Literature Review of Atherosclerosis Treatment with Hibiscus Sabdariffa as an Alternative for Statin Therapy

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Abstract. Coronary heart disease (CHD) ranks the second-highest cause of mortality after stroke, thereby emphasizing CHD as the most significant contributor to cardiovascular disease (CVD) mortality. Statin therapy serves as an efficacious treatment in regressing the number of CHD cases. However, current studies highlighted a prolonged side effect of statin therapy; thereby, a more effective, safe and alternative effort is required in addressing such notion. Hibiscus sabdariffa (HS) is currently an alternative herbal treatment to treat CHD due to atherosclerosis prevalence. Thus, this literature review examines HS potential as an alternative and less risky approach in statin therapy. In compiling this literature review, the PRISMA method was applied, cited through articles and journals sourced from 6 databases: PubMed, Google Scholar, NCBI, MDPI, ScienceDirect, and Springer-Link. Researches indicated that HS contained phytochemicals, depicted an active role in minimizing risk factors for atherosclerosis. Anthocyanins and polyphenols comprised the phytochemicals stored by HS. Anthocyanins worked as an inhibitor of Low-Density Lipoprotein (LDL) oxidation, acted as a potent antioxidant and a high blood pressure-lowering factor.

Meanwhile, polyphenol compounds played a role in overcoming hypercholesterolemia which generated a risk factor for atherosclerosis. These two compounds further proved that HS could offer an alternative treatment for CHD due to atherosclerosis prevalence. In sum, this literature review encouraged further researches highlighting the toxicity tests and the appropriate dose to observe HS potency while utilizing a broader sample of Hibiscus sabdariffa extract (HES) as an alternative for statin therapy.

Keywords: Atherosclerosis · Hibiscus sabdariffa · Statin

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1 Introduction

Coronary Heart Disease is generally alleged as the most significant contributor to cardiovascular disease mortality, accounting for 16% of the world's total deaths. Since 2000, the number of deaths generated by CHD has increasingly been demonstrated by more than 2 million to 8.9 million deaths in 2019 [1]. According to the 2016 Sample Registration System (SRS) Indonesia, CHD ranks the second highest cause of death after stroke, accounting for 13.3% of all the highest causes of death in Indonesia. This mortality rate has increased by 0.4% from 2014 [2, 3], which is following the growing number of CHD cases in Indonesia.

CHD occurs due to the prevalence of atherosclerosis, a chronic inflammation of the artery walls that triggers various diseases, such as heart attack, stroke, and peripheral artery disease [4]. Atherosclerosis arises due to various risk factors, including modifiable risk factors and non-modifiable risk factors [5]. Hypertension serves as a major modifiable risk factor for atherosclerosis, accounted for 28% to 33% of all CVD risks in Indonesia in 2018 [5, 6]. The prevalence of uncontrolled high blood pressure in individuals with hypertension has contributed to the increased risk of atherosclerosis.

Hence, appropriate medical treatment therapy should be administered to reduce the high number of cases of atherosclerosis.

Statin therapy is commonly regarded as an efficient drug in the treatment of atherosclerosis. Since the 1990s, statin therapy studies have indicated feasible results, proved with a decreasing emergence in low-density lipoprotein (LDL) cholesterol and plaque volume regression, associated with cardiovascular disease risk. However, the difference in the percentage of atheroma volume in patients with and without statin therapy was about 0.55%, leading to the failure of statin therapy. In addition, statin therapy was considered a failure due to its inability to meet the treatment targets and patient non-adherence to therapy. Patient non-compliance was thus assessed for the patient's anxiety of the side effects of statin therapy [7].

Side effects arising from statin therapy include the risk of rhabdomyolysis, diabetes mellitus, Statin Associated Muscle Symptoms (SAMS), and memory loss or dementia in certain patients [8]. This finding underlines that the use of statin therapy has yet proved a completely effective and safe means of treatment, further leading to worse effects for patients. This finding hence provides an approach for alternative therapy in CHD treatment with a prevalence of atherosclerosis. Research related to herbal medicine has been widely developed, considered positive and potential as a safe alternative treatment. This literature review thus aims to determine the potential application of HS as an alternative treatment for statin therapy in CHD.

2 Methods

2.1 Literature Review

This literature review applies the PRISMA method through navigating national and international journals or articles. The author utilizes the six databases in the search process, including PubMed, Google Scholar, NCBI, MDPI, ScienceDirect, and SpringerLink. Using the Boolean method, a total of 218 sources were obtained with keywords such as atherosclerosis, Hibiscus sabdariffa, and statin.

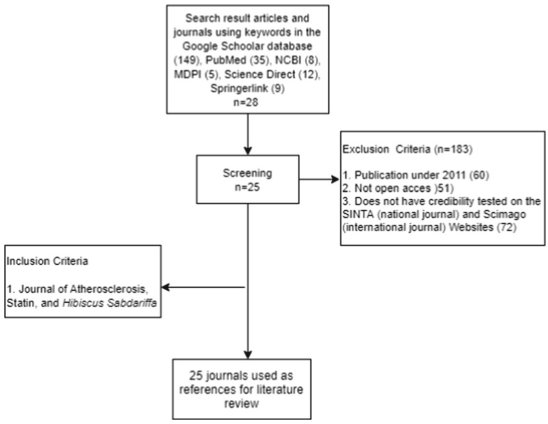

Fig. 1. Methode

Further, the 183 other sources were excluded due to being regarded as an inclusion criterion. Hence, the final results obtained were 25 journals applied as a reference source to complete this literature review (Fig. 1).

3 Result and Discussion

3.1 Statin Side Effect

Statin has been recognized as the drug, classified for its ability to lower fat blood levels, frequently administered to treat atherosclerotic cardiovascular disease [9]. In a systematic review, modern treatment of CVD has been administered with high doses (atorvastatin or simvastatin, typically around 80 mg) and with moderate doses (pravastatin 40 mg, simvastatin 10–40 mg, and atorvastatin 10 mg), has indicated to elevate the risk of diabetes mellitus by 4.4% and 4% in those who were administered with both therapies. In addition, it was found that there were more than 60 cases of statin side effects such as memory loss or dementia [10]. The results of another study conducted by S. Makinen et al. asserted that simvastatin affected the body metabolism, further compromising the muscles due to simvastatin role in increasing the formation of glucagon and absorption of glucose. Hence, simvastatin presents the risk to increase diabetes and muscle disorders [11].

Statins are most commonly associated with a mild muscle disorder called Statin Associated Muscle Symptoms (SAMS), which include myalgia, cramping of small muscles, myopathy, myositis, along with elevated Creatine Kinase (CK) [12]. Such symptoms are challenging to diagnose, depending on the administered timespan of statin, the type of complaint, and the severity. Symptoms involve large muscle groups, including the thighs, buttocks, back, and shoulders. The most severe effect, such as rhabdomyolysis, was proven from the case of a 72-year-old male patient who was daily administered with simvastatin 20 mg for an extended period. The typical symptoms that characterize the rhabdomyolysis he experienced, characterized by muscle cramps and pain in both legs along with a significant increase in CK [13].

3.2 The Content and Benefits of Hibiscus Sabdariffa as a Herbal Medicine

To minimize the risk of statin administration, other alternatives were included in the treatment. Indonesia, an area rich in biological resources, has traditionally utilized the existing plants as herbal medicines. HS or often called rosella is recognized as a plant, easily grows in tropical and subtropical areas. HS plants have traditionally been involved in food ingredients, flavoring or taste enhancers in the food industry, spices and herbal medicines [14]. In general, the red color of HS petals is due to the compounds delphinidin-sambubioside (red pigment) and cyanidin-sambubioside (pink pigment) as an alternative to synthetic dyes. Several phytochemical studies have proven that HS flower petals have bioactive compounds, such as flavonoids (quercetin, luteolin, glycosides), chlorogenic acid, gossypetin, and hibiscus acid, phenols, some phenolic acids, anthocyanins, delphinidin-3- sambubioside and cyanidin-3-). Sambubioside) [15]. Additionally, qualitative analysis has been utilized through the Thin Layer Chromatographic technique, reporting that each leaf, seed, flower, and root of HS contains the primary and secondary metabolites in the form of alkaloids and flavonoids phenolics, saponins, and glycosides [16].

In addition, several studies have reported that phenolic compounds are the most abundant compounds contained in HS. Particularly, flavonoids are regarded as one of the most abundant phenolic compounds in all parts of HS, acting as antioxidant agents [14, 16]. Flavonoids are also beneficial in lowering oxysterols (cholesterol derivatives) in bile acid metabolism, blocking fat accumulation in the liver. In addition, there are anthocyanins included in the flavonoid group, also serving as an antioxidant [17]. Several in vitro and in vivo trials have indicated that anthocyanins in HS are produced from the red pigment of the seeds themselves. A study affirms that HS flower petal extract could produce antioxidants, classified as strong level (IC50 = 50–100 ppm) [18]. Anthocyanin compounds are generally found in various forms, comprising cyanidin, delphinidin (increasing hydroxylation), peonidin, petunidin, and malvidin (increasing methoxylation). In a trial with a diabetic-induced mouse model, it was navigated that the content of cyanidin and delphinidin plays an important role as antioxidant activity, thereby overcoming hyperglycemia and insulin sensitivity [19]. Another trial with a dose of 200 mg/kg in a rat model induced by type II diabetes similarly indicated that the phenolic content of HS was capable of reducing hyperglycemia and hyperinsulinemia. The trial reported that HS could reduce Advanced Glycation End Products (AGEs) and fatty peroxides [20]. Diabetes mellitus becomes one of the risk factors for CHD, especially in atherosclerosis [3]. Therefore, HS demonstrates the potential benefit of overcoming the risk of diabetes mellitus and atherosclerosis in the future.

Antioxidant activity derived from phenolic compounds, especially anthocyanins, demonstrates an important role as anti-atherosclerosis to inhibit LDL oxidation, foam cell formation, and atherosclerotic plaques. However, antioxidants are inconclusive as to the cause of atherosclerosis. This notion is supported by the fact that atherosclerosis has been formed during childhood, potentially leading to a disease risk if accompanied by an increase in CHD risk factors [18]. A clinical trial highlighting the treatment of atherosclerosis through the consumption of tea from HS seed and leaf extract was capable of reducing LDL, triglycerides, cholesterol levels and increasing the amount of High-Density Lipoprotein (HDL) in plasma. Additionally, the anthocyanin compounds

in HS have been potential to lower blood pressure by inhibiting Angiotensin-Converting Enzyme 11 (ACE), generating the vasodilating effects. Anthocyanins further inhibit the formation of ACE to prevent the conversion of Angiotensin I into Angiotensin II. Anthocyanins further inhibit the opening of calcium channels in blood vessels. Blockage of calcium ions results in activation of the pathway protein kinase B, activating the nitric oxide (NO) enzyme synthesis.

Vascular smooth muscle responds to this activation mechanism by relaxing. Eventually, such a mechanism leads to vasodilation, decreasing blood pressure [21]. Hypertension serves as one of the risk factors for atherosclerosis. Meanwhile, most Indonesian people have hypertension, thus HS could offer an alternative treatment solutions [3]. Numerous studies have proven the effect of HS in patients with hypertension, observed through the consumption of HS tea at a dose of 1.25 g/day for one month in 46 hypertensive patients. The results indicate that the systolic and diastolic blood pressure of each individual has decreased [22]. In addition, in vivo trials in humans and animals indicate that the consumption of HS extract could reduce risk factors for CHD.

On the other hand, the polyphenol content in HS was capable of overcoming hypercholesterolemia. Polyphenols are responsible for lowering the body's cholesterol levels by inhibiting cholesterol absorption in the intestines. Within a similar timespan, polyphenols increase the production of bile acids in the body [19]. This finding is based on an in vivo trial of ethanol extract of a rat model for 35 days at daily doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg. The trial results reported that the ethanol extract could significantly reduce triglyceride levels in the control rat model. However, this significant decrease in triglycerides was not accompanied by a significant decrease in cholesterol. During the 14 days of observation, the decrease in cholesterol occurred at the same level daily [23].

3.3 Community Consumption of Hibiscus Sabdariffa

In general, people consume HS extract in an infusion or tea by brewing the dried HS seeds or leaves and adding honey [14]. Another relevant study demonstrates the resistance of HS secondary metabolites to degrees of temperature, thereby emphasizing that a temperature of 60 °C for a 20-min process was the best condition to extract anthocyanin compounds from HS. However, this anthocyanin compound degraded at a temperature of 80–100 °C [24]. Hence, further researches are encouraged to observe the maximum benefit of HS extract through a more proper process. However, from all the observed benefits, HS extract is not recommended for consumption by pregnant women. A review of the literature clarified that consuming HS during pregnancy potentially leads to pubertal delay. This statement is supported by a decrease in the fetus's maternal fluid and food intake, triggered by an increase in plasma Na + ion and corticosterone concentrations affecting fetus growth hormone [14]. Research focusing on the effective dose of HS for appropriate consumption is required to prevent overdose or poisoning. Instances include the consumption at high doses of HS (150–180 mg/kg/day), increasing several plasma enzymes, such as Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST). On the other hand, the administration of such dose had demonstrated no effect on Lactate Dehydrogenase (LDH) and Alkaline Phosphatase (ALP). However, the monthly consumption of 300 mg/kg dose might lead to liver disorders [21].

3.4 Hibiscus Sabdariffa Toxicity

Relevant studies regarding the toxicity of HS, however, have not yielded satisfactory results. Several in vivo studies utilizing Wistar rats indicated that consuming large doses of HS promotes weight loss. One of the referred studies includes a toxicity trial with a Wistar rat orally administered with HS extract with a total dose of 5000 mg/kg for two weeks. The trial results demonstrated that the maximum dose of HS extract did not significantly cause side effects. Thus far, HS has presented significant weight loss, especially in the liver and kidneys. However, the weight loss was within normal limits and did not cause any hematological changes in the rat organs[25].

4 Conclusions

Scientific evidence indicates that statin therapy is considered to have harmful and prolonged side effects in some CHD patients with a high prevalence of atherosclerosis. Side effects due to statin therapy are in the form of a high risk of diabetes mellitus, SAMS, dementia, and rhabdomyolysis. HS is thus regarded as a potential alternative in the therapeutic treatment of CHD with a prevalence of atherosclerosis, which is safer and more effective than statin therapy. In addition, prior studies affirm that HS, as an herbal plant cultivated in Indonesia, contains potential phytochemicals as an alternative therapy to reduce the risk of atherosclerosis. Phytochemical contents in the form of anthocyanins and polyphenols act as potent antioxidants, high blood pressure-lowering factors, and anti-atherosclerosis agents by inhibiting LDL oxidation.

5 Suggestion

Numerous works of literature have reported that HS offers a potential means as an alternative therapy for the treatment of CHD with a prevalence of atherosclerosis. However, further research is encouraged, emphasizing the toxicity potential of HS to navigate the beneficial application of HS as an alternative therapy for the treatment of CHD with a prevalence of atherosclerosis. In addition, appropriate dose-related studies and broader samples are required to examine the potential means of HS as an alternative therapy for the treatment of CHD with atherosclerosis prevalence.

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