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Honey-derived Flavonoids: Natural Products for the Prevention of Atherosclerosis and Cardiovascular Diseases

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Abstract

The ancient product honey produced by honeybees, particularly the species *Apis mellifera* from the nectar blossoms or from exudates of trees and plants. Honey contains a very high content of carbohydrates, mostly mono- and disaccharides but it also contains many members of the family of antioxidant flavonoids. Over the last several decade of studies on human disease processes it has become recognized that an elevated, unfavourable oxidation status and a states of chronic inflammation underlies multiple diseases most notably, cardiovascular disease (CVD). The underlying cause of most CVD is atherosclerosis, the trapping of lipids in the vessel wall by modified proteoglycans, followed by oxidation, a chronic immune response and the development and rupture of atherosclerotic plaques. Many of the flavonoids present in honey have actions which impact on the oxidative and other processes of atherosclerosis. In this review we describe the actions of many of the flavonoids present in honey and speculate on the manner in which these might aggregate to produce a favorable CVD protective effect of honey *per se*.

Keywords: Honey; Flavonoids; Anti-oxidants; Atherosclerosis; Proteoglycans; Inflammation

Introduction

Honey is a natural substance with a sweet flavour and viscous consistency that is produced by honeybees, particularly the species *Apis mellifera* [1], from the nectar blossoms or from exudates of trees and plants that produce nectar honeys or honeydews, respectively [2]. Different types of honey samples contain a number of flavonoids including catechin, quercetin, rutin, naringin, naringenin, kaempferol, apigenin, chrysin, acacetin, luteolin, myricetin, hesperitin, galanginsome of which have evolved as promising pharmacological or even therapeutic agents [3]. Flavonoids have been recognized as compounds with potent biological activities that may be active in the prevention of chronic diseases including atherosclerosis and cardiovascular diseases (CVDs) [4].

CVD is the largest single cause of premature mortality in developed countries and its underlying pathology is atherosclerosis [5]. An important initiating event for atherosclerosis is the transport of low-density lipoproteins (LDLs) across the endothelium into the artery wall [6]. Intimal lipids are trapped by modified proteoglycans with hyperelongated glycosaminoglycan (GAG) chains [7-9], the oxidation of the neointimal lipids leads to the release of oxidized immunogenic molecular species which initiate a chronic inflammatory process in the vessel wall.

Flavonoids have been reported to be potentially active in cardiovascular prevention mainly by decreasing oxidative stress and increasing nitric oxide (NO) bioavailability. These polyphenolic compounds are able to modulate the expression of genes associated with metabolism, stress defence, drug metabolizing enzymes, and detoxification and transporter proteins [10-12]. Their overall effect is protective in overcoming the deleterious effects of cardiovascular risk factors and in delaying the onset of atherosclerosis [13]. In this review, we considered the prominent honey flavonoids and their biological and pharmacological actions in the prevention and treatment of atherosclerosis and CVDs.

Flavonoids have several anti-atherosclerotic activities including anti-inflammatory, antioxidant, anti-proliferative and antiplatelet activities. Cholesterol-lowering and anti-hypertensive effects of flavonoids have also been described [4]. The central component of the oxidation hypothesis of atherogenesis is that oxidative modification of LDLs provides an immunogenic stimulus for monocyte recruitment to the vessel wall and phagocytic uptake of oxidized LDL by macrophages [14]. Extensive oxidation of LDLs leads to its aggregation [15,16] and that both of these modified forms of LDLs are present in the atherosclerotic lesion. Recent studies demonstrated that catechin and quercetin (two major honey flavonoids) [3,17] consumption exhibited inhibitory effect on development of aortic atherosclerotic lesions and on atherogenic modification of LDLs [18]. NO, produced by endothelial nitric oxide synthase (eNOS), is a major anti-atherogenic factor in the blood vessel. Oxidative stress plays an important role in the pathogenesis of CVDs including atherosclerosis. Decreased availability of endothelial NO promotes the progression of endothelial dysfunction and atherosclerosis. Rutin promotes NO production by inducing eNOS gene expression, eNOS protein synthesis and eNOS activity. Treatment with rutin also leads to increased gene and protein expression of basic fibroblast growth factor (bFGF). Therefore, up-regulation of eNOS expression by rutin may be mediated by bFGF [18]. The honey-derived flavonoid naringin inhibits hypercholesterolemia-induced intercellular adhesion molecule-1

(ICAM-1) expression on endothelial cells. Hypercholesterolemia causes fatty liver and an elevation of liver enzymes, effects which are prevented by naringin. Naringin also reduces fatty streak formation and neointimal macrophage infiltration and also inhibits the expression of ICAM-1 in endothelial cells, suggesting that suppression of ICAM-1 contributes to its vascular effects [19]. Naringenin decreases LDL and triglycerides levels as well as inhibiting glucose uptake, increase high density lipoproteins (HDLs), co-oxidation of NADH, suppression of protein oxidation, suppression macrophage inflammation, inhibits leukotriene B4 leading to reduced monocyte adhesion and foam cell formation and the down-regulate genes related to atherosclerosis [20]. Apigenin, commonly found in honey, improves various parameters of cardiovascular disease, stimulates the favorable aspects of the immune system and inhibits platelet aggregation [21]. Apigenin exhibits a pro-apoptotic effect on oxidized LDL (Ox LDL)-loaded murine peritoneal macrophages (MPMs) and increases the expression of pro-apoptotic Bax, cleaves caspase-3and it decreases the anti-apoptotic factors Mcl-1 and Bcl-2 (Figure 1). These results suggested that the anti-atherosclerotic effects of apigenin are associated with the up-regulation of apoptosis in OxLDL-loaded MPMs [22].

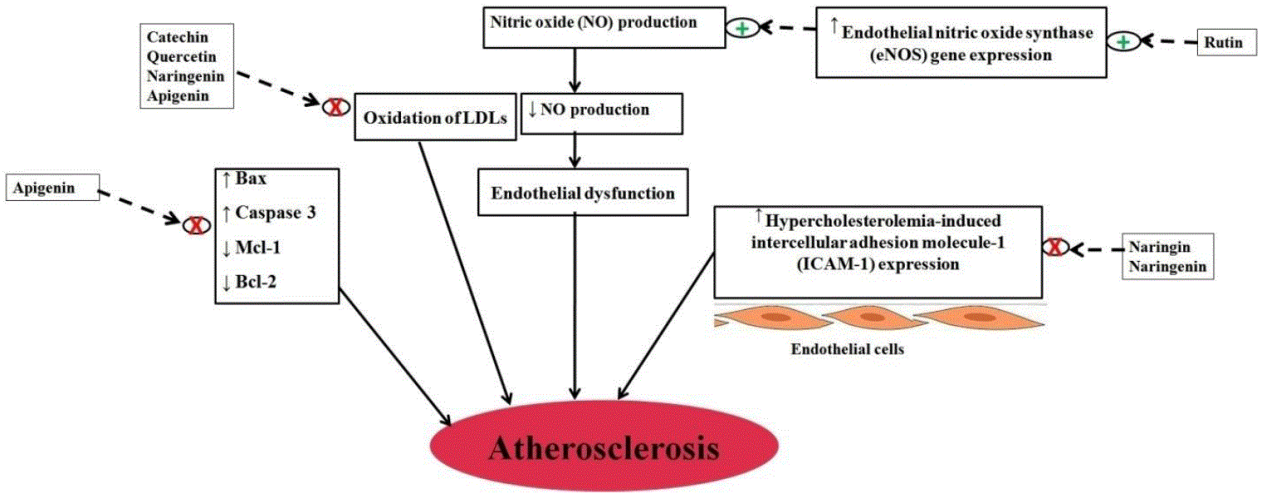

Figure 1: Potential anti-atherosclerotic effects of honey-derived flavonoids.

Atherosclerosis is widely considered to be a chronic inflammatory disease of the vessel wall and as such adhesion molecules which attract and stimulate infiltration of inflammatory cells play an important role in atherogenesis. A honey flavonoid kaempferol shows effects in this area by modulating the gene and protein expression of inflammatory molecules [23]. The honey flavonoid chrysin possesses multiple pharmacological activities some of which in the current context would be seen as anti-atherosclerotic. Chrysin is an inhibitor of foam cell formation that may stimulate cholesterol flow. Up-regulation of the classical peroxisome proliferator-activated receptor gamma (PPARγ)-liver X receptor alpha (LXR-α)-ATP-binding cassette, sub-family A1 (ABCA 1)/ATP-binding cassette, sub-family G1 (ABCG1) pathway and down-regulation of scavenger receptor A1 (SR-A1) and SR-A2 may participate the suppressive effect of chrysin on intracellular cholesterol accumulation thereby reducing the development of atherosclerosis [24]. Although many honey-derived flavonoids have actions which inhibit processes considered to be associated with the development of atherosclerosis, it is plausible that, through pharmacological synergy, these honey flavonoids might be confer an anti-atherosclerotic on honey *per se*.

Flavonoids decrease the risk of CVDs by improving coronary vasodilatation, decreasing the ability of platelets to clot and preventing LDLs from oxidizing [3]. CVDs involve multifactorial processes involving oxidative stress [25], abnormalities in lipid metabolism [26], disturbances in vascular tone platelet aggregation inflammation [27] and proliferation of vascular cells [28]. Catechin beneficially impacts many of these parameters including vascular dysfunction, including lipoprotein oxidation, blood platelet aggregation, vascular inflammation, vascular smooth muscle cell (VSMC) proliferation, altered lipid profile and vascular reactivity. Besides being antioxidants, catechins exert biological effects by modulating some cellular signaling pathways that lead to a reduction in inflammation, platelet aggregation, and an elevation of vascular reactivity [29]. The sources for the reactive oxygen species (ROS) production during CVD are uncoupling of mitochondrial electron transport, pro-inflammatory cytokines and induction of oxidative enzymes such as inducible nitric oxide synthase (iNOS) and xanthine oxidase (XO) [30]. Honey exerts is cardio protective effect mainly through antioxidant activities of catechin including ROS scavenging, chelating redox active transition-metal ions, inhibiting redox sensitive transcription factors, inhibiting pro-oxidant enzymes and inducing antioxidant enzymes [31,32]. Hyperlipidemia, resulting from the abnormalities of lipid metabolism, is one of the major risk factors for the development of CVDs. The elevated levels of plasma lipids such as fatty acids, cholesterol, phospholipids and triglycerides the accelerated development of atherosclerotic plaques. Catechins reduce blood cholesterol levels and prevent the deposition and/or accumulation of cholesterol in various tissues including liver and heart. The phenomena of endothelial dysfunction, mostly reduced availability of NO but also other factors, is widely associated with the pathogenesis and the precipitation of the clinical manifestations of CVDs. Experimental and clinical studies have shown that catechins improve endothelial function [29]. Quercetin is a naturally occurring flavonoid that exerts multiple pharmacological effects. Yoshizumi et al. [33] proposed that daily intake of bioflavonoids reduces the incidence of ischemic heart disease

(IHD). It was hypothesized that bioflavonoids may affect angiotensin-II (Ang-II)-induced MAP (mitogen activated protein) kinase activation in cultured rat aortic smooth muscle cells (RASMC). Ang-II stimulated rapid activation of extracellular signal-regulated kinase (ERK) 1/2, c-Jun N-terminal kinase (JNK), and p38 in RASMC. Ang-II induced JNK activation was inhibited by quercetin, whereas ERK1/2 and p38 activation by Ang-II were not affected by quercetin. Ang-II caused a rapid tyrosine phosphorylation of Src, which was inhibited by quercetin. This flavonoid compound also activated the PI3K/Akt pathway in RASMC. Moreover, a PI3K inhibitor and quercetin derivative inhibited Ang-II-induced JNK activation as well as Akt phosphorylation. These findings suggested that the inhibitory effect of quercetin on Ang-II-induced vascular smooth muscle cell (VSMC) hypertrophy are attributable, in part, to its inhibitory effect on PI3K-dependent JNK activation in VSMC. Therefore, inhibition of JNK by quercetin may imply its usefulness for the treatment of cardiovascular diseases (CVDs). Naringin shows a range of properties that help protect the cardiovascular system, including anti-hypertensive, lipid lowering, insulin-sensitizing, antioxidative and anti-inflammatory properties [34]. Naringin prevents the age-related increase in systolic blood pressure in stroke-prone spontaneously hypertensive rats, increases NO production, improves endothelial function and decreases cerebral thrombosis [35]. Further, naringin prevents oxidative stress in the hearts of rats with isoprenaline-induced myocardial infarction (MI) [36]. Another bioflavonoid, naringenin, is present in many honey types [37]. Naringenin inhibits the TNFα induced VSMC proliferation and migration, which is an important event in the generation of a neointima and in the restenosis following vascular injury or luminal reconstruction [38]. Naringenin also blocks the increased ROS generation induced by TNF-α. Oxidative stress and TNFα trigger the activation of MAP kinases, which are key regulatory factors for VSMC proliferation. Naringenin prevents ERK/MAP kinase and Akt phosphorylation, whereas p38 MAP kinase and JNKs remained unchanged. This overall effect is probably mediated via the induction of heme oxygenase 1 (HO-1) and reduction in oxidative stress [39]. Galangin has anti-oxidative effect on endothelial tissues, thus affects lipid peroxidation another favorable effect for the amelioration of CVD. Galangin has an interesting action to preserve other protective anti-oxidants such as vitamin E, vitamin C and other flavonoids. In CVDs, the protective effects of honey flavonoids include mainly anti-thrombotic, anti-ischemic, antioxidant and vasorelaxant [40]. Flavonoids in honeys along with other polyphenolic components and enzymes are the responsible elements for the favorable effects on the prevention and potentially the treatment of CVDs.

In recent years, the prevention of CVDs and its underlying cause atherosclerosis have been associated with the consumption of fresh fruits, vegetables or plants rich in natural antioxidants, because of the attractive features of such a strategy relative to the use of synthetic products [41,42]. Honey, a natural sweetener, therefore can be considered as a natural therapy against atherosclerosis and CVDs. Overall, the probable mechanisms by which honey exhibits its protective and curative actions against myocardial damage are via improved anti-oxidative status and lowered plasma cholesterol level. It might be concluded that major contributing agents of cardio protective and anti-atherosclerotic effects of honey are flavonoid constituents commonly present in natural honeys.

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