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Review

Effects of flavonoids on cholesterol efflux capability

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Abstract

Reverse cholesterol transport (RCT), which plays a critical role in the export of cholesterol from peripheral cells, is one of the processes employed in the management and treatment of atherosclerosis. RCT requires cholesterol efflux from macrophages in the subintima of the vessel wall. ATP-binding cassette transporters A1 and G1 transfer cholesterol from arterial macrophages to extracellular high-density lipoprotein cholesterol. The high-density lipoprotein (HDL) then carries the esterified cholesterol to the liver, where it is eliminated. HDL is an essential element in RCT and extracellular cholesterol excretion. By modifying the processes of RCT and cholesterol efflux, it is possible to inhibit atherogenesis, which might lead to innovative treatments for cardiovascular disease. New modifying factors for RCT and cholesterol efflux must be investigated. Through study, a deeper knowledge of RCT's molecular processes has been achieved, enabling the development of novel therapies that exploit RCT's pharmacological potential. This review aims to stimulate discourse on the possible influence of certain flavonoids on cholesterol efflux on the evolution of atherosclerosis.

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

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, oxidized low-density lipoprotein (ox-LDL) 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 (CE) and foam cells. Foam cells contribute to the earliest pathogenic alterations that result in atherosclerosis [2].

Multiple interdependent mechanisms participate in lipid metabolism, including hepatic production of very low-density lipoprotein, absorption of fatty acids by adipocytes, and lipolysis; skeletal muscle and/or adipose tissue; transfer outside of the liver by low-density lipoprotein (LDL); and removing excess cholesterol by high-density lipoprotein cholesterol (HDL-C). Cardiovascular events are the main cause of mortality in the world, and dyslipidemia (low-density lipoprotein cholesterol (LDL-C) and HDL-C levels) is a key contributor [3]. Cardiovascular disease (CVD) may be predicted by an increase in the quantity of LDL-C. HDL-C has an inverse correlation with coronary heart disease incidence [3].

The capacity to take cholesterol from cells and to induce reverse cholesterol transport (RCT) is the antiatherogenic activity of high-density lipoprotein (HDL) that is well understood. The RCT method has been studied a lot in both people and animal models of atherosclerosis and has been shown to be useful [4]. Cholesterol efflux capacity, an *in vitro* experiment created to quantify the first stage of RCT, has been demonstrated to correlate with cardiovascular risk in many human cohorts, suggesting the atheroprotective effect of RCT in humans. Statins, or inhibitors of hydroxymethyl glutaryl coenzyme A reductase, are one of the most often prescribed families of drugs globally. They have existed for about two decades. Generally, the majority of patients appear to be safe to utilize statin medications. However, individuals with various medical comorbidities are at a greater risk of statin-related side effects with long-term therapy [5]. Thus, the focus is now on plant-based substances that contain antiatherosclerotic 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 sub-

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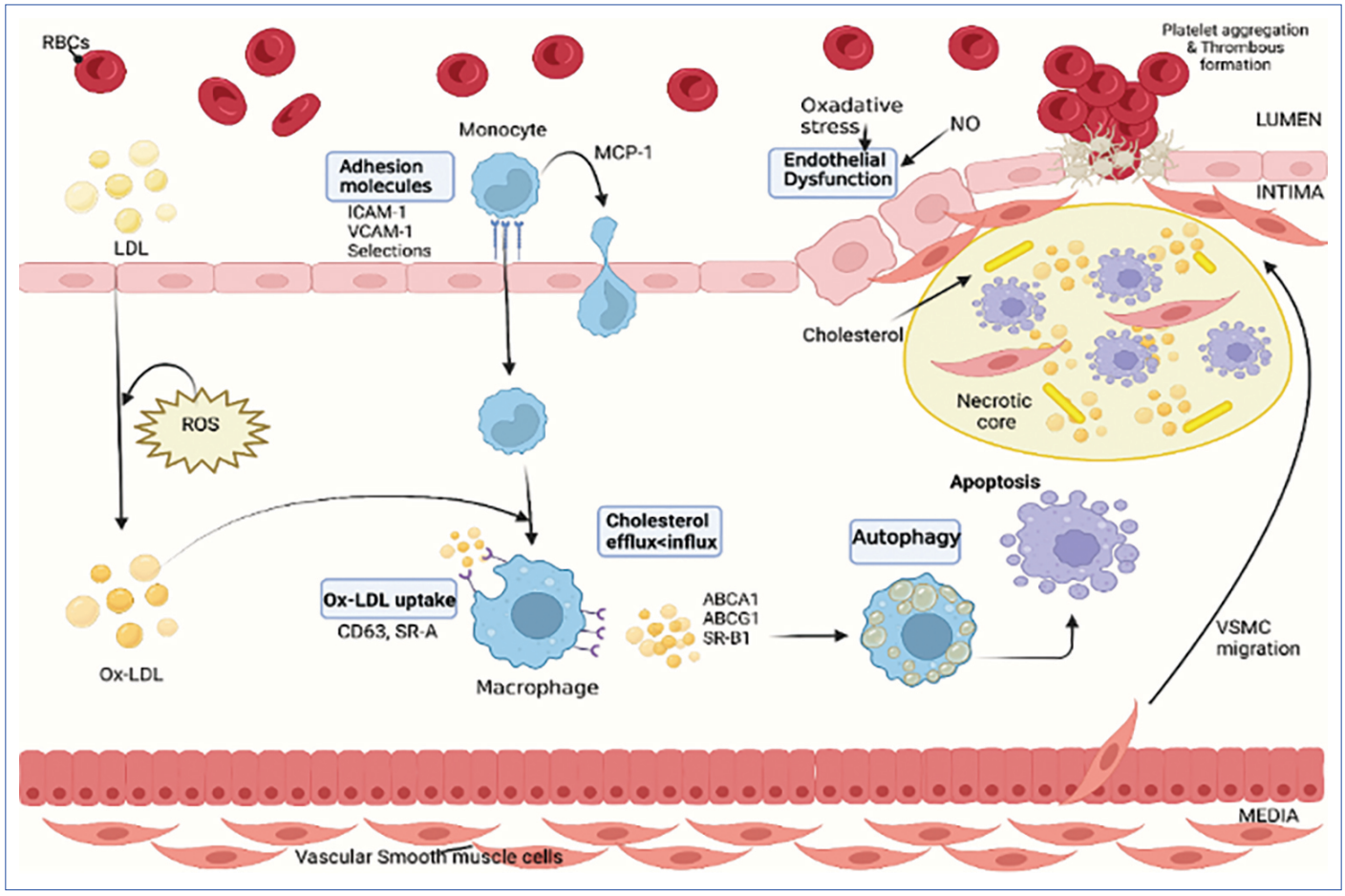

Figure 1. Mechanism of the atherosclerosis process. CD36 and SR-A increase ox-LDL uptake. In the case of atherosclerosis, cholesterol efflux and the levels of ABCA1, ABCG1, SR-B1 are decreased.

NO: Nitric oxide; ROS: Reactive oxygen species; LDL: Low-density lipoprotein; Ox-LDL: oxidized LDL; RBCs: Red blood cells; ICAM-1: Intercellular adhesion molecule 1; MCP-1: Monocyte chemoattractant protein-1; VCAM-1: Vascular cell adhesion molecule 1; CD36: CD36 molecule; SR-A: Class A macrophage scavenger receptor; ABCA1: ATP-binding cassette subfamily A member 1; ABCG1: ATP-binding cassette subfamily G member 1; SR-B1: Scavenger receptor class B type 1; VSMC: Vascular smooth muscle cells.

stances and their potential therapeutic properties have been conducted [6, 7]. 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 RCT on the development of atherosclerosis.

Two different treatments are available to increase the body's ability to excrete cholesterol. Improving cellular cholesterol efflux by targeting macrophages is one approach. The nuclear receptor liver-X-receptor (LXR) agonism is one of the mechanisms that increase macrophage efflux capability [7]. LXRα and LXRβ are nuclear receptors that have essential functions in the transcriptional regulation of lipid metabolism. In response to increased cellular cholesterol levels, The transcriptional activity of LXRs is stimulated. LXRs bind to and control the expression of genes encoding proteins that engage in cholesterol absorption, transport, efflux, excretion, and conversion to bile acids. The coordinated, tissue-specific activities of the LXR pathway govern immunological and inflammatory responses and preserve systemic cholesterol homeostasis [8].

Two of the first identified LXR responsive factors, ATP-binding cassette transporters ATP-binding cassette subfamily A member 1 (ABCA1) and ATP-binding cassette subfamily G member 1 (ABCG1), primarily promote cellular cholesterol efflux. Enhancing HDL cholesterol efflux acceptor functioning is another technique for increasing cholesterol efflux capacity. Infusions of apolipoprotein A-I (apoA-I) might be a novel treatment for preventing coronary artery disease (CAD) [9]. apoA-I is the predominant protein component of HDL particles, and it exerts important atheroprotective benefits against CAD, including antioxidant, anti-inflammatory, antithrombotic, and nitric oxide-promoting properties [10]. 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 [11]. Additionally, inhibition of CETPs might help improve efflux capability [12].

Flavonoids

Fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine contain flavonoids, a collection of naturally occurring chemicals with varying phenolic structures. Subgroups of flavonoids include flavones, flavonols, flavanones, flavanonols, flavanols, catechins, anthocyanins, and chalcones [13]. Epidemiological studies have demonstrated that flavonoid-rich diets may lower the incidence of CVD [14]. Dietary flavonoid consumption has been linked to a reduced risk of CVD because of its antioxidant and anti-inflammatory properties. It is possible that these characteristics may increase HDL-C, cholesterol efflux, and RCT. Flavonoids commonly found in foods and their mechanisms of action for increasing cholesterol efflux and reversing cholesterol transport are listed in the following sections.

Quercetin

For the treatment of CVDs, flavonoids such as quercetin (3,4,3,5,7-pentahydroxyflavone) have received a lot of interest [15, 16]. According to scientific research, flavonoid quercetin has anti-inflammatory, antioxidant, and lipid metabolic properties [17, 18]. Foam cell development and aberrant lipid metabolism are early indicators of atherosclerosis in patients with CVD [19, 20]. Because quercetin inhibits the production of foam cells, it may be an important factor in lowering the prevalence of atherosclerosis [21]. Regulation of ABCA1 gene expression has been linked to transcription factor-mediated mechanisms, as well as mitogen-activated protein kinase (MAPK) signaling pathways. MAPKs are essential upstream regulators of the NF-κB signaling cascade in inflammatory and immunological responses [22]. It has been shown that quercetin may have antiatherosclerosis 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 [23]. An essential lipid regulating protein, PCSK9, proprotein convertase subtilisin/kexin type 9 (PCSK9), is involved in lipid metabolism and the process of apoptosis [24]. Preliminary findings show that PCSK9 is increased in macrophages, resulting in an inflammatory reaction and an increase in cholesterol levels by blockage of RCT [25]. The overexpression of ABCA1 by PCSK9 inhibitors may also increase macrophage cholesterol efflux [26]. Quercetin therapy led to the downregulation of PCSK9 and CD36 protein expression and the overexpression of PPAR, LXRα, and ABCA1 protein expression in the aorta and hepatic tissue, respectively [27]. Furthermore, quercetin inhibits oxidative modification of LDL-induced lipid droplets in RAW264.7 cells by increasing ABCAI, ABCG1, and LXR and decreasing PCSK9 [28].

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 CVD [29, 30]. Furthermore, kaempferol increased the levels of ABCA1, ABCG1, and SR-BI protein expression in THP-1-derived macrophages in a dose-dependent manner [31]. Kaempferol stimulated macrophage cholesterol efflux and influenced the expression of LXR-related genes in macrophages, hepatocytes, and intestinal cells, according to Hoang et al. [32].

Myricetin

Several studies have revealed that myricetin (3,3,4,5,5,7-hexahydroxyflavone) has anti-inflammatory and antioxidative effects [33, 34]. However, myricetin'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. Because myricetin reduces CD36, it helps reduce cholesterol buildup in macrophages. Furthermore, Meng et al. [35] showed that myricetin-treated macrophages were less likely to form foam cells, which may be due to myricetin's ability to inhibit cholesterol esterification. Lian et al. [36] demonstrated that the treatment of U937-derived macrophages with myricetin reduced CD36 cell surface protein and mRNA expression.

Naringenin

Many studies have focused on the use of naringenin (4,5,7-trihydroxyflavanone) in the treatment of atherosclerosis [37-40]. There are several citrus flavanones, including naringenin, which may be found in citrus fruits such as oranges and grapefruits [37]. Some animal investigations have shown that naringenin raises HDL-C levels [38]. Naringenin improved cholesterol efflux by nearly five times as much as apoA-I 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 AMP-activated protein kinase (AMPK)-dependent mechanisms [39]. 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. [40]. 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 [40]. At the molecular and protein levels, Naringenin activated LXR in THP-1 macrophages, altering the expression of LXRα target genes ABCA1, ABCG1, and sterol regulatory element-binding protein 1c (SREBP-1c). LXRα and its target genes in human macrophages are upregulated by naringenin through AMPK modulation [37].

Catechin

Citrus juice, chocolate, tea, and wine contain flavanol or flavan-3-ol substances such as catechins [41]. 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. Catechins may have antiatherogenic benefits owing to increased expression of ABCA1, ABCA1, and scavenger receptor class B type I (SRB1) through stimulation of the liver X recep-

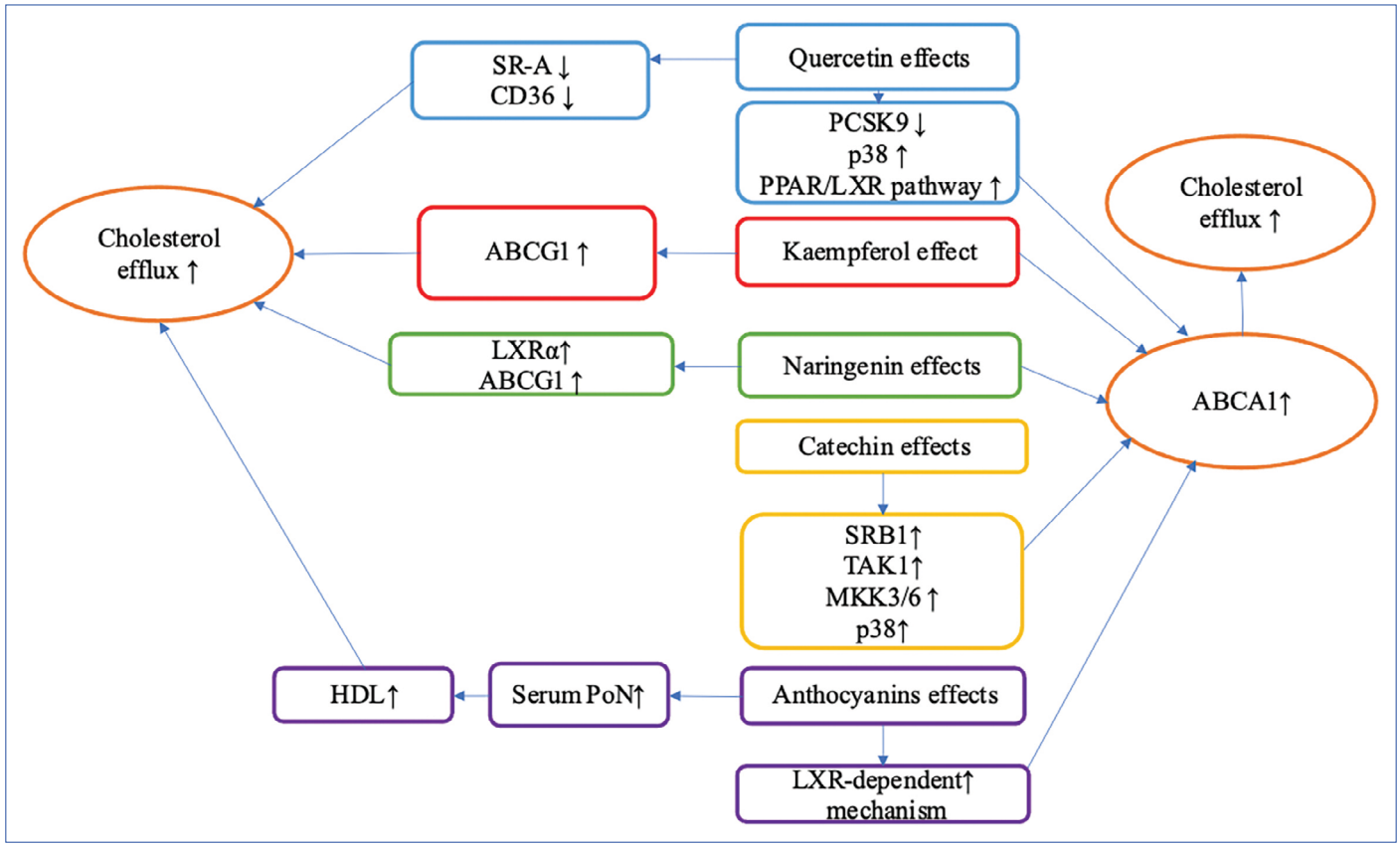

Figure 2. Effect of flavonoids on cholesterol efflux capacity.

SR-A: Class A macrophage scavenger receptor; CD36: CD36 molecule; ABCG1: ATP-binding cassette subfamily G member 1; LXR: Nuclear receptors liver-X-receptors; HDL: High-density lipoprotein; PON1: Paraoxonase-1; PCSK9: Proprotein convertase subtilisin/kexin type 9; PPAR/LXR pathway: Peroxisome proliferator-activated receptors/ Nuclear receptors liver-X-receptors pathway; SR-B1: Scavenger receptor class B type 1; TAK1: TGFβ activated kinase 1; MKK3/6: Mitogen-activated kinase 3/6; ABCA1: ATP-binding cassette subfamily A member 1.

tor signaling pathway. Hepatic SRB1 has been labeled as a positive regulator of macrophage RCT and as a receptor for HDL 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), IRAK1 and Tollip are inhibited. The suppression of nuclear receptors such as RARα-mediated GSK3 influences expression. As an antagonist, IRAK-M causes IRAK1 to regulate SRB1 and efflux cholesterol from the macrophage [42]. Catechins also stimulate TGFβ-activated kinase 1 (TAK1) and mitogen-activated 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 [43].

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 [44]. *In vitro*, anthocyanins promoted the efflux of cholesterol from lipid-laden macrophage foam cells [45]. 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 [46]. Treatment to raise serum PON1 activity improved HDL-mediated macrophage cholesterol efflux from arterial macrophage foam cells, thereby aiding to the regression of atherosclerosis [47]. Anthocyanins stimulate ABCA1 expression and cholesterol efflux through an LXR-dependent mechanism, according to Du et al. [48]. 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 in dyslipidemic patients [46]. Millar et al. [49] found that 24 weeks of anthocyanin intake increased apoE/mouse CEC by 64% and 85%, respectively. Protocatechuic acid is formed from the cyanidin-3-O-glucoside of anthocyanins, which are absorbed from the intestines and converted to various compounds, including anthocyanins (Cy-3-G).

Conclusion

The purpose of this study is to stimulate debate on the possible influence of certain flavonoids on cholesterol efflux in the course of atherosclerosis (Fig. 2). 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 RCT route without addressing the effectiveness of individuals' macrophages to efflux cholesterol or the hepatic absorption of macrophage-derived cholesterol in humans [50]. 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 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 apoA-I particles from the circulation, whereas ABCG1 is responsible for the removal of mature HDL particles. Raising HDL and apoA-I levels can stimulate 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.

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