# Anti-atherosclerotic effects of natural compounds targeting lipid metabolism and inflammation: Focus on PPARs, LXRs, and PCSK9

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## ARTICLE INFO

## ABSTRACT

A large body of evidence has shown that modulation of the nuclear receptors peroxisome proliferator-activated receptors (PPARs), the liver X receptors (LXRs), the proprotein convertase subtilisin/kexin type 9 (PCSK9) and inflammatory processes by natural compounds has hypolipidemic and anti-atherosclerotic effects. These beneficial outcomes are certainly related to the crucial function of these targets in maintaining cholesterol homeostasis and regulating systemic inflammation. Currently, the therapeutic scenario for cardiovascular diseases (CVD) offers a plethora of widely validated and functional pharmacological treatments to improve the health status of patients. However, patients are increasingly sceptical of pharmacological treatments which are often associated with moderate to severe side effects. The aim of our review is to provide a collection of the most recent scientific evidence on the most common phytochemicals, used for centuries in the Mediterranean diet and traditional chinese medicine that act on these key regulators of cholesterol homeostasis and systemic inflammation, which could constitute important tools for CVD management.

## 1. Introduction

Despite advances in medicine and drug development, the rising incidence of cardiovascular diseases (CVD) remains a major global health problem [1]. Atherosclerosis is a chronic inflammatory disease characterized by arterial narrowing and restricts blood flow due to the buildup of cholesterol-rich plaques, and it is associated with clinical outcomes including ischemic heart disease, ischemic stroke, and peripheral arterial disease-conditions. Activation of the inflammatory cascade is a well-established event promoting tissue and organ dysfunction in several pathological conditions [2] including atherosclerosis where it drives initiation, metaphase and advanced stages, and plaque rupture [3]. Inflammatory factors such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α) are consistently elevated in atherosclerosis. In addition, receptors involved in inflammation, such as the toll-like receptor (TLR), particularly TLR2 and TLR4, are increased in human atherosclerotic plaques [4]. Equally or more dangerous for the onset and development of atherosclerosis is dyslipidemia, characterized by high plasma levels of total cholesterol (TC) and triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C). It is known that low-density lipoproteins

cholesterol (LDL-C) or LDL particles and hypertriglyceridemia or TG-rich lipoproteins are major risk factors for this pathology [5,6]. The causal relationship between cholesterol and inflammation is not completely understood. Growing evidence has revealed that several molecular mechanisms implicated in cholesterol metabolism participate in multiple inflammatory signaling pathways [7]. In particular, inflammation causes significant adverse changes in lipoprotein metabolism, including increased oxidation of LDL and very low-density lipoproteins (VLDL), all of which are pro-atherogenic [8]. In the context of cholesterol metabolism, peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs) are nuclear receptors involved in regulating cholesterol homeostasis, besides promoting anti-inflammatory effects. The promotion of peroxisome proliferation by PPARs increases fatty acid catabolism as a result of enhanced expression of genes encoding proteins involved in lipid transport and fatty acid β-oxidation [9]. The distribution and function of PPARs show organ and cell specificity. PPARα is widely expressed in the heart, liver, skeletal muscle, and cardiovascular system; PPARβ/δ is mainly distributed throughout the body; PPARγ is highly expressed in white adipose tissue [10–12]. From a mechanistic point of view, PPARs form heterodimers with the retinoid X receptor (RXR) and bind to specific DNA regions of

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target genes (AGGTCAXAGGTCA, where X is a random nucleotide) called peroxisome proliferation hormone response elements. Activation by a ligand induces conformational changes in the PPAR-RXR complex, ultimately activating the transcription of target genes, including LXRs, responsible for encoding proteins involved in the cellular cholesterol efflux process [13]. Notably, PPARs are involved in the regulation of a large number of genes involved in cellular lipid metabolism and inflammation in the cardiovascular system [11], showing multiple anti-atherosclerotic functions, as observed in PPARα$^{-/-}$ mice with increased lipogenesis and inflammation [14]. The downregulation of PPARα expression has been associated with decreased *de novo* hepatic lipogenesis [15], while PPARβ activates carnitine palmitoyl transferase (CPT), which improves fatty acid transport across the mitochondrial membrane and subsequent β-oxidation [16]. Activated PPARs can interact with other inflammatory transcription factors, such as activator protein 1 (AP-1) and nuclear factor-kappa B (NF-κB), causing transcriptional repression [11,17]. For instance, activation of PPARα suppresses inflammatory responses in a variety of cells by inhibiting the TLR4/NF-κB and AP-1 signaling pathways [11,15–18]. In addition, PPARγ activation has been shown to suppress the release of pro-inflammatory factors via activation of adenosine monophosphate-activated protein kinase (AMPK) and inhibition of multiple signaling pathways, including TLR4, mitogen-activated protein kinase (MAPK), and wingless/integrated (WNT)/β-catenin [11]. Therefore, PPARs are considered important targets for the treatment of atherosclerosis and other CVD. LXRs have been identified in two isoforms, LXRα and LXRβ, which form heterodimers with RXR [19]. Both agonists and antagonists can modulate the activity of LXRs. After activation, LXRs bind to the LXR response element in the promoter region of target genes and regulate their expression. Examples include the adenosine triphosphate (ATP)-binding cassette (ABC) transporter genes A1 (ABCA1) and G1 (ABCG1), fatty acid synthase (FAS), sterol regulatory element-binding protein-1c (SREBP-1c), apolipoprotein E (ApoE), cholesteryl ester transfer protein, and carbohydrate regulatory element-binding protein, which are involved in cholesterol, fatty acid, lipid, and glucose metabolism [19]. Studies of LXRs knockout mice have shown that the absence of both isoforms of LXR associated with the pathogenesis of several diseases including lipid disorders, diabetes, atherosclerosis, obesity, cancer and Alzheimer's disease [20–22]. With respect to CVD, LXRs may have an impact on atherosclerosis by modulating several pathways involved in cholesterol homeostasis. Activation of LXRs decreases intestinal absorption of cholesterol and promotes reverse cholesterol transport by directly activating genes that control cellular cholesterol efflux, as also recently demonstrated in an *in vitro* hepatocyte model [23]. This may account for the reduction in atherosclerotic lesions observed with LXR agonists in the LDLR$^{-/-}$ mouse model of atherosclerosis [24]. LXRs are also involved in macrophage functions as they inhibit the action of pro-inflammatory genes that recruit NF-κB-negative coregulatory proteins [25]. In the LDLR$^{-/-}$ mouse model of atherosclerosis, the selective LXR agonist WAY-252623 has been shown to reduce lesion progression [24]. Because of the crucial role of these nuclear receptors in the regulation of lipid metabolism and anti-inflammatory processes, several synthetic modulators of PPARs and LXRs have been developed in view of their potential in the therapy of atherosclerosis. However, to date they have shown conflicting therapeutic results together with various side effects [26,27]. In the context of lipid metabolism, proprotein convertase subtilisin/kexin type 9 (PCSK9) is another important regulator of circulating cholesterol levels. PCSK9 is a type K serine protease secreted into the plasma by hepatocytes [28] able to bind to the low-density lipoprotein receptor (LDLR) in liver cells, preventing its recycling and increasing its degradation in endosomes and lysosomes. Therefore, by decreasing hepatic LDLR expression, PCSK9 reduces the uptake of circulating LDL particles and LDL-C, ultimately leading to elevated blood LDL-C levels [28]. Consistently, PCSK9 gain-of-function (GOF) mutations have been shown to cause elevated plasma LDL-C levels and increased risk of CVD [28]. Conversely,

loss-of-function (LOF) mutations are associated with lower LDL-C concentrations and CVD risk [29]. New pharmacological approaches targeting PCSK9 have been developed to effectively reduce plasma levels of LDL-C [28]. Currently, three PCSK9 inhibitors are available in market: two monoclonal antibodies alirocumab and evolocumab [30,31], and a small interfering RNA (siRNA), namely inclisiran, that inhibits the synthesis of PCSK9 protein in the liver [32]. PCSK9 inhibitors can be used as monotherapy or as adjunctive therapy in patients with familial hypercholesterolemia when maximum tolerated doses of statins combined with ezetimibe fail to achieve LDL-C targets [33] or in combination with these drugs used at low doses in patients who are intolerant to statins [33]. Several recent studies have suggested also a direct link between PCSK9 and inflammation. For example, PCSK9 levels were associated with white blood cell counts in patients with stable coronary heart disease (CHD) [34]. An experimental study conducted by Ricci et al. showed that recombinant PCSK9 induces TNF-α mRNA in bone marrow-derived macrophages primarily, but not exclusively, in an LDLR-dependent manner [35]. The siRNA for PCSK9 protects against inflammation by inhibiting NF-κB activation in THP-I-derived macrophages stimulated by oxidized LDL (oxLDL) [36]. On the other hand, there is also evidence that inflammation can influence PCSK9 expression [37]. The dual effect of PCSK9 on cholesterol homeostasis and inflammation discloses the crucial role of this protein as a pro-atherosclerotic agent. Indeed, as demonstrated by an *in vitro* study on macrophages, PCSK9 is able to downregulate ABCA1 expression reducing cholesterol efflux, suggesting a relevant influence in the pathogenesis of atherosclerosis [38]. Nutrition has been widely described as playing a pivotal role in the prevention of CVD, which led recent ESC/EAS guidelines to recommend the use of nutraceuticals as dietary supplements and functional foods for the management of mild dyslipidemia [39]. Nutraceuticals are food supplements recommended to complete the diet by providing a concentrated source of nutrients or other substances designed to support health benefits and physiological functions [40,41]. In particular, many nutraceutical compounds have shown beneficial effects on plasma lipoproteins levels [42]. In recent years, the overall use of nutraceuticals has become increasingly popular due to their safety and efficacy (even if they also are associated with some adverse effects and interactions with other substances and drugs). Patients tend to prefer them to hypolipidemic drugs, in the belief that they are "natural" products and therefore not harmful. Moreover, the media often overstate the potential adverse effects of lipid-lowering medications, especially statins, which are widely used as they can effectively lower LDL and prevent CVD [33]. Given the growing interest in anti-atherosclerotic dietary supplements, the aim of this review is to explore the role of major nutraceuticals, phytochemicals, and terrestrial and marine plant extracts in the treatment of atherosclerosis through the modulation of PPARs, LXRs, and PCSK9, focusing on their effects on the two crucial aspects of this pathology, lipid metabolism and inflammation (Fig. 1). The use of novel natural products through the modulation of these targets represents a readily accessible and safe therapeutic potential for the treatment of CVD.

## 2. Literature search methods

With this aim, the literature search was performed by the PubMed database, considering all manuscripts published in English language from 2020 until 2024. The following search strategy was applied as follow: ((natural compounds) OR polyphenols) OR alkaloids) OR terrestrial and marine plant extracts) AND PPARs) OR LXRs) OR PCSK9) OR inflammatory markers) AND lipid-lowering) OR anti-atherosclerosis) OR cardiovascular) OR cardiovascular disorder) OR cardiovascular health)). The literature search was repeated adding the keywords "supplementation" and "therapy" using Mesh terms. After this search, we selected clinical trials, *in vivo* and *in vitro* studies in which the natural compounds of interest were administered as isolated compounds or food supplements, showing an effect on the targets PPARs, LXRs,
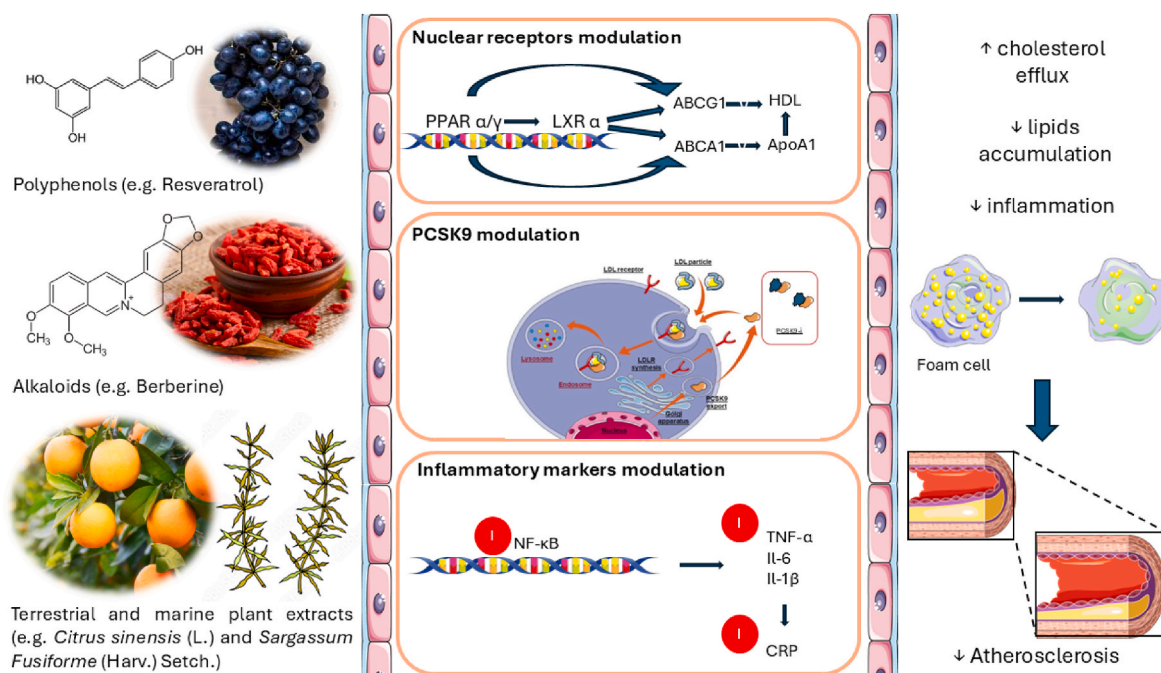
**Fig. 1.** Anti-atherosclerotic and hypolipidemic effects of the main classes of natural compounds through modulation of PPARs, LXRs, PCSK9 and inflammatory markers. This figure schematizes the mechanisms of action of natural bioactive molecules described in this review and their effects on atherosclerosis by targeting peroxisome proliferator-activated receptors (PPARs), liver X receptor α (LXRα), proprotein convertase subtilisin/kexin type 9 (PCSK9) and inflammatory markers. Notably, compounds activating PPARs/LXRα pathway lead to an increase in ATP-binding cassette transporter genes G1 (ABCG1) and A1 (ABCA1) expression, thus raising transporters-mediated cholesterol efflux from macrophage to high-density lipoproteins (HDL) and apolipoprotein A1 (ApoA1). Moreover, some phytochemicals are able to inhibit PCSK9 expression and secretion, increasing low-density lipoprotein receptor (LDLR) expression and consequently reducing LDL circulating cholesterol. In addition, all natural compounds considered have been demonstrated to modulate systemic inflammation, in particular by downregulating nuclear factor kappa B (NF-kB) transcription factor, thus reducing the production of pro-inflammatory cytokines as tumor necrosis factor-α (TNF-α), interleukin 6 and 1β (IL-6, IL-1β) and C-reactive protein (CRP) levels. All these effects result in an enhanced cholesterol efflux and a decreased lipid accumulation leading to a reduction in foam cell formation, slowing down plaque formation and ameliorating atherosclerosis outcome. Pictures were created by combining images from Smart Servier Medical Art (https://smart.servier.com, accessed on September 9, 2022). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/, accessed on September 9, 2022).

PCSK9 and inflammatory markers, as well as an anti-atherosclerotic and/or lipid-lowering effect.

## 3. Natural compounds with lipid-lowering and anti-atherosclerotic effects

### 3.1. Polyphenols

Polyphenolic compounds are an extensive range of plant-derived molecules found in nuts, herbs, seeds, spices, flowers, stems, roots, fruits and vegetables. They include different classes of compounds such as flavonoids, lignans, tannins and stilbenes and offer several beneficial effects [43]. A large body of evidence showed that polyphenol-enriched diet (as Mediterranean diet) is associated to antioxidant and ant-inflammatory activity, as well as to a modulation of lipid metabolism with positive effects on atherosclerosis and lipid disorders [43, 44]. Here are listed some of the most significant polyphenolic compounds that have been demonstrated to have an impact on these pathological conditions, as summarised in Table 1.

Curcumin is a polyphenolic compound majorly found in turmeric extracted from *Curcuma longa* L. (Zingiberaceae) rhizome. Many are the beneficial effects of this compound that exerts an antioxidant, anti-inflammatory and lipid-lowering activity through different mechanisms [86]. Clinical studies conducted on patients suffering from obesity showed a beneficial effect of curcumin as anti-atherosclerotic agent, given its significant impact in reducing LDL oxidation and foam cell formation at a daily dose of 500 and 750 mg [45]. A preclinical study conducted on hypercholesterolemic male rabbits showed that a diet

enriched with 0.2 % curcumin led to a reduction in serum TC, LDL-C, TG, thus decreasing atherogenic index of plasma, but with no effect on HDL levels [46]. From a mechanistic point of view, curcumin seems to exert a lipid-lowering effect by activating the Nrf/FXR/LXRα pathway, as observed in a high-fat and high-fructose fed murine model and in murine hepatocytes [27]. Moreover, both *in vitro* and *in vivo* evidence reported that curcumin treatment by promoting LXRα activity, increases the half-life and stability of ABCA1, one of the main transporters involved in the antiatherogenic process of cellular cholesterol efflux [47]. In another study, treatment with curcumin at 10 and 20 μM for 24 h reduced hepatocytes nuclear factor 1α (HNF-1α) which ultimately down-regulated the PCSK9 mRNA expression and secretion in HepG2 cells, thus increasing LDLR expression and LDL-C uptake. Moreover, curcumin counteracts the increase of statin-induced PCSK9 expression in the same cellular model, enhancing the cholesterol-lowering effect [48]. Curcumin plays also an antioxidant and anti-inflammatory role thanks to its polyphenolic structure. *In vitro* studies on THP-I cells evidence an inhibitory activity of curcumin on inflammatory cytokines' production (IL-6, IL-1β, and TNF-α) and M1 macrophage polarization, reducing foam cell formation in the atherosclerotic plaques. Moreover, the treatment also decreased the TLR-4 expression as well as the inhibition of extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), p38, and NF-kB phosphorylation, corroborating the anti-inflammatory and anti-atherosclerotic activity [49]. *In vivo* there are conflicting outcomes regarding curcumin treatment, probably because of the poor aqueous solubility and the limited bioavailability of this compound after oral administration [50]. For this reason, conjugated forms of curcumin have been developed to enhance its

**Table 1**

Summarised anti-atherosclerotic and hypolipidemic effects of polyphenols included in the review through PPARs, LXRs, PCSK9, and inflammatory markers modulation.

| Polyphenols | | | |
|---|---|---|---|
| **Compound** | **Main natural source** | **Biological activity** | **References** |
| Curcumin | *Curcuma longa* L. | Reduction of LDL oxidation and foam cell formation in patients with obesity. Reduction of cholesterol, LDL-C, triglycerides in hypercholesterolemic mice. Inhibition of Nrf/FXR/LXRα pathway in mice with metabolic syndrome. Promotion of LXRα and ABCA1 stability *in vitro* and *in vivo*. Reduction of HNF-1α and downregulation of PCSK9 in HepG2 cells. Inhibition IL-6, IL-1β, TNF-α, TLR4, ERK, JNK, p38, NF-kB in THP-I cells. | [27,45–51] |
| Resveratrol | *Veratrum grandiflorum* O. Loes., *Vitis vinifera* L., *Polygonum cuspidatum* Siebold & Zucc. | Amelioration of atherosclerosis and lipid profile in humans. Activation of PPARα/PPARγ, ABCA1 and ABCG1 in atherosclerotic mice model. Decrease of PCSK9 and increase of LDLR-mediated cholesterol uptake *in vitro*. Reduction of NF-kB and cytokines (IL-6, IL-1β, TNF-α) in clinical trials. | [26,52–54] |
| Epigallocatechin gallate | *Camellia sinensis* (L.) Kuntz | Reduction on LDL oxidation in healthy men. Reduction of TG, TC, LDL-C and increase in HDL-C in healthy smokers. ERK-mediated increase in LDLR levels in hepatocytes models. Upregulation of LDLR independent from 67 kDa laminin receptor in HepG2 cells. Inhibition of HNF-1α, activation of FoxO3a and reduction of PCSK9 in HFD-mice. | [42,55–58] |
| Eugenol | *Syzygium aromaticum* (L.) Merr. & L.M. Perry, *Origanum vulgare* L. | Decrease of plasma and hepatic LDL-C *in vivo*. Activation of PPARα pathway in diabetic rats. *In silico* and *in vitro* reduction of PCSK9 and increase in LDLR. | [59–61] |
| Emodin | *Rheum palmatum* L., *Rheum rhabarbarum* L., *Rheum officinale* L., and *Rheum rhaponticum* L. | Beneficial effect in CVDs in preclinical studies. Regulation of TC, TG, TNFα and IL-1β through PPARα *in vitro* and *in vivo*. Enhancement in AMPKα, LDLR, ABCA1, ABCG1 and downregulation of SREBP-2, PCSK9 and HMG-CoA reductase in hyperlipidemic zebrafish. Decrease in LDL-C in HFD-rats and suppression | [62–65] |

**Table 1** (*continued*)

| Polyphenols | | | |
|---|---|---|---|
| **Compound** | **Main natural source** | **Biological activity** | **References** |
| Chlorogenic acid | *Coffea arabica* L. *and canephora* Pierre ex A. Froehner | of SREBP-2, HNF-1α and PCSK9 *in vitro*. Reduction of hepatic LXRα expression in HFD-fed mice. Reduction of NPC1L1 and HMG-CoA reductase expression in HepG2 cells. Reduction of CRP, cytokines secretion and lipid peroxidation demonstrated in a meta-analysis. | [27,66,67] |
| Luteolin | *Reseda luteola* L. | Amelioration of atherosclerosis and inflammation in ApoE$^{-/-}$ HFD-mice. Suppression of LXR-SREBP-1c in HepG2 cells. Reduction of total cholesterol, LDL-C, TG via SREBP-2 inhibition in T2DM rats. | [68–70] |
| Naringin and Naringenin | *Citrus* L. | Reduction of plaque macrophages, plasma triglycerides and cholesterol in LDLR$^{-/-}$ and ApoE$^{-/-}$ mice. Inhibition of cholesterol synthesis through HMG-CoA reductase, ACAT, PPARα and γ in ApoE$^{-/-}$ HFD-fed mice. Increase in cholesterol efflux via LXRα activation in murine macrophages. Reduction of hepatic SREBP-1 and -2, PCSK9 and enhancement of LDLR expression in obese mice. | [71,72–74] |
| Quercetin | *Ginkgo biloba* L., *Hypericum perforatum* L., *Sambucus canadensis* L. | Increase in ABCA1 and LXRα, reduction of PCSK9 and cytokines in ApoE$^{-/-}$ mice. Activation of PPARγ-LXRα pathway with induction on ABCA1 in THP-I-derived foam cells and macrophages. Enhancement of cholesterol efflux in THP-I. Reduction of IL-1β, IL-6, IL-8 and TNFα, via suppression of NF-kB and JAK/STAT pathway in thymocytes and splenocytes. | [75–79] |
| Apigenin | *Matricaria chamomilla* L. | Reduction of total cholesterol, LDL-C and triglycerides in hyperlipidemic rats. Activation of PPARα and γ pathway with a reduced hepatic lipid accumulation in HuH7 cells. Inhibition of IL-1β, IL-6 and prostaglandin E2 release, ICAM-1 and VCAM-1 expression in endothelial cells. | [80–82] |

**Table 1** (*continued*)

| Polyphenols | | | |
| --- | --- | --- | --- |
| Compound | Main natural source | Biological activity | References |
| Genistein | *Glycine* max (L.) Merr | Regulation of lipid metabolism and inflammation through PPARα, PPARγ, SREBP-1 *in vivo*. Increase in LXRα in murine fibroblasts and human hepatocytes. Decrease of CRP, MMP-9 via ER-p38/ERK1/2-PPARγ-NF-kB pathway and ERβ stimulation. | [83–85] |

*Abbreviations:* ABCA1, ATP-binding cassette transporter genes A1; ABCG1, ATP-binding cassette transporter genes G1; ACAT, acyl-coenzyme A (CoA):cholesterol acyltransferases; AMPK, Adenosine monophosphate-activated protein kinase; ApoE, apolipoprotein ECOPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVDs, cardiovascular diseases; ER, estrogen receptor; ERK, extracellular signal-regulated kinases; FXR, farnesoid X receptor; HFD, high-fat diet; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HNF-1α, hepatocytes nuclear factor 1α; ICAM-1, intracellular adhesion molecule 1; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-8, interleukin 8; JAK/STAT, Janus kinase/signal transducers and activators of transcription; JNK, c-Jun N-terminal kinases; LDL-C, low-density lipoprotein cholesterol; LXR, liver X receptor; MMP-9, metalloproteinase 9; NF-kB, nuclear factor kappa B; NPC1L1, Niemann-pick C1-like 1; Nrf, Nuclear factor erythroid 2-related factor 2; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptor; SREBP, sterol regulatory element-binding protein; T2DM, type 2 diabetes mellitus; TLR4, toll-like receptor 4; TNF-α, tumour necrosis factor-α; VCAM-1, Vascular cell adhesion protein 1.

bioavailability. In this regard, as described by Grafender et al., treatment with micellar curcumin at a dose of 105 mg/day significantly reduced by about 10 % PCSK9 plasma concentrations, as well as specific markers of inflammation [51].

Among polyphenolic non-flavonoid compounds, resveratrol is a phytoalexin first isolated from the roots of *Veratrum grandiflorum* O. Loes. but mostly found in *Vitis vinifera* L. and *Polygonum cuspidatum* Siebold & Zucc. radix [71]. Several beneficial functions of resveratrol have been described, including amelioration of steatosis, improvement of lipoprotein metabolism, as well as inflammation [87]. In this regard, resveratrol supplementation at a mean dose of about 450 mg/day has been demonstrated to positively impact atherosclerosis and lipid profile, as highlighted in a review that examined the overall effect of several clinical trials [52]. Resveratrol treatment at 10 mg/kg of atherosclerotic mice lowered intestinal fatty acid accumulation via activation of PPARα/PPARγ, stimulating the ABCA1 and ABCG1 transporters' expression [26]. Moreover, *in vitro* evidence found that resveratrol treatment decreased PCSK9 levels, enhancing LDL receptor-mediated uptake through the estrogen receptor alpha (ERα)- and an LXR-mediated pathway, and it prevented the progression of atherosclerosis in Ovx/ApoE$^{-/-}$ mice at a dose of 250 and 500 mg/kg [53]. It is well-characterized also the ability of resveratrol to inhibit inflammation as described by Brenjian et al. in a clinical study where patients with polycystic ovary syndrome treated with 800 mg/day of resveratrol for 40 days showed lower serum levels of NF-kB (−9.96 %) and its downstream cytokines IL-6 (−16.29 %), IL-1β (−10.52 %) and TNF-α (−10.13 %) [54].

Epigallocatechin gallate (EGCG) is mainly extracted from green tea (*Camellia sinensis* (L.) Kuntze) that has exhibited hypocholesterolemic properties. A randomized, placebo-controlled clinical trial conducted on healthy men showed that the supplementation of epigallocatechin at 1 g/day led to a significant reduction in LDL oxidation, suggesting an antioxidant effect [55]. In addition, an anti-atherogenic role of EGCG has been demonstrated in a study where male smokers consuming 100 mL of green tea, containing high amounts of EGCG, three times a day for one year had lower TG, TC, LDL-C and higher HDL-C compared to smokers who did not take green tea extract [56]. Mechanistically, EGCG has been demonstrated to increase LDLR levels in an ERK-dependent pathway together with a reduction in the formation of ApoB in a hepatoma cell line, corroborating its involvement in cholesterol metabolism modulation [42]. Despite several evidence suggest an interaction with the 67 kDa laminin receptor, a recent study in HepG2 cells demonstrated that the EGCG-induced upregulation of LDLR does not occur through this mechanism [57]. Some researchers have observed that EGCG supplementation in a high-fat diet (HFD)-mice model inhibited HNF-1α and activated forkhead box class O 3a (FoxO3a), resulting in a reduced PCSK9 levels and a cholesterol-lowering effect [58]. Despite the several beneficial effects of EGCG, this molecule is characterized by low stability and thus poor *in vivo* bioavailability. For this reason, it may be of great importance to develop new strategies aimed at enhancing its ability to reach unaltered its target and exert biological activities [88]. Interestingly, a recent study took into consideration the stability of EGCG present in different tea infusions in *in vitro* model of digestion, showing that the phytocomplex can carry out a protective role against digestive enzymes, leading to an increased biological effect, thus preferring the administration of the total phytocomplex rather than the isolated molecule [89]. It needs to be noticed that there have been some concerns about EGCG consumption related to a potential hepatotoxicity; indeed, cases of liver injury have been reported after the consumption of this catechin at high dosages. In this regard, EFSA's scientific opinion concluded that EGCG doses equal or above 800 mg/day taken as food supplement cannot be considered safe, since it has been associated to a statistically significant increase of serum transaminases in interventional clinical trials [90].

Polyphenolic compounds include also some monoterpenoids as eugenol, a plant derivative mainly present in essential oils like clove oil (*Syzygium aromaticum* (L.) Merr. & L.M.Perry) and oregano essential oil (*Origanum vulgare* L.). A large body of evidence demonstrated that eugenol decreases both serum and hepatic cholesterol levels, protecting against fatty liver disease and atherosclerosis *in vivo* [59]. The hypolipidemic function of this compound seems to be related to the activation of PPARα, whose expression is enhanced after treating diabetic rats with eugenol for 4 weeks at a dose of 24 mg/kg [60]. In addition, *in silico* and *in vitro* studies found out that eugenol can influence PCSK9 expression and activity, reducing its production and possibly inducing a lipid-lowering effect [61]. It is necessary to consider that there are some concerns about eugenol hepatotoxicity when used as pure compound as cases of hepatic necrosis have been reported, however only in case of overdose, while it is not implicated in liver injury if used at therapeutic doses [91].

Emodin is an anthraquinone extracted from several chinese and european herbs, such as *Rheum palmatum* L., *Rheum rhabarbarum* L., *Rheum officinale* L., and *Rheum rhaponticum* L., which showed hypolipidemic and anti-atherosclerotic activity. Despite it has not been used yet in clinical trials, preclinical studies highlighted its beneficial effects in cardiovascular diseases [62]. In particular, there is strong evidence that the rhubarb extract, in which the predominant anthraquinone is emodin, regulates levels of TC, TG, TNF-α and IL-1β through pathways such as PPARα both *in vitro* and *in vivo* studies [63]. In this regard, experiments on hyperlipidemic zebrafish interestingly exhibited a decrease in TG and TC triggered by an enhancement in AMPKα, LDLR, ABCA1 and ABCG1 expression after emodin treatment for 10 days from a dose of 0.125 μg/mL, together with a down-regulation of SREBP-2, PCSK9 and 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA) expression [64]. The effect on PCSK9 was supported by findings obtained in HepG2 cells treated with elevated cholesterol concentrations as *in vitro* model of hyperlipidemia, where cells incubated with emodin-containing aloe extracts showed a decrease in HNF-1α pathway and thus cholesterol-lowering effect. The same study displayed a reduction in total and LDL-C in HFD-rats treated with aloe extracts at

100 mg/kg [65]. However, EFSA's expert panel indicates that emodin present in the extracts should be considered genotoxic and carcinogenic in the absence of specific data to the contrary, although some uncertainties still remain [92].

Chlorogenic acid is an ester of caffeic acid that can be found in coffee beans (*Coffea arabica* L. and *Coffea canephora* Pierre ex A.Froehner), but also in eggplants, peaches and prunes. It is known for its beneficial effects on CVD and dyslipidemia. Indeed, mice treated with a dose of 90 mg/kg chlorogenic acid for a 12-week period revealed a reduction in hepatic LXRα expression previously upregulated by HFD, preventing lipid hepatic accumulation [27]. According to other preclinical studies conducted on HepG2, chlorogenic acid treatment could reduce intracellular cholesterol levels by inhibiting pregnane X receptor (PXR) and SREBP-2, as well as the expression of Niemann-pick C1-like 1 (NPC1L1) and HMG-CoA reductase [66]. A meta-analysis pointed out that chlorogenic acid beneficial functions are also linked to a reduction in inflammation and oxidation, demonstrated by a drop in different inflammatory markers such as CRP, and different cytokines together with a reduction in lipid peroxidation [67].

Luteolin is a flavonoid compound that can be found mainly in *Reseda luteola* L., but also in a broad number of fruits, vegetables and herbs like spinach, celery, parsley and carrots. Among its numerous biological activities, it is mainly studied as a nutraceutical compound for its anti-inflammatory, anti-diabetic and anti-atherosclerotic properties. There is not much evidence *in vivo*, however a study conducted on ApoE$^{-/-}$ HFD-mice treated with luteolin-containing extracts showed an amelioration of atherosclerosis and inflammation [68]. Mechanistically, Luteolin is able to interact with α and β LXR receptors suppressing LXR-SREBP-1c activation in HepG2 cells, thus reducing lipid accumulation [69]. In addition, *in vivo* studies revealed that Luteolin administration at 50 mg/kg daily for 28 days reduced TC, LDL-C and TG via the inhibition of SREBP-2 in HFD-induced T2DM rats [70].

Naringin and its aglycone naringenin are flavones mainly found in citrus fruits (*Citrus* L.), oranges, grapefruits and tomatoes. These two bioactive compounds showed antioxidant, anti-inflammatory and hypolipidemic functions. In this regard, *in vivo* evidence on male LDLR$^{-/-}$ mice showed a reduction in plaque macrophage content, as well as plasma TG (−79.4 %) and TC (−83.2 %) after 12 weeks diet supplementation with 3 % w/w of naringenin [72]. A positive effect on atherosclerosis was observed also in another study in ApoE$^{-/-}$ HFD-fed mice treated with naringenin at a daily doses of 25, 50 or 100 mg/kg for 12 weeks [73]. The described effects are mediated by inhibition of cholesterol synthesis targeting HMG-CoA reductase, acyl-coenzyme A (CoA): cholesterol acyltransferases (ACAT), PPARα and γ, important regulators of lipid homeostasis. Moreover, naringenin enhanced LXRα mRNA expression and cholesterol efflux in murine macrophages, thus opposing foam cell formation [74]. In an obese mice model, naringin administration at doses of 25, 50 or 100 mg/kg/day for 8 weeks caused a reduction in hepatic SREBP-1, SREBP-2 and PCSK9 expression, thereby inducing LDLR expression. A similar finding was observed after treatment with naringenin, the active metabolite of naringin obtained by hydrolyzation after oral administration in mice models [71].

Quercetin is a flavonoid compound ubiquitous in vegetables and fruits, especially present in apples, berries, capers, grapes, tomatoes, onions, nuts and also herbs such as *Ginkgo biloba* L.*, Hypericum perforatum* L.*, Sambucus canadensis* L. Naturally, it is mainly found in its glycosylated form, which is then deglycosylated in the intestine after absorption. Quercetin is well-known for its anti-inflammatory, antioxidant and anti-atherosclerotic properties, and for this reason widely employed in traditional medicine and formulas [59]. A preclinical study performed in ApoE$^{-/-}$ mice fed with a HFD diet showed that signs of atherosclerosis were reversed after treatment with quercetin at 12.5 mg/kg/day. The treatment increased the expression of LXRα and ABCA1, while reducing the level of PCSK9 and different proinflammatory cytokines [75]. According to *in vitro* studies performed on THP-I-derived foam cells, quercetin treatment could also activate the PPARγ-LXRα pathway that consequently induced ABCA1 expression [76]. A similar result was obtained in another experiment conducted on RAW264.7 macrophages where incubation with quercetin inhibited lipid droplet formation induced by oxLDL through upregulation of LXRα, ABCA1, ABCG1, and downregulation of PCSK9 expression [77]. Recent evidence supports the involvement of LXRα signaling pathway activation in the anti-atherosclerotic effect of quercetin, able to enhance cholesterol efflux in THP-I cells [78]. Quercetin displays a fundamental role also in the modulation of inflammation, as described by Das et al., as primary thymocytes and splenocytes from rats treated with quercetin showed a decrease in both expression and release of several cytokines such as IL-1β, IL-6, IL-8 and TNF-α, via suppression of NF-kB and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. In addition, quercetin's immunomodulatory function unfolds also in the prevention of Nod-Like receptor family pyrin domain containing 3 (NLRP3) activation and enhancement of anti-inflammatory cytokine IL-10 [79].

Apigenin belongs to the flavonoids family and is commonly extracted from chamomile (*Matricaria chamomilla* L.) but is present also in many vegetables and fruits such as celery, onion, orange and malt. This compound seems to have many positive biological effects as a lipid metabolism regulator, as well as anti-inflammatory and antioxidant properties. A preclinical study showed a significant reduction in TC, LDL-C and TG in a model of hyperlipidemic rats after the treatment with apigenin at a dose of 50 mg/kg/day for 14 days [80]. Furthermore, apigenin treatment improved also hepatic lipid accumulation by activation of the autophagy-mitochondria route in HuH7 cells. Specifically, this effect was mediated by apigenin-induced up-regulation of the β-oxidation pathway, thus activation of PPARα and γ, with positive impact on lipid homeostasis maintenance [81]. Apigenin *in vitro* treatment also induced the inhibition of TNF-α-induced IL-1β, IL-6 and prostaglandin E$_2$ (PGE2) secretion and the decrease in the expression of intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells [82].

Genistein is an isoflavone present in soy (*Glycine* max (L.) Merr.) with many beneficial effects such as cardioprotective, anti-inflammatory, and antioxidant and estrogenic properties. It is well reported the ability of soy isoflavones to interact with estrogen receptors, both α and β, leading to the stimulation of lipolysis, ending in an anti-adipogenic effect. An *in vivo* study highlighted the positive influence of genistein supplementation at 500 mg/kg on the regulation of lipid metabolism and inflammatory response, modulating PPARα, PPARγ, SREBP-1, as well as TNF-α and IL-6 mRNA levels [83]. Moreover, murine fibroblasts and HepG2 cells treated with genistein showed increased levels of LXRα expression, corroborating the evidence of a modulation on lipid metabolism [84]. Another *in vitro* study showed that genistein decreased the expression of CRP and metalloproteinase 9 (MMP-9), two markers of inflammation strongly associated with atherosclerosis, and the effect was mediated by ER-p38/ERK1/2-PPARγ-NF-kB pathway and ERβ stimulation [85].

### 3.2. Alkaloids

Alkaloids are a variety of natural organic molecules that contain at least one nitrogen atom and different functional groups. They are produced by a wide range of organisms, mostly plants, but also fungi, bacteria and animals. Alkaloids' physiological function has not been understood yet, and they have been widely used in traditional medicine because of their multiple biological properties in humans. In this regard, they have demonstrated to be involved in modulating lipid homeostasis and inflammatory response, thereby being potentially included in nutraceuticals for the prevention of atherosclerosis and CVD [26], as summarised in Table 2.

Tetramethylpyrazine is an alkaloid present in food such as fermented Japanese food natto and chinese black vinegar, as well as in medicinal plants such as *Ligusticum chuanxiong* (for this reason, this compound is also known as Ligustrazine). Among its biological functions, it has

**Table 2**
Summarised anti-atherosclerotic and hypolipidemic effects of alkaloids included in the review through PPARs, LXRs, PCSK9, and inflammatory markers modulation.

| Alkaloids | | | |
| --- | --- | --- | --- |
| **Compound** | **Main natural source** | **Biological activity** | **References** |
| Tetramethylpyrazine | *Ligusticum chuanxiong* | Amelioration of lipid metabolism, inflammatory and oxidant markers in animal models. Increase of PPARs, LXRs and ABCA1 expression in hepatoma cells. Amelioration of vascular calcification via PPARγ activation in VSMC cells. Decrease of TLR4 and NF-kB expression in HUVEC cells and in mice. | [93–96] |
| Berberine | *Rhizoma coptidis, Berberis* L. | Reduction of total and LDL-C in clinical trials. Reduction of cholesterol uptake in macrophages. Activation of PPARα and γ with improvement of lipid metabolism in hypercholesterolemic mice. Amelioration of atherosclerosis and increase in PPARγ in ApoE$^{-/-}$ mice. Suppression of PCSK9 in HepG2 cells and in dyslipidemic subjects. Reduction of plasma cholesterol, LDL-C, triglycerides in a mouse model of atherosclerosis. Downregulation of NF-kB pathway and decrease of pro-inflammatory cytokines in HUVEC cells. Decrease the expression of ICAM-1, reduce inflammation and atherosclerosis. | [26, 97–105] |
| Caffeine | *Coffea arabica* L. *and canephora* Pierre ex A. Froehner, *Camellia sinensis* (L.) Kuntz | Inhibition of SREBP-2, PCSK9 and increase in LDLR in healthy volunteers and in hepatocytes models. Decrease in lipid droplet, adipogenesis and oxidative stress via PPARγ in a model of Graves' orbitopathy. Reduction of CRP and cytokines secretion and lipid peroxidation in clinical trials. | [67,106, 107] |
| Theobromine | *Theobroma cacao* L. | Downregulation of SREBP-1c, FAS, CD36, FABP4, PPARα, CPT1 *in vitro* and *in vivo*. | [108] |

*Abbreviations:* ABCA1, ATP-binding cassette transporter genes A1; CD36, cluster of differentiation 36; CPT-1, carnitine palmitoyltransferase; CRP, C-reactive protein; FABP4, fatty acid binding protein 4; FAS, fatty acid synthase; ICAM-1, intracellular adhesion molecule 1; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LXR, liver X receptor; NF-kB, nuclear factor kappa B; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptor; SREBP, sterol regulatory element-binding protein; TLR4, toll-like receptor 4.

described the ability to modulate lipid profile and inflammation, thus improving atherosclerosis [69]. In this regard, a meta-analysis collecting studies on animal models showed a significant improvement in endothelial function and a reduction in proliferation and migration of smooth muscle cells after treatment with tetramethylpyrazine at the dose of 50 mg/kg, with amelioration of inflammatory and oxidant markers and lipid metabolism [93]. The mechanism underlying these effects seems to be mediated by activation of PPARs and LXRα genes. This was confirmed by *in vitro* evidence where Ligustrazine treatment in hepatoma cells exhibited an increased expression of PPARγ and LXRα, resulting in a raised expression of the cholesterol transporter ABCA1 [94]. Similarly, a study conducted on vascular smooth cells showed an amelioration of vascular calcification after tetramethylpyrazine treatment via PPARγ pathway [95]. The anti-inflammatory effects of Ligustrazine were elucidated in a study where the alkaloid decreased the Toll-like receptor 4 (TLR4) expression and NF-kB translocation in HUVEC cells and in C57BL/6 mice [96].

Berberine (BBR) is a plant-derived isoquinoline alkaloid present in *Rhizoma coptidis* as well as in several species of *Berberis* L. and it can be usually employed as extract. It plays a well-established role in the regulation of lipid metabolism and inflammation, being currently used as a hypocholesterolemic agent. BBR has been tested in clinical trials alone or in combination with other nutraceuticals and according to a recent meta-analysis, it showed a significant reduction in total and LDL-C and TG, consistently with the hypolipidemic effect observed in preclinical studies [97,98]. In addition, it was observed a significant reduction of serum-mediated cholesterol uptake through micropinocytosis and thus intracellular cholesterol content lowering in macrophages treated with berberine [99]. From a mechanistic standpoint, BBR can interact with many mediators of lipid homeostasis and inflammatory response, including PPARs, as demonstrated by many *in vitro* studies [100]. Indeed, BBR can interact with PPARα in the liver improving lipid oxidation and avoiding lipid accumulation, as well as with PPARγ in the adipose tissue of hypercholesterolemic mice, promoting its remodelling and thermogenesis [26]. In accordance with this evidence, an *in vivo* study on ApoE$^{-/-}$ mice demonstrated a significant amelioration of atherosclerosis with a concurrent increase in PPARγ expression after treatment with *Coptis* extract [101]. One of the most studied BBR targets is PCSK9, a crucial regulator of cholesterol metabolism. In this regard, a wide range of evidence showed that BBR treatment suppresses PCSK9 expression accelerating the degradation of HNF-1α protein in a hepatoma cell model [102]. Interestingly, BBR seems to be able to counteract the statin-mediated PCSK9 plasma levels increase when given in a nutraceutical combination containing 531.25 mg of BBR [103]. In addition, BBR exerts also an anti-inflammatory and antioxidant function through the inhibition of the NF-kB signaling pathway, leading to a reduction in proinflammatory cytokines (IL-6, IL-8, IL-1β) expression in HUVEC cells [104]. This anti-inflammatory activity is corroborated by an *in vivo* study where BBR treatment at 100 mg/kg/day decreased the expression of ICAM-1 and interferon regulatory factor 3 in partially ligated carotid arteries of mice, suggesting an attenuation of vascular endothelial inflammation with a potential positive impact on atherosclerosis progression [105]. A study conducted on BBR extracts provides also crucial information about the bioaccessibility and general safety of this compound. It was shown a possible interaction with P-gp, responsible for a low intestinal absorption rate, and with different cytochrome P450 isoforms, suggesting a strong metabolism and thus a low bioavailability. Moreover, BBR is characterised by an absence of cytotoxicity at 50 and 100 μg/mL, suggesting a good tolerability. Given this evidence, it may be necessary to work on BBR formulation to enhance its bioavailability [109].

Caffeine is a trimethylxantine (1,3,7) found in plants, mostly in coffee (*Coffea arabica* L. and *Coffea canephora* Pierre ex A.Froehner) and tea (*Camellia sinensis* (L.) Kuntz). It is well-known as a stimulant of the central nervous system; however, it also seems to have a positive effect on the cardiovascular system by exerting beneficial functions on lipid

homeostasis, oxidative stress and inflammatory markers. Caffeine was administered in healthy volunteers at a dose of 400 mg/kg and the treatment resulted in the inhibition of SREBP-2, the decrease in PCSK9 levels together with an increase in LDLR expression and LDL-C clearance. In the same study, it was observed that caffeine decreased PCSK9 expression and secretion in two different models of hepatocytes through inhibition of SREBP-2 [106]. In addition, an *in vitro* study conducted in a model of Graves' orbitopathy caffeine treatment led to a decrease in lipid droplet formation and inhibition of the PPARγ pathway, decreasing adipogenesis and oxidative stress [107]. Moreover, a clinical trial showed the anti-inflammatory and antioxidant properties of caffeine, as it reduced the secretion of the main proinflammatory cytokines, CRP and lipid peroxidation, carrying out an anti-atherosclerotic action [67].

Theobromine is a dimethylxantine (3,7) in the cacao plant (*Theobroma cacao* L.) that has shown many biological effects, such as regulation of lipid metabolism, and antioxidative and anti-inflammatory properties. *In vitro* and *in vivo* evidence showed that theobromine treatment resulted in the downregulation of the expression of SREBP-1c, fatty acid synthase (FAS), CD36, and fatty acid binding protein 4 (FABP4), as well as PPARα and carnitine palmitoyltransferase (CPT1), all genes regulating lipid metabolism and thereby leading to an improvement in dyslipidemia and amelioration of non-alcoholic fatty liver disease [108]. Besides the above-mentioned evidence about theobromine effect on lipid metabolism, up to now there is a lack of information about its activity on other modulators of cholesterol homeostasis, such as LXRs and PCSK9, which may be interesting to be further elucidated.

### 3.3. Terrestrial and marine plant extracts

Botanical extracts, consisting of a complex mixture of molecules obtained directly from crude terrestrial and marine plants, are a promising source of bioactive compounds for research and development of new drugs [47]. The bioactive components contained in plant extracts, which have been used for centuries in traditional chinese medicine [110–112], and extracts from algae growing in the oceans, with their unique environment and enormous biodiversity, are a rich source of diverse natural products with proven pharmacological activities [113]. Compared to synthetic compounds, natural extracts cover a wide range of biodiversity and functionality due to their ability to interact with multiple proteins or other biological targets [114]. In addition, they usually do not manifest the side effects commonly associated with synthetics modulating the same targets.

In detail, several compounds found in plant extracts have been shown to modulate the activity of nuclear receptors and PCSK9, and also affect inflammation [71,115,116]. In the scenario of dyslipidemic diseases, these natural extracts may thus have potential therapeutic effects as summarised in Table 3.

*Citrus sinensis* (L.) Osbeck extracts are known for their abundance of bioactive compounds, including anthocyanins, flavonoids and phenolic acids, which offer various health benefits [117]. Several studies have shown that *Citrus sinensis* extracts can positively influence lipid metabolism. In *in vivo* models, these extracts indeed promote lipolysis likely through the modulation of cellular signaling pathways involved in fat metabolism by the bioactive compounds [117,118]. Moreover, it was observed that Moro orange juice (200 mL/daily) induced a significant reduction of TC (−14 %) and LDL-C (−16.2 %), as well as an increase in HDL-C (p < 0.05) after a treatment of 28 days in obese and diabetic rats [119]. Orange extracts have been also shown to actively modulate PPARs. Specifically, this mechanism seems to be dependent on the effect of naringenin, that increases AMPK which in turn activates PPARγ in isolated mitochondria from liver, and also decreases the expression of LXRs, SREBP-1c and SREBP-1a in the liver, preventing steatosis in diabetic male rats fed with a HFD, and supplemented with 100 mg/kg/day of naringenin [116]. Other evidence supports the ability of anthocyanins to differentially regulate genes such as PPARα, PPARδ [116]. The

**Table 3**
Summarised anti-atherosclerotic and hypolipidemic effects of terrestrial and marine plant extracts included in the review through PPARs, LXRs, PCSK9, and inflammatory markers modulation.

| Terrestrial and marine plant extracts | | | |
|---|---|---|---|
| **Extract** | **Main natural compounds** | **Biological activity** | **References** |
| *Citrus sinensis* (L.) Osbeck | Anthocyanins, flavonoids (naringenin, hesperetin), phenolic acids | Reduction of body fat and augmented lipolysis *in vivo*. Increase in AMPK and activation of PPARγ in isolated mitochondria. Prevention of steatosis by decrease of LXRs, SREBP-1c, SREBP-1a in diabetic male rats. Activation of PPARα and δ in HFD-fed mice. Reduction of TNF-α and IL-6 in macrophages. | [116–119] |
| Bergamot (*Citrus bergamia (Risso) Risso & Poit)*) | Polyphenols, flavonoids (neoeriocitrin, naringin, melitidin), essential oils | PPARα-mediated hypolipidemic effects in rats. Downregulation of PCSK9 with increase in LDLR expression and LDL-C clearance in HFD rats. Reduction of HNF-1α and PCSK9 in HepG2 cells Decrease in CRP secretion in overweight adults. | [120–124] |
| *Morus alba* L. (*Moraceae*) | Organic acids, alkaloids, isoquercetrin, quercetin-3-triglucoside, moracetin, rutin, cudraflavone B, prenylflavore, tannic acid, phosphorous, calcium, iron, β-carotene, coumarins, vitamin C, amino acids, dihydroxycoumarin, oxyresveratrol, protein, zinc and magnesium | Downregulation of PCSK9 expression, increase in LDLR and LDL-C uptake in liver cell model. Inhibition of PPARγ improving insulin sensitivity and lipid metabolism in diabetic rats. Reduction of inflammatory markers (MCP-1, mTOR, NF-kB) in rats. Reduction of CRP and MDA and increase of HDL-C in humans. | [125,126, 127] |
| *Aquilaria sinensis* (Lour.) Spreng. (*Thymelaeaceae*) | Flavonoids, triterpenoids, phenolic acids | Inhibition of atherosclerosis progression in HFD-fed diet ApoE$^{-/-}$ mice. Reduction of TG, LDL-C and increase in HDL-C reducing CVD risk *in vivo*. Activation of PPARs leading to fatty acid catabolism and elimination in | [114,128, 129] |

**Table 3** (*continued*)

| Extract | Main natural compounds | Biological activity | References |
|---|---|---|---|
| | | differentiated myoblast cells. Possible anti-inflammatory action via LXRs activation in differentiated myoblast cells. | |
| Magnolia L. (*Magnolia officinalis*) | Lignans (honokiol, obovatolins-A and B, magnolol) | Modulation of LXRs, promotion of cholesterol efflux via ABCA1 in macrophages. Downregulation of PCSK9 in hepatocytes model. Anti-inflammatory activity by decreasing IL-1β, COX-2 and iNOS in rats. | [69,130, 131] |
| *Garcinia* L. (Clusiaceae) | Hydroxycitric acid (HCA), Flavonoids (Garcinia biflavonoid 1 (GB1)) | Reduction of TC, TG and increase in HDL-C through ATP-citrate lyase inhibition *in vitro* and in humans. Upregulation of PPARα expression in HepG2 cells. Anti-inflammatory properties *in vitro* and *in vivo*. Inhibition of NF-kB and JAK/STAT pathway in LPS-stimulated in macrophages. Reduction of MPO activity, COX-2 and iNOS expression and IL-1β levels *in vivo*. | [132–135] |
| Brown algae (*Phaeophyceae*) | Polysaccharides (alginate, fucoidan), proteins (phycobiliproteins), polyphenols (phlorotannins), carotenoids (fucoxanthin), phytosterols (fucosterol, 24S-sarin-gosterol), n-3 long-chain polyunsaturated fatty acids (eicosapentaenoic acid) | Improvement of atherosclerosis through regulation of autophagy-mediated macrophage polarization in LDLR$^{-/-}$ HFD mice. Reduction of acid synthase, diacylglycerol acyltransferase, SREBP-1, perilipin-2 in NAFLD and NASH rats. Activation of LXRs in a mouse model of AD. Modulation of PPARα/γ in 3T3-L1 cells. Anti-inflammatory properties and enhancement of cholesterol efflux in THP-I cells. | [115, 136–139] |

*Abbreviations:* ABCA1, ATP-binding cassette transporter genes A1; AD, Alzheimer's disease; AMPK, Adenosine monophosphate-activated protein kinase;

ApoE, apoliprotein E; COX-2, Cyclooxygenase-2 CRP, C-reactive protein; CVDs, cardiovascular diseases; HFD, high fat diet; HDL-C, high-density lipoprotein cholesterol; HNF-1α, hepatocytes nuclear factor 1α; IL-1β, interleukin 1β; IL-6, interleukin 6; iNOS, nitric oxide synthases; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LXR, liver X receptor; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MPO, myeloperoxidase; mTOR, mechanistic target of rapamycin; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-kB, nuclear factor kappa B; PLA$_2$, phospholipase A$_2$; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptor; SREBP, sterol regulatory element-binding protein; TNF-α, tumour necrosis factor-α.

activation of these receptors promotes fatty acid oxidation and reduces fat accumulation while improving insulin sensitivity. In addition, Moro orange extracts have significant anti-inflammatory properties. Chronic inflammation is often associated with visceral fat accumulation and altered metabolic conditions. The bioactive compounds in Moro orange, in particular naringenin and hesperetin, reduce the production of inflammatory mediators such as TNF-α and IL-6, tested *in vitro* [116], possibly contributing to an improved inflammatory profile and potentially reducing the risk of obesity-related metabolic disorders.

Bergamot (*Citrus bergamia* (Risso) Risso & Poit) is native to the Calabria region, in south Italy. Known for its unique chemical composition, the peel of bergamot is rich in polyphenols, flavonoids, and essential oils that contribute to its various therapeutic properties [140]. Already used in the nutraceutical field and for the production of essential oils [120], bergamot has gained attention in recent years for its potential health benefits, particularly in managing cardiovascular risk factors. One of the most notable actions of bergamot extract is its anti-atherogenic and hypocholesterolemic effect. In particular, the flavonoids neoeriocitrin, naringin and hesperetin have been shown to reduce serum cholesterol levels in *in vivo* studies as well as in humans (a reduction in TC from 12.3 % to 31.3 %, in LDL-C from 7.6 % to 40.8 %, and in TG from 11.5 % to 39.5 % were reported in humans by Itziar Lamiquiz-Moneo and colleagues), by modulating key enzymes involved in lipid metabolism: for example is well known the effect of bergamot extract on HMG-CoA reductase [121,122]. As already observed for *Citrus sinensis* extracts, naringenin contained in bergamot extract has shown a hypolipidemic activity and anti-adiposity effects in rats through PPARα regulation mechanism [123]. A recent *in vivo* study in rats fed with a hyperlipidemic diet has highlighted the ability of bergamot polyphenolic fraction (10 mg/kg given orally for 30 consecutive days) to modulate also the expression of PCSK9, downregulating its expression [124]. Moreover, in recent work by Lupo M.G. and colleagues, isolated compounds from bergamot peel extract, hesperetin-7-*O*-neohesperidoside and naringenin-7-*O*-rutinoside, showed to reduce intracellular sterols and the expression of the PCSK9 transcription factor HNF1-α in HepG2 cells [122]. These findings support the use of bergamot extracts as a potential strategy for cholesterol management, complementing traditional lipid-lowering approaches. In addition, the anti-inflammatory properties of bergamot extract are of great interest in the context of cardiovascular health. In a pilot study including 80 overweight adults with the diagnosis of metabolic syndrome, following a personalized low calories Mediterranean diet, the supplementation with 1 tablet per day for 6 months of a bioactive phytocomplex from bergamot fruit (200 mg dry extract), particularly rich in flavonoids, has been shown to reduce the production of inflammatory markers such as CRP (−40 %) [120]. This activity further supports the cardiovascular benefits of bergamot extract by reducing the inflammatory processes that contribute to plaque formation and vascular damage.

*Morus alba* L., commonly known as white mulberry, is a deciduous tree native to China, but now widely cultivated in various parts of the world, particularly in Asia, Europe and North America. The leaves, fruit and bark of *Morus alba* have long been used in traditional medicine for their therapeutic properties. In particular, the plant extract is rich in bioactive compounds, including organic acids, alkaloids, isoquercitrin,

quercetin-3-trigluco-side, moracetin, rutin, cudraflavone B, prenyl-flavone, tannic acid, phosphorous, calcium, iron, β-carotene, coumarins, vitamin C, amino acids, dihydroxycoumarin, oxyresveratrol, protein, zinc and magnesium [125]. These compounds contribute to *Morus alba* wide range of pharmacological effects, including anti-atherosclerotic, anti-inflammatory, antioxidant, antidiabetic, and lipid-lowering activities, as demonstrated in several recent *in vivo* studies on mice and humans [125,141,142]. These effects could be explained by the modulatory action of *Morus alba* extract of important key regulators of cholesterol homeostasis. In a study comparing the effects of various natural extracts, *Morus alba* leaves extract was found to significantly downregulate the expression of PCSK9 ($-59.3$ %) *in vitro* using liver cell lines. This resulted in increased LDLR expression, suggesting that *Morus alba* extract may contribute to improved LDL clearance and lower circulating LDL-C levels [126]. In addition, *Morus alba* showed a modulation effect on PPARs. A study focusing on a diabetic rat model demonstrated that *Morus alba* leaves extract (5 % incorporated in the diet) down-regulated PPARγ activity in the kidney, resulting in improved insulin sensitivity and lipid metabolism. Activation of PPARγ by *Morus alba* in this *in vivo* model also reduced expression of the inflammatory marker, monocyte chemoattractant protein-1 (MCP-1), mechanistic target of rapamycin (mTOR), and the transcription factor NF-κB, further corroborating the beneficial effects of *Morus alba* in metabolic disorders [127]. Furthermore, *Morus alba* leaves extract (300 mg) administered for 12 weeks significantly reduced CRP and malondialdehyde (MDA) levels, and significantly increased HDL-C in humans [125].

*Aquilaria sinensis* (Lour.) Spreng., from *Thymelaeaceae* family, also known as the agarwood tree, is used in traditional chinese medicine for its therapeutic properties. The tree is native to China, where it has long been valued for the production of agarwood, its resin secretion. However, the flowers of *Aquilaria sinensis* are gaining attention for their potential health benefits, particularly in the treatment of metabolic disorders [114]. Agarwood from Aquilaria sinensis at a dose of 75–150 mg/kg per day inhibits atherosclerosis progression in ApoE$^{-/-}$ mice under a HFD [128]. This could be due to the presence of bioactive compounds, including flavonoids, triterpenoids, and phenolic acids, that have been shown to regulate key modulators involved in lipid metabolism, such as PPARs and LXRs. These compounds indeed help to reduce TC levels, lower LDL-C, and increase HDL-C, positively impacting on CVD risk [129]. Most recently, the modulating effects of *Aquilaria sinensis* flowers extract on PPARs and LXRs were investigated. In particular, *in vitro* activation of PPARs by *Aquilaria sinensis* flowers extract promotes fatty acid catabolism and reduces fat accumulation, thereby improving insulin sensitivity and glucose uptake in differentiated myoblast cells [114]. In the same work, the flowers extract showed also to activate LXRs, an effect not associated with increased adipogenesis [114]. In addition, *Aquilaria sinensis* leaves and flowers extracts have been shown to have significant anti-inflammatory properties [114], probably due to the activity of the bioactive compounds present in the extracts on PPARs and LXRs, but this association still needs to be investigated.

*Magnolia* L. extract, derived primarily from the bark and flowers of the *Magnolia officinalis* tree, has been widely traditionally used for its therapeutic properties. Native to east Asia, the extract of this plant is rich in bioactive compounds, particularly honokiol and magnolol, which have been shown to have antioxidant, anti-inflammatory and lipid-regulating effects [143]. In recent years, research has focused on the potential of *Magnolia* extract to modulate lipid metabolism and its impact on key molecular targets involved in cholesterol homeostasis. In an *in vitro* model of macrophages, honokiol has been shown to activate LXRs, promoting cholesterol efflux and reducing intracellular cholesterol accumulation by regulating the expression of ABCA1 [69]. However, further research is needed to confirm its efficacy *in vivo*. Recently, *Magnolia* extract has been also investigated as a natural modulator of PCSK9. The components obovatolins-A and B and magnolol could

indeed downregulate PCSK9 expression in HepG2 cells [130]. Furthermore, *Magnolia* extract has demonstrated *in vivo* potent anti-inflammatory properties in rats. In detail, a single dose of *Magnolia officinalis* extract decreased the expression of IL-1β, cyclooxygenase-2 and nitric oxide synthase at 6 and 24 h post-treatment, suggesting that such extract could be an alternative preventive treatment for inflammatory diseases [131].

*Garcinia* L. is a tropical fruit native to Southeast Asia and India. Its fruit rind is a rich source of several bioactive compounds such as organic acids, amino acids, benzophenones, xanthones, and flavonoids [132]; the most relevant component is hydroxycitric acid (HCA), which is widely studied for its anti-atherogenic effect, as its hypolipidemic property [133]. HCA, by inhibiting ATP-citrate lyase, the enzyme involved in fatty acid and cholesterol synthesis, promotes a reduction in plasma lipid profile; as reported in a recent systematic review and meta-analysis, HCA reduced levels of TC (confidence interval (CI): $-12.39$ to $-0.59$, $p = 0.032$), and TG (CI: $-37.84$ to $-10.58$, $p < 0.001$), and increased plasma HDL-C levels (CI: 2.01 to 3.89, $p < 0.001$) [132, 133], probably due to the action of *Garcinia* on PPARs. In fact, in an *in vitro* study, treatment of HepG2 with Garcinia biflavonoid 1 (GB1), one of the active chemical components of *Garcinia kola*, increased the expression level of PPARα [134]. In addition to its metabolic benefits, *Garcinia* exhibits significant anti-inflammatory properties both *in vitro* and *in vivo* [132], thanks to the presence of bioactive compounds such as HCA, flavonoids, and benzophenones, by targeting pathways involving PPAR-γ and potentially LXRs. These findings position Garcinia as a promising natural intervention for managing obesity, metabolic syndrome, and associated inflammatory conditions. Several compounds isolated from *Garcinia cambogia* have also shown anti-inflammatory activity *in vitro*. Garcinol (5 μM) inhibited NF-κB and/or JAK/STAT-1 activation in lipopolysaccharide (LPS)-stimulated macrophages [135]. Interestingly, *in vivo* oral administration of 500 and 1000 mg/kg of an extract from the peel of the fruit containing 51.2 % HCA showed anti-inflammatory activity in a rat model of colitis, ameliorating macroscopic damage and causing a significant reduction in myeloperoxidase (MPO) activity and expression of cyclooxygenase (COX)-2 and iNOS. The extract also reduced IL-1β levels in the colon of rats without producing toxic effects [135].

With a long fossil history, algae are a widespread group of autotrophic organisms, which consist at least of 30,000 species [144]. They are found worldwide and in all climate zones, from cold polar regions to warm tropical waters. Algae are classified into three main groups: *Rhodophyceae* (red algae), *Phaeophyceae* (brown algae), and *Chlorophyceae* (green algae), each of which has specific nutritional, biological, and chemical characteristics. Brown algae are known to contain the highest amount of bioactive compounds [145] among which polysaccharides (e.g., alginate, fucoidan), proteins (e.g., phycobiliproteins), polyphenols (e.g., phlorotannins), carotenoids (e.g., fucoxanthin), phytosterols (e.g., fucosterol and 24S-saringosterol) and n-3 long-chain polyunsaturated fatty acids (e.g., eicosapentaenoic acid) [146]. Brown seaweed extracts have been shown to play an important anti-atherogenic role by regulating autophagy-mediated macrophage polarization [136], and playing a role in modulating lipid metabolism. In particular, a nutraceutical formulation containing an algal extract of *Ascophyllum nodosum* (L.) Le Jolis and *Fucus vesiculosus* (L.) (titled in 20 % of polyphenols) reduced mRNA levels of fatty acid synthase, diacylglycerol acyltransferases, the sterol-binding protein SREBP-1, and the lipid transporter perilipin-2, in rats with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) [137]. The regulation of lipid metabolism is strictly dependent on the activation of LXRs. Several marine-derived phytosteroids have indeed been reported as ligands of LXRs. Fucosterol and 24S-Saringosterol could promote the transactivation of both LXR isoforms, α and β. However, saringosterol from seaweed *Sargassum fusiforme* (Harv.) Setch., used for centuries in traditional medicine and known as "antiaging vegetable" [110], acts as a selective LXRβ agonist, making this extract a potential

anti-atherosclerotic strategy, without showing any potential adverse effects on liver fat content [138]. Brown seaweed extracts also modulate PPARs activity. The most potent activator of PPARα/γ transcriptional activity was the organic extract of the brown alga *Sargassum yezoense* (Yamada) Yoshida & T.Konno, as observed in 3T3-L1 cells. Additionally, the brown alga *Lessonia spicata* Bory de Saint-Vincent extract, because of its composition rich in polyunsaturated fatty acids, activated all the three PPARs isoforms [139]. In a recent *in vivo* work, the seaweed supplementation with *Himanthalia elongata* (L.) S.F. Gray (192 μg/g saringosterol and 3760 μg/g fucosterol), a brown seaweed species original from north Europe, and an extract of *Sargassum fusiforme* (304 μg/g saringosterol and 4797 μg/g fucosterol) administered for 12 weeks increased intracellular content of desmosterol, an LXR agonist with anti-inflammatory properties, and enhanced cholesterol efflux from THP-I macrophages [115]. The *Himanthalia elongata* extract also reduced pro-inflammatory cytokine production in LPS-stimulated macrophages [115].

### 3.4. Alpha-linolenic acid

Our discussion about lipid-lowering agents cannot be comprehensive without considering also alpha-linolenic acid (ALA), an essential fatty acid of the omega-3 series which can be mostly found in walnuts, flaxseed, vegetable oils, including sesame oil. Indeed, according to EFSA statement, dietary supplements with ALA carry out anti-atherosclerotic and cardioprotective effects potentially reducing the risk of CVD [147]. In this regard, a recent clinical trial highlighted that a long-term supplementation with walnuts entailed a significant reduction in LDL-C ($-9.07$ mg/dL (95 % CI: 12.87; $-5.73$); p = 0.010) in a healthy elder population [148]. The positive effect of ALA on CVD was observed also in a ApoE$^{-/-}$ mice subjected to a HFD supplemented with 5 % w/w flaxseed oil (containing 3.3 % w/w ALA-plant sterol) for 18 weeks, showing an improvement in atherosclerosis in terms of lipid profile and inflammation [149]. Similarly, a study conducted on mice under HFD showed a reduction in TG levels ($-15.67$ %) and LDL-C ($-10.02$ %), a downregulation of FAS and SREBP-1c, together with an increase in PPARα expression [150]. Mechanistically, it has been proved through an *in vitro* study on HepG2 cells that ALA is responsible of PPARα transactivation at concentrations ranging from 50 to 125 μM, that may explain the positive effect on lipid metabolism [151]. Nevertheless, it was demonstrated by another *in vitro* study on human macrophages that the activity of ALA on cholesterol homeostasis is independent from PPARα and ACAT expression, suggesting the need for further evaluations to better elucidate the molecular mechanism underpinning ALA's regulation of cholesterol homeostasis [152]. In addition, the beneficial effects of sesame oil containing ALA on atherosclerosis, with particular focus on the modulation of inflammatory biomarkers by regulating PGE2, NF-kB and PPARγ has been recently highlighted [153].

### 4. Conclusions

The use of dietary supplements and functional foods for the treatment of mild dyslipidemia is a preventive strategy that is nowadays supported by numerous studies and included in the most recent ESC/EAS guidelines for the management of CVD [39]. In this context, there is an increasingly active effort to identify new pharmacological targets whose modulation leads to the regulation of lipid metabolism, particularly cholesterol homeostasis and the reduction of the inflammatory state, both phenomena involved in the development and progression of atherosclerosis [8]. Indeed, a large body of *in vivo* evidence has shown that the modulation of PPARs and LXRs nuclear receptors, PCSK9, and inflammation are of particular interest [18,154,155]. PPARs are important regulators of lipogenesis and inflammation [14] and LXRs have an impact on atherosclerosis by modulating several genes involved in cholesterol metabolism, including efflux [23], the pathway opposing foam cell formation. PCSK9, beyond its hepatic function, exerts several

pleiotropic effects on macrophages, in particular the downregulation of ABCA1 expression, thus reducing cholesterol efflux, and the enhancement of the inflammatory response. This suggests a relevant influence of this protein in the pathogenesis of atherosclerosis [38]. For all these reasons, the targets described in this review provide an important starting point for the development of new therapeutic strategies based on the use of natural compounds. The consumption of foods rich in polyphenols, fundamental components of the Mediterranean diet, and alkaloids as well as extracts from terrestrial and marine plants, used for centuries in traditional chinese medicine, have always been known for their benefits on cardiovascular health, as demonstrated by numerous studies [26,43,76]. This review focused specifically on natural compounds that have been demonstrated to modulate PPARs and LXRs, the protein PCSK9 and inflammatory mediators, leading to anti-atherosclerotic effects [53,72], in order to offer novel plant-based pharmacological alternatives to current prevention and/or treatment strategies in CVD. However, the development of treatments based on natural compounds has some drawbacks, one of which is that natural products are available in limited quantities, depending on the yield of the plant and linked to the light and temperature conditions under which the vegetation grows [144]. In addition, there are also issues of stability and solubility of some naturally occurring molecules, which are characterised by poor bioavailability when administered as such *in vivo* [50]. In this context, new advanced and more efficient, sophisticated and accurate extraction methods together with the synthesis of compounds with structures that mimic naturally occurring compounds, represent good strategies to overcome these problems [23]. However, these aspects were not explored in this review. Finally, in regard to natural compounds efficacy, other important aspects that are worth considering are the characterization of the pharmacokinetic profiles of the natural compound or extract, with particular attention to metabolites formation [156] and the evaluation of clinical efficacy in placebo-controlled, double-blind studies. The phytochemicals included in this review represent a picture of the compounds of current scientific interest and, in our opinion, might represent an important starting point for the development of new strategies for anti-atherosclerotic prevention or treatment based on natural compounds.

### Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### References

[1] Nebuwa C, Omoike OJ, Fagbenro A, Uwumiro F, Erhus E, Okpujie V, et al. Rising cardiovascular Mortality Despite increased Resource utilization: Insights from the Nationwide Inpatient Sample database. Cureus 2024;16:e57856. https://doi.org/10.7759/cureus.57856.

[2] Quispe R, Michos ED, Martin SS, Puri R, Toth PP, Al Suwaidi J, et al. High-sensitivity C-reactive protein Discordance with atherogenic lipid Measures and incidence of atherosclerotic cardiovascular disease in primary prevention: the ARIC study. J Am Heart Assoc 2020;9:e013600. https://doi.org/10.1161/JAHA.119.013600.

[3] Botts SR, Fish JE, Howe KL. Dysfunctional vascular Endothelium as a driver of atherosclerosis: Emerging Insights into pathogenesis and treatment. Front Pharmacol 2021;12:787541. https://doi.org/10.3389/fphar.2021.787541.

[4] Yoon W, Kim E-J, Park Y, Kim S, Park Y-K, Yoo Y. Bacterially Delivered miRNA-mediated toll-like receptor 8 gene Silencing for combined therapy in a murine model of Atopic Dermatitis: therapeutic effect of miRTLR8 in AD. Microorganisms 2021;9. https://doi.org/10.3390/microorganisms9081715.

[5] Zhang B, Hao Z, Zhou W, Zhang S, Sun M, Li H, et al. Formononetin protects against ox-LDL-induced endothelial dysfunction by activating PPAR-γ signaling

based on network pharmacology and experimental validation. Bioengineered 2021;12:4887–98. https://doi.org/10.1080/21655979.2021.1959493.

[6] Qiao Y-N, Zou Y-L, Guo S-D. Low-density lipoprotein particles in atherosclerosis. Front Physiol 2022;13:931931. https://doi.org/10.3389/fphys.2022.931931.

[7] Yvan-Charvet L, Bonacina F, Guinamard RR, Norata GD. Immunometabolic function of cholesterol in cardiovascular disease and beyond. Cardiovasc Res 2019;115:1393–407. https://doi.org/10.1093/cvr/cvz127.

[8] Tekin IO, Orem A, Shiri-Sverdlov R. Oxidized LDL in inflammation: from bench to bedside. Mediators Inflamm 2013;2013:762759. https://doi.org/10.1155/2013/762759.

[9] Sun J, Yu L, Qu X, Huang T. The role of peroxisome proliferator-activated receptors in the tumor microenvironment, tumor cell metabolism, and anticancer therapy. Front Pharmacol 2023;14:1184794. https://doi.org/10.3389/fphar.2023.1184794.

[10] Gross B, Pawlak M, Lefebvre P, Staels B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. Nat Rev Endocrinol 2017;13:36–49. https://doi.org/10.1038/nrendo.2016.135.

[11] Miao M, Wang X, Liu T, Li Y-J, Yu W-Q, Yang T-M, et al. Targeting PPARs for therapy of atherosclerosis: a review. Int J Biol Macromol 2023;242:125008. https://doi.org/10.1016/j.ijbiomac.2023.125008.

[12] Corrales P, Vidal-Puig A, Medina-Gómez G. PPARs and metabolic disorders associated with Challenged adipose tissue Plasticity. Int J Mol Sci 2018;19. https://doi.org/10.3390/ijms19072124.

[13] Wang M, Xiang Q, Sun W, Zhang H, Shi R, Guo J, et al. Qihuang Zhuyu formula attenuates atherosclerosis via targeting PPARγ to regulate cholesterol efflux and endothelial cell inflammation. Oxid Med Cell Longev 2022;2022:2226168. https://doi.org/10.1155/2022/2226168.

[14] Hinds TDJ, Kipp ZA, Xu M, Yiannikouris FB, Morris AJ, Stec DF, et al. Adipose-specific PPARα knockout mice have increased lipogenesis by PASK-SREBP1 signaling and a polarity Shift to inflammatory macrophages in white adipose tissue. Cells 2021;11. https://doi.org/10.3390/cells11010004.

[15] Yang X, Wang J, Chang C-Y, Zhou F, Liu J, Xu H, et al. Leukemia inhibitory factor suppresses hepatic de novo lipogenesis and induces cachexia in mice. Nat Commun 2024;15:627. https://doi.org/10.1038/s41467-024-44924-w.

[16] Koga T, Peters JM. Targeting peroxisome proliferator-activated receptor-β/δ (PPARβ/δ) for the treatment or prevention of alcoholic liver disease. Biol Pharm Bull 2021;44:1598–606. https://doi.org/10.1248/bpb.b21-00486.

[17] Cheang WS, Tian XY, Wong WT, Huang Y. The peroxisome proliferator-activated receptors in cardiovascular diseases: experimental benefits and clinical challenges. Br J Pharmacol 2015;172:5512–22. https://doi.org/10.1111/bph.13029.

[18] Mirza AZ, Althagafi II, Shamshad H. Role of PPAR receptor in different diseases and their ligands: physiological importance and clinical implications. Eur J Med Chem 2019;166:502–13. https://doi.org/10.1016/j.ejmech.2019.01.067.

[19] Savla SR, Prabhavalkar KS, Bhatt LK. Liver X receptor: a potential target in the treatment of atherosclerosis. Expert Opin Ther Targets 2022;26:645–58. https://doi.org/10.1080/14728222.2022.2117610.

[20] Dixon ED, Nardo AD, Claudel T, Trauner M. The role of lipid sensing nuclear receptors (PPARs and LXR) and metabolic Lipases in obesity, diabetes and NAFLD. Genes 2021;12. https://doi.org/10.3390/genes12050645.

[21] Tavazoie MF, Pollack I, Tanqueco R, Ostendorf BN, Reis BS, Gonsalves FC, et al. LXR/ApoE activation restricts Innate Immune suppression in cancer. Cell 2018; 172:825–840.e18. https://doi.org/10.1016/j.cell.2017.12.026.

[22] Kang J, Rivest S. Lipid metabolism and neuroinflammation in Alzheimer's disease: a role for liver X receptors. Endocr Rev 2012;33:715–46. https://doi.org/10.1210/er.2011-1049.

[23] Zhan N, Wang B, Martens N, Liu Y, Zhao S, Voortman G, et al. Identification of side chain oxidized sterols as novel liver X receptor agonists with therapeutic potential in the treatment of cardiovascular and Neurodegenerative diseases. Int J Mol Sci 2023;24. https://doi.org/10.3390/ijms24021290.

[24] Zhang Y, Breevoort SR, Angdisen J, Fu M, Schmidt DR, Holmstrom SR, et al. Liver LXRα expression is crucial for whole body cholesterol homeostasis and reverse cholesterol transport in mice. J Clin Invest 2012;122:1688–99. https://doi.org/10.1172/JCI59817.

[25] Lo Sasso G, Murzilli S, Salvatore L, D'Errico I, Petruzzelli M, Conca P, et al. Intestinal specific LXR activation stimulates reverse cholesterol transport and protects from atherosclerosis. Cell Metab 2010;12:187–93. https://doi.org/10.1016/j.cmet.2010.07.002.

[26] Zhang Y, Zhang XY, Shi SR, Ma CN, Lin YP, Song WG, et al. Natural products in atherosclerosis therapy by targeting PPARs: a review focusing on lipid metabolism and inflammation. Front Cardiovasc Med 2024;11. https://doi.org/10.3389/fcvm.2024.1372055.

[27] Domínguez-Avila JA. Dietary phenolic compounds exert some of their health-promoting Bioactivities by targeting liver X receptor (LXR) and retinoid X receptor (RXR). Foods 2023;12. https://doi.org/10.3390/foods12234205.

[28] Catapano AL, Pirillo A, Norata GD. New pharmacological approaches to target PCSK9. Curr Atheroscler Rep 2020;22:24. https://doi.org/10.1007/s11883-020-00847-7.

[29] Ogura M. PCSK9 inhibition in the management of familial hypercholesterolemia. J Cardiol 2018;71:1–7. https://doi.org/10.1016/j.jjcc.2017.07.002.

[30] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after Acute coronary syndrome. N Engl J Med 2018; 379:2097–107. https://doi.org/10.1056/NEJMoa1801174.

[31] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22. https://doi.org/10.1056/NEJMoa1615664.

[32] Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two Phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med 2020; 382:1507–19. https://doi.org/10.1056/NEJMoa1912387.

[33] Grześk G, Dorota B, Wołowiec Ł, Wołowiec A, Osiak J, Kozakiewicz M, et al. Safety of PCSK9 inhibitors. Biomed Pharmacother 2022;156:113957. https://doi.org/10.1016/j.biopha.2022.113957.

[34] Li S, Guo Y-L, Xu R-X, Zhang Y, Zhu C-G, Sun J, et al. Association of plasma PCSK9 levels with white blood cell count and its subsets in patients with stable coronary artery disease. Atherosclerosis 2014;234:441–5. https://doi.org/10.1016/j.atherosclerosis.2014.04.001.

[35] Ricci C, Ruscica M, Camera M, Rossetti L, Macchi C, Colciago A, et al. PCSK9 induces a pro-inflammatory response in macrophages. Sci Rep 2018;8:2267. https://doi.org/10.1038/s41598-018-20425-x.

[36] Tang Z, Jiang L, Peng J, Ren Z, Wei D, Wu C, et al. PCSK9 siRNA suppresses the inflammatory response induced by oxLDL through inhibition of NF-κB activation in THP-1-derived macrophages. Int J Mol Med 2012;30:931–8. https://doi.org/10.3892/ijmm.2012.1072.

[37] Ding Z, Pothineni NVK, Goel A, Lüscher TF, Mehta JL. PCSK9 and inflammation: role of shear stress, pro-inflammatory cytokines, and LOX-1. Cardiovasc Res 2020;116:908–15. https://doi.org/10.1093/cvr/cvz313.

[38] Pia M, Cipollari E, Favari E, Zanotti I, Zimetti F, Corsini A, et al. Inhibitory effect of PCSK9 on Abca1 protein expression and cholesterol ef fl ux in macrophages. Atherosclerosis 2017;256:1–6. https://doi.org/10.1016/j.atherosclerosis.2016.11.019.

[39] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2019;41:111–88. https://doi.org/10.1093/eurheartj/ehz455. 2020.

[40] Tang Y. Editorial: nutraceuticals. Curr Opin Pharmacol 2022;66:102265. https://doi.org/10.1016/j.coph.2022.102265.

[41] Biagi M, Pecorari R, Appendino G, Miraldi E, Magnano AR, Governa P, et al. Herbal products in Italy: the Thin line between Phytotherapy, nutrition and Parapharmaceuticals; A Normative overview of the Fastest growing market in Europe. Pharmaceuticals 2016;9. https://doi.org/10.3390/ph9040065.

[42] Singh S, Sharma H, Ramankutty R, Ramaswamy S, Agrawal N. Natural proprotein convertase subtilisin/kexin type 9 inhibitors: a review. Comb Chem High Throughput Screen 2023;26:2668–78. https://doi.org/10.2174/1386207326666230627122630.

[43] Potì F, Santi D, Spaggiari G, Zimetti F, Zanotti I. Polyphenol health effects on cardiovascular and Neurodegenerative disorders: a review and meta-analysis. Int J Mol Sci 2019;20. https://doi.org/10.3390/ijms20020351.

[44] Zanotti I, Dall'Asta M, Mena P, Mele L, Bruni R, Ray S, et al. Atheroprotective effects of (poly)phenols: a focus on cell cholesterol metabolism. Food Funct 2015; 6:13–31. https://doi.org/10.1039/c4fo00670d.

[45] Campos-Cervantes A, Murillo-Ortiz B, Alvarado-Caudillo Y, Perez-Vazquez V, RamírezEmiliano J. Curcumin decreases the oxidative damage Indexes and increases the Adiponectin levels in serum of obese Subjects. Free Radic Biol Med - Free Radic BIOL MED 2011;51. https://doi.org/10.1016/j.freeradbiomed.2011.10.463.

[46] Majeed ML, Ghafil FA, Fatima G, Hadi NR, Mahdi HF. Anti-atherosclerotic and anti-inflammatory effects of curcumin on hypercholesterolemic male rabbits. Indian J Clin Biochem 2021;36:74–80. https://doi.org/10.1007/s12291-019-00858-5.

[47] Wang D, Hiebl V, Xu T, Ladurner A, Atanasov AG, Heiss EH, et al. Impact of natural products on the cholesterol transporter ABCA1. J Ethnopharmacol 2020; 249:112444. https://doi.org/10.1016/j.jep.2019.112444.

[48] Tai MH, Chen PK, Chen PY, Wu MJ, Ho CT, Yen JH. Curcumin enhances cell-surface LDLR level and promotes LDL uptake through downregulation of PCSK9 gene expression in HepG2 cells. Mol Nutr Food Res 2014;58:2133–45. https://doi.org/10.1002/mnfr.201400366.

[49] Singh L, Sharma X, Xu S, Tewari D, Fang J. Curcumin as a natural remedy for atherosclerosis: a pharmacological review. Molecules 2021;26:1–14. https://doi.org/10.3390/molecules26134036.

[50] Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The essential medicinal Chemistry of curcumin. J Med Chem 2017;60:1620–37. https://doi.org/10.1021/acs.jmedchem.6b00975.

[51] Grafeneder J, Derhaschnig U, Eskandary F, Buchtele N, Sus N, Frank J, et al. Micellar curcumin: pharmacokinetics and effects on inflammation markers and PCSK-9 concentrations in healthy Subjects in a double-blind, randomized, active-controlled, Crossover trial. Mol Nutr Food Res 2022;66:1–9. https://doi.org/10.1002/mnfr.202200139.

[52] Santana TM, Ogawa LY, Rogero MM, Barroso LP, Alves de Castro I. Effect of resveratrol supplementation on biomarkers associated with atherosclerosis in humans. Complement Ther Clin Pract 2022;46:101491. https://doi.org/10.1016/j.ctcp.2021.101491.

[53] Jing Y, Hu T, Yuan J, Liu Z, Tao M, Ou M, et al. Resveratrol protects against postmenopausal atherosclerosis progression through reducing PCSK9 expression via the regulation of the ERα-mediated signaling pathway. Biochem Pharmacol 2023;211:115541. https://doi.org/10.1016/j.bcp.2023.115541.

[54] Brenjian S, Moini A, Yamini N, Kashani L, Faridmojtahedi M, Bahramrezaie M, et al. Resveratrol treatment in patients with polycystic ovary syndrome decreased pro-inflammatory and endoplasmic reticulum stress markers. Am J Reprod Immunol 2020;83:1–10. https://doi.org/10.1111/aji.13186.

[55] Suzuki-Sugihara N, Kishimoto Y, Saita E, Taguchi C, Kobayashi M, Ichitani M, et al. Green tea catechins prevent low-density lipoprotein oxidation via their

accumulation in low-density lipoprotein particles in humans. Nutr Res 2016;36: 16–23. https://doi.org/10.1016/j.nutres.2015.10.012.

[56] Kanu VR, Pulakuntla S, Kuruvalli G, Aramgam SL, Marthadu SB, Pannuru P, et al. Anti-atherogenic role of green tea (Camellia sinensis) in South Indian smokers. J Ethnopharmacol 2024;332:118298. https://doi.org/10.1016/j.jep.2024.118298.

[57] Zanka K, Kawaguchi Y, Okada Y, Nagaoka S. Epigallocatechin gallate induces upregulation of LDL receptor via the 67 kDa laminin receptor-independent pathway in HepG2 cells. Mol Nutr Food Res 2020;64:1–7. https://doi.org/10.1002/mnfr.201901036.

[58] Cui CJ, Jin JL, Guo LN, Sun J, Wu NQ, Guo YL, et al. Beneficial impact of epigallocatechingallate on LDL-C through PCSK9/LDLR pathway by blocking HNF1α and activating FoxO3a. J Transl Med 2020;18:1–13. https://doi.org/10.1186/s12967-020-02362-4.

[59] Waiz M, Alvi SS, Salman Khan M. Potential dual inhibitors of Pcsk-9 and Hmg-R from natural sources in cardiovascular risk management. EXCLI J 2022;21:47–76. https://doi.org/10.17179/excli2021-4453.

[60] Kokabiyan Z, Yaghmaei P, Jameie SB, Hajebrahimi Z. Effect of eugenol on lipid profile, oxidative stress, sex hormone, liver injury, ovarian failure, and expression of COX-2 and PPAR-α genes in a rat model of diabetes. Mol Biol Rep 2023;50: 3669–79. https://doi.org/10.1007/s11033-022-08108-3.

[61] Zia S, Batool S, Shahid R. Could PCSK9 be a new therapeutic target of Eugenol? In vitro and in silico resolution of hypothesis. Med Hypotheses 2020;136:109513. https://doi.org/10.1016/j.mehy.2019.109513.

[62] Wang X, Yang S, Li Y, Jin X, Lu J, Wu M. Role of emodin in atherosclerosis and other cardiovascular diseases: pharmacological effects, mechanisms, and potential therapeutic target as a phytochemical. Biomed Pharmacother 2023;161: 114539. https://doi.org/10.1016/j.biopha.2023.114539.

[63] Wu L, Wang X, Jiang J, Chen Y, Peng B, Jin W. Mechanism of rhubarb in the treatment of hyperlipidemia: a recent review. Open Med 2023;18. https://doi.org/10.1515/med-2023-0812.

[64] He LF, Wang C, Zhang YF, Guo CC, Wan Y, Li YX. Effect of emodin on hyperlipidemia and hepatic lipid metabolism in zebrafish Larvae fed a high-cholesterol diet**. Chem Biodivers 2022;19. https://doi.org/10.1002/cbdv.202100675.

[65] Su Z li, zhou Hang P, Hu J, Zheng Y yang, qi Sun H, Guo J, et al. Aloe-emodin exerts cholesterol-lowering effects by inhibiting proprotein convertase subtilisin/kexin type 9 in hyperlipidemic rats. Acta Pharmacol Sin 2020;41:1085–92. https://doi.org/10.1038/s41401-020-0392-8.

[66] Meng C, Zhou L, Huang L, Gu Q, Du X, Wang C, et al. Chlorogenic acid regulates the expression of NPC1L1 and HMGCR through PXR and SREBP2 signaling pathways and their interactions with HSP90 to maintain cholesterol homeostasis. Phytomedicine 2024;123. https://doi.org/10.1016/j.phymed.2023.155271.

[67] Surma S, Sahebkar A, Banach M. Coffee or tea: anti-inflammatory properties in the context of atherosclerotic cardiovascular disease prevention. Pharmacol Res 2023;187. https://doi.org/10.1016/j.phrs.2022.106596.

[68] Liu F, Shan S, Li H, Shi J, Hao R, Yang R, et al. Millet shell polyphenols prevent atherosclerosis by protecting the gut barrier and remodeling the gut microbiota in ApoE(-/-) mice. Food Funct 2021;12:7298–309. https://doi.org/10.1039/d1fo00991e.

[69] She J, Gu T, Pang X, Liu Y, Tang L, Zhou X. Natural products targeting liver X receptors or farnesoid X receptor. Front Pharmacol 2022;12:1–42. https://doi.org/10.3389/fphar.2021.772435.

[70] Shehnaz SI, Roy A, Vijayaraghavan R, Sivanesan S. Luteolin Mitigates diabetic dyslipidemia in rats by modulating ACAT-2, PPARα, SREBP-2 proteins, and oxidative stress. Appl Biochem Biotechnol 2023;195:4893–914. https://doi.org/10.1007/s12010-023-04544-4.

[71] Adorni MP, Zimetti F, Lupo MG, Ruscica M, Ferri N. Naturally occurring PCSK9 inhibitors. Nutrients 2020;12. https://doi.org/10.3390/nu12051440.

[72] Burke AC, Sutherland BG, Telford DE, Morrow MR, Sawyez CG, Edwards JY, et al. Naringenin enhances the regression of atherosclerosis induced by a chow diet in Ldlr(-/-) mice. Atherosclerosis 2019;286:60–70. https://doi.org/10.1016/j.atherosclerosis.2019.05.009.

[73] Zhao R, Xiao H, Jin T, Xu F, Li Y, Li H, et al. Naringenin promotes cell autophagy to improve high-fat-diet-induced atherosclerosis in ApoE-/- mice. Brazilian J Med Biol Res = Rev Bras Pesqui Medicas e Biol 2021;54:e9764. https://doi.org/10.1590/1414-431X20209764.

[74] Yang Y, Trevethan M, Wang S, Zhao L. Beneficial effects of citrus flavanones naringin and naringenin and their food sources on lipid metabolism: an update on bioavailability, pharmacokinetics, and mechanisms. J Nutr Biochem 2022;104: 1–27. https://doi.org/10.1016/j.jnutbio.2022.108967.

[75] shan Li S, Cao H, Shen D zhu, Chen C, Xing S li, fang Dou F, et al. Effect of quercetin on atherosclerosis based on expressions of ABCA1, LXR-α and PCSK9 in ApoE-/- mice. Chin J Integr Med 2020;26:114–21. https://doi.org/10.1007/s11655-019-2942-9.

[76] Wang S, Yuan R, Liu M, Zhang Y, Jia B, Ruan J, et al. Targeting autophagy in atherosclerosis: advances and therapeutic potential of natural bioactive compounds from herbal medicines and natural products. Biomed Pharmacother 2022;155:113712. https://doi.org/10.1016/j.biopha.2022.113712.

[77] Cao H, Jia Q, Yan L, Chen C, Xing S, Shen D. Quercetin suppresses the progression of atherosclerosis by regulating MST1-mediated autophagy in ox-LDL-induced RAW264.7 macrophage foam cells. Int J Mol Sci 2019;20. https://doi.org/10.3390/ijms20236093.

[78] Huwait EA, Saddeek SY, Al-Massabi RF, Almowallad SJ, Pushparaj PN, Kalamegam G. Antiatherogenic effects of quercetin in the THP-1 macrophage

model in vitro, with Insights into its signaling mechanisms using in silico analysis. Front Pharmacol 2021;12:1–14. https://doi.org/10.3389/fphar.2021.698138.

[79] Das D, Banerjee A, Mukherjee S, Maji BK. Quercetin inhibits NF-kB and JAK/STAT signaling via modulating TLR in thymocytes and splenocytes during MSG-induced immunotoxicity: an in vitro approach. Mol Biol Rep 2024;51:1–13. https://doi.org/10.1007/s11033-024-09245-7.

[80] Hasnat H, Shompa SA, Islam MM, Alam S, Richi FT, Emon NU, et al. Flavonoids: a treasure house of prospective pharmacological potentials. Heliyon 2024;10: e27533. https://doi.org/10.1016/j.heliyon.2024.e27533.

[81] Hsu MC, Guo BC, Chen CH, Hu PA, Lee TS. Apigenin ameliorates hepatic lipid accumulation by activating the autophagy-mitochondria pathway. J Food Drug Anal 2021;29:240–54. https://doi.org/10.38212/2224-6614.3269.

[82] Al-Khayri JM, Sahana GR, Nagella P, Joseph BV, Alessa FM, Al-Mssallem MQ. Flavonoids as potential anti-inflammatory molecules: a review. Molecules 2022; 27. https://doi.org/10.3390/molecules27092901.

[83] Yang L, Zhao M, Liu M, Zhang W, Zhi S, Qu L, et al. Effects of genistein on lipid metabolism, antioxidant activity, and Immunity of common Carp (Cyprinus carpio L.) fed with high-carbohydrate and high-fat diets. Aquac Nutr 2023;2023. https://doi.org/10.1155/2023/9555855.

[84] Luo T, Miranda-Garcia O, Sasaki G, Wang J, Shay NF. Genistein and daidzein decrease food intake and body weight gain in mice, and alter LXR signaling: in vivo and in vitro. Food Funct 2018;9:6257–67. https://doi.org/10.1039/c8fo01718b.

[85] Xu L, Liu J tian, Li K, Wang S yu, Xu S. Genistein inhibits Ang II-induced CRP and MMP-9 generations via the ER-p38/ERK1/2-PPARγ-NF-κB signaling pathway in rat vascular smooth muscle cells. Life Sci 2019;216:140–6. https://doi.org/10.1016/j.lfs.2018.11.036.

[86] Khayatan D, Zare K, Khanahmadi M, Momtaz S, Butler AE, Jamialahmadi T, et al. The role of natural products as PCSK9 modulators: a review. Phyther Res 2024: 4081–98. https://doi.org/10.1002/ptr.8260.

[87] Shafabakhsh R, Reiner Ž, Hallajzadeh J, Mirsafaei L, Asemi Z. Are anti-inflammatory agents and nutraceuticals - novel inhibitors of PCSK9? Crit Rev Food Sci Nutr 2021;61:325–36. https://doi.org/10.1080/10408398.2020.1731678.

[88] Mehmood S, Maqsood M, Mahtab N, Khan MI, Sahar A, Zaib S, et al. Epigallocatechin gallate: Phytochemistry, bioavailability, utilization challenges, and strategies. J Food Biochem 2022;46:e14189. https://doi.org/10.1111/jfbc.14189.

[89] Governa P, Manetti F, Miraldi E, Biagi M. Effects of in vitro simulated digestion on the antioxidant activity of different Camellia sinensis (L.) Kuntze leaves extracts. Eur Food Res Technol 2022;248:119–28. https://doi.org/10.1007/s00217-021-03864-1.

[90] Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, Filipič M, et al. Scientific opinion on the safety of green tea catechins. EFSA Journal Eur Food Saf Auth 2018;16:e05239. https://doi.org/10.2903/j.efsa.2018.5239.

[91] National Institute of Diabetes and Digestive and Kidney Diseases. In: LiverTox: clinical and research information on drug-induced liver injury [Internet]; 2012. Bethesda, Maryland.

[92] Younes M, Aggett P, Aguilar F, Crebelli R, Filipič M, Frutos MJ, et al. Safety of hydroxyanthracene derivatives for use in food. EFSA Journal Eur Food Saf Auth 2018;16:e05090. https://doi.org/10.2903/j.efsa.2018.5090.

[93] Li S, Liu P, Feng X, Wang Y, Du M, Wang J. The role and mechanism of tetramethylpyrazine for atherosclerosis in animal models: a systematic review and meta-analysis. PLoS One 2022;17:e0267968. https://doi.org/10.1371/journal.pone.0267968.

[94] Chen J, Tian J, Ge H, Liu R, Xiao J. Effects of tetramethylpyrazine from Chinese black vinegar on antioxidant and hypolipidemia activities in HepG2 cells. Food Chem Toxicol an Int J Publ Br Ind Biol Res Assoc 2017;109:930–40. https://doi.org/10.1016/j.fct.2016.12.017.

[95] Li H, Yang M. Ligustrazine activate the PPAR-γ pathway and play a protective role in vascular calcification. Vascular 2022;30:1224–31. https://doi.org/10.1177/17085381211051477.

[96] Lei J, Xiang P, Zeng S, Chen L, Zhang L, Yuan Z, et al. Tetramethylpyrazine Alleviates endothelial Glycocalyx degradation and promotes Glycocalyx Restoration via TLR4/NF-κB/HPSE1 signaling pathway during inflammation. Front Pharmacol 2021;12:791841. https://doi.org/10.3389/fphar.2021.791841.

[97] Hernandez AV, Hwang J, Nasreen I, Sicignano D, Pasupuleti V, Snow-Caroti K, et al. Impact of berberine or berberine combination products on lipoprotein, triglyceride and biological safety marker concentrations in patients with hyperlipidemia: a systematic review and meta-analysis. J Diet Suppl 2024;21: 242–59. https://doi.org/10.1080/19390211.2023.2212762.

[98] Ma C-Y, Shi X-Y, Wu Y-R, Zhang Y, Yao Y-H, Qu H-L, et al. Berberine attenuates atherosclerotic lesions and hepatic steatosis in ApoE(-/-) mice by down-regulating PCSK9 via ERK1/2 pathway. Ann Transl Med 2021;9:1517. https://doi.org/10.21037/atm-20-8106.

[99] Zimetti F, Adorni MP, Ronda N, Gatti R, Bernini F, Favari E. The natural compound berberine positively affects macrophage functions involved in atherogenesis. Nutr Metab Cardiovasc Dis 2015;25:195–201. https://doi.org/10.1016/j.numecd.2014.08.004.

[100] Sharma S, Sharma D, Dhobi M, Wang D, Tewari D. An insight to treat cardiovascular diseases through phytochemicals targeting PPAR-α. Mol Cell Biochem 2024;479:707–32. https://doi.org/10.1007/s11010-023-04755-7.

[101] Zhou M-X, Xu H, Chen K-J. [Effect of Coptis root extract on gene expressions of perilipin and PPAR-gamma in aortic vulnerable atherosclerotic plaque of ApoE-gene knockout mice]. Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chinese J Integr Tradit West Med 2008;28:532–6.

[102] Dong B, Li H, Singh AB, Cao A, Liu J. Inhibition of PCSK9 transcription by berberine involves down-regulation of hepatic HNF1α protein expression through the ubiquitin-proteasome degradation pathway. J Biol Chem 2015;290:4047–58. https://doi.org/10.1074/jbc.M114.597229.

[103] Adorni MP, Ferri N, Marchianò S, Trimarco V, Rozza F, Izzo R, et al. Effect of a novel nutraceutical combination on serum lipoprotein functional profile and circulating PCSK9. Ther Clin Risk Manag 2017;13:1555–62. https://doi.org/10.2147/TCRM.S144121.

[104] Chen L, Fan X-D, Qu H, Bai R-N, Shi D-Z. Berberine protects against TNF-α-Induced injury of human Umbilical Vein endothelial cells via the AMPK/NF-κB/YY1 signaling pathway. Evid Based Complement Alternat Med 2021;2021:6518355. https://doi.org/10.1155/2021/6518355.

[105] Lv Y, Yang H, Ye P, Qian Z, Wang D, Kong C, et al. Berberine inhibits low shear stress-induced vascular endothelial inflammation via decreasing phosphorylation of Akt and IRF3. Tissue Cell 2022;79:101946. https://doi.org/10.1016/j.tice.2022.101946.

[106] Lebeau PF, Byun JH, Platko K, Saliba P, Sguazzin M, MacDonald ME, et al. Caffeine blocks SREBP2-induced hepatic PCSK9 expression to enhance LDLR-mediated cholesterol clearance. Nat Commun 2022;13. https://doi.org/10.1038/s41467-022-28240-9.

[107] Ko J, Kim J-Y, Kim J-W, Yoon JS. Anti-oxidative and anti-adipogenic effects of caffeine in an in vitro model of Graves' orbitopathy. Endocr J 2020;67:439–47. https://doi.org/10.1507/endocrj.EJ19-0521.

[108] Wei D, Wu S, Liu J, Zhang X, Guan X, Gao L, et al. Theobromine ameliorates nonalcoholic fatty liver disease by regulating hepatic lipid metabolism via mTOR signaling pathway in vivo and in vitro. Can J Physiol Pharmacol 2021;99:775–85. https://doi.org/10.1139/cjpp-2020-0259.

[109] Rigillo G, Cappellucci G, Baini G, Vaccaro F, Miraldi E, Pani L, et al. Comprehensive analysis of Berberis aristata DC. Bark extracts: in vitro and in silico evaluation of bioaccessibility and safety. Nutrients 2024;16. https://doi.org/10.3390/nu16172953.

[110] Chen Z, Liu J, Fu Z, Ye C, Zhang R, Song Y, et al. 24(S)-Saringosterol from edible marine seaweed Sargassum fusiforme is a novel selective LXRβ agonist. J Agric Food Chem 2014;62:6130–7. https://doi.org/10.1021/jf500083r.

[111] Li L, Bonneton F, Chen XY, Laudet V. Botanical compounds and their regulation of nuclear receptor action: the case of traditional Chinese medicine. Mol Cell Endocrinol 2015;401:221–37. https://doi.org/10.1016/j.mce.2014.10.028.

[112] Feng X, Sureda A, Jafari S, Memariani Z, Tewari D, Annunziata G, et al. Berberine in cardiovascular and metabolic diseases: from mechanisms to therapeutics. Theranostics 2019;9:1923–51. https://doi.org/10.7150/thno.30787.

[113] Carazo A, Mladěnka P, Pávek P. Marine ligands of the pregnane X receptor (PXR): an overview. Mar Drugs 2019;17. https://doi.org/10.3390/md17100554.

[114] Chae H-S, Dale O, Mir TM, Avula B, Zhao J, Khan IA, et al. A Multitarget approach to evaluate the efficacy of Aquilaria sinensis flower extract against metabolic syndrome. Molecules 2022;27. https://doi.org/10.3390/molecules27030629.

[115] Martens N, Zhan N, Yam SC, Leijten FPJ, Palumbo M, Caspers M, et al. Supplementation of seaweed extracts to the diet reduces Symptoms of Alzheimer's disease in the APPswePS1ΔE9 mouse model. Nutrients 2024;16. https://doi.org/10.3390/nu16111614.

[116] de Lima LP, de Paula Barbosa A. A review of the lipolytic effects and the reduction of abdominal fat from bioactive compounds and moro orange extracts. Heliyon 2021;7:e07695. https://doi.org/10.1016/j.heliyon.2021.e07695.

[117] Montalbano G, Mania M, Guerrera MC, Laurà R, Abbate F, Levanti M, et al. Effects of a flavonoid-rich extract from citrus sinensis juice on a diet-induced obese zebrafish. Int J Mol Sci 2019;20. https://doi.org/10.3390/ijms20205116.

[118] Gandhi GR, Vasconcelos ABS, Wu D-T, Li H-B, Antony PJ, Li H, et al. Citrus flavonoids as promising phytochemicals targeting diabetes and related Complications: a systematic review of in vitro and in vivo studies. Nutrients 2020;12. https://doi.org/10.3390/nu12102907.

[119] Magalhães ML, de Sousa RV, Miranda JR, Konig IFM, Wouters F, Souza FR, et al. Effects of Moro orange juice (Citrus sinensis (l.) Osbeck) on some metabolic and morphological parameters in obese and diabetic rats. J Sci Food Agric 2021;101:1053–64. https://doi.org/10.1002/jsfa.10714.

[120] Di Folco U, Pollakova D, De Falco D, Nardone MR, Tubili F, Tubili C. Effects of a nutraceutical multicompound including bergamot (Citrus Bergamia Risso) juice on metabolic syndrome: a pilot study. Med J Nutrition Metab 2018;11. https://doi.org/10.3233/MNM-17186. 119–26.

[121] Lamiquiz-Moneo I, Giné-González J, Alisente S, Bea AM, Pérez-Calahorra S, Marco-Benedí V, et al. Effect of bergamot on lipid profile in humans: a systematic review. Crit Rev Food Sci Nutr 2020;60:3133–43. https://doi.org/10.1080/10408398.2019.1677554.

[122] Ferrarese I, Giovanna Lupo M, Rossi I, Sut S, Loschi F, Allegrini P, et al. Bergamot (Citrus bergamia) peel extract as new hypocholesterolemic agent modulating PCSK9 expression. J Funct Foods 2023;108:105724. https://doi.org/10.1016/j.jff.2023.105724.

[123] Cho KW, Kim YO, Andrade JE, Burgess JR, Kim Y-C. Dietary naringenin increases hepatic peroxisome proliferators–activated receptor α protein expression and decreases plasma triglyceride and adiposity in rats. Eur J Nutr 2011;50:81–8. https://doi.org/10.1007/s00394-010-0117-8.

[124] Mollace R, Macrì R, Tavernese A, Gliozzi M, Musolino V, Carresi C, et al. Comparative effect of bergamot polyphenolic fraction and red yeast rice extract in rats fed a hyperlipidemic diet: role of antioxidant properties and PCSK9 expression. Nutrients 2022;14. https://doi.org/10.3390/nu14030477.

[125] Taghizadeh M, Mohammad Zadeh A, Asemi Z, Farrokhnezhad AH, Memarzadeh MR, Banikazemi Z, et al. Morus Alba leaf extract affects metabolic profiles, biomarkers inflammation and oxidative stress in patients with type 2 diabetes mellitus: a double-blind clinical trial. Clin Nutr ESPEN 2022;49:68–73. https://doi.org/10.1016/j.clnesp.2022.03.027.

[126] Lupo MG, Macchi C, Marchianò S, Cristofani R, Greco MF, Dall'Acqua S, et al. Differential effects of red yeast rice, Berberis aristata and Morus alba extracts on PCSK9 and LDL uptake. Nutr Metab Cardiovasc Dis 2019;29:1245–53. https://doi.org/10.1016/j.numecd.2019.06.001.

[127] Gurukar MSA, Chilkunda ND. Morus alba leaf bioactives modulate peroxisome proliferator activated receptor γ in the kidney of diabetic rat and Impart beneficial effect. J Agric Food Chem 2018;66:7923–34. https://doi.org/10.1021/acs.jafc.8b01357.

[128] Ma J, Wang L, Zhao Y, Gao Y, Yin Z, Zhao M, et al. 2-(2-Phenylethyl)chromone-enriched extract of Chinese agarwood (Aquilaria sinensis) inhibits atherosclerosis progression through endoplasmic reticulum stress-mediated CD36 expression in macrophages. J Ethnopharmacol 2024;320:117411. https://doi.org/10.1016/j.jep.2023.117411.

[129] Min L, Wang G, Tong X, Yang H, Sun H, Zhang Z, et al. Feeding Aquilaria sinensis leaves modulates lipid metabolism and improves the Meat Quality of Goats. Foods 2023;12. https://doi.org/10.3390/foods12030560.

[130] Aguchem RN, Okagu IU, Okorigwe EM, Uzoechina JO, Nnemolisa SC, Ezeorba TPC. Role of CETP, PCSK-9, and CYP7-alpha in cholesterol metabolism: potential targets for natural products in managing hypercholesterolemia. Life Sci 2024;351:122823. https://doi.org/10.1016/j.lfs.2024.122823.

[131] Vega-García A, Rocha L, Guevara-Guzmán R, Guerra-Araiza C, Feria-Romero I, Gallardo JM, et al. Magnolia officinalis reduces inflammation and damage induced by Recurrent status Epilepticus in Immature rats. Curr Pharm Des 2020;26:1388–401. https://doi.org/10.2174/1381612826666200320121813.

[132] Baky M H, Fahmy H, Farag MA. Recent advances in Garcinia cambogia nutraceuticals in relation to its hydroxy citric acid level. A comprehensive review of its bioactive production, formulation, and analysis with Future perspectives. ACS Omega 2022;7:25948–57. https://doi.org/10.1021/acsomega.2c02838.

[133] Amini MR, Rasaei N, Jalalzadeh M, Akhgarjand C, Hashemian M, Jalali P, et al. The effects of Garcinia cambogia (hydroxycitric acid) on lipid profile: a systematic review and meta-analysis of randomized controlled trials. Phytother Res 2024;38:1028–43. https://doi.org/10.1002/ptr.8102.

[134] Chen H-X, Yang F, He X-Q, Li T, Sun Y-Z, Song J-P, et al. Garcinia biflavonoid 1 improves lipid metabolism in HepG2 cells via regulating PPARα. Molecules 2022;27. https://doi.org/10.3390/molecules27061978.

[135] Semwal RB, Semwal DK, Vermaak I, Viljoen A. A comprehensive scientific overview of Garcinia cambogia. Fitoterapia 2015;102:134–48. https://doi.org/10.1016/j.fitote.2015.02.012.

[136] Li X-Y, Wang Y-J, Chen S, Pan L-H, Li Q-M, Luo J-P, et al. Laminaria japonica polysaccharide suppresses atherosclerosis via regulating autophagy-mediated macrophage polarization. J Agric Food Chem 2022;70:3633–43. https://doi.org/10.1021/acs.jafc.1c07483.

[137] Gabbia D, Roverso M, Zanotto I, Colognesi M, Sayaf K, Sarcognato S, et al. A nutraceutical formulation containing Brown algae reduces hepatic lipid accumulation by modulating lipid metabolism and inflammation in experimental models of NAFLD and NASH. Mar Drugs 2022;20. https://doi.org/10.3390/md20090572.

[138] Martens N, Schepers M, Zhan N, Leijten F, Voortman G, Tiane A, et al. 24(S)-Saringosterol prevents Cognitive decline in a mouse model for Alzheimer's disease. Mar Drugs 2021;19. https://doi.org/10.3390/md19040190.

[139] D'Aniello E, Amodeo P, Vitale RM. Marine natural and Nature-Inspired compounds targeting peroxisome proliferator activated receptors (PPARs). Mar Drugs 2023;21. https://doi.org/10.3390/md21020089.

[140] Gattuso A, Mafrica R, Cannavò S, Mafrica D, De Bruno A, Poiana M. Quality evaluation of bergamot juice produced in different Areas of Calabria region. Foods 2024;13. https://doi.org/10.3390/foods13132080.

[141] Peng D, Zhuge F, Wang M, Zhang B, Zhuang Z, Zhou R, et al. Morus alba L. (Sangzhi) alkaloids mitigate atherosclerosis by regulating M1/M2 macrophage polarization. Phytomedicine 2024;128:155526. https://doi.org/10.1016/j.phymed.2024.155526.

[142] Kim N-Y, Thomas SS, Hwang D-I, Lee J-H, Kim K-A, Cha Y-S. Anti-obesity effects of Morus alba L. and Aronia melanocarpa in a high-fat diet-induced obese C57BL/6J mouse model. Foods 2021;10. https://doi.org/10.3390/foods10081914.

[143] Chen D, Chen T, Chen Y, Zhang Z, Li B, Tian S. Bio-source substances against postharvest diseases of fruits: mechanisms, applications and perspectives. Postharvest Biol Technol 2023;198:112240. https://doi.org/10.1016/j.postharvbio.2023.112240.

[144] Vanbrabant K, Van Meel D, Kerksiek A, Friedrichs S, Dubbeldam M, Schepers M, et al. 24(R, S)-Saringosterol - from artefact to a biological medical agent. J Steroid Biochem Mol Biol 2021;212:105942. https://doi.org/10.1016/j.jsbmb.2021.105942.

[145] Keleszade E, Patterson M, Trangmar S, Guinan KJ, Costabile A. Clinical efficacy of Brown seaweeds Ascophyllum nodosum and Fucus vesiculosus in the prevention or Delay progression of the metabolic syndrome: a review of clinical trials. Molecules 2021;26. https://doi.org/10.3390/molecules26030714.

[146] Olsthoorn SEM, Wang X, Tillema B, Vanmierlo T, Kraan S, Leenen PJM, et al. Brown seaweed food supplementation: effects on Allergy and inflammation and its Consequences. Nutrients 2021;13. https://doi.org/10.3390/nu13082613.

[147] Bertoni C, Abodi M, D'Oria V, Milani GP, Agostoni C, Mazzocchi A. Alpha-linolenic acid and cardiovascular events: a Narrative review. Int J Mol Sci 2023;24. https://doi.org/10.3390/ijms241814319.

[148] Gil-Zamorano J, Cofán M, López de Las Hazas M-C, García-Blanco T, García-Ruiz A, Doménech M, et al. Interplay of walnut consumption, changes in

circulating miRNAs and reduction in LDL-cholesterol in elders. Nutrients 2022; 14. https://doi.org/10.3390/nu14071473.

[149] Han H, Yan P, Chen L, Luo C, Gao H, Deng Q, et al. Flaxseed oil containing α -linolenic acid ester of plant sterol improved atherosclerosis in ApoE Deficient mice. Oxid Med Cell Longev 2015;2015:958217. https://doi.org/10.1155/2015/958217.

[150] Wang Q, Wang X. The effects of a low linoleic acid/α-linolenic acid Ratio on lipid metabolism and Endogenous fatty acid distribution in obese mice. Int J Mol Sci 2023;24. https://doi.org/10.3390/ijms241512117.

[151] Popeijus HE, van Otterdijk SD, van der Krieken SE, Konings M, Serbonij K, Plat J, et al. Fatty acid chain length and saturation influences PPARα transcriptional activation and repression in HepG2 cells. Mol Nutr Food Res 2014;58:2342–9. https://doi.org/10.1002/mnfr.201400314.

[152] Zavar Reza J, Nahangi H, Mansouri R, Dehghani A, Mojarrad M, Fathi M, et al. The effect of Unsaturated fatty acids on molecular markers of cholesterol homeostasis in THP-1 macrophages. Iran Red Crescent Med J 2013;15:554–9. https://doi.org/10.5812/ircmj.11780.

[153] Hadipour E, Emami SA, Tayarani-Najaran N, Tayarani-Najaran Z. Effects of sesame (Sesamum indicum L.) and bioactive compounds (sesamin and sesamolin) on inflammation and atherosclerosis: a review. Food Sci Nutr 2023;11:3729–57. https://doi.org/10.1002/fsn3.3407.

[154] Goel D, Vohora D. Liver X receptors and skeleton: current state-of-knowledge. Bone 2021;144:115807. https://doi.org/10.1016/j.bone.2020.115807.

[155] Peng C, Li J, Chen Y, Zhang H-R, Li T-X, Jiang Y-H, et al. PCSK9 aggravated carotid artery stenosis in ApoE(-/-) mice by promoting the expression of tissue factors in endothelial cells via the TLR4/NF-κB pathway. Biochem Pharmacol 2024;225:116314. https://doi.org/10.1016/j.bcp.2024.116314.

[156] Favari C, Rinaldi de Alvarenga JF, Sánchez-Martínez L, Tosi N, Mignogna C, Cremonini E, et al. Factors driving the inter-individual variability in the metabolism and bioavailability of (poly)phenolic metabolites: a systematic review of human studies. Redox Biol 2024;71:103095. https://doi.org/10.1016/j.redox.2024.103095.