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Review

A systematic review of the protective role of swertiamarin in cardiac and metabolic diseases

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ABSTRACT

Background: Swertiamarin, is a secoiridoid glycoside found in genera of *Enicostemma Species* (*Enicostemma littorale* and *Enicostemma axillare*) belonging to the family of gentianaceae, which has been reported to cure many diseases such as diabetes, hypertension, atherosclerosis, arthritis, malaria and abdominal ulcers. However, to the best of our knowledge, till date systematic studies to understand the molecular basis of cardiac and metabolic disease preventing properties of swertiamarin has not been reported.

Aim of the review: The present review aims to compile an up-to-date information on the progress made in the protective role of swertiamarin in cardiac and metabolic diseases with the objective of providing a guide for future research on this bioactive molecule.

Materials and methods: Information on the swertiamarin was collected from major scientific databases (Pubmed, Springer, google scholar, and Web of Science) for publication between1974-2016. In this review, the protective role of swertiamarin on cardiac and metabolic diseases was discussed.

Results: Swertiamarin reported to exhibit a wide range of biological activities such as anti-atherosclerotic, antidiabetic, anti-inflammatory and antioxidant effects. These activities were mainly due to its effect on various signaling pathways associated with cardiac remodeling events such as inhibition of NF-kB expression, LDL oxidation, apoptosis, inflammatory and lipid peroxidation markers and stimulation of antioxidant enzymes.

Conclusion: Sweriamarin exhibit a wide range of biological activities. This review presents evidence supporting the point of view that swertiamarin should be considered a potential therapeutic agent against cardiac and metabolic diseases, giving rise to novel applications in their prevention and treatment.

Abbreviations: AA, adjuvant arthritis; ABTS, 2,2-azino-bis(3-Ethylbenzothiazoline-6-sulfonic acid) diammonium salt; ACC, acetyl-CoA-carboxylase; ALP, alkaline phosphatase; CAT, catalase; CK-MB, creatinine kinase type muscle brain; Con A, concanavalin A; CPT-1α, carnitine palmitoyl transferase-1α; D-GaIN, D-galactosamine; DN, diabetic nephropathy; DTH, delayed type hypersensitivity; FFA, free fatty acid; FLS, fibroblast-like synoviocytes; GSH, glutathione; HA, hemagglutinating antibody; HbA1c, glycated hemoglobin; HC, hypercholesterolaemic; HDL, high-density lipoprotein; HF, high fructose; HMG-Co A, 3-hydroxy-3-methyl-glutaryl-CoA reductase; HMIO, 3, 4-dihydro-5-(hydroxymethyl) isochroman-1-one; IR, insulin receptor; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; JAK, janus kinase; K_{ITT}, insulin sensitivity index; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; LPS, lipopolysaccharide; MDA, malondialdehyde; MMP, matrix metalloproteinase; NEFA, non-esterified free fatty acid; NF-dB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIDDM, non-insulin dependent diabetic mellitus; NO, nitric oxide; OGTT, oral glucose tolerance test; P-407, poloxamer-407; PEPCK, phosphoenolpyruvate carboxykinase; PFC, plaque forming cells; PI3K, phosphatidylinositide 3-kinase; PPARγ, peroxisome proliferator activated receptor gamma; ROS, reactive oxygen species; SC, swertia corymbosa; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SOD, superoxide dismutase; SRBC, sheep red blood cells; SREBP-1c, sterol regulatory element-binding protein-1c; STAT, signal transducer and activator of transcription; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; VCAM-1, vascular cell adhesion molecules-1; WHF, World Heart Federation; WHO, World Health Organization.

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Contents

1. Introduction

Cardiovascular complications are the leading cause of morbidity and mortality in patients with type 2 diabetes, hypertension and atherosclerosis. The number 1 killer in terms of diseases and health-related problem in Malaysia is coronary heart disease. According to WHO statistics in 2011, the total number of deaths in Malaysia due to coronary heart disease was 22,701 people which contribute to 22.18% of the total deaths in Malaysia. The narrowing or blockage of coronary arteries is the most common cause of coronary heart disease. Smoking, hypertension, lipoproteins, hyperglycemia and etc. are the major causes of atherosclerosis (Fig. 1) [1].

Epidemiological studies have demonstrated that obesity associated with hypertension, inflammation and other metabolic aberrations are the major risk factor for diabetes mellitus and cardiovascular disease. Free fatty acid (FFA) has the ability to disturb with a hepatic clearance of insulin through reduced the number of insulin receptors due to the internalization of receptor and decreases in insulin degradation. Patients with obesity was associated with a decreased hepatic clearance of insulin [2]. Arrants demonstrated the relationship between tissue insulin resistance and compensatory hyperinsulinemia cause early atherosclerosis and an increased cardiovascular risk for the non-insulin dependent diabetic individual [3]. Adachi et al. [4] has conducted a study on cardiovascular risk factors in hyperinsulinemia Japanese patients without diabetes. They conclude that several risk factors for cardiovascular disease have occurred in hyperinsulinemia patients without diabetes.

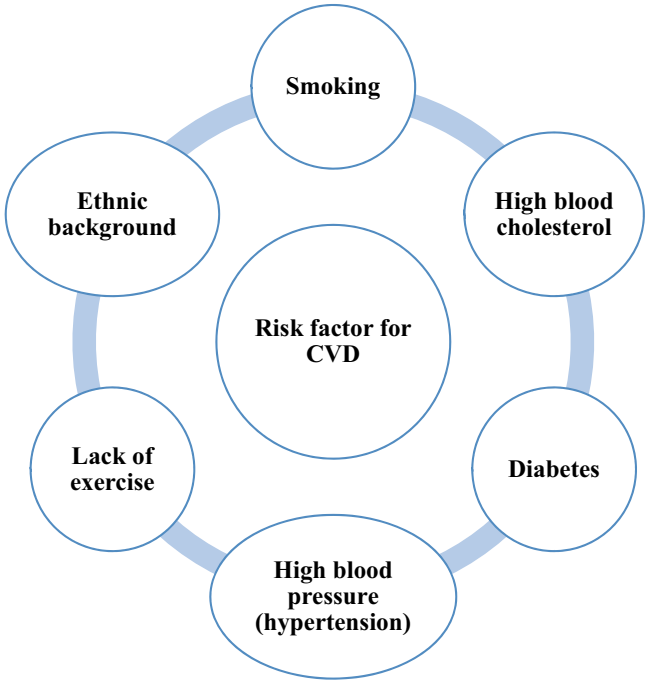

Fig 1. The risk factor for cardiovascular disease (CVD).

Stages such as initiation, growth and complication of the atherosclerotic plaques are considered as a type of inflammatory response towards injury. Oxidation of low-density lipoprotein lead to apoptosis of atherosclerotic plaque cap and lead to plaque vulnerability. Activation of macrophages, T lymphocytes, and smooth muscle cells leads to the release of additional mediators, including adhesion molecules, cytokines, chemokines, and growth factors, all of which play important roles in atherogenesis (i.e, rupture of plaque) [1,5]. The mechanism mostly starts from the expression of vascular cell adhesion molecules-1 (VCAM-1). When VCAM-1 attracts monocytes and migrates through the endothelial layer into arterial intima. The monocytes in the arterial intima undergo several inflammatory changes to form foam cells, whereas cytokines from T lymphocytes initiate the inflammatory activity. Therefore, the initial lesion of atherosclerosis and fatty streak are formed [6,7].

Based on the World Heart Federation (WHF), hypertension lead to atherosclerosis by narrow down the blood vessel through obstruction of blood clots which lining along the blood vessel wall. Thus, hypertension is a risk factor for coronary heart disease and the single most important risk factor for stroke. According to WHF, the systolic pressure will be the key determinant risk factor of cardiovascular disease in elderly patients. Sowers et al. suggest diabetes patient with cardiovascular complication has high mortality rate and hypertension is commonly found in diabetes patients than non-diabetes patients [8]. Accelerated atherosclerotic vascular disease is the leading cause of mortality in patients with diabetes mellitus. The increases of oxidative injury in diabetes mellitus patients associated with a weakened defense due to reduced endogenous antioxidants [9].

Current therapy to alleviate cardiovascular diseases is not optimal and thus efforts have made to develop effective and better drugs, led to the discovery of natural agents. Herbal remedies are natural products derived from plants and plant extracts that have been traditionally used to treat various diseases. During the last decade, the use of traditional medicine has expanded globally and it's gaining property. Herbs have been widely used for therapeutic purpose due to expensive and unaffordable of the conventional drug in the rural area because herbal remedies are readily available and cheap. Hence, urban dwellers are more preferred on herbs for therapeutic purposes. According to the WHO, herbal medicines serve the health needs of about 80% of the world's population, especially for millions of people in the vast rural areas of developing countries. Many researchers are focusing on natural