 doi:10.20944/preprints202208.0205.v1

Review

The Antiatherogenic Effects of Flavonoid on Cholesterol Efflux Capacity

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Abstract

One of the mechanisms used in the management and cure of atherosclerosis is reverse cholesterol transfer (RCT), which plays a vital role in the export of cholesterol from peripheral cells. Cholesterol efflux from macrophages in the subintima of the vessel wall is a critical part of RCT. ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) are involved in the transfer of cholesterol from arterial macrophages to extracellular high-density lipoprotein cholesterol (HDL). The HDL then transports esterified cholesterol to the liver for elimination. An important factor in the reverse cholesterol transport and excretion of extracellular cholesterol is HDL. Atherogenesis can be prevented by altering the processes of RCT and cholesterol efflux, and this might lead to novel treatment options for cardiovascular disease. Research of novel modifying variables for RCT and cholesterol efflux is necessary. A better understanding of RCT's molecular processes has been gained via research, allowing for the creation of new treatments that make use of RCT's potential for pharmacological improvement. The purpose of this review is to provoke discussion on the potential impact of selected flavonoids on cholesterol efflux on the progression of atherosclerosis.

Keywords: Cholesterol efflux; flavonoids; HDL; quercetin; reverse cholesterol transport

Introduction

Cardiovascular and cerebrovascular illnesses and lipid metabolic abnormalities are both linked to the development and progression of atherosclerosis. A buildup of macrophages in blood arteries causes macrophages to become foam cells, which release intracellular cholesterol, causing the development of atherosclerosis (Fig. 1.) [1]. When atherosclerosis first begins, oxidative modification of low-density lipoprotein (oxLDL) and other inflammatory mediators stimulate the conversion of mononuclear cells to macrophages in the endothelium gap. As a result, macrophages take up ox-LDL, resulting in the production of cholesterol ester and foam cells. Foam cells contribute to the earliest pathogenic alterations that result in atherosclerosis [2].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 August 2022 doi:10.20944/preprints202208.0205.v1

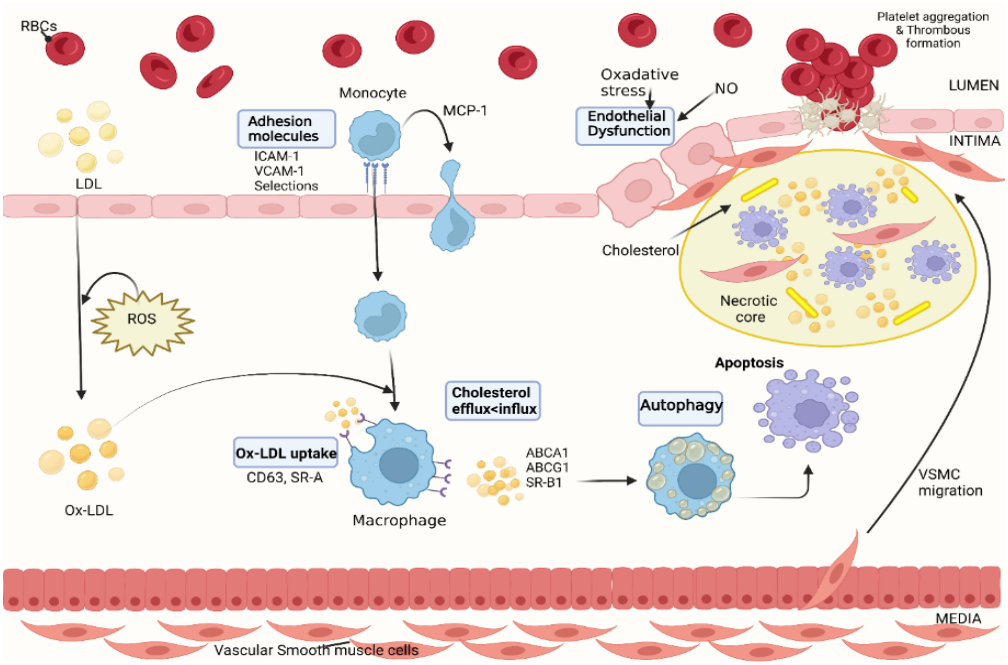

Figure 1. Mechanism of the atherosclerosis process.

By carrying excess cholesterol from peripheral tissues to the liver and small digestive tract, reverse cholesterol transport (RCT) is thought to play a crucial role in the initiation and progression of atherosclerotic vascular disease [3]. Cardiovascular events are the main cause of mortality in the world, and dyslipidemia (high low-density lipoprotein cholesterol (LDL-c) and low high-density lipoprotein-cholesterol (HDL-c) levels) is a key contributor [4]. Cardiovascular disease may be predicted by an increase in the quantity of LDL-c [5]. HDL-c has an inverse correlation with coronary heart disease incidence [4].

HDL's atheroprotective function is mostly due to its participation in RCT, which removes excess cholesterol from macrophages in the artery wall and inhibits foam cell production and the earliest phases of atherosclerotic plaque development [6]. RCT is the primary mechanism for the excretion of cholesterol in animals, and apolipoprotein AI (apoA-I), the predominant protein component of HDL, is a critical facilitator of this process. apoA-I and HDL particle interactions increase free cholesterol efflux via a range of passive and active mechanisms in the first phase of RCT, which includes cellular cholesterol mobilization [7]. Cellular cholesterol efflux seems to be supported by ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1). In macrophages, ABCA1 and ABCG1 are responsible for about 50% and 20% of the total cholesterol efflux from cells, respectively [8]. ABCA1 effluxes phospholipids and free cholesterol to lipid-free apoA-I in the extracellular space, creating nascent HDL particles [9]. HDL biogenesis is helped by ABCA1, which then serves as an effective substrate for the lecithin-cholesterol acyltransferase-mediated esterification of free cholesterol into cholesteryl esters (CE) (LCAT) [10].

Cholesterol may be given to the liver in two ways: directly and indirectly. In the first case, mature HDL-c molecules in the liver engage with SR-B1 to facilitate the transport of cholesterol from the liver to the rest of the body. Following RCT, the HDL-c molecule may return to the bloodstream and be used again [7], [11]. Additionally, cholesterol may be delivered indirectly via the liver's low-density lipoprotein (LDL) receptor when CE is transferred from HDL particles to apo B-100 (apo B-100), particularly to LDL [12], [13]. The enzyme cholesteryl ester transfer protein is involved in this process (CETP). Because of this, these lipoproteins can interact with their liver receptors and distribute their cholesterol load [7], [11]. *Very-low-density lipoprotein* (VLDL)-to-LDL particle transition is aided by CETP, a circulating glycoprotein that facilitates the bidirectional transfer of

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cholesterol esters (CEs), triacylglycerols (TGs), and phospholipids (PL) from HDL to apoB-containing LDL particles [14]. In humans, RCT relies heavily on this indirect channel [12], but not so much in rats, who lack CETP activity [15]. The RCT method has been studied a lot in both people and animal models of atherosclerosis, and it has been shown to be useful [16].

Liver damage and muscle toxicity are two side effects of statin therapy that should be avoided [17]. Acute renal failure, myopathy, and rhabdomyolysis are some of the additional severe effects [18]. Thus, the focus is now on plant-based substances that contain antiarthrosclerotic action and may benefit human health. This may ultimately prevent potential adverse health consequences of long-term statin use. Over the last few decades, several studies on bioactive substances and their potential therapeutic properties have been conducted [19], [20]. Bioactive substances have shown promising outcomes in certain trials, but further research on functional foods and bioactive molecules is needed. Therefore, this review aims to stimulate debate on the possible influence of certain flavonoids on reverse cholesterol transport on the development of atherosclerosis.

Enhancing the ability to excrete cholesterol

Two different treatments are available to increase the body's ability to excrete cholesterol. Improving cellular cholesterol efflux by targeting macrophages is one approach. LXR agonism is one of the mechanisms that increases macrophage efflux capability [21]. The expression of ABCA1 and ABCG1 cellular receptors is controlled by liver X receptors (LXR), including LXRα and LXRβ [22]. Enhancing HDL cholesterol efflux acceptor functioning is another technique for increasing cholesterol efflux capacity [21]. Increased apoA-I expression raises HDL levels in the blood and improves HDL function, which reduces the risk of heart disease and stroke [23]. Nuclear receptors such as the peroxisome proliferator-activated receptor- γ (PPAR- γ) are abundant in atherosclerotic plaque macrophages and foam cells. They have been linked to an increase in ABCA1 expression and apoA-I activity. Autonomous apoE plays a vital function in cellular cholesterol homeostasis among various lipoproteins. In mice, the absence of the apoE receptor gene led to an increase in atherosclerosis [24]. Additionally, inhibition of CETPs might help improve efflux capability [25].

Flavonoids

More than 5,000 subclass members of the most prevalent polyphenol, flavonoids, are found in fruits, tea, berries, wine, and chocolate, among other foods and beverages [26]. Flavonoids may be further split into flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanins, and chalcones, which are all subgroups of flavonoids [27]. Epidemiological studies have demonstrated that flavonoid-rich diets may lower the incidence of cardiovascular disease [28]. Dietary flavonoid consumption has been linked to a reduced risk of cardiovascular disease (CVD) because of its antioxidant and anti-inflammatory properties. It is possible that these characteristics may raise HDL cholesterol, cholesterol efflux, and RCT. Flavonoids commonly found in foods and their mechanisms of action for increasing cholesterol efflux and reversing cholesterol transport are listed below.

Quercetin

For the treatment of cardiovascular diseases, flavonoids like quercetin (3,4,3,5,7-pentahydroxyflavone) have received a lot of interest [29], [30]. According to scientific research, the flavonoid quercetin has anti-inflammatory, anti-oxidant, and lipid metabolic properties [31]. In RAW264.7 cells, it may prevent atherosclerosis by modulating lipid metabolism, boosting the expression of ABCA1 and encouraging macrophage cholesterol efflux, and preventing foam cell formation [32]. Foam cell development and

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aberrant lipid metabolism are early indicators of atherosclerosis in patients with cardiovascular disease [33], [34]. Because quercetin inhibits the production of foam cells, it may be an important factor in lowering the prevalence of atherosclerosis [2]. The apoAI-mediated cholesterol efflux from macrophages is controlled by ABCA1 [35], [36]. In prior research [37], overexpression of ABCA1 in LDL receptor-deficient mice has been found to minimize fat buildup in the arterial wall in prior research. Consequently, the stimulation of ABCA1 expression is seen as a successful approach to combating atherosclerosis. ABCA1 expression is controlled by nuclear transcription factors LXR and retinoid X receptor (RXR), which are involved in the transcription of ABCA1 [38], [39]. By binding to the ABCA1 promoter, LXR produces heterodimers with its natural ligand, oxysterols, and thereby activates gene expression. Regulation of ABCA1 gene expression has been linked to transcription factor-mediated mechanisms, as well as mitogen-activated protein kinase (MAPK) signaling pathways [40], [41]. This family of enzymes includes extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun N-terminal kinase 1/2 (JNK1/2), and p38 [42]. Inhibition of ERK activation raises ABCA1 mRNA and protein stabilities, ending in ABCA1 expression activation [40]. According to Chang et al. (2012), upregulation of ABCA1 expression by quercetin protects against cholesterol efflux through upregulating p38-dependent Sp1 and LXR binding to the ABCA1 promoter [43]. It has been shown that quercetin may have anti-atherosclerosis advantages by inhibiting the expression of scavenger receptors such as SR-A and CD36 in macrophages and preventing the free radical-mediated oxidative alteration of LDL [44], [45]. ABCA1 expression can be increased by quercetin activating the PPAR/LXR pathway, which increases the amount of protein PPAR and its transcription [46]. An essential lipid regulating protein, PCSK9, Proprotein convertase subtilisin/kexin type 9 (PCSK9), is involved in lipid metabolism as well as the process of apoptosis [47]. Preliminary findings show that PCSK9 is increased in macrophages, resulting in an inflammatory reaction and an increase in cholesterol levels by blockage of RCT [48]. The overexpression of ABCA1 by PCSK9 inhibitors may also increase macrophage cholesterol efflux [49]. Quercetin has been shown to reduce the expression of PCSK9 in hepatocytes and increase the outflow of cholesterol from macrophages [50]. Furthermore, according to Shanshan et al. (2018), quercetin inhibits oxLDL-induced lipid droplets in RAW264.7 cells by increasing ABCAl, ABCG1, LXR and decreasing PCSK9 [51]. Additionally, quercetin may enhance RCT by increasing HDL cholesterol-accepting capacity, increasing protein expression levels relevant to RCT such as (ABC) A1 and G1, and enhancing HDL's antioxidant activity [30].

Kaempferol

Kaempferol (3,4,5,7-tetrahydroxyflavone) has been the subject of several studies, and the results demonstrate that consuming foods high in kaempferol lowers the risk of cardiovascular disease [52], [53]. Furthermore, kaempferol increased the levels of ABCA1, ABCG1, and SR-BI protein expression in THP-1-derived macrophages in a dose-dependent manner [54]. Kaempferol stimulated macrophage cholesterol efflux and influenced the expression of LXR-related genes in macrophages, hepatocytes, and intestinal cells, according to Hoang et al. (2018) [55].

Myricetin

Several studies have revealed that myricetin (3,3,4,5,5,7-hexahydroxyflavone) has anti-inflammatory and anti-oxidative effects [56], [57]. However, myceritin's role in lipid metabolism and atherosclerosis is still a mystery. When myricetin was used to treat macrophages, it was revealed that CD36 expression was reduced, which is consistent with the decreased ability of macrophages to accept modified LDL [58]. Because myricetin reduces CD36, it helps reduce cholesterol buildup in macrophages. Furthermore, Meng et al. 2019, showed that myricetin-treated macrophages were less likely to form foam cells, which may be due to myricetin's ability to inhibit cholesterol esterification [58]. Lian et al. (2008), demonstrated that the treatment of U937-derived macrophages with myricetin reduced CD36 cell surface protein and mRNA expression [59].

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Naringenin

Many studies have focused on the use of naringenin (4,5,7-trihydroxyflavanone) in the treatment of atherosclerosis. There are several citrus flavanones, including naringenin, which may be found in citrus fruits like oranges and grapefruits [60]. Some animal investigations have shown that naringenin raises HDL cholesterol levels [61], [62]. Naringenin improved cholesterol efflux by nearly five times as much as apoA1 individually, in accordance with elevated ABCA1 and ABCG1 expression. For macrophages, naringenin upregulated LXRα mRNA and protein levels as well as its target genes via AMPK-dependent mechanisms [63]. Naringenin enhanced cholesterol efflux to both apoA-I and HDL and gene expressions of ABCA1, ABCG1 and LXR in RAW264.7 macrophages, as shown by Xu et al. 2019. The effects of naringenin were attributed to its ability to block the ER stress-ATF6 pathway. The modulation of cholesterol efflux by naringenin was mediated through the ATF6 component of ER stress and the PI3K/AKT pathway [64]. At the molecular and protein levels, Naringenin activated LXR in THP-1 macrophages, altering the expression of LXRα target genes ABCA1, ABCG1, and SREBP-1c (sterol response element binding protein 1c). LXRα and its target genes in human macrophages are up-regulated by naringenin through AMP-activated protein kinase (AMPK) modulation [60].

Catechin

Citrus juice, chocolate, tea, and wine all contain flavanol or flavan-3-ol substances such as catechins [65]. Catechin intake is associated with an increase in HDL levels and a decrease in atherosclerosis that may be due to the ABCG1 and ABCA1 genes being activated [45]. Catechins may have anti-atherogenic benefits owing to increased expression of ABCA1, ABCA1, and scavenger receptor class B type I (SRB1) through stimulation of the liver X receptor signaling pathway [39]. Hepatic SRB1 has been labeled as a positive regulator of macrophage RCT and as a receptor for HDL cholesterol ester (CE). SRB1 is required for the macrophage RCT to function. Catechins promote cholesterol efflux at all dosages through upregulated mRNA ABCA1. ABCA1, ABCG1, and SRB1 are expressed through the interleukin-1 receptor-associated kinase 1 (IRAK1) and toll-interacting protein (TIP) pathways (Tollip). By suppressing the expression of nuclear receptors such as retinoic acid receptor α (RARα) regulated by glycogen synthase kinase-3β (GSK3β), IRAK-1 and Tollip are inhibited. The suppression of nuclear receptors such as RARα-mediated GSK3 influences expression. As an antagonist, IRAK-M causes IRAK-1 to regulate SRB1 and efflux cholesterol from the macrophage [66]. Catechins also stimulate TGF β activated kinase 1 (TAK1) and mitogen-activated kinase kinase 3/6 (MKK3/6) to increase ABCA1 expression. The phosphorylation of p38 is induced by TAK1 signaling and MKK3/6. Activated p38 increases ABCA1 expression by making it easier for SP1 and LXR to bind to the ABCA1 promoter [67].

Anthocyanins

According to several studies, phenolic flavonoids such as anthocyanins, which are the major water-soluble pigments in a wide variety of berries and red and blue vegetables, are the most abundant water-soluble pigments in the world. In vitro, anthocyanins promoted the efflux of cholesterol from lipid-laden macrophage foam cells [68]. *Paraoxonase-1 (*PON1) activity alterations in hypercholesterolemic HDL suggest that HDL's cholesterol efflux capacity has improved, which might be related to anthocyanin's cardioprotective properties [69]. Treatment to raise serum PON1 activity improved HDL-mediated macrophage cholesterol efflux

 doi:10.20944/preprints202208.0205.v1

from arterial macrophage foam cells, thereby aiding to the regression of atherosclerosis [70]. Anthocyanins stimulate ABCA1 expression and cholesterol efflux through an LXR-dependent mechanism, according to Du et al. (2015) [71]. Increasing the dosage of anthocyanin supplementation has been shown to promote cholesterol efflux in many experimental models. A daily anthocyanin supplementation dose of 320 mg improved the lipid profiles and cholesterol efflux capacity (CEC) in dyslipidemic patients [69]. Millar et al. (2018) found that 24 weeks of anthocyanin intake increased apoE/mouse CEC by 64 and 85 percent, respectively [72]. Protocatechuic acid (PCA) is formed from the cyanidin-3-O-glucoside of anthocyanins, which are absorbed from the intestines and converted to a variety of compounds, including anthocyanins (Cy-3-G). A model of an animal without apoE suggests that PCA may be important for anthocyanins to protect the blood vessels [73].

Methods for measuring cholesterol efflux capacity

Serum A-lipoproteins (HDL) have been recognized for over 30 years for their ability to efficiently remove cholesterol molecules from cells [74]. Researchers spent a great amount of time and resources investigating this concept in the years following, and in particular, trying to understand how cholesterol molecules are transported from cells to external acceptors [75]. To measure cholesterol efflux, the methods used are virtually always the same. Standard techniques employ cultured cells containing cholesterol labeled by radioisotopes to test HDL's efflux capacity, or ability to remove cholesterol from the serum [75], [76]. For example, J774, Raw264, or differentiated THP-1 cells are tagged with [3 H] cholesterol ([3H]C) and then treated with serum HDL, after which the radioactivity of [3H]C emitted by cells is assessed [77]. Due to the complexity of this treatment, it cannot be used in a clinical situation. HDL capacity may now be measured in a more efficient and time-saving manner. Instead of using radioactive isotopes, the researchers used fluorescent dyes to label cholesterol in blood samples from test patients [78]. They added HDL to the blood serum and measured the fluorescence intensity to determine how much cholesterol HDL was able to take. "Uptake capacity" was the team's nickname for this method's cholesterol marker [78]. Cholesterol tagged with stable isotopes is another alternate approach for measuring CEC without radioisotopes (RI) [79]–[83]. This approach permits the measurement of natural and stable isotope-labeled cholesterol independently; it may also be used for substances other than cholesterol, such as phospholipids (24). However, it is not appropriate for clinical applications since it requires laborious pretreatment processes, such as cholesterol derivatization for Mass Spectrometry (MS) analysis and cholesterol ester hydrolysis.

Conclusion

There are a few limitations to the cholesterol efflux capacity test that must be considered. It is difficult to standardize cellular tests, making them unsuitable for clinical use. As a result, the test assesses just one component of the reverse cholesterol transport route without addressing the effectiveness of individuals' macrophages to efflux cholesterol or the hepatic absorption of macrophage-derived cholesterol in humans [84]. The bioactive substances indicated in the study exhibited limited bioavailability and/or considerable gastrointestinal metabolism, which made it difficult to translate the in vitro findings to human physiology. Because of this, tests on animals and in people are needed to confirm the promising results seen in vitro.

Transporters are used by polyphenols to remove cholesterol from macrophages. RCT starts with the effluxion of cholesterol from macrophage foam cells. ABCA1 is responsible for the removal of lipid-free or lipid-poor apoA1 particles from the circulation, whereas ABCG1 is responsible for the removal of mature HDL particles. Raising HDL and apoA-I levels can stimulate the cholesterol efflux, increasing pathways involving ABCA1/G1 and SR-BI. Each of these routes might benefit from the addition of phytochemicals. This review demonstrates that several phytochemicals have a positive effect on cholesterol efflux. If the ability to get rid of cholesterol is a big part of preventing atherosclerosis, then other pathways that may be controlled by the same bioactive metabolites may play a role in protecting against atherosclerosis.

Conflicts of interest:

The author declares that no competing interests exist.

Funding information

This research received no external funding.

Author's contribution

The author confirms sole responsibility for the following: study conception and design, data collection, and manuscript preparation.

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