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REVIEW: THE ROLE OF HERBAL AS A THERAPY FOR ENDOTHELIAL DYSFUNCTION IN CARDIOVASCULAR DISEASES: NARRATIVE REVIEW

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ABSTRACT

Atherosclerosis, diabetes mellitus, hypertension, and aging are examples of cardiovascular illnesses, the pathogenesis of which is affected by endothelial dysfunction. Many patients with cardiovascular disease already use herbs or combine herbs with medications prescribed by doctors. Herbs have emerged as alternative treatments for health maintenance. Herbs are in increasing demand by patients and health professionals. An overview of the role of herbal plants, their active substances, and their mechanisms of action as therapies for endothelial dysfunction to prevent the worsening of cardiovascular disease is presented in this review. The research was carried out by reviewing published scientific papers using online sources, such as PubMed and Google Scholar. Herbs can be used as a therapy for endothelial dysfunction to prevent the worsening of cardiovascular disease through various mechanisms, including inhibition of oxidative stress through the COX-2 and NOX2 pathways, inhibition of NADPH oxidase, inhibition of ROS formation through Src/EGFR/Akt, and increasing nitric oxide (NO) production by activating eNOS. The benefits and potential of herbal plants in dysfunction therapy to prevent cardiovascular disease need to be further developed for plants that grow widely in Indonesia. Furthermore, it is necessary to develop mechanisms for other targets, such as immunomodulatory therapy, to prevent cardiovascular disease from worsening.

Keywords: Herbals, Endothelial Dysfunction, Cardiovascular Disease

INTRODUCTION

Under normal conditions, endothelial cells maintain blood vessel homeostasis in a stable state when vasoconstriction occurs. In addition to intrinsic physical stimuli such as stress, temperature, and transmural pressure, the endothelium can respond to external stimuli such as temperature, psychological stress, and drugs (Widmer and Lerman, 2014). Endothelial homeostasis encompasses a number of acute responses such as adaption of flow to tissue demand *via* mechanosensing and acute modulation of vascular tone *via* production of autocoids, including nitric oxide (NO), which are affected by sympathetic tone (Heiss, Rodriguez-Mateos and Kelm, 2015).

Endothelial dysfunction has been discussed in the literature over the past 25 years. Vasoactive properties and vasodilator capacity in the endothelium are compromised during endothelial dysfunction, which can affect the endothelium's vasoprotective function (Little et al., 2021). The pathogenesis of cardiovascular disease involves endothelial dysfunction (Boulanger, 2016). Endothelial dysfunction can lead to various cardiovascular diseases by reducing nitric oxide (NO) production, resulting in vasoconstriction and increased blood pressure. Endothelial dysfunction increases the production of endothelin-1 (ET-1), activation of coagulation factors, activation of inflammation, and increased membrane permeability, which can trigger inflammation and plaque formation in the blood vessels (Maruhashi and Higashi, 2021). Heart failure, diabetes mellitus, hypertension, atherosclerosis, aging, and hyperbolemia are cardiovascular conditions linked to a reduction in endothelial vasodilation (S.W.S. Leung and P.M. Vanhoutte, 2015; Suryavanshi and Kulkarni, 2017).

An important substance produced by the endothelium, nitric oxide (NO), has decreased bioavailability due to the pathophysiology of endothelial dysfunction. Along with controlling the tone of vascular smooth muscle, moreover, NO inhibits leukocyte adhesion, vascular smooth muscle migration, oxidative stress, inflammation, and platelet aggregation (Chhabra, 2009). In the use of conventional drugs to prevent worsening due to endothelial dysfunction, in their use, various kinds of obstacles are found, including side effects (Hina, Rizwani and Naseem, 2011) and relatively expensive drug prices (Jahan et al., 2016). Therefore, there is a need for alternative medicines derived from natural ingredients, known as herbal medicines, to complement conventional treatments, which tend to be safer, more affordable, and have a strong therapeutic effect.

Herbal products with active compounds obtained from a single plant or a combination of plants are known as herbal medicines, and include herbal mixtures and ingredients (Organization, 2017). Historically, herbs have been medicines derived from natural resources, such as plants (Ara Tachjian, Viqar Maria and Arshad Jahangir, 2011). The WHO Global Survey on National Policies and Regulations on Herbal Medicines (2005) showed that over 100 countries have regulations on the use of herbal medicines as over-the-counter medicines, prescription medicines, food supplements, and healthy foods. Current research into plant bioactive compounds has produced new medicines derived from herbs (Davison and Brimble, 2019; Otvos *et al.*, 2019).

Based on data from Basic Health Research in 2018, there was a notable increase (48%) in the use of herbal or traditional medicines in Indonesia (Riset Dinas Kesehatan, 2018). Currently, herbal medicine is an alternative treatment for several cardiovascular diseases (Shaito et al., 2020). Many patients with cardiovascular disease already use herbal medicines or combine herbal medicines with medicines prescribed by doctors (Villaescusa et al., 2023). However, herbal medicines are often not scientifically proven effective in treating cardiovascular diseases (R et al., 2017). In contrast, most herbs appear to affect biological mechanisms involved in cardiovascular disease.

Herbal medicines used in cardiovascular diseases are unlike prescription medicines, which have characteristic active ingredients. Many active components of herbal treatments, including fibers, terpenoids, flavonoids, alkaloids, polyphenols, and saponins, may target different pathways linked to the etiology of cardiovascular disease (Ekor, 2014; Hassen *et al.*, 2022). This review aimed to collect and analyze data on the use of herbal medicines and their mechanisms of action in cardiovascular treatment. Additionally, it seeks to identify and evaluate existing research on the active components of herbal medicines and their mechanisms in the treatment of cardiovascular diseases. This review discusses cardiovascular diseases caused by endothelial dysfunction, herbal medicines as alternative treatments, active components in herbal medicines, the mechanisms of action of these active components, and the effectiveness of herbal components in treating cardiovascular diseases associated with endothelial dysfunction.

RESEARCH METHOD

A literature review was conducted to gather data sources and material search methodologies for the review article. In October 2023, a thorough search was performed using PubMed and Google Scholar using the search strategy '(herbs) OR (phytochemicals) AND (Endothelial Dysfunction) AND (cardiovascular) OR (CVD) OR (hypertension) OR

(Diabetes Mellitus). This narrative review will include original publications and research published in Indonesian and English in the last ten years that describes various plants or herbal extracts used for endothelial dysfunction therapy in cardiovascular disease, as well as their mechanisms of action. This narrative evaluation excluded reports of plant preparations and herbal extracts that did not show efficacy as inhibitors of endothelial dysfunction in cardiovascular diseases. Seven articles were selected from 16 search results. A total of 24 records were found in PubMed and Google Scholar. Furthermore, 17 entries were eliminated because they contained publications other than the original research, such as reviews or conference proceedings. Additional literature searches were undertaken manually on the article search engines Google Scholar and PubMed using custom keywords to collect additional data related to the review article's topic and previously obtained content. Manual search results from Google Scholar and PubMed yielded four and three publications, respectively. Fourteen articles were collected and used to prepare the discussion for this review article.

RESULTS AND DISCUSSION

This review article aims to determine the plants and their active compounds that can be used to manage endothelial dysfunction and prevent the worsening of cardiovascular disease. Based on the review of the article, researchers gained an idea of what plant variations could be used in research regarding the content of active substances that have an effect on endothelial dysfunction. The results of the review from several journals are summarized in Table I.

In the first article, the red grape plant, with its active polyphenol compounds, was proven effective as a therapy for endothelial dysfunction. The stages carried out in this study started with red grape extract, after which the bioactive compound content of the plant was tested. Extracts from red grapes include 88.6 mg/g of catechin, 8.7 mg/G of epicatechin, dimers (B1:6.99 mg/g, B2:8.00 mg/G, B3:20.77 mg/g, and B4:0.77 mg/g), anthocyanins (malvidin-3-glucoside:111.77 mg/g,peonidin-3-glucoside:00.666 mg/g, and cyanidin-3-glucoside: 0.06 mg/g), and phenolic acids (gallic acid: 5.00 mg/g, caffeic acid: 2.55 mg/g, and caftaric acid: 12.5 mg/g). After testing the compound content, an in vivo activity test was performed using Ang II-treated mice induced with angiotensin II. In this study, it was concluded that red grape polyphenols can successfully lower blood pressure and endothelial dysfunction caused by Angiotensin II in mice. This is due to the ability of red grape polyphenols to stimulate the synthesis of unmodified endothelial NO and inhibit the development of NADPH oxidase in damaged arteries, thereby reducing vascular oxidative stress (Sarr et al., 2006).

Centella asiatica contains asiaticoside, a monomeric saponin. In this study, the tests were performed both in vivo and in vitro. Forty adult mice (weight range 180-200 g) were used in the in vivo experiment. Cyclic guanosine monophosphate (cGMP), NO, prostacyclin (PGI2), and endothelin (ET)-1 were all measured in vivo. Then, in vitro tests were performed using HAFECs; cell culture was carried out before use. The results of this study showed that asiaticoside can activate IOS through the PI3K/Akt mechanism in HPAECs, which enhances NO generation in vivo as well as in vitro (Wang et al., 2018). Centella Asiatica and its triterpenoids have been shown to have cardioprotective effects (Razali, Ng and Fong, 2019). Asiatic acid can lower NF-κB production, p388MAPK andeERK1/2 activation, and inflammatory cytokines liketTGF-β1 and TNF-α (Bunaim et al., 2021). Furthermore, L-NAME-induced hypertension and cardiac injury can be avoided by Centella Asiatica, an action similar to that of captopril (Papparella et al., 2008).

Endothelial dysfunction has been shown to be ameliorated by catechins found in green tea extracts. Testing was conducted in this study both in vitro and in vivo. Researchers have found that green tea extracts counteracted the generation of Reactive Oxygen Species (ROS) in the pathway involving Src/EGFR/Akt, which Ang II activates, thereby avoiding cardiac hypertrophy caused by angiotensin II (Higashi, 2022). Oxidative stress, induced by

ROS generation, can lead to endothelial malfunction. Therefore, the suppression of ROS production can prevent oxidative stress (He, 2017). Catechins have a high antioxidant content due to the presence of hydroxyl groups and inhibit ROS production, leading to increased bioavailability of nitric oxide and vasodilators. To prevent ACE from catalyzing reactions, catechins bind to zinc ions or amino acids at the active site. This allows catechins to function as ACEI (Kim *et al*, 2020; Nitiéma *et al* 2019).

Lannea macrocarpa is a plant that grows in the savannas of Sudan and Guinea in Africa. In this study, we investigated the efficacy of the ethyl acetate fraction of the Lannea macrocarpa plant in reducing angiotensin II-induced hypertension in rats. The tests were performed both in vivo and ex vivo. Research has examined how isolated aortas respond to ex vivo exposure to acetylcholine (ACh) and calcium chloride (CaCl2), as well as their hemodynamic and echocardiographic characteristics in vivo. The results of the study revealed that lannea macrocarpa could prevent vascular dysfunction and hypertension caused by Ang II by decreasing oxidative stress associated with the COX-2 and NOX-2 pathways and preventing calcium influx (Ahmad et al., 2023). The flavonoid, alkaloid, and triterpenoid contents of Phaleria macrocarpa provide a vasodilation effect on blood vessels. It inhibits the action of ACE inhibitors, which can inhibit the change of angiotensin I to angiotensin II so that Phaleria macrocarpa can lower blood pressure (Kukongviriyapan et al., 2015).

Antidesma thwaitesianum grows in tropical and subtropical regions. Atidesma thwaitesianum contains many polyphenolic compounds. This study examined the antioxidant antihypertensive activity of the antidesma thwaitesianum plant in vivo in mice that were first administered fednNG-Nitro-L-Arginine-methylLester (L-NAME) and then administered antidesma thwaitesianum extract orally for three weeks at a dose of 100–3000 mg/kg body weight. The findings of this study demonstrate that A. thwaitesianum has an antihypertensive effect and protects blood vessels by inhibiting O2 production, decreasing protein oxidation and lipid peroxidation, and enhancing eNOS protein expression (Udomkasemsab et al., 2018). In addition, antidesma thwaitesianum extract has been proven to prevent tissue damage in the heart in vivo in mice. The mechanism involves inhibition of oxidative stress and increased antioxidant capacity. Pro-inflammatory genes, such as tTNF-α, iIL-6, iVCAM-1, iMCP-1, and eNOS, can be enhanced by antidesma thwaitesianum extract (Fauzy et al., 2019).

The Southeast Asian tropical plant Piper sarmentosum is well known for its traditional use as a medicine and has the ability to treat a wide range of illnesses, including hypertension. Piper sarmentosum has been shown to have antihypertensive properties in earlier studies; nevertheless, its exact mechanism of action remains unclear. The objective of this study was to test the effectiveness of Piper sarmentosum in protecting the vascular endothelial system in hypertensive rats. Oral administration of sarmentosum extract has been shown to lower endothelin 1 (ET-1) levels, increase nitric oxide (NO) levels, and control diastolic and systolic blood pressure levels (Alwi et al., 2018). The water extract from Piper sarmentosum leaves was proven to have anti-hypertensive activity by testing white mice that had previously been induced with hypertension drugs. The extract was administered orally at doses of 125, 250, and 500 mg/kg orally. This dose variation results in a lower blood pressure (Sargowo et al., 2018). Piper sarmentosum leaf extract has been shown in studies by Moh Zainudin to have antioxidant action to prevent oxidative stress, boost NO production, and lower cholesterol and blood pressure.

Originating from Ganoderma lucidum, the active compound found in the Polysaccharide Peptide (PsP) is β-glucan. This study was conducted using clinical trial methods on 34 stable patients and 37 high-risk individuals with angina. The concentrations of superoxide dismutase (SOD) and malondialdehyde (MDA), along with the quantity of EPC (endotheliall progenitor cells) and CEC (circulating endotheliall cells), were theestudy's parameters. The results of this study indicated a significant decrease in MDA, CEC, and EPC concentrations, and a significant increase in SOD in the group of high-risk angina patients treated with PsP. As a result, in high-risk individuals with stable angina, ganoderma lucidum functions as a strong antioxidant that inhibits the progression of atherosclerosis (Nisha I.

ParikhDitri, 2017). Ganoderma Lucidum (Lingzhi Mushroom) contains an extract of the active compound β-D glucan, which works to reduce cholesterol levels in blood plasma and plays an influential role as an anti-inflammatory antioxidant, anti-lipid, and anti-endothelial dysfunction. This is very important for preventing atherogenesis process so as to decrease the risk of coronary heart disease (Wegener, 2017).

Table I. Plants that Have Potential as Therapy for Endothelial Dysfunction in Cardiovascular Disease

Author	Plant	Active substance	Results
Sarr M, *et al* 2006	Red grape	Polyphenols	Inhibits NADPH oxidase Inhibits Angiotensin II.
Wang X *et al* 2018	Centela Asiatica	Asiaticoside (saponin)	Increasing NO production through eNOS
Papparella I, *et al* 2008	Green Tea	Catechins (epigallocatechin-3-gallate and epicatechin)	Inhibits ROS formation through the Src/EGFR/Akt pathway
Mathieu Nitiéma *et al* 2019	Lannea macrocarpa	sterols, triterpenes, coumarins, and anthraquinones	Prevents oxidative stress through the COX-2 and NOX2 pathways
Kukongviriyapan U, *et al.* 2015	Antidesma thwaitesianum	Polyphenols	Inhibits superoxide production, increases NO production via eNOS.
Fauzy *et al.*, 2019	Piper sarmentosum	Flavonoids	Improves endothelial dysfunction through increasing NO production and reducing arterial resistance levels
Sargowo D, *et al* 2018	Ganoderma lucidum	Polysaccharide Peptide (PsP)	As an antioxidant to prevent atherosclerosis by improving endothelial dysfunction

The limitations of this review include the variability of research methods, heterogeneity of animal test populations, limited clinical data, complexity of chemical compositions, variability in active ingredient content, and lack of standardized dosages. Further studies are needed to understand the therapeutic potential of plants and their active compounds in the treatment of endothelial dysfunction and cardiovascular diseases.

CONCLUSION

Various studies have used herbal plants as therapies for endothelial dysfunction, with various mechanisms of action. The plants and their ingredients can provide treatment effects for endothelial dysfunction, including red grape, Centella Asiatica, Green tea, Lannea macrocarpa, Antidesma thwaitesianum, Piper sarmentosum and Ganoderma lucidum. The components of herbal plants that function most as antioxidants are polyphenols, saponins, flavonoids, sterols, triterpenes, coumarins, anthraquinones, catechins, and Polysaccharide Peptides (PSP). The effectiveness of this plant as a therapy for endothelial dysfunction involves various mechanisms such as increasing NO, preventing the production of ROS, and inhibiting NADPH oxidase, which ultimately inhibits the occurrence of oxidative stress. One of the reasons for endothelial dysfunction is oxidative stress.

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