also accounts for approximately 25% of the global pharmaceutical market (Chang et al., 2020). Indonesia is a world that have biodiversity, making it a global hotspot for biological diversity. With over 17,000 islands and a wide variety of ecosystems, this natural abundance includes thousands of medicinal plant species, many of which remain scientifically unexplored for their pharmacological potential. Indonesia as a country with a long tradition of using natural resources for healing in traditional remedies, such as jamu. Many native medicinal plants are believed to offer health benefits, ranging from treating minor ailments to preventing several disease such as diabetes, hypertension, and cardiovascular conditions (Wahyuningrum et al., 2022).

ATHEROSCLEROSIS AS THE LEADING CAUSE OF MYOCARDIAL INFARCTION

Atherosclerosis occurs when plaques are formed due to the accumulation of lipids in the arteries. These plaques consist of a mixture of cholesterol, fats, blood cells, and other components, which can disrupt the flow of oxygen-rich blood to vital tissues in the body (*Atherosclerosis - What Is Atherosclerosis? | NHLBI, NIH*, n.d.). There are condition progression of atherosclerosis including initiation: Endothelial Dysfunction; LDL Oxidation and Inflammation; Formation of Atherosclerotic Plaque; Plaque Complications: Rupture and Thrombosis; Progression and Clinical Manifestations. Myocardial infarction is commonly caused by

thrombotic occlusion resulting from the rupture of plaques (Ojha & Dhamoon, 2023). This condition, causes death of cardiomyocyte and necrosis in myocardial area, followed by inflammation and fibrosis (Leancă et al., 2022). Necrosis spreads from the sub-endocardium to the sub-epicardium. The infarcted area can heal through scar formation, a natural compensatory response due to the limited regenerative capacity of the myocardium (Ojha & Dhamoon, 2023).

The therapy for myocardial infarction aims to prevent left ventricular remodeling (molecularm cellular, and size, shape and function of heart) by reducing the size of the infarct in cardiac injury (Leancă et al., 2022). After acute myocardial infarction, the inflammatory response plays a crucial role in the healing process of the infarcted myocardium and the development of adverse remodeling. Several cytokines were tigered by myocardial necrosis including TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6) (Leancă et al., 2023). Certain cytokines have been identified as potential therapeutic targets for modulating myocardial inflammation (Leancă et al., 2022). The levels of pro-inflammatory cytokines correlate with the progression of left ventricular remodeling after myocardial infarction. IL-1β secretion is stimulated following ischemic events in mice (Leancă et al., 2023).

Several specific factors that increase an individual's risk of myocardial infarction due to atherosclerosis include gender (more common in men), obesity, smoking, and the presence of cardiovascular-related conditions such as diabetes mellitus, hypertension, and dyslipidemia (Wells et al., 2015).

The etiology of myocardial infarction is primarily caused by a reduction in blood flow to the coronary arteries. This reduction in blood flow leads to an unmet oxygen demand in the heart, resulting in myocardial ischemia. The decrease in coronary blood flow may be due to the rupture of atherosclerotic plaques within the cardiac circulation, which forms lesions and triggers thrombosis in the heart muscle cells. Thrombosis is also a significant cause of acute reductions in blood flow, as it narrows the vessels supplying the coronary arteries. In addition to atherosclerotic plaques and thrombosis, myocardial ischemia can be induced by cocaine use, coronary abnormalities, or coronary vasospasm (Massberg & Polzin, 2018).

Myocardial infarction (MI) occurs due to oxidative stress caused by a large number of free radicals in myocardial cells from the oxidation of certain chemical compounds, lipid peroxidation, hyperlipidemia, and hyperglycemia (Zhang et al., 2022). This leads to atherosclerotic plaque rupture, triggering a cascade of monocyte and macrophage inflammation, thrombus formation, and platelet aggregation. The coronary arteries experience reduced oxygen delivery, leading to decreased myocardial oxygenation and reduced oxygen supply to heart cells. This also impairs the heart's ability to generate energy in

the mitochondria, causing an ischemic condition and causes in apoptosis in cell. Cardiac muscle cell death begins in the endocardium. As the duration of occlusion increases, myocardial cell death extends from the endocardium to the myocardium and eventually reaches the epicardium (Kurian et al., 2016).

THE POTENTIAL OF INDONESIAN MEDICINAL PLANTS AS ANTIATHEROSCLEROTIC AGENT

The collection of information on several Indonesian medicinal plants that have the potential as antiatherosclerosis is based on research reports on the effects of several of these plants, including as lowering blood cholesterol and some have been confirmed to have anti-atherosclerosis effects. The plants included in this article are easy to find, there are ten plants that we have successfully collected information on regarding their safety and effectiveness data so that they are considered to have the potential as antiatherosclerosis.

Pinus eldarica

Study was perform by Huseini, the findings show that *P. eldarica* nut extract can reduce fasting blood cholesterol and aortic atherosclerotic involvements at doses 200 and 100 mg/kg/day in rabbit (Huseini et al., 2015). The safety was confirmed by acute (200 mg/kg) and sub acute toxicity study may have relatively non toxic at doses 125 and 250 mg/kg (Ghadirkhomi et al., 2016). The oil substances primary reported from *P. eldarica* including mono and sesquiterpenoid fraction especially caryophyllene oxide (14.0%), δ-3-carene (10.7%), α-pinene (24.6%), (E)-β-caryophyllene (7.9%), and myrtenal (3.1%) (Iravani & Zolfaghari, 2014).

Garlic (*Allium sativum*)

Clinical study was found from high dose garlic powder with time for uses along 48 months can decrease volume of atherosclerotic plaque by 5-18% with ultrasonography evaluation. (Koscielny et al., 1999). Garlic extract was reported to have an LC50 of 7.48 ppm at 96 hours for *T. blochii*. According to the results of this investigation, pompano can be safely treated with aqueous garlic extract up to 5 ppm for preventive purposes (Erazo-Pagador, 2021). Garlic may decrease the absorption of cholesterol, and the synthesis of cholesterol and fatty acid, and thereby reduces the level of cholesterol (Sun et al., 2018).

Echinodorus grandifloras

E. grandiflorus leaves might prevent rabbits from developing atherosclerosis and could be a novel herbal remedy that has direct therapeutic and preventive potential for atherosclerotic disease (reduction serum lipid) (Gasparotto et al., 2019). Diterpenoids and flavonoids metabolites have been reported from crude *E. grandiflorus* extracts (Marques et al., 2017). Toxicity studies of aqueous extract of *Echinodorus grandiflorus* in pregnant rats show that treatment with 1,000 mg of extract caused anemia, leukocytosis, and

an increase in AST and in cholesterol, but it does not alter the reproductive performance (Brugiolo et al., 2010).

Basella alba

One study was investigate the use of hypercholesterolemia-induced rabbits to study the hypocholesterolemic and antiatherosclerotic properties of Basella alba (*B. alba*). The findings of the current investigation demonstrated that *B. alba* extract (200 mg/kg) efficiently lowers Total Cholesterol, LDL, and TG levels while increasing HDL and antioxidant enzyme levels. B. alba leaf extract did not harm the liver or the muscles, showing that it is safe to eat. (Baskaran et al., 2015). The alcoholic extract of *B. alba* contains alkaloids, tannins, flavanoids, and polyphenols as phytochemicals.

Aloe vera

Aloe vera contains a variety of nutrients, including vitamins (A, C, and E), enzymes, lignins, saponins, anthraquinones, phytosterols, monosaccharides, and polysaccharides (glucomannans and acemannans) (Huga et al., 2019). In rabbits fed a high-cholesterol diet, aloe vera leaf gel dramatically reduced Total Cholesterol (TC), decreased the development of atherosclerotic lesions in the aorta and blood levels of C-Reactive Protein (CRP) (Dana et al., 2012). Many forms of *Aloe vera* preparations, including extracts, gels, and powdered capsules, are effective as blood lipid reducers (R. S. Singh & Silitonga, 2021). Information about lethal dose (LD_{50}) of *Aloe vera* in Swiss albino mice was 120.65 mg/kg (Guo & Mei, 2016). Polysaccharides in *Aloe vera* gel such as Mannose-6-phosphate and C-glucosyl chromone have anti-inflammatory and anti-oxidant effect (Dana et al., 2012).

Morinda citrifolia

Mechanism of antiatherosclerotic property of *Morinda citrifolia* leaf extract through lipids elimination and anti-inflammatory activity (at dose 500 mg and 1000 mg/kg) (Chong et al., 2018). *Morinda citrifolia* contained a broad spectrum of secondary metabolites such as alkaloids, saponins and steroid, phenol, tannin and terpenoids (Nagalingam et al., 2012). ***Morinda citrifolia*** have possibility to inhibit of cholesterol biosynthesis by inhibition of HMG Co-A. This enzyme plays a key role in controlling lipid levels in plasma and other tissue (Mandukhail et al., 2010).

Pomegranate (*Punica granatum*)

Pomegranate is a source of some very potent antioxidants (tannins, anthocyanins), which are also thought to be potent anti-atherogenic agents. These antioxidants prevent oxidation of both high-density lipoprotein (HDL, "the good cholesterol") and low-density lipoprotein (LDL, "the bad cholesterol"), which slows the development of atherosclerosis and the subsequent cardiovascular events (Aviram & Rosenblat, 2013). At 4 months of age, Atherosclerotic E0 mice were supplemented for 2 months with 31

µL of PJ (equal to 0.875 moles of total polyphenols/mouse/day, or around one glass-8Oz/person/day), and their results were compared to age-matched mice that received a placebo. By shrinking the atherosclerotic lesion size by 17% in contrast to the age-matched placebo-treated mice, PJ supplementation to 4-month-old E0 mice was still able to slow the course of the illness (Aviram & Rosenblat, 2012). Pomegranate extract treatment was used in another trial to lower the size of atherosclerotic plaques in the aortic sinus and the percentage of coronary arteries with occlusive atherosclerotic plaques (Al-Jarallah et al., 2013).

Turmeric (*Curcuma longa*)

Curcumin, shows potent antioxidant, anti-inflammatory, anti-cancer, and anti-atherosclerotic properties (L. Singh et al., 2021). According to the available articles, the dose-response meta-analysis indicated an effective dosage of curcumin between 0 to 347 mg/kg BW per day, which was both safe and nontoxic. The underlying processes were also explored, and they could be connected to changes in lipid transport, inflammation, and indirect changes in other tissues in arterial wall cells (Lin et al., 2020). In a 90-day repeated dose subchronic toxicity study, the safety of NR-INF-02 (a standardized extract of Curcuma longa) was assessed in Wistar rats at oral doses of 250, 500, and 1000 mg/kg. The no-observed adverse effect level (NOAEL) for albino Wistar rats was determined to be 1000 mg/kg body weight based on research findings (Murugan et al., 2021). Curcumin was shown to increase activation of PPAR-γ, which suppressed expression of the LDL-C receptor gene, and could thereby reduce plasma LDL-C concentrations (Qin et al., 2017). Numerous studies have shown that curcumin has a positive impact on the signaling pathways that control oxidative stress, inflammation, apoptosis, and cell growth (Pourbagher-Shahri et al., 2021).

Moringa oleifera

M. oleifera leaf extract can decrease of IL-1 and TNF-alfa, indicate potential as antiinflammatory and antidyslipidemia effect (Wahyuni & Yasa, 2017). Treatment with the methanolic extract of *M. oleifera* leaves (MEML) reduced abnormalities in the antioxidant status, alleviated abnormalities in serum biochemical parameters, and restored the normal histological structure of the heart, particularly in the case of higher concentrations (at doses of 200 mg/kg/bw and 400 mg/kg/bw). The leaves of the moringa oleifera tree may hold promise for the treatment of obesity and associated consequences, such as cardiac issues (Mabrouki et al., 2020). Moringa oleifera is genotoxic at supra-supplementation levels of 3,000 mg/kg b.wt (Asare et al., 2012). Phenolic acids, flavonoids, alkaloids, phytosterols, have been reported from *M. oleifera* (Saini et al., 2016).

Avocado (*Persea americana*)

According to a clinical study, eating more avocados (about two servings per week) was linked to a lower risk of coronary heart disease and CVD in two sizable prospective cohorts of US men and women. Avocado could reduce the risk of CVD if certain fat-containing foods were substituted for them (Pacheco et al., 2022). Avocado seed has antioxidant capabilities and has high concentrations of phenolic chemicals. Studies on the impact of avocado seed flour (ASF) on the lipid levels in mice fed a hyperlipidemic diet have revealed that ASF may have a hypocholesterolemic effect in mice with hyperlipidemia due to the antioxidant activity of its phenolic components and dietary fiber (Ramos et al., 2012). Peptone, b-galactoside, glycosylated abscisic acid, alkaloids, cellulose, polygalacto urease, polyuronoids, cytochrome *P*-450, and volatile oils have been reported from Avocado (Yasir et al., 2010).

PROSPECTS FOR THE DEVELOPMENT OF INDONESIAN MEDICINAL PLANTS AS ANTIATHEROSCLEROTIC AGENTS

Medicinal plants in Indonesia have promising prospects for development as anti-atherosclerosis agents. Several natural product effects responsible for atherosclerosis include antioxidant, anti-inflammatory, antiplatelet, and antihyperlipidemic activities. One of the challenges faced in developing drugs from natural sources is the difficulty in isolating active chemical compounds with therapeutic effects. Information about the activity of pure compounds is crucial in pharmacology to understand the mediated mechanisms that produce anti-atherosclerotic effects. However, with advances in science and technology, these challenges should not hinder the discovery of compounds from natural sources. Nature offers hundreds of compounds with significant potential for further exploration.

Phytomedicine accounts for approximately 25% of the drug population in the global pharmaceutical market (Chang et al., 2020). Pharmacological research in the preclinical context utilizing natural products is considered highly effective and provides valuable contributions. Natural products, particularly secondary metabolites derived from medicinal plants, are significant sources of new chemical entities that can be used in pharmacological research, especially for inflammatory and infectious diseases (Ribeiro-Filho et al., 2022). The discovery of safe and effective drugs remains a hot topic in the cardiovascular field (Atanasov et al., 2021; Ooi et al., 2018). A high safety profile is one of the advantages of developing drugs from natural sources. Accumulating evidence indicates that flavonoids, phenolics, and saponins from medicinal plants can reduce oxidative stress, making them promising candidates for cardiovascular drugs (Chang et al., 2020). Oxidative stress is a mechanism widely involved in various disease conditions. In the context of myocardial infarction, oxidative stress arises from an imbalance between

reactive oxygen species (ROS), which are primary triggers of myocardial damage during ischemia/reperfusion, and the body's natural antioxidant defenses. Therefore, approaching natural sources with potential antioxidant properties, particularly exogenous antioxidants, could provide a scientific basis for their development as cardiovascular drug candidates.

The unique structural diversity of natural compounds also adds value as a source of new drugs and therapeutic agents. Hydroxytyrosol from olive oil and resveratrol derived from red grapes are bioactives shown to prevent cardiovascular diseases by inhibiting the production of reactive oxygen species (ROS) (Ooi et al., 2018). Thus, relevant and comprehensive studies, including in vitro, in vivo, and in silico investigations, can enable the development of these natural substances into phytopharmaceuticals, which implies a clinically based application. The integration of traditional and modern medicine, if executed thoughtfully, can certainly enhance the success of therapies and improve patient outcomes. Exploring natural products can serve as a promising therapeutic approach for the prevention and treatment of cardiovascular-related diseases.

ANTIATHEROSCLEROSIS AS CARDIOPROTECTIVE AGENT

"*All mechanisms and means that contribute to the protection of the heart by limiting or even avoiding myocardial damage*" are included in the definition of cardioprotection, directly or indirectly support myocardial preservation must be categorized as "cardioprotective"(Kubler and Haass, 1996). For illustrate, individuals with coronary heart disease are currently treated with three major groups of anti-ischaemic medications: nitrates, calcium channel blockers, and beta adrenoceptor blockers. It is generally known that they are effective in easing symptoms and lowering the occurrence of myocardial ischaemia. Indonesia is one of the countries that has various sources of medicinal plants that have the potential as cardioprotective agents. In the drug development process, these safety requirements can be shown from the result of the toxicity test at the preclinical stage (Prasesti, 2021).

Cardioprotection including primary and secondary prevention of coronary artery disease, cardiac surgical procedures, and thrombolysis in acute myocardial infarction (Kubler & Haass, 1996). Cardioprotection can help mitigate cardiac damage and improve prognosis and clinical outcomes for patients experiencing a heart attack. Efforts to identify and implement effective cardioprotective strategies are integral to the management of patients with myocardial infarction. This review also aims to arrange the information about alternative drugs that can prevent more severe cardiac damage (cardioprotective) that have evidence base as antiatherosclerotic so that heart function can be preserved and mortality from heart attacks can be reduced.

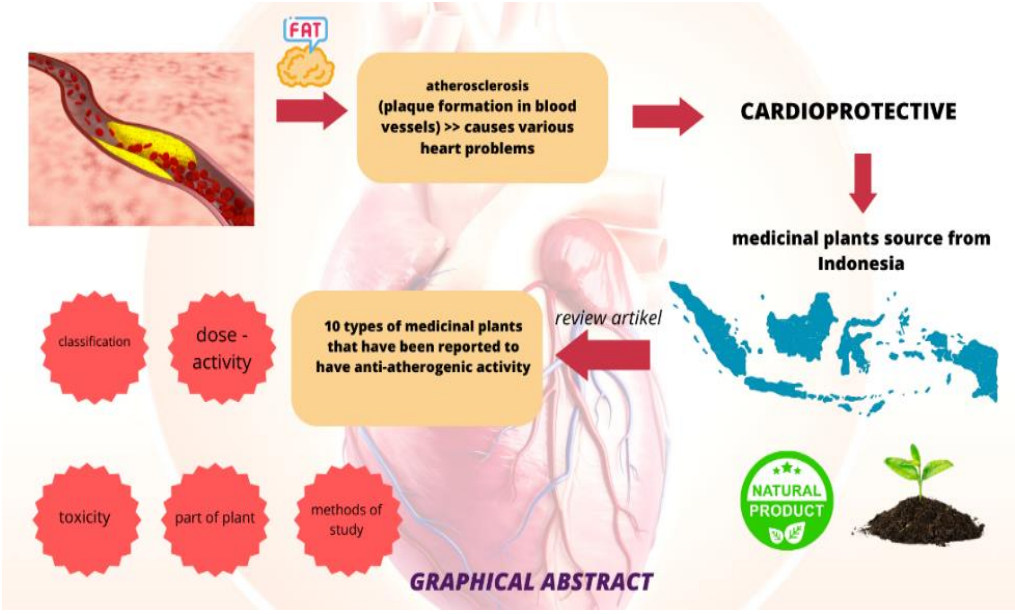

Figure 1. Indonesia as a source of medicinal plants for atherosclerosis. In this review we collect data about 10 types medicinal plants that have been reported to have anti-atherogenic activity from Indonesia. The data about classification, dose-activity, toxicity, part of plant and methods used in that study.

The importance of the role of cardioprotective agents in atherosclerotic conditions is shown in Figure 1.

PLANT BASED ACTIVE COMPOUND AS ANTIATHEROSCLEROSIS

In particular, by lowering cholesterol, preventing an increase in free radicals, and subsequently lowering vascular plaque and vascular resistance, plant-based active compounds, such as phenols (Pedret et al., 2018) (Alotaibi et al., 2021) (Vázquez-Ruiz et al., 2022), flavonoids (Ciumărnean et al., 2020) (Khan et al., 2021) (Kozłowska & Szostak-Węgierek, 2022), and antioxidants (Hu et al., 2022) (Castro, 2022) (Mirmiran et al., 2022) (Zhou et al., 2021) (Valaei et al., 2021) (Cammisotto et al., 2021), can be effective on atherosclerosis predisposing factors and preventing this disease and its harmful complications. Therefore, by lowering cholesterolemia, free radicals, inflammation, vascular resistance, and certain enzymes, medicinal herbs can help treat atherosclerosis and stop it from progressing. They can therefore be helpful for patients with hyperlipidemia and accompanying consequences, either alone or in combination with hypocholesterolemic medications (Sedighi et al., 2017).

CONCLUSION

Atherosclerosis is one of the causes of problems in the cardiovascular system especially myocardial infarction. This condition can be prevented by using natural products, one of which is medicinal plants.. In the context of modern drug development, Indonesia holds significant potential for exploring these plants as sources of active compounds for pharmaceutical applications. Scientific studies of these natural materials are

crucial for identifying bioactive components and understanding their mechanisms of action. With the right approach, Indonesia's natural resources could form the basis for developing new, safer, and more effective drugs.

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