Current Applied Science and Technology e-ISSN: 2586-9396

Curr. Appl. Sci. Technol. ….., Vol... (No...), e0267568

Review article

Protein Targets and the Roles of Natural Compounds in the Treatment and Management of Hypercholesterolemia: A Comprehensive Review

Ja'far Umar[1,3], Turhadi Turhadi[1], Titin Andri Wihastuti[2] and Fatchiyah Fatchiyah[1,3]

[1]Biology Department, Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Malang, East Java, Indonesia
[2]Nursing Department, Faculty of Health Sciences, Universitas Brawijaya, Malang, East Java, Indonesia
[3]Research Center of Smart Molecule of Natural Genetics Resource, Universitas Brawijaya, Malang, East Java, Indonesia

Received: 11 May 2025, Revised: 29 July 2025, Accepted: 2 September 2025, Published: 14 May 2026

Abstract

Hypercholesterolemia, a condition characterized by elevated cholesterol levels, has been identified as a major risk factor for cardiovascular disease, which is recognized as the leading cause of mortality on a global scale. Whereas statins remain the cornerstone of pharmacological treatment for hypercholesterolemia, their long-term use is often limited by side effects such as myopathy and hepatotoxicity. Natural bioactive compounds derived from medicinal plants and foods have emerged as promising alternatives for treating hypercholesterolemia due to their multi-target mechanisms, reduced side effects, and wide availability. These compounds, including polyphenols, flavonoids, terpenoids, and plant sterols, have demonstrated efficacy in regulating major cholesterol metabolic pathways, such as reducing intestinal cholesterol absorption, inhibiting cholesterol synthesis, regulating transcription factors, and increasing cholesterol excretion. This review discusses the molecular mechanisms through which previous natural compounds regulate cholesterol homeostasis, focusing on their interactions with proteins such as HMGCR, NPC1L1, PCSK9, and the transcription factor SREBP-2.

Keywords: cardiovascular disease prevention; cholesterol metabolism; hypercholesterolemia; natural bioactive compounds; npc1l1 inhibition

1. Introduction

Hypercholesterolemia is characterized by elevated levels of cholesterol in the bloodstream. The disease constitutes a significant global health concern, given its strong association with cardiovascular disease (CVD) (Pirillo & Norata, 2023), the foremost cause of mortality worldwide (Vučević et al., 2016; Upadhyay, 2023). The prevalence of hypercholesterolemia

*Corresponding author: E-mail: fatchiya@ub.ac.id
https://doi.org/10.55003/cast.2026.267568
Copyright © 2024 by King Mongkut's Institute of Technology Ladkrabang, Thailand. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

continues to rise, driven by changing dietary patterns (Carson et al., 2020), increased consumption of processed foods rich in saturated fats (DiNicolantonio et al., 2016), sedentary lifestyles (Park et al., 2020), and the exacerbating global burden of metabolic disorders (Saklayen, 2018). This escalating trend underscores the necessity for effective prevention and treatment strategies that extend beyond conventional pharmacological approaches. In the absence of adequate management, hypercholesterolemia has been demonstrated to significantly contribute to the development of atherosclerosis, a condition that increases the risk of myocardial infarction, stroke, and other cardiovascular complications (Boudoulas et al., 2016; Alloubani et al., 2021).

Pharmacological interventions, most notably statins, have been widely implemented as the gold standard for the management of hypercholesterolemia, predicated on the proven efficacy of these medications in lowering *low-density lipoprotein cholesterol* (LDL-c) levels and, by extension, minimizing the risk of CVD (Bardolia et al., 2021; Mormone et al., 2024). Statins function by selectively inhibiting *3-hydroxy-3-methylglutaryl-CoA reductase* (HMGCR), the rate-limiting enzyme in cholesterol biosynthesis, thereby resulting in a reduction in hepatic cholesterol production (Gesto et al., 2020). Despite their effectiveness, statins are often associated with adverse effects, including myopathy (Ramkumar et al., 2016) and hepatotoxicity (Ward et al., 2019), which can limit their long-term use and patient compliance (Newman et al., 2019). Furthermore, a subset of patients exhibits statin intolerance or resistance (Mancini et al., 2016), requiring alternative therapeutic strategies to address hypercholesterolemia while minimizing adverse effects. These challenges highlight the pressing need for complementary or alternative interventions that are both safe and effective.

Natural bioactive compounds derived from food sources and medicinal plants have emerged as promising alternatives for hypercholesterolemia management (Hunter & Hegele, 2017). These compounds offer several advantages, including multitarget mechanisms (Makhoba et al., 2020), fewer side effects, broad availability, and potential synergistic interactions with conventional treatments (Chaachouay, 2025). Previous studies have demonstrated that various classes of natural compounds—such as polyphenols (Upadhyay & Dixit, 2015), phenolic acids, phytosterols, terpenoids (Sut & Dall'Acqua, 2023), plant sterols (Jayaraman et al., 2021), and bioactive peptides possess lipid documented biological activities. For example, polyphenols such as quercetin and curcumin have been shown to inhibit cholesterol absorption via modulation of intestinal transporters such as NPC1L1, while also suppressing cholesterol biosynthesis through downregulation of HMGCR expression (Zhao et al., 2018; Kobayashi, 2019). Phytosterols are structurally similar to cholesterol and compete with it for incorporation into mixed micelles, thereby reducing its intestinal absorption (Jayaraman et al., 2021). Notably, numerous in vivo and clinical studies have reported that these compounds significantly improve cholesterol profiles by reducing total cholesterol (TC), lowering low-density lipoprotein cholesterol (LDL-c), increasing high-density lipoprotein cholesterol (HDL-c), and decreasing triglyceride (TG) levels. For example, curcumin supplementation has been associated with a marked reduction in LDL-c and TG while increasing HDL-c in hyperlipidemic subjects (Panahi et al., 2018; Aldalou, 2021). Similarly, plant sterols and stanols have been shown to reduce LDL-c levels in both healthy and hypercholesterolemic individuals (Trautwein et al., 2018; Ruuth et al., 2020). These physiological effects strengthen the translational value of molecular findings and reinforce their potential application in cardiovascular disease prevention. The regulation of cholesterol homeostasis is a complex, tightly controlled process involving multiple pathways and molecular mediators (Luo et al., 2020; Kumar et al., 2024). Cholesterol metabolism is regulated by a series of key enzymes, transporters, and transcription factors. These include

HMGCR and 3-*hydroxy-3-methylglutaryl-CoA synthase 1* (HMGCS1), which play a pivotal role in de novo cholesterol synthesis (Kou et al., 2022); *Niemann-Pick C1-like 1* (NPC1L1), which is involved in intestinal absorption (Yamanashi et al., 2018); and *ATP-binding cassette, subfamily G member 5 and member 8* (ABCG5/G8), which facilitate cholesterol efflux (Wang et al., 2020). Furthermore, *sterol regulatory element-binding proteins* (SREBPs) govern lipid gene expression, while *proprotein convertase subtilisin/kexin type 9* (PCSK9) controls the degradation of *low-density lipoprotein receptor* (LDLR), affecting plasma LDL-c levels (Cesaro et al., 2020). Despite these findings, the molecular mechanisms underlying their effects have not been fully elucidated. Many bioactives affect core pathways involved in cholesterol homeostasis, including modulated inhibition of cholesterol absorption in the gut, hepatic cholesterol synthesis, and regulation of lipoprotein metabolism (Gianazza et al., 2023). A comprehensive understanding of the interaction between natural bioactive compounds and these pathways is imperative for optimizing their therapeutic potential and developing targeted interventions for hypercholesterolemia.

The present review aims to systematically investigate the target proteins and major molecular pathways involved in the regulation of cholesterol metabolism, which play a role in the pathogenesis of hypercholesterolemia. It also aims to review the findings of natural compounds that specifically inhibit target proteins, evaluating the cholesterol regulatory pathways most frequently targeted for therapy. In addition, the focus on interprotein interactions within relevant molecular networks is aimed at elucidating the complexities of the mechanisms underlying the therapeutic effects of bioactive compounds. This approach is expected to provide a conceptual foundation for the classification and development of natural compounds into nutraceuticals or pharmaceutical agents for the management of hypercholesterolemia (Ghosh & Mukherjee, 2019; Paul & Kumar, 2024).

2. Modulation of Intestinal Cholesterol Absorption

The intestine plays a vital role in cholesterol regulation, with NPC1L1 acting as the primary transporter responsible for the absorption of dietary cholesterol (Iqbal et al., 2017b) (see Table 1 and Figure 1). The present review analysis, as seen in Table 2, identifies seven polyphenols reported to inhibit NPC1L1 through different mechanisms. Luteolin, curcumin, cyanidin-3-glucoside, chlorogenic acid, and catechin primarily inhibit NPC1L1 expression, while luteolin and quercetin inhibit its transport function (Kobayashi, 2019). Luteolin and quercetin exert dual modulatory effects by attenuating both the transcriptional activity and functional capacity of NPC1L1, indicating interference at the gene expression and protein transport levels (Kobayashi, 2019). Curcumin, cyanidin-3-glucoside, chlorogenic acid, and catechin predominantly downregulate NPC1L1 mRNA expression, leading to reduced protein synthesis and diminished cholesterol uptake across the apical membrane of enterocytes (Kobayashi, 2019). Notably, piperine demonstrates a multi-target regulatory profile by simultaneously repressing the expression of NPC1L1, acyl-CoA:cholesterol acyltransferase 2 (ACAT2), and microsomal triglyceride transfer protein (MTP), suggesting coordinated inhibition of cholesterol absorption, esterification, and lipoprotein assembly (Zhao et al., 2018). These findings underscore the mechanistic diversity of phytochemicals in modulating cholesterol homeostasis and support their potential as adjunctive agents in molecular-targeted strategies for hypercholesterolemia management.

Table 1. Key protein targets in hypercholesterolemia and their roles in cholesterol metabolism

Protein Target	Location	Primary Function	Role in Cholesterol Metabolism	Reference
ACAT2	Intestine, liver	Enzyme	Esterifies cholesterol for incorporation into chylomicrons and VLDL	(Zhao et al., 2018; Ibrahim et al., 2020)
NPC1L1	Small intestine. liver	Cholesterol transporter, Cholesterol absorption	Rate-limiting transporter for intestinal cholesterol absorption	(Kikuchi et al., 2016; Kobayashi, 2019; Zhao et al., 2023)
HMGCS1	Liver	Enzyme	Catalyzes the condensation of acetyl-CoA with acetoacetyl-CoA to form HMG-CoA	(Ma et al., 2022)
HMGCR	Liver	Enzyme	Catalyzes the rate limiting step in cholesterol biosynthesis (conversion of HMG-CoA to mevalonate)	(Baskaran et al., 2015; Grande et al., 2021)
MTP	Intestine, Liver	Transfer protein	Facilitates the assembly and secretion of apoB-containing lipoproteins	(Zhao et al., 2018)
PCSK9	Liver	Protein convertase	Promotes degradation of LDLR, leading to elevated LDL cholesterol levels	(Lammi et al., 2014; Kim et al., 2020; Ferrari, 2024)
LDLR	Liver, peripheral tissues	Receptor	Mediates the uptake of LDL particles from circulation; main pathway of LDL clearance	(Luchetti et al., 2021)
SREBP-1c	Liver	Transcription factor	Controls expression of genes involved in biosynthesis of fatty acids	(Miyata et al., 2015; Vallianou & Hadzopoulou-Cladaras, 2016)
SREBP-2	Liver	Transcription factor	Primary regulator of cholesterol biosynthesis genes, including HMGCR and SQLE; enhances PCSK9 transcription	(Liang et al., 2014; Vallianou & Hadzopoulou-Cladaras, 2016; Feng et al., 2025)

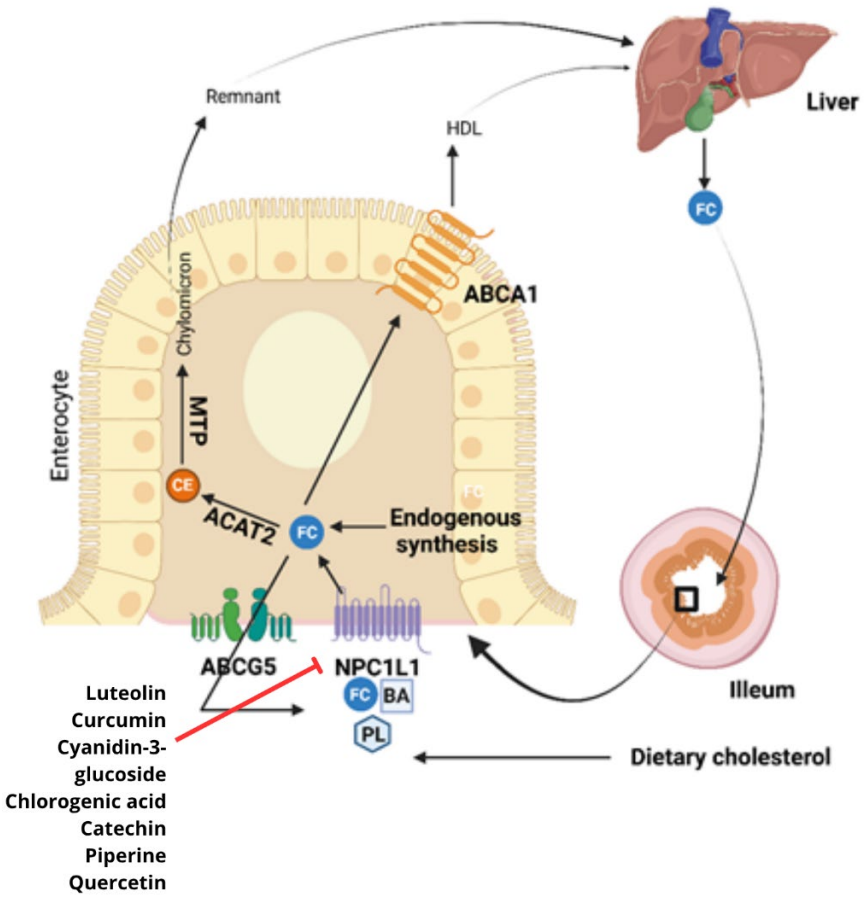


Figure 1. NPC1L1 regulates the uptake of dietary cholesterol within enterocytes, while ABCG5/8 facilitates cholesterol excretion. ACAT2 esterifies cholesterol, facilitating its incorporation into chylomicrons. These particles subsequently transport the cholesterol to the liver for processing. NPC1L1: Niemann-Pick C1-Like 1, ABCG5 – ATP-Binding Cassette Sub-Family G Member 5, ABCA1:ATP-Binding Cassette Sub-Family A Member 1, ACAT2:Acyl-CoA:Cholesterol Acyltransferase 2, MTP:Microsomal Triglyceride Transfer Protein, HDL:High-Density Lipoprotein, FC:Free Cholesterol, CE:Cholesteryl Ester, PL:Phospholipid, BA: Bile Acid

3. Targeting Cholesterol Synthesis Pathway

The inhibition of de novo cholesterol synthesis is a key mechanism through which natural compounds exert hypocholesterolemic effects (Cerqueira et al., 2016). This pathway is subject to regulation by the mevalonate cascade, plays a central role in the endogenous cholesterol production process, and serves as a major target for intervention strategies (Hashemi et al., 2017). Natural compounds frequently modulate multiple enzymes within the cholesterol synthesis pathway (Zhang et al., 2024). For example, chlorogenic acid and polyphenols downregulate both HMGCR and NPC1L1 via the PXR and SREBP-2

Table 2. Classification of natural compounds by their target mechanisms in hypercholesterolemia

Protein Target	Current Drug Interventions	Natural Compound Interventions	Mechanism of Action	Reference
ACAT2	No approved drugs	Piperine	Downregulation of intestinal ACAT2; reduces cholesterol esterification	(Zhao et al., 2018; Ibrahim et al., 2020)
NPC1L1	Ezetimibe	Luteolin, Curcumin, Cyanidin-3-glucoside, Chlorogenic acid, Catechin, Quercetin, Piperine	Inhibition of cholesterol transporter; reduces intestinal cholesterol absorption	(Zhao et al., 2018; Kobayashi, 2019; Meng et al., 2024)
HMGCS1	No approved drugs	Ursolic acid	Forms covalent bonds with Cys-129; inhibits catalytic activity	(Ma et al., 2022)
HMGCR	Statins	Naringin, Hesperidin, Chlorogenic acid	Competitive inhibition of catalytic domain; blocks conversion of HMG-CoA to mevalonate	(Iqbal et al., 2017a; Grande et al., 2021; Meng et al., 2024)
MTP	Lomitapide	Piperine	Inhibits lipoprotein assembly and secretion	(Vallianou & Hadzopoulou-Cladaras, 2016; Zhao et al., 2018)
PCSK9	Evolocumab, Alirocumab	Hypericin, Lupin protein/peptides, Piceatannol, Tetrahydroberberrubine	Prevents PCSK9-mediated degradation of LDLR; enhances LDL clearance	(Lammi et al., 2016; Kim et al., 2020; Ferrari, 2024; Feng et al., 2025)
SREBP-2	No approved drugs	Anhydroicaritin, xanthohumol, tetrahydroberberrubine, camphene	Inhibition of transcription factors; reduces expression of lipogenic genes	(Miyata et al., 2015; Vallianou & Hadzopoulou-Cladaras, 2016; Zheng et al., 2016; Feng et al., 2025)

pathways, thereby inhibiting cholesterol biosynthesis and promoting absorption regulation (Meng et al., 2024) (see Table 1 and Figure 2). Citrus flavonoids, such as naringin and hesperidin, function as natural HMGCR inhibitors that exhibit binding affinities that are comparable to those of statins, rendering them promising alternatives for the 5–20% of patients who are intolerant to statins (Peluso et al., 2015; Grande et al., 2021).

Another promising compound, ursolic acid, a triterpenoid, has been shown to inhibit cholesterol synthesis through a novel upstream mechanism. Ursolic acid has been demonstrated to inhibit HMGCS1, an enzyme that catalyzes an earlier step in the mevalonate pathway. The ursolic acid epoxide metabolite forms a covalent bond with Cys-129 in HMGCS1, thereby disrupting its catalytic activity and reducing cholesterol synthesis (Ma et al., 2022). This irreversible inhibition provides a unique therapeutic approach, with the potential to overcome drug resistance in the treatment of hypercholesterolemia and complement existing statin-based therapies.

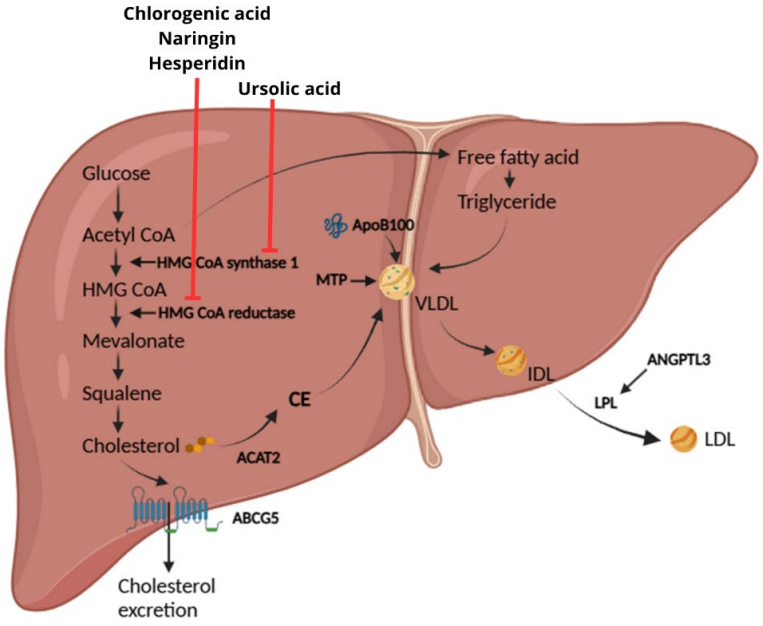


Figure 2. HMGCS1 initiates cholesterol biosynthesis in the liver by converting acetyl-CoA to HMG-CoA, which is then processed by HMGCR to produce mevalonate. MTP is essential for the assembly of VLDL particles, which combine cholesterol and triglycerides for transport: lipoprotein lipase (LPL) hydrolyzes triglycerides contained within lipoproteins, releasing free fatty acids for utilization by peripheral tissue. *Angiopoietin-like protein 3* (ANGPTL3) regulates lipoprotein lipase (LPL) activity, ensuring proper lipid metabolism and triglyceride balance in the liver. ACAT2: Acyl-CoA:Cholesterol Acyltransferase 2, ABCG5: ATP-Binding Cassette Subfamily G Member 5, HMG CoA: 3-Hydroxy-3-Methylglutaryl-Coenzyme A, HMG CoA reductase: Key rate-limiting enzyme in cholesterol biosynthesis, HMG CoA synthase 1: Enzyme catalyzing the formation of HMG CoA, CE: Cholesterol Ester, MTP: Microsomal Triglyceride Transfer Protein, $ApoB_{100}$: Apolipoprotein B100, VLDL: Very-Low-Density Lipoprotein, IDL: Intermediate-Density Lipoprotein, LDL: Low-Density Lipoprotein, LPL: Lipoprotein Lipase, ANGPTL3: Angiopoietin-like 3.

4. PCSK9 Inhibition and LDLR Regulation

The regulation of the PCSK9–LDLR axis has significantly transformed therapeutic strategies for cholesterol management (Xu et al., 2023). PCSK9 has been shown to promote the lysosomal degradation of LDL receptors (LDLR), thereby reducing the liver's capacity to clear circulating low-density lipoprotein cholesterol (LDL-C) (Tavori et al., 2015) (see Table 1 and Figure 3). Monoclonal antibodies, such as alirocumab and evolocumab, reduce plasma LDL-C levels by binding to PCSK9 and preventing its interaction with LDLR (Fitzgerald & Kiernan, 2018). Nevertheless, their high manufacturing costs and limited accessibility impede their extensive clinical implementation (Svatikova & Kopecky, 2017). These limitations have given rise to a growing interest in the use of natural bioactive compounds as more affordable alternatives. Hypericin, a constituent of *Hypericum perforatum*, exhibits a robust binding affinity for the PCSK9 site, which facilitates its interaction with LDLR. This interaction potentially contributes to the stabilization of LDLR expression on liver cells, akin to the mechanism observed with monoclonal antibodies. Furthermore, proteins derived from lupin have been demonstrated to regulate PCSK9 gene expression, indicating a correlation between plant-based diets and enhanced cholesterol management (Islam et al., 2021). Elucidating the mechanism by which these compounds exert their action, whether through direct PCSK9 inhibition or by altering gene transcription, could inform the development of functional foods and nutraceuticals as potential alternative or complementary treatments for dyslipidemia (Vekic et al., 2022).

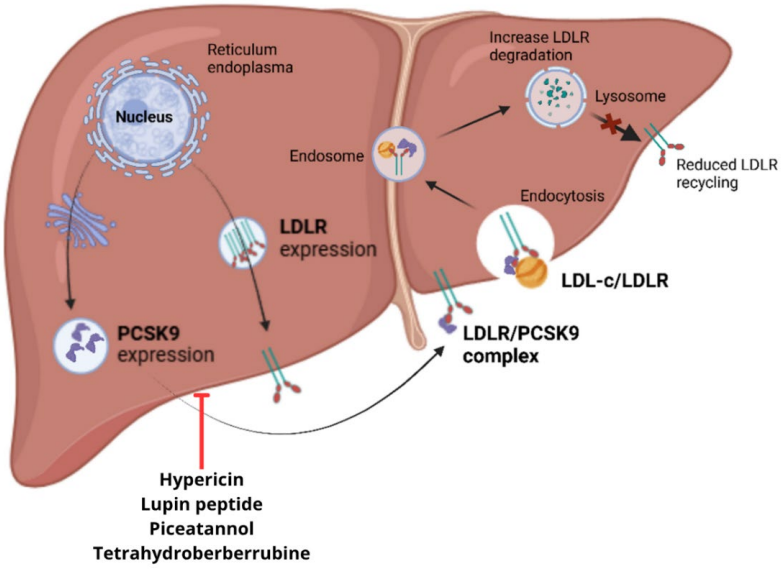


Figure 3. PCSK9 expression regulates the expression of LDLR. The formation of LDLR/PCSK9 occurs, and through the process of endocytosis, LDL-c is internalized along with LDLR. The complex undergoes degradation by lysosomes, leading to decreased LDLR recycling and increased LDLR degradation. This mechanism reduces the availability of LDLR on the cell surface, thereby decreasing cholesterol uptake. PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9, LDLR: Low-Density Lipoprotein Receptor, LDL-c: Low-Density Lipoprotein Cholesterol.

5. Transcription Factor Regulation

Targeting transcription factors like SREBP-1c and SREBP-2 is one strategic approach to modulating lipid homeostasis by regulating multiple genes involved in fatty acid and cholesterol biosynthesis (Shimano & Sato, 2017; Li et al., 2023) (see Table 1 and Figure 4). SREBP-2 plays a central role in the regulation of enzymes involved in de novo cholesterol synthesis and lipoprotein metabolism, making it a key target in the management of hypercholesterolemia and related disorders (Li et al., 2017). A number of naturally occurring compounds, including anhydroicaritin, xanthohumol, tetrahydroberberrubine, and camphene, have been identified as modulators of the SREBP pathway. Among these, xanthohumol from *Humulus lupulus* has been shown to inhibit SREBP activity, thereby reducing both cholesterol and fatty acid synthesis (Miyata et al., 2015). Xanthohumol's extensive metabolic consequences suggests its potential as a therapeutic agent for not only hypercholesterolemia but also metabolic syndrome and NAFLD. It has been demonstrated to suppress lipogenesis and cholesterol production through the process of transcriptional regulation.

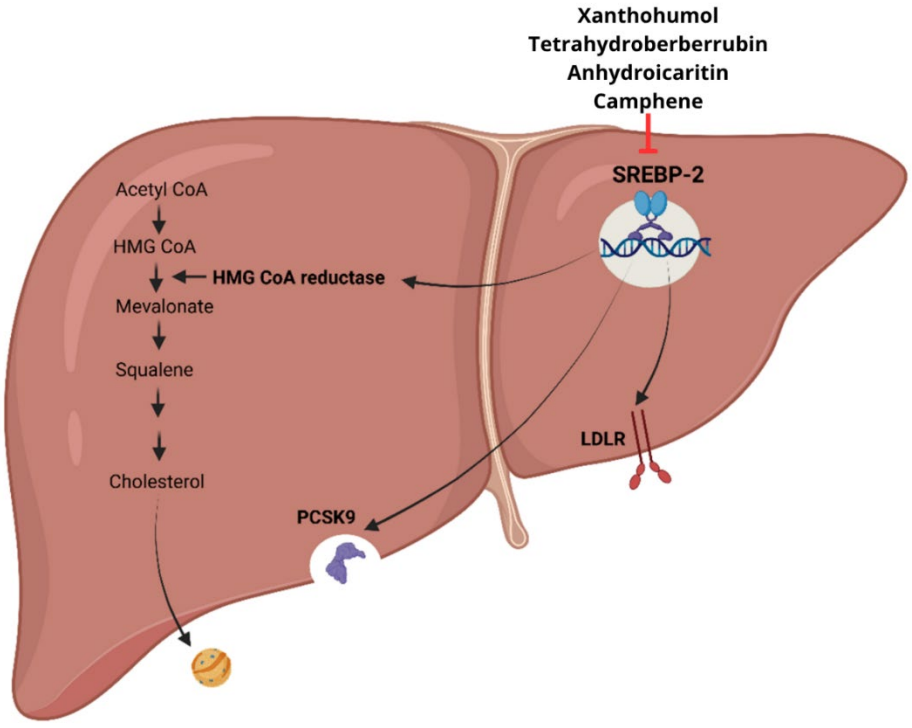


Figure 4. SREBP-2 regulates cholesterol biosynthesis in the liver by activating the expression of genes involved in the mevalonate pathway, including HMGCR. The pathway, which leads to cholesterol production, can also affect the expression of LDLR. Furthermore, PCSK9 expression may interact with LDLR to modulate LDL uptake. SREBP-2: Sterol Regulatory Element-Binding Protein 2, HMG CoA: 3-Hydroxy-3-Methylglutaryl-Coenzyme A, HMG CoA reductase: Acetyl CoA: Acetyl Coenzyme A, LDLR: Low-Density Lipoprotein Receptor, PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9, LDL-c: Low-Density Lipoprotein Cholesterol

Tetrahydroberberrubine is another notable compound that exerts lipid-lowering effects through the AMP-activated protein kinase (AMPK) pathway, a central regulator of energy and lipid metabolism (Feng et al., 2025). The modulation of SREBP2, PCSK9, or LDLR by tetrahydroberberrubine has been demonstrated to enhance LDL-C clearance and reduce cholesterol synthesis. The activation of AMPK suggests a broader potential for metabolic interventions, including the improvement of insulin resistance and energy balance. The incorporation of natural SREBP modulators into lipid-lowering therapies offers a safer alternative to synthetic drugs by influencing multiple transcriptional pathways simultaneously (Shi & Han, 2025). Future research should prioritize validating their efficacy, bioavailability, and pharmacokinetics, as well as exploring combination therapies. Ultimately, leveraging natural SREBP-targeting compounds has the potential to facilitate a comprehensive approach to the management of hypercholesterolemia, complemented by a range of metabolic improvements.

6. Protein Target of Hypercholesterolemia Interaction

The protein-protein interaction (PPI) network of key molecular targets involved in cholesterol metabolism under hypercholesterolemic conditions was illustrated using STRINGdb (Szklarczyk et al., 2021) (Figure 5). The PPI network provides a systems biology perspective that enhances our understanding of the molecular mechanisms underlying disease (Safari-Alighiarloo et al., 2014). The results of the PPI study indicated that a highly interconnected core module consisting of SREBP-2, HMGCR, HMGCS1, SREBP-1c, and NPC1L1 is central to cholesterol biosynthesis, transcriptional regulation, and uptake. SREBP-2 has been identified as a critical transcriptional regulator, regulating key enzymes, including HMGCR and HMGCS1, within the mevalonate pathway. HMGCR demonstrated the most significant interactions with other proteins implicated in cholesterol metabolism (Figure 5). NPC1L1 modulates cholesterol uptake through biosynthesis regulation. Peripheral proteins such as PCSK9, ANGPTL3, and ABCG5, despite their lack of direct modulation, play important roles in the regulation of LDL receptors, the metabolism of triglyceride, and the excretion of cholesterol. MTP and ACAT2 are associated with the regulation of cholesterol and triglyceride through the process of lipid packaging and esterification. The thickness of the edges is indicative of the conviction of strong interactions, while the overlapping node colors highlight multifunctional roles across metabolic, biosynthetic, homeostatic, and absorption pathways. This network underscores the importance of targeting central and peripheral regulators for effective cholesterol management and supports multi-target therapeutic strategies.

7. Complex Extracts with Multifaceted Actions

Recent studies have primarily focused on isolated bioactive compounds. Mounting evidence highlights the superior hypolipidemic potential of complex plant extracts, attributable to synergistic interactions among multiple phytochemicals (Pham et al., 2020). In contrast to single-compound therapies, plant extracts contain a variety of bioactive compounds, including flavonoids, terpenoids, polyphenols, and alkaloids. These compounds modulate lipid metabolism through complementary mechanisms. For instance, hawthorn extract, which is abundant in triterpenoids and flavonoids, has been demonstrated to improve lipid profiles, safeguard hepatic function, and reduce oxidative stress associated with hypercholesterolemia (Rezaei-Golmisheh et al., 2015). As shown in Table 3, natural compounds and extracts exert a significant influence on multiple lipid-

regulatory processes. The prevalent mechanisms include NPC1L1 inhibition/downregulation (36.9%), SREBP pathway modulation (21%), and PCSK9 inhibition/modulation (10.5%). Other targets include MTP, HMGCR, and ACAT2. While pharmaceuticals tend to consist of single, purified compounds, plant extracts offer broader metabolic benefit by addressing cholesterol synthesis, lipoprotein metabolism, oxidative stress, and inflammation. However, challenges related to standardization, extraction methods, and pharmacokinetics must be addressed to fully realize the clinical potential of plant-based therapies.

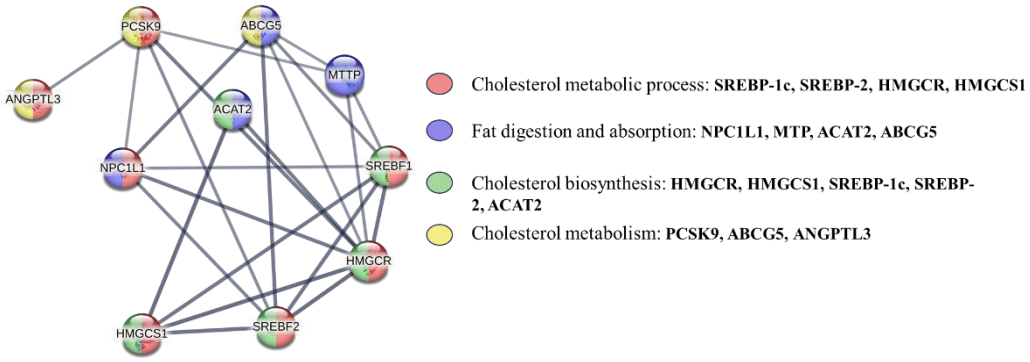


Figure 5. Protein target interaction of hypercholesterolemia in cholesterol metabolism result using STRINGdb. PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9, ABCG5: ATP-Binding Cassette Subfamily G Member 5, MTTP: Microsomal Triglyceride Transfer Protein, SREBF1 (SREBP-1): Sterol Regulatory Element-Binding Protein 1, SREBF2 (SREBP-2): Sterol Regulatory Element-Binding Protein 2, HMGCR: 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase, HMGCS1: 3-Hydroxy-3-Methylglutaryl-Coenzyme A Synthase 1, ACAT2: Acyl-CoA:Cholesterol Acyltransferase 2, ANGPTL3: Angiopoietin-Like 3, NPC1L1: Niemann-Pick C1-Like 1

Table 3. Distribution of major cholesterol regulation mechanisms targeted by natural compound

Mechanism	Number of Compounds	Percentage
NPC1L1 inhibition	7	36.9%
SREBP pathway modulation	4	21%
HMGCR inhibition	3	15.7%
PCSK9 inhibition	2	10.5%
ACAT2 downregulation	1	5.3%
HMGCS1 inhibition	1	5.3%
MTP inhibition	1	5.3%
Total	**19**	**100%**

8. Limitations and Research Gaps

Notwithstanding the promising results, significant challenges persist before natural compounds and plant extracts can be widely adopted clinically. The preponderance of extant evidence derives from in vitro and animal studies, with a paucity of rigorous human trials to substantiate efficacy, optimal dosing, long-term safety, and pharmacokinetics (Bondemark & Ruf, 2015). Moreover, numerous bioactive molecules, such as polyphenols and flavonoids, exhibit suboptimal bioavailability and poor absorption, although advanced formulations, such as nanoencapsulation, have emerged as potential solutions to address these challenges (Murthy et al., 2018; Chen et al., 2022). The complexity of plant extracts poses significant challenges to standardization and quality control processes (Srivastava & Misra, 2018). The potential interactions between natural compounds and lipid-lowering medications highlight the necessity for comprehensive pharmacological studies. Future research should prioritize large-scale clinical trials, standardized extraction protocols, improved formulations, and drug-interaction studies. Addressing these gaps has the potential to establish natural compounds that could emerge as effective and evidence-based alternatives or adjuncts to conventional lipid-lowering therapies, thereby contributing to the advancement of cardiovascular disease prevention.

9. Conclusions

Natural bioactive compounds derived from herbs and food plants, including polyphenols, flavonoids, terpenoids, and plant sterols, have demonstrated the capacity to modulate these protein targets through various mechanisms. These compounds have been shown to exert multitargeted actions by modulating key protein regulators of cholesterol metabolism. Specifically, they inhibit cholesterol synthesis via HMGCR and HMGCS1, reduce intestinal cholesterol absorption by targeting NPC1L1, and enhance LDL clearance through PCSK9 inhibition. Furthermore, their influence on transcription factors such as SREBP-2 serves to amplify their cholesterol-lowering effects. Notably, decrease in LDL accumulation was achieved indirectly through the contribution of multiple compounds. Given their multi-targeted action, wide availability, and generally favorable safety profile, natural compounds hold significant promise as complementary or alternative therapies in the management of hypercholesterolemia. Subsequent research endeavors should focus on clinical validation, bioavailability optimization, and formulation strategies to fully leverage their therapeutic potential.

10. Acknowledgements

We would like to thank the Research Center of Smart Molecules of Natural Genetic Resources at Brawijaya University, for their invaluable guidance and support.

11. Authors' Contributions

JU: Conceptualization, methodology, investigation, data curation, initial draft writing. TT: Methodology refinement, validation, review & editing. TAW: Supervision, validation, revision. FF: Conceptualization, supervision, revision. All authors have read and approved the final manuscript.

ORCID
Ja'far Umar https://orcid.org/0009-0005-7860-2516
Titin Wihastuti https://orcid.org/0000-0001-6476-0541
Fatchiyah Fatchiyah https://orcid.org/0000-0001-6241-9665

12. Conflicts of Interest

The authors declare no conflict of interest.

13. AI Declaration

During the preparation of this work, the authors used ChatGPT and Claude to extract the data, improve the clarity and coherence of the manuscript. After using these tools, the authors carefully reviewed and edited the content as needed and took full responsibility for the content and conclusions presented in this publication.

References

Aldalou, A. R. (2021). Hypolipidemic effects of curcumin, cinnamon, vitamin C and simvastatin in domestic rabbits. *GSC Biological and Pharmaceutical Sciences*, *15*(1), 119-131. https://doi.org/10.30574/gscbps.2021.15.1.0103

Alloubani, A., Nimer, R., & Samara, R. (2021). Relationship between hyperlipidemia, cardiovascular disease and stroke: a systematic review. *Current Cardiology Reviews*, *17*(6), Article e0511211890015. https://doi.org/10.2174/1573403X16999201210200342

Bardolia, C., Amin, N. S., & Turgeon, J. (2021). Emerging non-statin treatment options for lowering low-density lipoprotein cholesterol. *Frontiers in Cardiovascular Medicine*, *8*, Article 789931. https://doi.org/10.3389/fcvm.2021.789931

Baskaran, G., Salvamani, S., Ahmad, S. A., Shaharuddin, N. A., Pattiram, P. D., & Shukor, M. Y. (2015). HMG-CoA reductase inhibitory activity and phytocomponent investigation of *Basella alba* leaf extract as a treatment for hypercholesterolemia. *Drug Design, Development and Therapy, 9*, 509-517. https://doi.org/10.2147/DDDT.S75056

Bondemark, L., & Ruf, S. (2015). Randomized controlled trial: the gold standard or an unobtainable fallacy? *European Journal of Orthodontics*, *37*(5), 457-461. https://doi.org/10.1093/ejo/cjv046

Boudoulas, K. D., Triposkiadis, F., Geleris, P., & Boudoulas, H. (2016). Coronary atherosclerosis: pathophysiologic basis for diagnosis and management. *Progress in Cardiovascular Diseases*, *58*(6), 676-692. https://doi.org/10.1016/j.pcad.2016.04.003

Carson, J. A. S., Lichtenstein, A. H., Anderson, C. A. M., Appel, L. J., Kris-Etherton, P. M., Meyer, K. A., Petersen, K., Polonsky, T., & Van Horn, L. (2020). Dietary cholesterol and cardiovascular risk: a science advisory from the American Heart Association. *Circulation*, *141*(3), e39-e53. https://doi.org/10.1161/CIR.0000000000000743

Cerqueira, N. M., Oliveira, E. F., Gesto, D. S., Santos-Martins, D., Moreira, C., Moorthy, H. N., Ramos, M. J., & Fernandes, P. A. (2016). Cholesterol biosynthesis: a mechanistic overview. *Biochemistry*, *55*(39), 5483-5506. https://doi.org/10.1021/acs.biochem.6b00342

Cesaro, A., Bianconi, V., Gragnano, F., Moscarella, E., Fimiani, F., Monda, E., Scudiero, O., Limongelli, G., Pirro, M., & Calabrò, P. (2020). Beyond cholesterol metabolism: the pleiotropic effects of proprotein convertase subtilisin/kexin type 9 (PCSK9). Genetics, mutations, expression, and perspective for long-term inhibition. *Biofactors*, *46*(3), 367-380. https://doi.org/10.1002/biof.1619

Chaachouay, N. (2025). Synergy, additive effects, and antagonism of drugs with plant bioactive compounds. *Drugs and Drug Candidates*, *4*(1), Article 4. https://doi.org/10.3390/ddc4010004

Chen, L., Cao, H., Huang, Q., Xiao, J., & Teng, H. (2022). Absorption, metabolism and bioavailability of flavonoids: A review. *Critical Reviews in Food Science and Nutrition*, *62*(28), 7730-7742. https://doi.org/10.1080/10408398.2021.1917508

DiNicolantonio, J. J., Lucan, S. C., & O'Keefe, J. H. (2016). The evidence for saturated fat and for sugar related to coronary heart disease. *Progress in Cardiovascular Diseases*, *58*(5), 464-472. https://doi.org/10.1016/j.pcad.2015.11.006

Feng, J., Xu, R., Dou, Z., Hao, Y., Xu, R., Khoso, M. A., Shi, Y., Liu, L., Sun, H., Chen, C., Li, X., Liu, H., Han, W., Cheng, M., Tang, P., Li, J., Zhang, Y., & Liu, X. (2025). Tetrahydroberberrubine improves hyperlipidemia by activating the AMPK / SREBP2 / PCSK9 / LDL receptor signaling pathway. *European Journal of Pharmacology*, *989*, Article 177228. https://doi.org/10.1016/j.ejphar.2024.177228

Ferrari, I. V. (2024). Unraveling the potential of hypericin: A novel approach to targeting PCSK9 mutations in cholesterol management. *bioRxiv*, https://doi.org/10.1101/2024.10.06.616901

Fitzgerald, G., & Kiernan, T. (2018). PCSK9 inhibitors and LDL reduction: pharmacology, clinical implications, and future perspectives. *Expert Review of Cardiovascular Therapy*, *16*(8), 567-578. https://doi.org/10.1080/14779072.2018.1497975

Gesto, D. S., Pereira, C. M. S., Cerqueira, N. M. F. S., & Sousa, S. F. (2020). An atomic-level perspective of HMG-CoA-reductase: The target enzyme to treat hypercholesterolemia. *Molecules*, *25*(17), Article 3891. https://doi.org/10.3390/molecules25173891

Ghosh, D., & Mukherjee, P. K. (2019). *Natural medicines: clinical efficacy, safety and quality*. CRC Press. https://doi.org/10.1201/9781315187853

Gianazza, E., Brioschi, M., Iezzi, A., Paglia, G., & Banfi, C. (2023). Pharmacometabolomics for the study of lipid-lowering therapies: opportunities and challenges. *International Journal of Molecular Sciences*, *24*(4), Article 3291. https://doi.org/10.3390/ijms24043291

Grande, F., Occhiuzzi, M. A., Perri, M. R., Ioele, G., Rizzuti, B., Statti, G., & Garofalo, A. (2021). Polyphenols from Citrus Tacle ® extract endowed with HMGCR inhibitory activity: An antihypercholesterolemia natural remedy. *Molecules*, *26*(18), Article 5718. https://doi.org/10.3390/molecules26185718

Hashemi, M., Hoshyar, R., Ande, S. R., Chen, Q. M., Solomon, C., Zuse, A., & Naderi, M. (2017). Mevalonate cascade and its regulation in cholesterol metabolism in different tissues in health and disease. *Current Molecular Pharmacology*, *10*(1), 13-26. https://doi.org/10.2174/1874467209666160112123746

Hunter, P. M., & Hegele, R. A. (2017). Functional foods and dietary supplements for the management of dyslipidaemia. *Nature Reviews Endocrinology*, *13*(5), 278-288. https://doi.org/10.1038/nrendo.2016.210

Ibrahim, A., Shafie, N. H., Mohd Esa, N., Shafie, S. R., Bahari, H., & Abdullah, M. A. (2020). *Mikania micrantha* extract inhibits HMG-CoA reductase and ACAT2 and ameliorates hypercholesterolemia and lipid peroxidation in high cholesterol-fed rats. *Nutrients*, *12*(10), Article 3077. https://doi.org/10.3390/nu12103077

Iqbal, J., Al Qarni, A., & Hawwari, A. (2017a). Regulation of intestinal cholesterol absorption: a disease perspective. *Advances in Biological Chemistry*, *7*(1), 60-75. https://doi.org/10.4236/abc.2017.71004

Iqbal, D., Khan, A., Ansari, I. A., & Khan, M. S. (2017b). Investigating the role of novel bioactive compound from *Ficus virens* Ait on cigarette smoke induced oxidative stress and hyperlipidemia in rats. *Iranian Journal of Pharmaceutical Research*, *16*(3), 1089-1103.

Islam, S. U., Ahmed, M. B., Ahsan, H., & Lee, Y.-S. (2021). Recent molecular mechanisms and beneficial effects of phytochemicals and plant-based whole foods in reducing

LDL-C and preventing cardiovascular disease. *Antioxidants*, *10*(5), Article 784. https://doi.org/10.3390/antiox10050784

Jayaraman, S., Roy, A., Vengadassalapathy, S., Sekar, R., Veeraraghavan, V. P., Rajagopal, P., Rengasamy, G., Mukherjee, R., Sekar, D., & Manjunathan, R. (2021). An overview on the therapeutic function of foods enriched with plant sterols in diabetes management. *Antioxidants*, *10*(12), Article 1903. https://doi.org/10.3390/antiox10121903

Kikuchi, T., Orihara, K., Oikawa, F., Han, S., Kuba, M., Okuda, K., Satoh, A., Osaki, Y., Takeuchi, Y., Aita, Y., Matsuzaka, T., Iwasaki, H., Yatoh, S., Sekiya, M., Yahagi, N., Suzuki, H., Sone, H., & Nakagawa, Y. (2016). Intestinal CREBH overexpression prevents high- cholesterol diet-induced hypercholesterolemia by reducing Npc1l1 expression. *Molecular Metabolism*, *5*(11), 1092-1102. https://doi.org/10.1016/j.molmet.2016.09.004

Kim, H., Lee, J., Chung, M., Hong, S., Ho, J., Lee, S., Wook, S., Choi, H., & Hwang, J. (2020). Piceatannol reduces resistance to statins in hypercholesterolemia by reducing PCSK9 expression through p300 acetyltransferase inhibition. *Pharmacological Research*, *161*, Article 105205. https://doi.org/10.1016/j.phrs.2020.105205

Kobayashi, S. (2019). The effect of polyphenols on hypercholesterolemia through inhibiting the transport and expression of Niemann - Pick C1-Like 1. *International Journal of Molecular Sciences, 20*(19), Article 4939. https://doi.org/10.3390/ijms20194939

Kou, Y., Geng, F., & Guo, D. (2022). Lipid metabolism in glioblastoma: from de novo synthesis to storage. *Biomedicines*, *10*(8), Article 1943. https://doi.org/10.3390/biomedicines10081943

Kumar, R., Chhillar, N., Gupta, D. S., Kaur, G., Singhal, S., & Chauhan, T. (2024). Cholesterol homeostasis, mechanisms of molecular pathways, and cardiac health: a current outlook. *Current Problems in Cardiology*, *49*(1), Article 102081. https://doi.org/10.1016/j.cpcardiol.2023.102081

Lammi, C., Zanoni, C., Calabresi, L., & Arnoldi, A. (2016). Lupin protein exerts cholesterol-lowering effects targeting PCSK9: From clinical evidences to elucidation of the in vitro molecular mechanism using HepG2 cells. *Journal of Functional Foods*, *23*, 230-240. https://doi.org/10.1016/j.jff.2016.02.042

Lammi, C., Zanoni, C., Scigliuolo, G. M., D'Amato, A., & Arnoldi, A. (2014). Lupin peptides lower low-density lipoprotein (LDL) cholesterol through an up-regulation of the LDL receptor/sterol regulatory element binding protein 2 (SREBP2) pathway at HepG2 cell line. *Journal of Agricultural and Food Chemistry*, *62*(29), 7151-7159. https://doi.org/10.1021/jf500795b

Li, N., Li, X., Ding, Y., Liu, X., Diggle, K., Kisseleva, T., & Brenner, D. A. (2023). SREBP regulation of lipid metabolism in liver disease, and therapeutic strategies. *Biomedicines*, *11*(12), Article 3280. https://doi.org/10.3390/biomedicines11123280

Li, Y., Song, Y., Zhao, M., Guo, Y., Yu, C., Chen, W., Shao, S., Xu, C., Zhou, X., Zhao, L., Zhang, Z., Bo, T., Xia, Y., Proud, C. G., Wang, X., Wang, L., Zhao, J., & Gao, L. (2017). A novel role for CRTC2 in hepatic cholesterol synthesis through SREBP-2. *Hepatology*, *66*(2), 481-497. https://doi.org/10.1002/hep.29206

Liang, Y., Gao, Y., Lin, Q., Luo, F., Wu, W., Lu, Q., & Liu, Y. (2014). A review of the research progress on the bioactive ingredients and physiological activities of rice bran oil. *European Food Research and Technology*, *238*, 169-176. https://doi.org/10.1007/s00217-013-2149-9

Luchetti, F., Crinelli, R., Nasoni, M. G., Benedetti, S., Palma, F., Fraternale, A., & Iuliano, L. (2021). LDL receptors, caveolae and cholesterol in endothelial dysfunction: oxLDLs accomplices or victims? *British Journal of Pharmacology*, *178*(16), 3104-3114. https://doi.org/10.1111/bph.15272

Luo, J., Yang, H., & Song, B.-L. (2020). Mechanisms and regulation of cholesterol homeostasis. *Nature Reviews, Molecular Cell Biology*, *21*(4), 225-245. https://doi.org/10.1038/s41580-019-0190-7

Ma, X., Bai, Y., Liu, K., Han, Y., Zhang, J., Liu, Y., Hou, X., Hao, E., Hou, Y., & Bai, G. (2022). Ursolic acid inhibits the cholesterol biosynthesis and alleviates high fat diet-induced hypercholesterolemia via irreversible inhibition of HMGCS1 in vivo. *Phytomedicine*, *103*, Article 154233. https://doi.org/10.1016/j.phymed.2022.154233

Makhoba, X. H., Viegas, C. Jr., Mosa, R. A., Viegas, F. P. D., & Pooe, O. J. (2020). Potential impact of the multi-target drug approach in the treatment of some complex diseases. *Drug Design, Development and Therapy*, *14*, 3235-3249. https://doi.org/10.2147/DDDT.S257494

Mancini, G. B. J., Baker, S., Bergeron, J., Fitchett, D., Frohlich, J., Genest, J., Gupta, M., Hegele, R. A., Ng, D., Pearson, G. J., Pope, J., & Tashakkor, A. Y. (2016). Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian consensus working group update (2016). *Canadian Journal of Cardiology*, *32*(7), S35-S65. https://doi.org/10.1016/j.cjca.2016.01.003

Meng, C., Zhou, L., Huang, L., Gu, Q., Du, X., Wang, C., Liu, F., & Xia, C. (2024). 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*, *123*, Article 155271. https://doi.org/10.1016/j.phymed.2023.155271

Miyata, S., Inoue, J., Shimizu, M., & Sato, R. (2015). Xanthohumol improves diet-induced obesity and fatty liver by suppressing sterol regulatory element-binding protein (SREBP) activation. *Journal of Biological Chemistry*, *290*(33), 20565-20579. https://doi.org/10.1074/jbc.M115.656975

Mormone, A., Tortorella, G., Esposito, F., Caturano, A., Marrone, A., Cozzolino, D., Galiero, R., Marfella, R., Sasso, F. C., & Rinaldi, L. (2024). Advances in pharmacological approaches for managing hypercholesterolemia: A comprehensive overview of novel treatments. *Biomedicines*, *12*(2), Article 432. https://doi.org/10.3390/biomedicines12020432

Murthy, K. N. C., Monika, P., Jayaprakasha, G. K., & Patil, B. S. (2018). Nanoencapsulation: An advanced nanotechnological approach to enhance the biological efficacy of curcumin. In G. K. Jayaprakasha, B. S. Patil, & G. Gattuso (Eds.). *Advances in plant phenolics: From chemistry to human health* (pp. 383-405). ACS Publications. https://doi.org/10.1021/bk-2018-1286.ch021

Newman, C. B., Preiss, D., Tobert, J. A., Jacobson, T. A., Page, R. L., Goldstein, L. B., Chin, C., Tannock, L. R., Miller, M., Raghuveer, G., Duell, P. B., Brinton, E. A., Pollak, A., Braun, L. T., & Welty, F. K. (2019). Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arteriosclerosis*, *Thrombosis, and Vascular Biology*, *39*(2), e38-e81. https://doi.org/10.1161/ATV.0000000000000073

Panahi, Y., Ahmadi, Y., Teymouri, M., Johnston, T. P., & Sahebkar, A. (2018). Curcumin as a potential candidate for treating hyperlipidemia: A review of cellular and metabolic mechanisms. *Journal of Cellular Physiology*, *233*(1), 141-152. https://doi.org/10.1002/jcp.25756

Park, J. H., Moon, J. H., Kim, H. J., Kong, M. H., & Oh, Y. H. (2020). Sedentary lifestyle: overview of updated evidence of potential health risks. *Korean Journal of Family Medicine*, *41*(6), 365-373. https://doi.org/10.4082/kjfm.20.0165

Paul, T., & Kumar, K. J. (2024). Standardization of herbal medicines for lifestyle diseases. In A. K. Dhara, & S. C. Mandal (Eds.). *Role of herbal medicines* (pp. 545-557). Springer. https://doi.org/10.1007/978-981-99-7703-1_27

Peluso, I., Palmery, M., & Serafini, M. (2015). Association of flavonoid-rich foods and statins in the management of hypercholesterolemia: a dangerous or helpful combination? *Current Drug Metabolism*, *16*(9), 833-846. https://doi.org/10.2174/1389200216666151015113828

Pham, D.-C., Shibu, M. A., Mahalakshmi, B., & Velmurugan, B. K. (2020). Effects of phytochemicals on cellular signaling: reviewing their recent usage approaches. *Critical Reviews in Food Science and Nutrition*, *60*(20), 3522-3546. https://doi.org/10.1080/10408398.2019.1699014

Pirillo, A., & Norata, G. D. (2023). The burden of hypercholesterolemia and ischemic heart disease in an ageing world. *Pharmacological Research*, *193*, Article 106814. https://doi.org/10.1016/j.phrs.2023.106814

Ramkumar, S., Raghunath, A., & Raghunath, S. (2016). Statin therapy: review of safety and potential side effects. *Acta Cardiologica Sinica*, *32*(6), 631-639. https://doi.org/10.6515/acs20160611a

Rezaei-Golmisheh, A., Malekinejad, H., Asri-Rezaei, S., Farshid, A. A., & Akbari, P. (2015). Hawthorn ethanolic extracts with triterpenoids and flavonoids exert hepatoprotective effects and suppress the hypercholesterolemia-induced oxidative stress in rats. *Iranian Journal of Basic Medical Sciences*, *18*(7), 691-699.

Ruuth, M., Äikäs, L., Tigistu-Sahle, F., Käkelä, R., Lindholm, H., Simonen, P., Kovanen, P. T., Gylling, H., & Öörni, K. (2020). Plant stanol esters reduce LDL (low-density lipoprotein) aggregation by altering LDL surface lipids: the blood flow randomized intervention study. *Arteriosclerosis, Thrombosis and Vascular Biology*, *40*(9), 2310-2321. https://doi.org/10.1161/ATVBAHA.120.314329

Safari-Alighiarloo, N., Taghizadeh, M., Rezaei-Tavirani, M., Goliaei, B., & Peyvandi, A. A. (2014). Protein-protein interaction networks (PPI) and complex diseases. *Gastroenterology and Hepatology from Bed to Bench*, *7*(1), 17-31.

Saklayen, M. G. (2018). The global epidemic of the metabolic syndrome. *Current Hypertension Reports*, 20(2), Article 12. https://doi.org/10.1007/s11906-018-0812-z

Shi, Z., & Han, S. (2025). Personalized statin therapy: Targeting metabolic processes to modulate the therapeutic and adverse effects of statins. *Heliyon*, *11*(1), Article e41629. https://doi.org/10.1016/j.heliyon.2025.e41629

Shimano, H., & Sato, R. (2017). SREBP-regulated lipid metabolism: convergent physiology-divergent pathophysiology. *Nature Reviews Endocrinology*, *13*(12), 710-730. https://doi.org/10.1038/nrendo.2017.91

Srivastava, S., & Misra, A. (2018). Quality control of herbal drugs: Advancements and challenges. In B. Singh, & K. Peter (Eds.). *New age herbals: resource, quality and pharmacognosy* (pp. 189-209). Springer. https://doi.org/10.1007/978-981-10-8291-7_10

Sut, S., & Dall'Acqua, S. (2023). Food-derived nutraceuticals for hypercholesterolemia management, mode of action and active ingredients. *Food Bioscience*, *54*, Article 102866. https://doi.org/10.1016/j.fbio.2023.102866

Svatikova, A., & Kopecky, S. L. (2017). Cholesterol management in the era of PCSK9 inhibitors. *Current Cardiology Reports*, *19*, Article 83. https://doi.org/10.1007/s11886-017-0891-5

Szklarczyk, D., Gable, A. L., Nastou, K. C., Lyon, D., Kirsch, R., Pyysalo, S., Doncheva, N. T., Legeay, M., Fang, T., Bork, P., Jensen, L., & von Merring, C. (2021). The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Research*, *49*(D1), D605-D612. https://doi.org/10.1093/nar/gkab835

Tavori, H., Rashid, S., & Fazio, S. (2015). On the function and homeostasis of PCSK9: reciprocal interaction with LDLR and additional lipid effects. *Atherosclerosis*, *238*(2), 264-270. https://doi.org/10.1016/j.atherosclerosis.2014.12.017

Trautwein, E. A., Vermeer, M. A., Hiemstra, H., & Ras, R. T. (2018). LDL-cholesterol lowering of plant sterols and stanols-which factors influence their efficacy? *Nutrients*, *10*(9), Article 1262. https://doi.org/10.3390/nu10091262

Upadhyay, R. K. (2023). High cholesterol disorders, myocardial infarction and its therapeutics. *World Journal of Cardiovascular Diseases*, *13*(8), 433-469. https://doi.org/10.4236/wjcd.2023.138040

Upadhyay, S., & Dixit, M. (2015). Role of polyphenols and other phytochemicals on molecular signaling. *Oxidative Medicine and Cellular Longevity*, *2015*(1), Article 504253. https://doi.org/10.1155/2015/504253

Vallianou, I., & Hadzopoulou-Cladaras, M. (2016). Camphene, a plant derived monoterpene, exerts its hypolipidemic action by affecting SREBP-1 and MTP expression. *PLoS One*, *11*(1), Article e0147117. https://doi.org/10.1371/journal.pone.0147117

Vekic, J., Zeljkovic, A., Stefanovic, A., Bogavac-Stanojevic, N., Ilias, I., Silva-Nunes, J., Stoian, A. P., Janez, A., & Rizzo, M. (2022). Novel pharmaceutical and nutraceutical-based approaches for cardiovascular diseases prevention targeting atherogenic small dense LDL. *Pharmaceutics*, *14*(4), Article 825. https://doi.org/10.3390/pharmaceutics14040825

Vučević, D., Đorđević, D., Stanojević, M., Jorgačević, B., Đorović, D., Radak, Đ., & Radosavljević, T. (2016). Hypercholesterolemias: Pathogenesis and pathophysiological implications. *Medicinska Istraživanja*, *50*(2), 30-43. https://doi.org/10.5937/MedIst1602030V

Wang, H. H., Liu, M., Portincasa, P., & Wang, D. Q.-H. (2020). Recent advances in the critical role of the sterol efflux transporters $ABCG_5$/G8 in health and disease. *Advances in Experimental Medicine and Biology*, *1276*, 105-136. https://doi.org/10.1007/978-981-15-6082-8_8

Ward, N. C., Watts, G. F., & Eckel, R. H. (2019). Statin toxicity: mechanistic insights and clinical implications. *Circulation Research*, *124*(2), 328-350. https://doi.org/10.1161/CIRCRESAHA.118.312782

Xu, J., Wang, T., Shu, H., Shi, S., Tao, L., & Li, J.-J. (2023). Insight into the role of PCSK9 in glucose metabolism. *Clinica Chimica Acta*, *547*, Article 117444. https://doi.org/10.1016/j.cca.2023.117444

Yamanashi, Y., Takada, T., & Suzuki, H. (2018). Associations between lifestyle-related diseases and transporters involved in intestinal absorption and biliary excretion of cholesterol. *Biological and Pharmaceutical Bulletin*, *41*(1), 1-10. https://doi.org/10.1248/bpb.b17-00690

Zhang, S., Ren, X., Zhang, B., Lan, T., & Liu, B. (2024). A systematic review of statins for the treatment of nonalcoholic steatohepatitis: safety, efficacy, and mechanism of action. *Molecules*, *29*(8), Article 1859. https://doi.org/10.3390/molecules29081859

Zhao, W., Xu, S., & Weng, J. (2023). $ASGR_1$: an emerging therapeutic target in hypercholesterolemia. *Signal Transduction and Targeted Therapy*, *8*(1), Article 43. https://doi.org/10.1038/s41392-023-01319-5

Zhao, Y., Liu, J., Hao, W., He, Z., Zhu, H., Liang, N., Ma, K. Y., He, W.-S., Yang, Y, & Chen, Z.-Y. (2018). Plasma cholesterol-lowering activity of piperine is mediated by inhibition on cholesterol absorption via down-regulation of intestinal ACAT2 and MTP. *Journal of Functional Foods*, *49*, 465-471. https://doi.org/10.1016/j.jff.2018.09.014

Zheng, Z., Zhou, Y., Zhang, X., Myat, P., Xie, Z., Lu, C., Pang, T., Xue, B., Xu, D., Chen, Y., Chen, X., Li, H., & Xu, X. (2016). Anhydroicaritin improves diet-induced obesity and hyperlipidemia and alleviates insulin resistance by suppressing SREBPs activation. *Biochemical Pharmacology*, *122*, 42-61. https://doi.org/10.1016/j.bcp.2016.10.016