Escola Superior
de Tecnologia
da Saúde
Politécnico de Coimbra

Rita Rafaela Galinha Costa

DRUG-FOOD INTERACTIONS OF LIPID-LOWERING STATIN DRUGS AND MEDITERRANEAN-BASED DIETARY SUPPLEMENTS: FRIENDS OR FOES?

Dissertação no âmbito do Mestrado em Farmácia – Especialização em Farmacoterapia Aplicada orientada pelo Doutor João Malva, pela Professora Doutora Sofia Andreia Domingues Viana e pelo Doutor Flávio Nelson Fernandes Reis e apresentada na Escola Superior de Tecnologia da Saúde do Politécnico de Coimbra para obtenção do grau de Mestre.

Setembro de 2024

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Resumo

Contexto: Alterações no estilo de vida, como a adoção de padrões alimentares saudáveis associados à Dieta Mediterrânea (MedDiet), são fundamentais em qualquer plano de tratamento, incluindo em pacientes medicados com estatinas. O número de consumidores que recorrem ao uso de alimentos fortificados com componentes MedDiet e/ou nutracêuticos tem vindo a aumentar, não obstante a probabilidade de ocorrência de efeitos adversos potencialmente graves aquando combinação de ambos os componentes. Um exemplo paradigmático prende-se com os suplementos alimentares enriquecidos em polifenóis, uma classe de metabolitos secundários com propriedades anti-dislipidémicas amplamente disponível no mercado sem necessidade de prescrição médica. Com efeito, a co-administração de estatinas e polifenóis parece potenciar a incidência de miopatia induzida por estatinas por meio da inibição das proteínas OATP, CYP450 e HMG-CoA redutase. No entanto, há elevada probabilidade de existirem alvos biológicos concorrentes a mediar estas interações, potencialmente influenciando tanto as respostas farmacodinâmicas quanto farmacocinéticas das estatinas. Por outro lado, subsistem dúvidas quanto ao consumo crónico de suplementos à base de polifenóis poder alcançar concentrações plasmáticas suficientes para desencadear alterações da farmacocinética das estatinas relevantes na clínica. O presente trabalho tem como objetivo mapear as interações relatadas entre as estatinas e os polifenóis e identificar os principais alvos biológicos envolvidos, com o objetivo de elucidar o seu impacto na farmacocinética, eficácia e toxicidade das estatinas.

Métodos: Foi realizada uma revisão *scoping* utilizando as bases de dados PubMed/Medline, Scopus e Web of Science. Este trabalho foi desenhado de acordo com o PRISMA-ScR. O protocolo da revisão foi registado no Open Science Framework (https://doi.org/10.17605/OSF.IO/PYB4R).

Resultados: Dos 134 registos identificados, 38 foram incluídos na análise. A rosuvastatina, sinvastatina e atorvastatina foram as três estatinas mais comumente utilizadas nos estudos incluídos. Todos os polifenóis usados pertencem à classe dos flavonoides, exceto um classificado como estilbeno. Oitenta e quatro porcento (84,2%) dos estudos reportam Interações entre as estatinas e polifenóis. O OATP foi o alvo biológico mais frequentemente identificado como responsável por essas interações (n=16), seguido pela inibição das

proteínas CYP450 (n=9), P-glicoproteína (n=3), HMG-CoA redutase (n=2) e esterases intestinais (n=1). Os parâmetros farmacocinéticos que descrevem as interações entre estatinas e polifenóis demonstraram considerável variabilidade e inconsistência entre os estudos, sublinhando o potencial aumento tanto da eficácia terapêutica quanto dos efeitos adversos.

Conclusões: As interações entre estatinas e polifenóis ocorrem por meio do transporte de fármacos mediado pelas proteínas OATPe P-glicoproteína bem como do metabolismo dependente das enzimas CYP450 e esterases intestinais, afetando vias bioquímicas críticas do metabolismo lipídico, como a via do mevalonato, essencial para a biossíntese do colesterol. Este trabalho avança o conhecimento ao fornecer um *framework* mecanístico que pode orientar investigação futura relacionada com a otimização da eficácia terapêutica das estatinas-polifenóis por forma a evitar quer resultados terapêuticos sub-ótimos, quer o aumento do risco de efeitos adversos. Em última análise, este estudo pretende consciencializar investigadores, doentes, prestadores de serviços de saúde e sistemas de farmacovigilância sobre a necessidade de sistematizar recomendações práticas sobre como prevenir e/ou gerir interações entre estatinas e polifenóis no contexto clínico.

Palavras-chave

Estatinas; Polifenóis; Flavonóides; Interações Fármaco-Alimento; Modulação Farmacodinâmica e Farmacocinética

Abstract

Background: Lifestyle modifications, particularly the adoption of healthy dietary patterns like the Mediterranean Diet (MedDiet), are foundational in any treatment plan, including for patients prescribed first-line statin therapy for hypercholesterolemia. However, with the increasing use of MedDiet-fortified foods and nutraceuticals by health-conscious consumers, combining these products with statins could lead to potentially serious adverse effects. A prominent example involves polyphenol supplements, a class of secondary metabolites with lipid-lowering properties, widely available over the counter. Drug-food interactions between statins and polyphenols can significantly impact both therapeutic efficacy and the incidence of adverse effects. Changes in statin pharmacokinetics due to polyphenol co-administration are well-documented and are implicated in statin-induced myopathy through the modulation of OATP, CYP450, and HMG-CoA reductase. However, additional biological targets may also play a role in these interactions, potentially influencing both pharmacodynamic and pharmacokinetic responses and ultimately affecting the success of lipid-lowering therapy. Furthermore, it remains uncertain whether chronic consumption of polyphenol-based supplements can achieve plasma concentrations sufficient to meaningfully alter statin pharmacokinetics in clinical settings. This work aims to systematically map the reported statin-polyphenol interactions and identify the key biological targets involved, with the goal of elucidating their impact on statin pharmacokinetics, efficacy and toxicity.

Methods: A scoping review was conducted using the PubMed/Medline, Scopus and Web of Science databases. This work was designed in accordance with PRISMA-ScR. Review protocol was registered in the Open Science Framework (https://doi.org/10.17605/OSF.IO/PYB4R).

Results: Out of the 134 records identified, 38 were included in the analysis. Rosuvastatin, simvastatin, and atorvastatin were the three most commonly used statins in the enrolled studies. All polyphenols belonged to the flavonoid class, except for one, which was a stilbene. Statin-polyphenol interactions were reported in 84.2% of the studies analyzed. OATP inhibition was the most frequently identified biological target responsible for these interactions (n=16), followed by the inhibition of CYP enzymes (n=9), P-glycoprotein (n=3), HMG-CoA reductase (n=2), and intestinal esterases (n=1). The pharmacokinetic outcomes

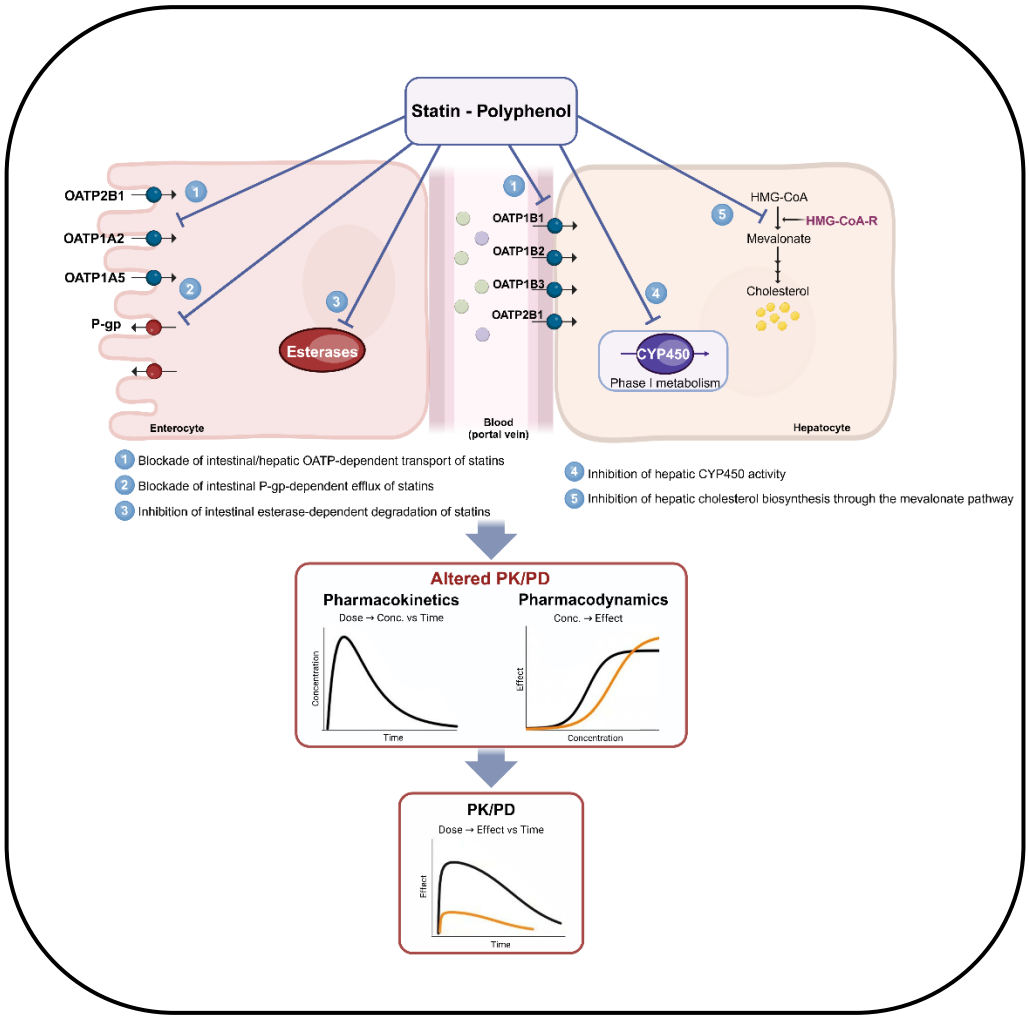
of statin-polyphenol interactions demonstrated considerable variability and inconsistency across the studies, underscoring the potential enhancement of both therapeutic efficacy and adverse effects.

Conclusions: Statin-polyphenol interactions occur through OATP/P-glycoprotein-mediated drug transport and CYP450/esterase-dependent metabolism, affecting critical biochemical pathways involved in lipid metabolism, such as the mevalonate pathway, which is essential for cholesterol biosynthesis. This work advances knowledge by providing a mechanistic framework that can guide further research on the optimization of statin-flavonoid therapeutic efficacy to avoid both suboptimal treatment outcomes and increased risk of adverse effects. Ultimately, it raises awareness among researchers, consumers, healthcare providers, and pharmacovigilance systems, emphasizing the need for practical recommendations on how to prevent and/or manage statin-polyphenol interactions.

Keywords

Statins; Polyphenols; Flavonoids; Drug-food interactions; Pharmacodynamic and Pharmacokinetic Modulation

Graphical abstract



List of abbreviations

AUC – Area under the curve

BMI – body mass index

CHD – Coronary heart disease

CL/F – clearance adjusted for bioavailability

Cmax – maximum plasma concentration

CoA – Coenzyme A

CVD – Cardiovascular disease

CYP – cytochrome P450

EGCG – Epigallocatechin-3-gallate

EGFR – Epidermal growth factor receptor

EMA – European Medicines Agency

ER – Endoplasmic reticulum

FAs – Fatty acids

FDA – Food and Drug Administration

HDL – High-density lipoprotein

HMG-CoA – 3-hydroxy-3-methylglutaryl coenzyme A

HMG-CoA-R – 3-hydroxy-3-methylglutaryl coenzyme A reductase

LDL – Low-density lipoprotein

LMD – Lipid metabolism disorder

NADPH - Nicotinamide adenine dinucleotide phosphate

NEFAs – Non-esterified fatty acids

OATPs – Organic anion-transporting polypeptides

P-gp – P-glycoprotein

PCC – Participants-Concept-Context

PMDA – Pharmaceuticals and Medical Devices Agency

PPAR – Peroxisome proliferator-activated receptor

PPB - plasma protein binding

SAS – Statin-associated symptoms

SAMS – Statin-Associated Muscle Symptoms

$T_{1/2}$ – Half-life

Tmax – Time to reach maximum plasma concentration

VECs – Vascular endothelial cells

VLDL – Very-low-density lipoprotein

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Chapter I | **INTRODUCTION**

1.1. Lipid dysmetabolism and Human Diseases

1.1.1. Lipid functions

Lipids are organic compounds insoluble in aqueous solvents that are mostly stored in adipose tissue and serve as a high caloric density energy source. From a chemical standpoint, they are esterified forms of fatty acids commonly found as triglycerides, phospholipids and/or steroids. Lipids are mostly stored in adipose tissue and can protect human organs such as the spleen, liver, heart, and kidneys, from damage (Natesan & Kim, 2021). They are key biological molecules that display important roles in different active functions of our body. Accordingly, lipids are fundamental structural elements of cellular membranes acting as a selective barrier separating the cell from the environment while ensuring subcellular compartmentalization. Moreover, they are chief molecules in energy metabolism to fuel the cell and serve as a high caloric density energy source. As such, they display important roles in different active functions of our body, such as fat-soluble nutrient transportation, hormone regulation, nerve impulse transmission, to name just a few (Mutlu, Duffy, & Wang, 2021).

1.1.2. Lipid metabolism and transport

The liver plays a key and vital role in lipid metabolism as it serves as a reservoir for storing extensive quantities of excessive fat. Through prolonged energy overload, the unspent excess energy is stored in adipose tissue and in hepatocytes in the form of neutral lipids, mainly triglycerides and sterol/cholesterol esters (Mutlu et al., 2021). Triglycerides are glycerolipids consisting of three fatty acids (FAs) attached to glycerol. Biosynthesis of triglycerides begin with glycerol-3-phosphate acyltransferase that combines glycerol-3-phosphate, a phosphorylated glycerol, with coenzyme A-bound FAs (acyl-CoA) to generate lysophosphatidic acid. A second acyl-CoA can be added by acyl-CoA:1-acylglycerol-3-phosphate acyltransferase to generate phosphatidic acid that is further hydrolyzed by lipins to generate diacylglyceride. A third esterification step catalyzed by diacylglyceride acyltransferase (DGAT) produces the triglyceride final form. In regards to cholesterol esters, they can be synthesized by two types of enzymes: acyl-CoA:cholesterol

acyltransferase and lecithin:cholesterol acyltransferase. Within the cell, neutral lipids are stored in organelles termed lipid droplets that play a crucial role in energy metabolism and signal transduction. Degradation processes of neutral lipids rely mainly on lipolysis and lipophagy (Pan, Shi, Yu, Mamtimin, & Zhu, 2023). Lipolysis involves metabolization of lipids via lipid droplet-associated lipases: ATGL toward triglycerides, diacylglycerol lipase (DAGL) and HSL toward diacylglyceride, and monoacylglycerol lipase (MAGL) toward monoglyceride. Lipophagy also contributes to lipid metabolization from lipid droplets, during which autophagosomes engulf lipid droplets and fuse with lysosomes towards lipid hydrolysis by lysosomal acid lipases. The resultant free FAs are subjected to further degradation through mitochondrial or peroxisomal β-oxidation generating ATP via the tricarboxylic acid cycle and oxidative phosphorylation (Natesan & Kim, 2021).

Given their abundance, it is also important to highlight the phospholipids and fatty acyls lipidic classes. The two most abundant membrane phospholipids are glycerophospholipids and sphingolipids, in which FA chains and polar head groups are linked to either a glycerol or sphingosine base, respectively. While glycerophospholipids are derivatives of phosphatidic acid with phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylinositol, and cardiolipin polar head groups, sphingolipids have a ceramide base (Bacle et al., 2020).

Being hydrophobic molecules, lipids need to be transported by lipoproteins in the blood as they do not dissolve in water-based environments like blood plasma. Several lipoproteins encapsulate these lipids within a hydrophilic outer layer, a transport system that facilitate the transportation of lipids from the intestine to the liver (the primary site of lipid conversion) and other peripheral tissues or removed from circulation when necessary, maintaining lipid balance and preventing harmful accumulation in the arteries (Kempegowda, Sugur, & Thimmulappa, 2024). Lipoproteins are complex particles composed of lipids and proteins, classified by their density including low-density lipoprotein (LDL), high-density lipoprotein (HDL) and very-low-density lipoprotein (VLDL). Each lipoprotein type has a distinct role in lipid transport and metabolism. LDL is often referred to as "bad cholesterol" because it transports cholesterol from the liver to peripheral tissues, where it can contribute to plaque buildup in the arteries. Conversely, HDL, or "good cholesterol," helps remove cholesterol from tissues and transport it back to the liver for excretion or recycling (Duranton et al., 2019).

1.1.3. Lipid metabolism disorder

Lipid metabolism disorder (LMD) is a common condition characterized by abnormal blood levels of lipids or lipoproteins and are significant contributors to global disease burden (Natesan & Kim, 2021). LMD is a well-established risk factor for systemic atherosclerosis, cardiovascular and cerebrovascular diseases. Other risk factors, such as obesity, diabetes, and sedentary lifestyles, exacerbate lipid abnormalities and their health outcomes (Pan et al., 2023). In addition, research has shown that the composition and functionality of lipoproteins are also affected by inflammation and oxidative stress, which can impair the protective functions of HDL and enhance the atherogenic potential of LDL. Moreover, new therapeutic strategies, including the use of statins and PCSK9 inhibitors, aim to lower LDL levels and improve the balance between different lipoproteins, offering promising approaches to reduce the incidence of cardiovascular diseases (Kempegowda et al., 2024). In low- and middle-income countries, the rising incidence of lipid disorders, often linked to dietary shifts and urbanization, is particularly concerning, with projections indicating a growing burden on healthcare systems (Kaneko et al., 2021).

Lipid dysmetabolism is often found in conditions such as Diabetes Mellitus, cardiovascular and cerebrovascular diseases. Diabetic dyslipidemia is featured by a pattern of lipoprotein deviations extremely atherogenic with clinical irregularities taking place at a range of plasma triglyceride levels above the upper normal range or mild hypertriglyceridemia (>1.5 mmol/L) (Natesan & Kim, 2021). Hyperinsulinemia typically yields to increased release of non-esterified fatty acids (NEFAs) to plasma as well as enhanced plasmatic ketone bodies concentration, further contributing to lipid dysmetabolism (Natesan & Kim, 2021; Poznyak et al., 2020). Elevated triglyceride levels are also commonly associated with an increased risk of cardiovascular and cerebrovascular disease, especially in the presence of low HDL cholesterol levels. The pathophysiological mechanisms are closely related to direct infiltration of the arterial wall, inflammation, oxidative stress, endothelial dysfunction, and impaired fibrinolysis (Natesan & Kim, 2021). Saturated fatty acyls induce various abnormal phenomena on vascular endothelial cells (VECs), such as oxidative stress, inflammatory response, endoplasmic reticulum (ER) stress, apoptosis, and autophagy, thereby impairing VECs barrier function, increasing permeability, promoting leukocyte adhesion and migration, and leading to atherosclerosis

formation. In addition, saturated fatty acyls can also alter VECs biological characteristics by affecting membrane fluidity, protein palmitoylation, mitochondrial function, among other mechanisms. Meanwhile, unsaturated fatty acyls have the opposite effects. They protect VECs from oxidative stress, the inflammatory response, ER stress, apoptosis, and autophagy damage, thereby maintaining VECs barrier function, reducing permeability, inhibiting leukocyte adhesion and migration, and preventing atherosclerosis development (Pan et al., 2023).

1.2. Lipid dysmetabolism and lipid-lowering drugs: A focus on statins

1.2.1. Lipid-lowering drugs: An overview

Several classes of lipid-modifying drugs are available worldwide, mostly including: i) bile acid-binding resins (e.g. cholestyramine, colestipol, colesevalam), ii) nicotinic acid (niacin), iii) fibrates (e.g. fenofibrate, clofibrate, gemfibrozil, bezafibrate), iv) cholesterol-absorption inhibitors (e.g. ezetimibe) (Zodda, Giammona, & Schifilliti, 2018). Given their preponderant role in the clinical management of lipid dysmetabolism, statins are analyzed in more detailed in section 1.2.2.

i) Bile acid-binding resins: including cholestyramine, colesevelam, and colestipol, they are orally administered anion-exchange resins that are neither absorbed systemically nor metabolized by digestive enzymes. At the intestinal level, they bind to the two main biliary acids (glycocholic acid and taurocholic acid) making an insoluble complex that is partially removed from the enterohepatic circulation and excreted in feces. Cholestyramine and colestipol are two hygroscopic molecules with high molecular weight (>1,000,000). They are effective in lowering total and LDL-C, reducing mortality and cardiovascular events (Othman, Myrie, & Jones, 2013). However, they are usually not well tolerated since they show significant gastrointestinal side effects, including abdominal pain, heartburn, bloating and constipation (Freese & Lysne, 2023).

ii) Nicotinic acid: also termed as niacin, vitamin B3 or PP, nicotinic acid significantly raises HDL levels while decreasing those of VLDL and LDL through mechanisms that do not involve cholesterol biosynthesis or catabolism. It is a powerful inhibitor of the intracellular lipase system, generating multiple effects that prevent lipolysis in adipose tissue. Moreover, it stimulates the activity of lipoprotein lipase, thus increasing the clearance of VLDL (Freese & Lysne, 2023). Niacin is approved for the treatment of hypercholesterolemia and hypertriglyceridemia. The reduction of triglycerides can be already observed several hours after the intake of niacin, while the effects on cholesterol decrease take a few days. Gastrointestinal intolerance is an effect that can be minimized by administering the drug with meals. The association of niacin with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors may lead to an increased risk of myopathy and rhabdomyolysis, whereas with bile acid sequestrants, it may reduce the bioavailability of niacin if the administrations are not spaced (Saboori, Yousefi Rad, Tammam, Thondre, & Coe, 2024).

iii) Fibrates: this class of lipid-lowering drugs encompass fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil, to name a few. They activate the peroxisome proliferator-activated receptor (PPAR)-alpha, bezafibrate also an agonist of PPAR gamma and delta isoforms. Fibrates decrease triglyceride levels and increase HDL-C levels, the latter effect more pronounced in patients with hypertriglyceridemia (Kounatidis et al., 2024). Fibrates have near 100% oral bioavailability, although fenofibrate, in its immediate release form, display a marked reduction (60%). Clofibrate and fenofibrate differ as they are dosed in the prodrug forms. Fenofibric acid is the circulating pharmacological active moiety following the oral administration of the ester of fenofibric acid (fenofibrate). Fenofibrate as monotherapy decreases serum TG levels by 20–50% and increases HDL-C levels by 10–50% (Jin et al., 2023).

iv) Ezetimibe: is the first drug capable of selectively inhibiting the intestinal absorption of dietary cholesterol and phytosterols. The ezetimibe molecular target is a sterol transport, Niemann-Pick C1-Like 1 (NPC1L1), responsible for intestinal cholesterol and sterol uptake. The molecule appears to be selective because it does not interfere with the absorption of triglycerides, liposoluble vitamins, fatty acids, bile acids, progesterone, and ethinyl estradiol (McPherson, Adreak, & Sharma, 2024). Ezetimibe is rapidly absorbed and extensively metabolized (Cmax 2–3 h). It is indicated both in association with statins to

reduce circulating levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apoB) in patients with primary hypercholesterolemia (family or non-familial heterozygosity) that are not adequately controlled with statins alone. In addition, it is also indicated for homozygous familial hypercholesterolemia in combination with atorvastatin or simvastatin, and homozygous familial sitosterolemia. In all cases, patient should not have responded to diet, physical activity, and other non-pharmacological measures (Soleimani et al., 2024).

1.2.2. Statins: A chemical perspective

In 1972, Dr. Akiro Endo, a Japanese scientist working at the pharmaceutical company Sankyo in Tokyo, made a groundbreaking discovery in the field of cholesterol management. His research focused on identifying compounds capable of inhibiting cholesterol synthesis, and after testing hundreds of microbial samples, he isolated a compound from the fungus *Penicillium citrinum* that inhibited cholesterol production. This compound, originally called ML-236B, is now known as mevastatin. This discovery paved the way for the development of other statins: chemical modification of fungal compounds (e.g., simvastatin), microbial modification of fungal compounds (e.g., pravastatin), and full chemical synthesis (e.g., fluvastatin, atorvastatin, cerivastatin, pitavastatin, and rosuvastatin) (Freese & Lysne, 2023).

All currently marketed statins contain a structure resembling HMG-CoA (Figure 1, highlight in orange) which is essential for their mechanism of action (Shitara & Sugiyama, 2006). For instance, lovastatin and simvastatin have a lactone ring, which is converted into the active open acid form in the body. Conversely, pravastatin is administered in its active open acid form from the outset. Fluvastatin, however, is unique as it is entirely synthetic, featuring a mevalonolactone derivative structure with a fluorophenyl-substituted indole ring. Later statins, developed after fluvastatin, also contain similar fluorophenyl groups, and all synthetic statins exist in the open acid form (Schachter, 2005). The structural differences between statins influence their affinity for the enzyme HMG-CoA reductase, which in turn affects their pharmacological activity and pharmacokinetic properties, such as tissue distribution, metabolic stability, and interactions with enzymes and transporters. Consequently, understanding the physicochemical characteristics of each statin is key to

predicting their pharmacokinetic behavior and potential drug interactions (Shitara & Sugiyama, 2006).

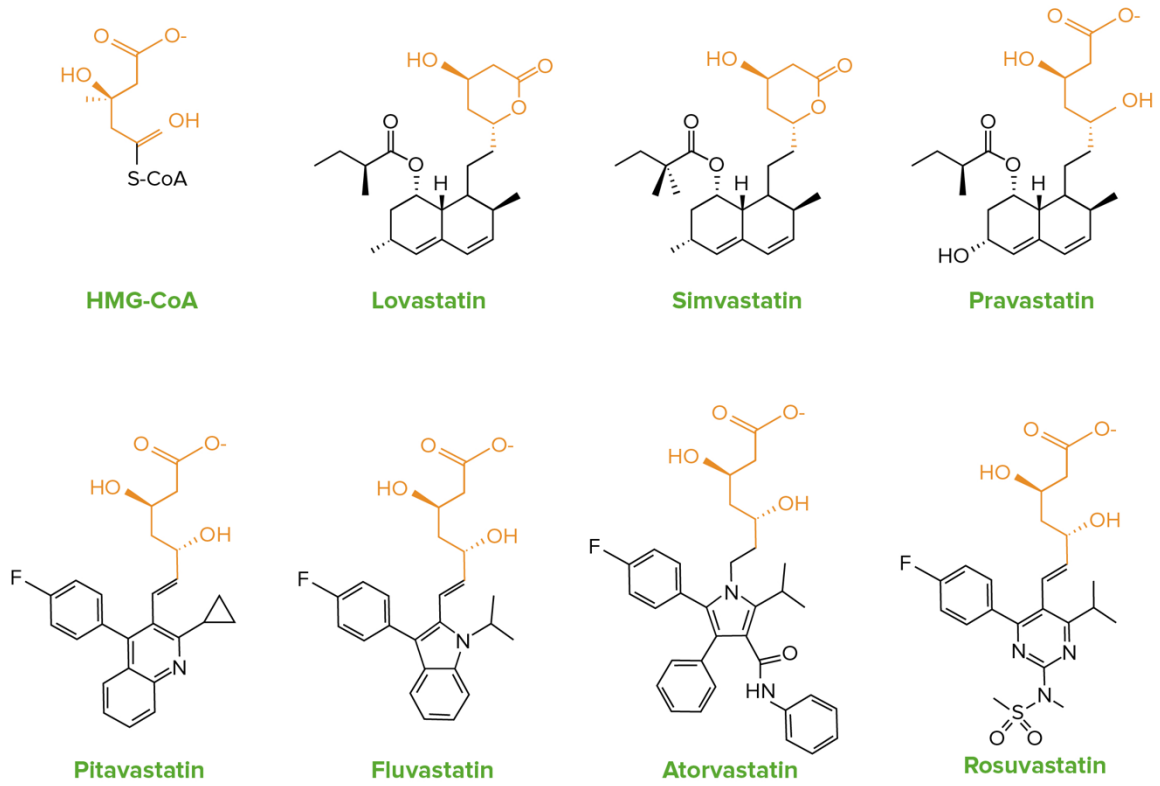

Figure 1. Statins chemical structure (HMG-CoA-structural moiety highlighted in orange).

1.2.3. Statins Pharmacodynamics: Mechanism of action and clinical use

On the basis of clinical trial evidence, the most commonly prescribed lipid-modifying therapies are the HMG-CoA reductase inhibitors, more commonly known as the statins. HMG-CoA reductase catalyses the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol synthesis (Attardo, Musumeci, Velardo, & Toscano, 2022; Sirtori, 2014).

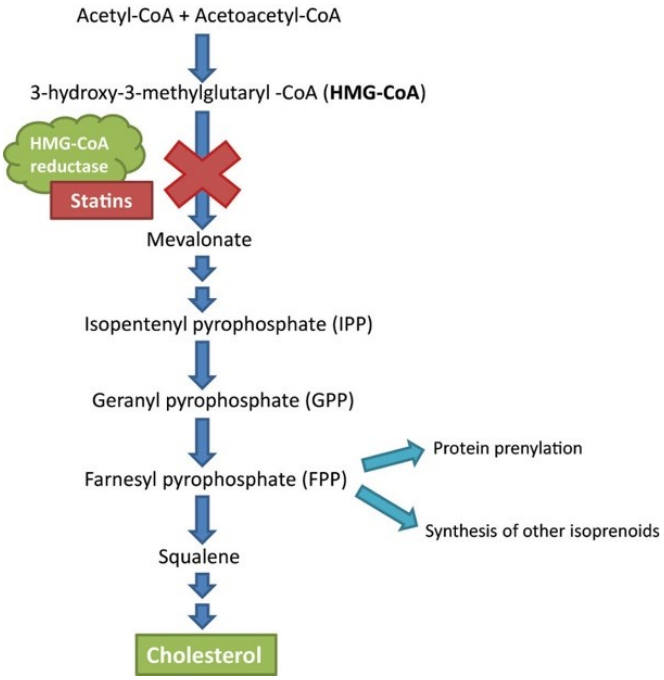

Figure 2. Statins modulation of the mevalonate pathway. Retrieved from (Sirtori, 2014).

Statins are competitive antagonists of HMG-CoA reductase as they reversibly compete with HMG-CoA (the endogenous substrate) for the active site within the enzyme. Still, they do not compete for that of the co-enzyme NADPH, suggesting that their HMG-CoA-like moieties bind to the HMG-CoA-binding portion of the enzyme active site (Davies et al., 2016). Conformational changes decrease cholesterol production and reduces the intracellular cholesterol stores of the hepatocytes (Davies et al., 2016). To counteract the decline in intracellular cholesterol, the LDL-receptor becomes overexpressed at hepatocyte cell surface and free LDL-C is endocyted and degraded at lysosomes, culminating in the reduction of circulating LDL-C levels (Figure 3).

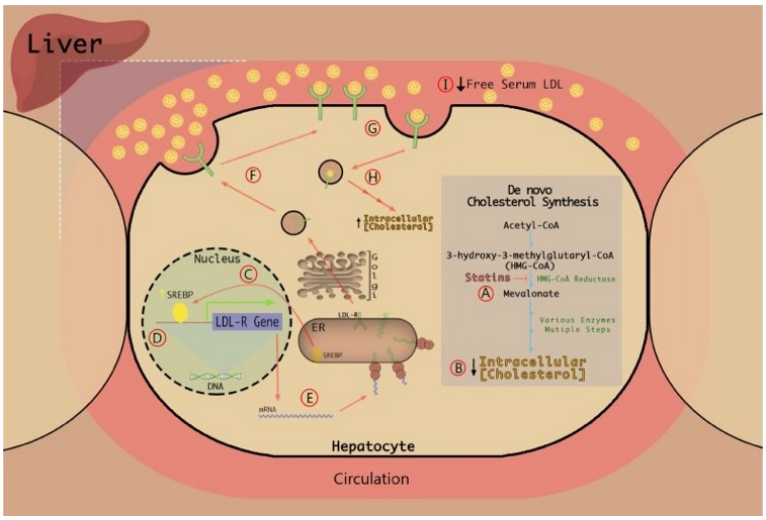

Figure 3. Statin mechanism of action. A) Inhibition of HMG-CoA reductase enzymatic activity; B) Reduction of intracellular cholesterol; C-D) SREBP nuclear translocation and LDL-R gene expression; E-F) LDL-R gene transcription, translation and translocation to the cell membrane; G) Intracellular degradation of LDL-C; H) Intracellular cholesterol increase; I) reduction of circulating LDL-C levels. Retrieved from (Davies et al., 2016).

Secondary mechanisms by which statins may reduce levels of atherogenic lipoproteins include inhibition of hepatic synthesis of apolipoprotein B100 and a reduction in the synthesis and secretion of triglyceride-rich lipoproteins. In addition, statins may exert beneficial cardiovascular effects independent of their lipid-modifying properties. These pleiotropic properties may be explained by inhibition of synthesis of nonsteroidal isoprenoid compounds, which are also produced from mevalonic acid, and include improvement of endothelial cell function, modification of inflammatory responses, and reduction of smooth muscle cell proliferation and cholesterol accumulation (Schachter, 2005).

Statins are commonly prescribed medications for patients with dyslipidemia and are also widely used in those with conditions such as coronary artery disease, diabetes mellitus, stroke, hypertension, and chronic kidney disease, regardless of whether they have dyslipidemia. Among the currently available statins, rosuvastatin is the most potent in lowering LDL-C, with reductions of up to 63% reported at a daily dose of 40 mg. Comparative studies confirm that, on a milligram-per-milligram basis, rosuvastatin is the most effective statin for reducing LDL-C, followed by atorvastatin, simvastatin, and pravastatin. Statins also raise HDL-C levels to varying extents, though a consistent dose–

response relationship is not always evident. In a comparative study of patients with hypercholesterolemia, rosuvastatin at doses of 10–40 mg increased HDL-C by 7.7–9.6%, compared to 2.1–5.7% for atorvastatin (10–80 mg), 5.2–6.8% for simvastatin (10–80 mg), and 3.2–5.6% for pravastatin (10–40 mg) (Schachter, 2005).

The benefits of statins extend beyond merely lowering cholesterol levels, as they offer various additional positive effects (pleiotropic effects), which include anti-inflammatory, antioxidant, anti-proliferative, apoptotic, cell cycle regulatory, and immunomodulatory properties (Attardo et al., 2022; Freese & Lysne, 2023; Pawelec & Gouttefangeas, 2006)). While high LDL-C plays a crucial role in the development of atherosclerosis, cholesterol is still an essential component of the cell membrane and the precursor of steroid hormones. Thus, statin therapy must strike a balance between the cholesterol excess and the physiological cholesterol needs (Freese & Lysne, 2023).

Several randomized clinical trials have demonstrated a significant reduction in cardiovascular disease (CVD) risk with statin use, both in primary and secondary prevention settings. For instance, in the PROSPER study focusing on a population over the age of 70 at risk of developing Coronary Heart Disease and stroke, the composite endpoint of coronary heart disease (CHD) death, myocardial infarction and stroke was significantly reduced by 23% with statin treatment (Loeffen et al., 2015). Moreover, the lipid-lowering arm of the ASCOT study was stopped given the observed benefits in the statin-treated group. ASCOT assessed the effects of statins in primary prevention of CHD in hypertensive patients with average or lower-than-average cholesterol levels but at least 3 other cardiovascular risk factors. It was observed an overall 36% risk reduction with statin treatment and a significant 27% risk reduction for fatal and non-fatal stroke (Loeffen et al., 2015; Sever et al., 2012). The link between elevated LDL-C and the onset of CVD and CHD, along with the proven benefits of statin treatments in improving health by lowering LDL-C levels and reducing CVD-related mortality rates, is therefore well established. As a preventive measure for those at high risk, statins help maintain normal LDL-C levels. For individuals with existing CVD, statins are used as a secondary preventive strategy, effectively lowering LDL-C and minimizing the risk of life-threatening cardiovascular events (Davies et al., 2016).

1.2.4. Statins Pharmacodynamics: Adverse drug reactions

Statins have been shown to be safe medications, though they can cause adverse effects, particularly affecting muscles, metabolism, liver, and the nervous system, with muscle-related issues being the most commonly reported. These side effects are collectively referred to as statin-associated symptoms (SAS). Most SAS are dose-dependent, and nearly half of patients on high-dose statins discontinue the medication within a year due to these symptoms. The likelihood of drug interactions increases with age and the number of medications a patient is taking. Other factors that increase the risk of statin intolerance include frailty, surgery, infections, female gender, physical exertion, hypothyroidism, chronic kidney disease, and genetic predispositions (Mollazadeh et al., 2021).

Besides HMG-CoA-reductase, statins interact with various membrane and cytosolic kinases, including epidermal growth factor receptor (EGFR), MET proto-oncogene, receptor tyrosine kinase (MET), SRC proto-oncogene and/or non-receptor tyrosine kinase (Src), to name a few. At higher doses, they also interact with calcium ATPases and peroxisome proliferator-activated receptor α. Additionally, statins can affect mitochondrial function both directly - by impairing complexes in the electron transport chain - and indirectly, by depleting metabolites from the mevalonate pathway, such as CoQ10 and isoprenoids. Increasing evidence suggests that SAS are primarily caused not by the cholesterol-lowering effect itself, but by disruptions to mitochondrial activity, as supported by findings in cell cultures, animal models, and human studies (Mollazadeh et al., 2021). Statins thus act as inhibitors of kinases, calcium ATPases, and mitochondrial complexes, while simultaneously activating PPAR-alpha. These off-target interactions may contribute to the side effects seen in patients on statin therapy, such as muscle and liver-related issues. Interestingly, some of these off-target effects may also explain potential beneficial outcomes, including the possible repurposing of statins for treating inflammatory conditions and cancer (Lagunas-Rangel et al., 2024). Given their clinical relevance, skeletal muscle adverse effects (i), peripheral neuropathy and sleep disturbances (ii) and autoimmune illnesses (iii) will be further assessed.

i) Skeletal Muscle Adverse Effects

Statin intolerance is most frequently associated with a wide range of side effects in the skeletal muscle, the so-called “Statin-Associated Muscle Symptoms” (SAMS). SAMS are quite difficult to be diagnosed and managed because there are no validated biomarkers or tests that can be used to confirm their presence, but also because muscle symptoms could originate from other comorbidities. Observational studies estimate that 10–15% of statin users develop statin-related muscular side effects, ranging from myalgia and fatigue to more severe muscle symptoms with significant creatine kinase (CK) elevations (Shitara & Sugiyama, 2006). Symptoms usually occur after 4–6 weeks of treatment initiation but sometimes after many years (Mollazadeh et al., 2021).

A recent study of Abed et al. evaluated the incidence of myopathy in patients under statins during an observation period of 12 months, showing that the incidence of statin-induced myopathy was 27.4%, highest with simvastatin and lowest with fluvastatin and rosuvastatin. Statins side effects are likely to occur more frequently in elderly patients, because of multiple comorbidities and use of other drugs that may interact negatively with statins. SAMS has a highly variable clinical presentation including more frequently muscle symptoms (myopathy, myalgia, cramps), neuromuscular junction disorders or, more rarely, peripheral neuropathies. Myopathy usually appears in patients who receive high doses of statins, especially when taking simvastatin 80 mg daily, which lead to higher plasma levels of active statins metabolites, especially in the first year of treatment or after having increased the dosage. Muscle disorders are often reversible after statin withdrawal. Moreover, an important condition that may occur in patients taking statins is immune-mediated necrotizing myopathy characterized by autoantibodies directed against HMG-CoA-reductase. This condition usually does not improve with statin withdrawal but needs specific immunosuppressive therapy (Rastegar, Khan, & Christopher-Stine, 2024). The risk of SAMS is higher with lipophilic statins such as simvastatin, atorvastatin, and lovastatin, because of their ability to not selectively diffuse into extrahepatic tissues as skeletal muscles. Myotoxicity may also depend on the statins metabolic profile. In fact, according to Catapano et al. co-administration of drugs may inhibit the cytochrome P450 (CYP) enzymes, responsible for metabolizing statins, or interact with the organic anion-transporting polypeptides (OATPs), responsible for statin uptake into hepatocytes,

substantially increasing the risk of developing myotoxicity. Accordingly, atorvastatin and rosuvastatin are both good choices in order to reduce the occurrence of statin myopathy, because they have long half-lives enabling alternate day or twice weekly dosing strategy (Attardo et al., 2022).

ii) Peripheral Neuropathy and sleep disturbances

The increased distribution of statins within the nervous system (CNS) may cause neural toxicological effects, including peripheral neuropathy and sleep disturbances. Still, increasing data suggest that statins have properties that are potentially neuroprotective, that is, endothelial protection via actions on the nitric oxide synthase system, as well as antioxidant, anti-inflammatory and antiplatelet effects. Thus, statins can be used also for the treatment of CNS diseases as well.

Many studies found that the duration of statin therapy is a significant risk factor to the development of sensory neuropathy and sleep disturbances. Patients on statin therapy may develop a peripheral neuropathy, complaining of numbness, tingling, pain, and tremor at hands or feet, as well as unsteadiness during walking upon long-term therapy (>1 year). Moreover, the incidence of polyneuropathy has been reported more frequently with atorvastatin than with fluvastatin. (Attardo et al., 2022). In regard to sleep disturbance, this side effect is observed upon simvastatin and lovastatin administration, but not with pravastatin, an effect that seems to correlate with the ability of statins to permeate blood-brain barrier (Shitara & Sugiyama, 2006).

iii) Autoimmune Illnesses

A rare side effect of statins is the possible induction of autoimmune illnesses. Even though the underlying mechanisms remain elusive, statins or exacerbate myasthenia gravis (MG) presentation, an autoimmune disorder characterized by muscle weakness due to an altered transmission at the neuromuscular junction, with autoantibodies against acetylcholine receptor (AChRAb) or, less commonly, against a muscle-specific tyrosine kinase (MuSKAb). In addition, another rare muscle condition associated with statin treatment is the immune-mediated necrotizing myopathy, a severe autoimmune myopathy presenting distinct clinical subtypes. Accordingly, statins appear to display immunomodulatory effects changing autoantigen processing (Attardo et al., 2022).

1.2.5. Statin Pharmacokinetics

Statins have different pharmacokinetic profiles that are associated with their physicochemical properties. Simvastatin and lovastatin, which are administered as prodrugs with a lactone ring, have higher lipophilicity values than other statins with open acid structures. Among them, the lipophilicity of pravastatin is the lowest. Generally, compounds with high lipophilicity values can easily cross lipid bilayer membranes by passive diffusion and, thus, distribute to tissues nonspecifically (via passive diffusion) (Shitara & Sugiyama, 2006). This is the case of lipophilic statins (lovastatin, simvastatin, fluvastatin, atorvastatin, and pitavastatin) that can cross cell membranes by passive diffusion and are relatively non-selective for hepatic tissues. Hydrophilic statins (rosuvastatin and pravastatin) are unable to cross cell membranes and therefore require activated carrier-mediated transport (Attardo et al., 2022).

All statins are absorbed rapidly following administration, reaching peak plasma concentration (T_{max}) within 4h (Cilla, Gibson, Whitfield, & Sedman, 1996). Absorption is faster for lipophilic drugs like atorvastatin, simvastatin, fluvastatin, pitavastatin, and lovastatin than hydrophilic statins like rosuvastatin or pravastatin (Climent, Benaiges, & Pedro-Botet, 2021). While atorvastatin is completely absorbed after oral administration, it undergoes extensive first-pass metabolism, and the bioavailability is about 12%. The bioavailability of pitavastatin is highest (>60%), followed by rosuvastatin (20%), while simvastatin has <5% bioavailability (Filppula et al., 2021). Overall, the currently available statins generally possess a low systemic bioavailability, indicating extensive first-pass extraction (Schachter, 2005).

Most statins exhibit high plasma protein binding (PPB), except for pravastatin, which has a PPB of around 50% (Freese & Lysne, 2023). The hepatic uptake of statins is influenced by both their lipophilicity and specific drug transporters. Due to their lipophilic nature, lovastatin and simvastatin can easily cross the plasma membrane. The key statin transporter in the liver is SLCO1B1 (also known as OATP1B1, OATPC/LST-1, SLC21A6), while SLCO1B3 plays a role in pitavastatin uptake (Schachter, 2005). Statins are also excreted through bile via specific transporters. For example, multidrug resistance-associated protein 2 (ABCC2), multidrug resistance 1 (ABCB1), and breast cancer resistance protein (ABCG2) are essential for the hepatic excretion of pravastatin and pitavastatin. Atorvastatin is taken

up by the heart through the SLCO2B1 transporter, which is found in the vascular endothelium of the human heart (Wessler, Grip, Mendell, & Giugliano, 2013).

Statins are primarily metabolized by cytochrome P450 (CYP450) enzymes. Specifically, the CYP3A4 isoenzyme, found in both intestinal and hepatic cells, is responsible for metabolizing lovastatin, simvastatin, and atorvastatin. Fluvastatin is metabolized by CYP2C9, while pravastatin and rosuvastatin do not undergo CYP-mediated metabolism. The elimination half-lives of rosuvastatin and pitavastatin are approximately 19 hours and 11 hours, respectively (Schachter, 2005). Due to their extensive metabolism, statins are minimally excreted in unchanged form via the kidneys and are primarily excreted in bile and feces (Wiggins et al., 2016).

1.3. Lipid dysmetabolism and Mediterranean-based dietary interventions: a focus on polyphenols

1.3.1. Polyphenols: Classification and main dietary sources

In recent years, the therapeutic potential of Mediterranean-based dietary interventions and the phytochemicals they contain has garnered significant interest. The most abundant and widely distributed bioactive compounds - polyphenols - are found in large quantities in various foods, including olive oil, herbs, fruits, vegetables, seeds, nuts, whole-grain cereals, and wine, which are often credited for the health benefits of the Mediterranean diet (Pollicino, Veronese, Dominguez, & Barbagallo, 2023). Such food groups are particularly rich in specific classes of polyphenols: phenolic acids are predominant in cereals and whole grains such as oats, rice, corn, wheat, and triticale; catechins, hydroxycinnamic acids, anthocyanins, and proanthocyanidins are present in red wine; fruits such as apples, mangoes, and pomegranates contain flavonoids, phenolic acids, and dihydrochalcones; flavones and hydroxycinnamic acids are found in dried herbs like oregano and peppermint; while berries are rich in anthocyanins, which are responsible for their distinct pigmentation and aroma. The Mediterranean diet, in fact, is associated with the consumption of colorful meals, made up of a wide variety of plant-based foods, whose sensory and nutritional qualities—such as astringency, color, and scent—are partly derived from the polyphenols they contain (Ferreira et al., 2024).

Polyphenols, as a chemical family, can be categorized into at least 10 distinct classes based on their fundamental chemical structure. The most common and significant low molecular weight phenolic compounds are simple phenolic derivatives and flavonoids (Figure 4). Phenolic acids, which include molecules like caffeic acid, vanillin, and coumaric acid, represent about one-third of the total polyphenol intake in the diet, while flavonoids make up the remaining two-thirds. Flavonoids structure is based on a 15-carbon C6-C3-C6 structural skeleton, where the A and B rings have a phenolic form, and a C heterocyclic pyrane ring (Goszcz, Duthie, Stewart, Leslie, & Megson, 2017). To highlight the complexity of these groupings, flavonoids themselves can be divided into 13 subclasses, with over

5,000 compounds identified. Most polyphenols are found in glycosidic forms in plants (Martin & Appel, 2009).

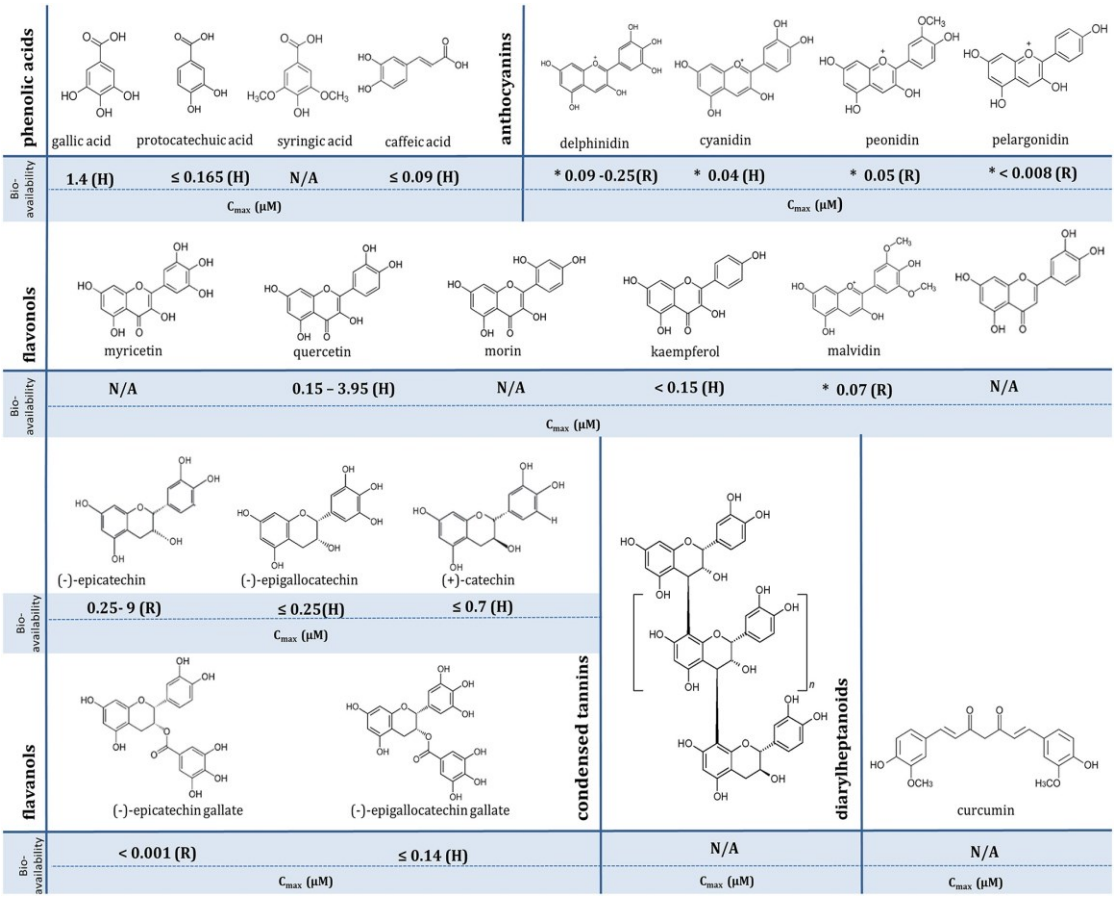

Figure 4. Chemical structures and bioavailability in plasma of representative polyphenols with high antioxidant potential. Retrieved from(Goszcz et al., 2017).

Factors such as sun exposure, rainfall, how vegetables are cultivated, and their ripeness can affect the polyphenol content in foods, thereby impacting the levels consumed by humans. Additionally, the methods used to process food in the kitchen significantly change the polyphenol concentrations, as these compounds are sensitive to heat (Antony & Farid, 2022).

1.3.2. Polyphenols bioavailability

The estimated daily intake of polyphenols for the general population is around 900 mg. For polyphenols to have any biological effect, they must reach the target tissues in a bioavailable form. The bioavailability of polyphenols is primarily influenced by their chemical structure, absorption, distribution, metabolism, and excretion (ADME), as well as the food matrix and form of consumption. Pharmacokinetic studies indicate that different PC classes exhibit varying levels of bioavailability, with the following order: phenolic acids > isoflavones > flavonols > catechins > flavanones, proanthocyanidins > anthocyanins.

Polyphenols commonly found in the human diet are not necessarily the most biologically active in the body. In fact, only about 5-10% of ingested polyphenols reach systemic circulation (Schachter, 2005). Polyphenols interact with other dietary components, such as proteins, carbohydrates, fiber, fats, and alcohol, which can affect their absorption. Most polyphenols are present in foods in their glycosylated form and need to be hydrolyzed by gut bacteria before they can be absorbed, reducing their bioavailability. Anthocyanins, found in red wine, are an exception and can be absorbed without hydrolysis (Dias, 2020). The diversity of gut microbiota species also plays a crucial role in polyphenol biotransformation, as it produces enzymes like deglycosylation. Thus, high polyphenol content in food does not necessarily equate to high bioavailability, as bioavailability is impacted by their chemical diversity and gut microbiota transformations.

Small polyphenols can be absorbed directly in the small intestine, while larger, complex polyphenols remain undigested until reaching the large intestine. There, gut microbes convert them into low-molecular-weight metabolites, which become bioavailable through methylation, sulfation, and glucuronidation. These microbial-derived secondary metabolites act as prebiotic-like compounds, influencing the growth of certain bacterial strains. Polyphenols also interact with food components in the gut, forming chemical complexes with fibers, which can either enhance or reduce their bioavailability. Polyphenols absorbed from the small intestine are typically in their aglycone form. Once absorbed, polyphenols undergo methylation, sulfation, and glucuronidation, processes that increase their hydrophilicity and facilitate their excretion through urine. Additionally, polyphenols support a healthy gut microbiome, which may help prevent lifestyle-related diseases like diabetes (Lippolis, Cofano, Caponio, De Nunzio, & Notarnicola, 2023).

Aside from microbial hydrolysis in the colon, enzymes like lactase phlorizin hydrolase and cytoplasmic beta-glucosidase in the small intestine can hydrolyze dietary polyphenols. The activity of these enzymes varies between individuals, contributing to differences in polyphenol absorption and bioavailability. After passing through the portal system, most polyphenols are conjugated in the liver, facilitating their elimination via urine and bile. In circulation, polyphenols bind strongly to albumin and other serum proteins, limiting their availability to tissues and further reducing their bioavailability (Dias, 2020).

1.3.3. Polyphenols: Biological activities and healthy outcomes

Studies have demonstrated that dietary polyphenols are biologically active substances, with therapeutic effects in cells and/or tissues. Phenolic compounds provide a wide spectrum of bioactivities: Aside from their broadly de- scribed free radical scavenging properties, the existence of both hydrophobic and hydrophilic domains within polyphenols enables them to potentially interact with, and diffuse through biological membranes, and to bind to receptors and enzymes to exert intracellular signalling effects (Goszcz et al., 2017).

The beneficial, health-promoting effect of flavonoids is supported by many studies, which have proven a positive, multi-directional effect of flavonoid intake on the improvement of health parameters. Their pleiotropic effect results from the ability to interact with many cellular targets and antioxidant properties, thus limiting the negative effects of oxidative stress accompanying inflammation and cancer. The broad spectrum of flavonoid biological activity, including many signaling pathways, leads to considering this group of compounds as structures with both chemopreventive and therapeutic properties, as highlighted in Figure 5 (Golonko, Olichwier, Swislocka, Szczerbinski, & Lewandowski, 2022).

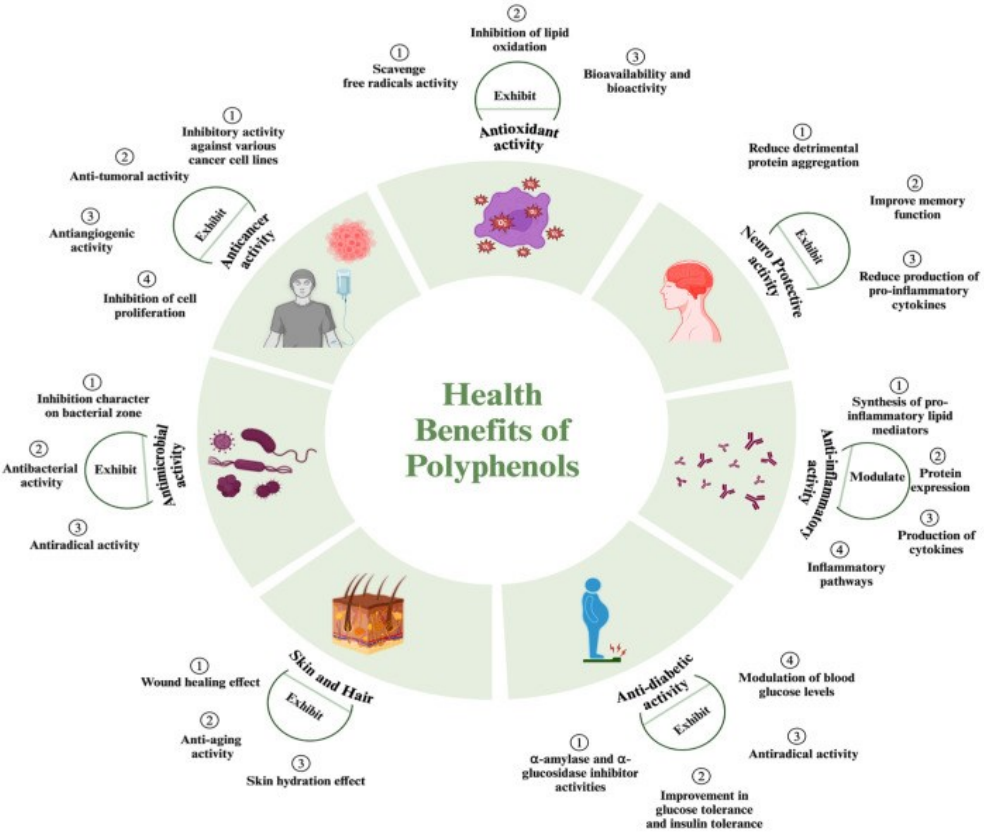

Figure 5. Pleiotropic actions and health benefits of polyphenols. Retrieved from (Bolat et al., 2024).

The health benefits of polyphenols are linked to their chemical structure, including the number, position, and type of substituents, as well as the degree of polymerization around the chromane ring. Additionally, the high level of hydroxylation in the B-ring of catechins and anthocyanidins enhances their bioactivity and ability to induce metabolic changes (Ferreira et al., 2024). Polyphenols from dietary sources have been recognized for their strong free radical-scavenging properties, initially thought to primarily serve as antioxidants protecting against lipid peroxidation (D'Archivio, Filesi, Vari, Scazzocchio, & Masella, 2010). They also influence NF-κB and MAPKs signaling pathways and increase the activity of phase II detoxification and antioxidant enzymes, such as heme oxygenase-1 (HO-1), glutathione peroxidase (GSH-Px), glutathione-S-transferase (GST), catalase, and superoxide dismutase (SOD), through the activation of the Nrf2 nuclear redox factor. Nrf2 activation, along with its binding to the electrophile response element (EpRE), also known as the antioxidant response element (ARE), plays a crucial role in defending against oxidative and electrophilic stress (Dias, 2020). However, in recent years, it has become clear that the modes of action of polyphenols are more complex than initially thought. These

compounds exhibit a range of biological effects beyond antioxidant activity, including anti-inflammatory, antimicrobial, antidiabetic, anti-aging, anticancer, and cytotoxic properties. These functions help reduce the risk of chronic diseases and can impact the treatment of existing conditions. Furthermore, polyphenols have demonstrated benefits for cardiovascular health and cognitive function, potentially helping to prevent neurodegenerative diseases (Jiang et al., 2024).

Finally, polyphenols have been emerging as important therapeutic options to manage lipid dysmetabolism. In vitro studies highlight the ability of polyphenols to modulate the transcription, translation and/or activity of peroxisome proliferator activated receptor γ, adenosine-monophosphate-activated protein kinase, uncoupling proteins 1 and 2, CCAAT/enhancer binding protein α, peroxisome proliferator activator receptor gamma activator 1-alpha, sirtuin 1, sterol regulatory element binding protein-1c, and nuclear factor-κB, key-factors that regulate adipogenesis (Alqarni et al., 2024). Likewise, they have been shown to stimulate lipolysis and fatty acid β-oxidation while reducing triglyceride accumulation (Nagao, Hase, & Tokimitsu, 2007; Wang et al., 2014).

Limited human studies have been conducted. In the randomized PREDIMED study, it was observed that a greater polyphenol intake may reduce body weight in elderly people at high cardiovascular risk (Guo et al., 2017). A long-term study conducted in the Netherlands found that women who consumed higher amounts of dietary flavones (flavonols) and catechins had a lower body mass index (BMI) (Hughes et al., 2008). Additionally, a meta-analysis revealed that resveratrol intake leads to a significant reduction in weight, BMI, and fat mass (Tabrizi et al., 2020). Nevertheless, results across studies remain inconsistent.

1.4. Statin-Polyphenol Interactions: Candidate biological targets

The most well-known biological targets through which statins and polyphenols interact are OATP, CYP450, and HMG-CoA reductase, as these pathways are closely linked to myotoxicity (Zechner, Britza, Farrington, Byard, & Musgrave, 2022).

1.4.1. OATP interactions

The human OATP family consists of 11 proteins. Even though certain organic anions have a clear preference for one transporter over another, multispecific transporters of the OATPs family display overlapping substrate specificity, transporting numerous structurally diverse organic anions (Nigam & Granados, 2023). Among the hepatic OATPs, OATP1B1 and OATP1B3 are considered highly relevant in clinical settings. When statins are co-administered with OATP1B inhibitors like cyclosporine or rifampicin, this can result in elevated systemic levels of the affected drug, potentially leading to side effects ranging from mild myopathy to serious, life-threatening rhabdomyolysis. Due to the numerous reported cases of adverse events linked to impaired OATP1B function, regulatory bodies such as the FDA, EMA, and PMDA recommend testing new drugs for potential drug-drug interactions mediated by OATP (Ciuta et al., 2023).

Notably, most statins rely on OATP uptake and polyphenols are OATP inhibitors (Luo et al., 2022). Hydrophilic statins such as rosuvastatin and pravastatin are primarily dependent on OATP1B1 for entry into cells while lipophilic statins can permeate through cell walls, though OATP1B1 still plays a role (Zechner et al., 2022).

1.4.2. Inhibition of Cytochrome P450

Cytochrome P450 (CYP) enzymes are a vital superfamily of heme-containing monooxygenases that play a crucial role in metabolizing a wide range of endogenous and foreign substances, including hormones, bile acids, sterols, and numerous drugs. CYPs facilitate hydroxylation and oxidation reactions, generally increasing the hydrophilicity of their substrates. In the case of drugs, this process can sometimes activate prodrugs, but

more often it leads to the formation of molecular structures that are more suitable for further conjugation in the body, such as glucuronidation, sulfation, or glutathionylation. (Loos, Beijnen, & Schinkel, 2022).

While the liver is the primary site of CYP-mediated drug metabolism, there are varying levels of CYP expression in other tissues, particularly in the small intestine, but also in the kidneys, lungs, and brain. The human CYP1, CYP2, and CYP3 families are most relevant to drug detoxification, metabolizing about 80% of all clinically used drugs. Simvastatin, lovastatin, and atorvastatin are substrates of CYP3A4, while fluvastatin, rosuvastatin, pravastatin, and pitavastatin are substrates of CYP2C9 (Zechner et al., 2022). Accordingly, CYP3A4 and CYP2C9 inhibitors can alter systemic exposure to statins. This is the case of polyphenols (Kimura, Ito, Ohnishi, & Hatano, 2010). For instance, both caffeic acid and quercetin are competitive inhibitors of CYP2C9 (Ki = 0.95 and 1.67 µM, respectively). Quercetin was also found to exert potent inhibitory effects on CYP3A4 (Ki=4.12 µM) (Rastogi & Jana, 2014).

1.4.3. Inhibition of HMG-CoA reductase

Statins, widely regarded for their effectiveness, are the most commonly used cholesterol-lowering drugs due to their ability to inhibit HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway. As such, they are considered the cornerstone of cardiovascular disease treatment (Somers, Siddiqi, Morshuis, Russel, & Schirris, 2023). Interestingly, flavonoids have the potential to inhibit HMG-CoA reductase, both directly and indirectly, which could interfere with statin therapy, necessitating careful monitoring of drug levels (Hemmerlin, Huchelmann, Tritsch, Schaller, & Bach, 2019).

Chapter II | **AIMS**

Dyslipidemia is a key pathogenic driver of various metabolic, cardiovascular, and cerebrovascular diseases. Lifestyle modifications, particularly the adoption of healthy dietary patterns like the Mediterranean Diet, are foundational in any treatment plan, including for patients prescribed first-line statin therapy for hypercholesterolemia. However, with the increasing use of MedDiet-fortified foods and nutraceuticals by health-conscious consumers, combining these products with statins could lead to potentially serious adverse effects. A prominent example involves polyphenol supplements, a class of secondary metabolites with lipid-lowering properties, widely available over the counter.

Interactions between statins and polyphenols can significantly affect both therapeutic efficacy and the incidence of adverse effects. Alterations in statin pharmacokinetics are well-documented with polyphenol co-administration and are implicated in statin-induced myopathy through the modulation of OATPs, CYP450, and HMG-CoA reductase. Nonetheless, other biological targets may also mediate these interactions, potentially influencing both pharmacodynamic and pharmacokinetic responses, and ultimately impacting the success of lipid-lowering therapy. Moreover, it remains unclear whether chronic consumption of polyphenol-based supplements can achieve plasma concentrations sufficient to alter statin pharmacokinetics meaningfully.

To address these concerns, a comprehensive scoping review will be conducted to assess reported statin-polyphenol interactions and identify the key biological targets involved, with the aim of elucidating their impact on statin pharmacokinetics, efficacy and toxicity. Ultimately, this work aims to provide a mechanistic framework that can guide the evaluation of the interaction potential between statins and polyphenols.

Chapter III | **METHODS**

3.1. Scoping Review Protocol

This scoping review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) and guided by the PRISMA-ScR checklist (https://doi.org/10.7326/M18-0850).The review protocol was registered in the Open Science Framework (OSF; https://osf.io/pyb4r/) on september 6, 2024 (https://*doi*.org/*10.17605/OSF.IO/PYB4R*).

3.1.1. Research Question

The research question for this scoping review was: **" What are the features of reported interactions between statins and polyphenols with respect to pharmacodynamic and pharmacokinetic outcomes?".**

3.1.2. Search Strategy

The search strategy was designed using the Participants-Concept-Context (PCC) framework, using keywords such as "Polyphenols", "Statins", "Interactions", combined with Boolean operators and the following syntax: ((Polyphenols OR Flavonoids) AND (Statins) AND (Interactions)). The search profile will include text terms in title, abstract, MeSH terms and subheadings. The literature search was conducted from 2014 to 2023 in the PubMed, Scopus, Web of Science databases.

3.1.3. Eligibility criteria

Only quasi-experimental and experimental studies published in English were considered, limited to those utilizing *in vitro* studies, animal models or human participants to explore Statin-Polyphenol interactions. Studies not focusing on the interaction between polyphenols and statins were excluded. Additionally, non-original research articles, such as systematic reviews, meta-analyses, and other review articles, were excluded in the analysis.

Data extraction focused on relevant study characteristics (e.g. Polyphenol classes; Statins; Type of study; Biological targets for interaction; Pharmacokinetic outcomes). A customized data-extraction form was constructed and integrated into the Covidence software (https://www.covidence.org/), and duplicate entries were removed. Titles and abstracts identified by the search were independently screened in duplicate by two independent reviewers against the eligibility criteria. Disagreements between the two reviewers during the screening and data extraction process were discussed and resolved by a third reviewer. Reasons for exclusion of full-text studies that do not meet the inclusion criteria were recorded and reported in the scoping. The results of the study selection process will be reported in full in the final systematic review and presented in a PRISMA-ScR flow diagram (Figure 6). Articles that passed the initial screening were subjected a full-text review based on the inclusion criteria detailed above. Any disagreements that arise between the reviewers at each stage of the study selection process were resolved through discussion, or with a third reviewer.

3.1.4. Synthesis of results

Results of this scoping review were synthesized as descriptive and quantitative measures of study outcomes frequencies with percentages. The studies were grouped by i) *polyphenols classes;* ii) *statins;* iii) and iii) *type of studies, i*v) *number of studies according to the presence or absence of reported interactions*. Subsequently, identified biological targets for interaction and pharmacokinetic outcomes were synthesized and systematized in two separate evidence tables.

Chapter IV | **RESULTS AND DISCUSSION**

4.1. Overview of the literature search

A total of 134 references that potentially addressed interactions between polyphenol-based dietary supplements and statins were yielded from literature search. To ensure the inclusion of eligible studies, the titles and abstracts of all records were independently screened by two team members to exclude irrelevant studies based on the pre-defined inclusion and exclusion criteria. After applying inclusion and exclusion criteria, a final total of 38 studies were included in the scoping review process for further analysis. The selection process, illustrated by the PRISMA flow diagram (Figure 6), involved the removal of duplicates and a thorough assessment of full texts, with any discrepancies resolved through discussion between reviewers.

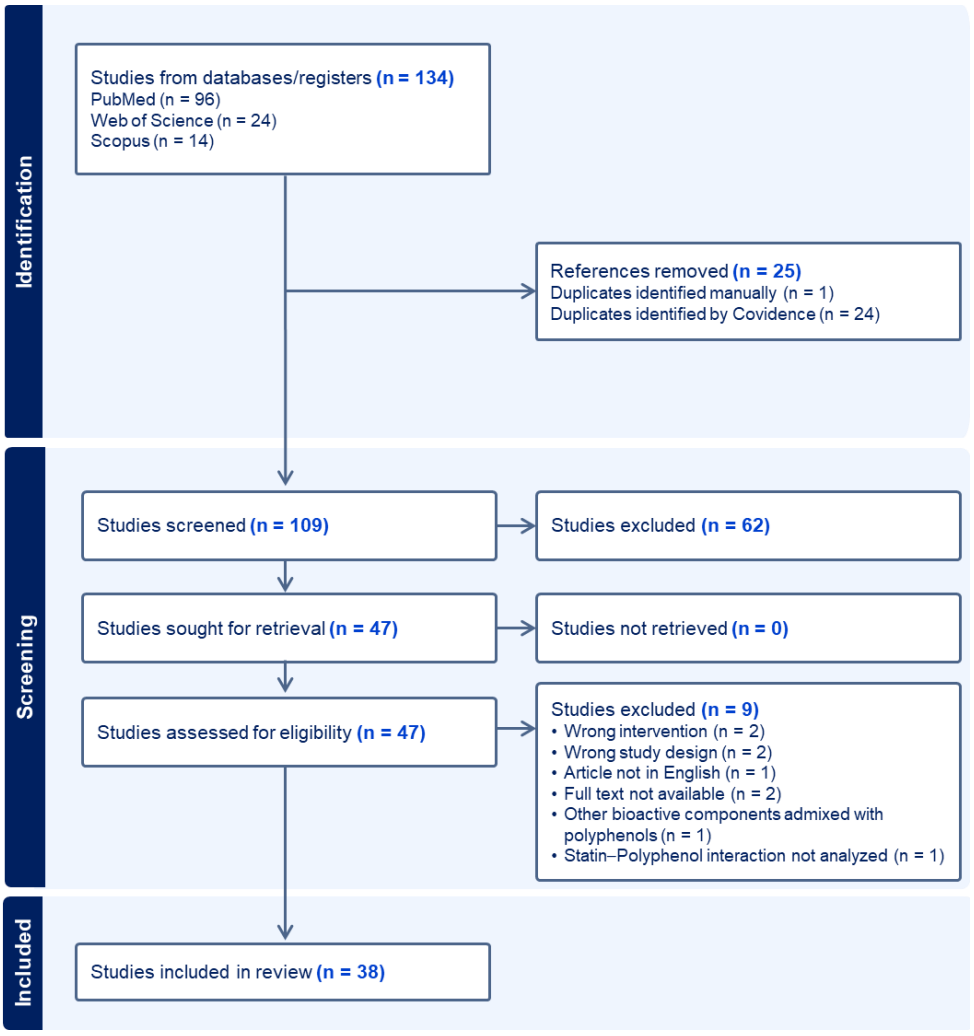

Figure 6. PRISMA flow diagram of study selection process.

4.2. Characterization of statins and polyphenol classes reported in the literature search

Figure 7 summarizes the number of enrolled studies that involved each statin: rosuvastatin was the most frequently studied statin, employed in 12 studies, followed by simvastatin (11 studies), atorvastatin (9 studies) lovastatin (3 studies), fluvastatin (3 studies), pravastatin and pitavastatin (2 studies each).

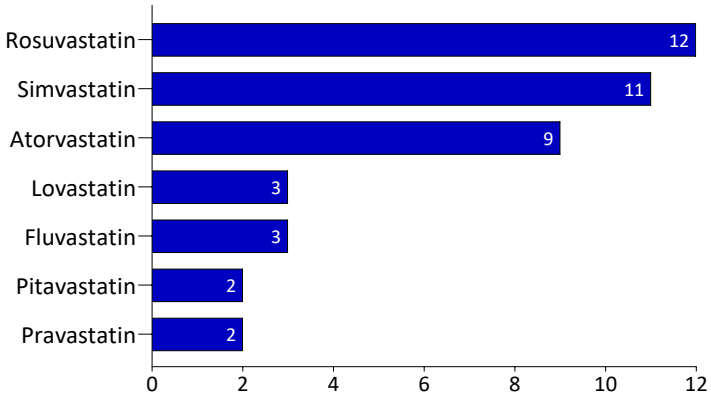

Figure 7. Statins employed in enrolled studies from literature search.

The distribution of the main polyphenol classes reported in the included studies is presented in Figure 8. Ninety four percent (97%, n=28) of studies focused on flavonoids. The remaining 3% (n=1) included 1 stilbene named resveratrol.

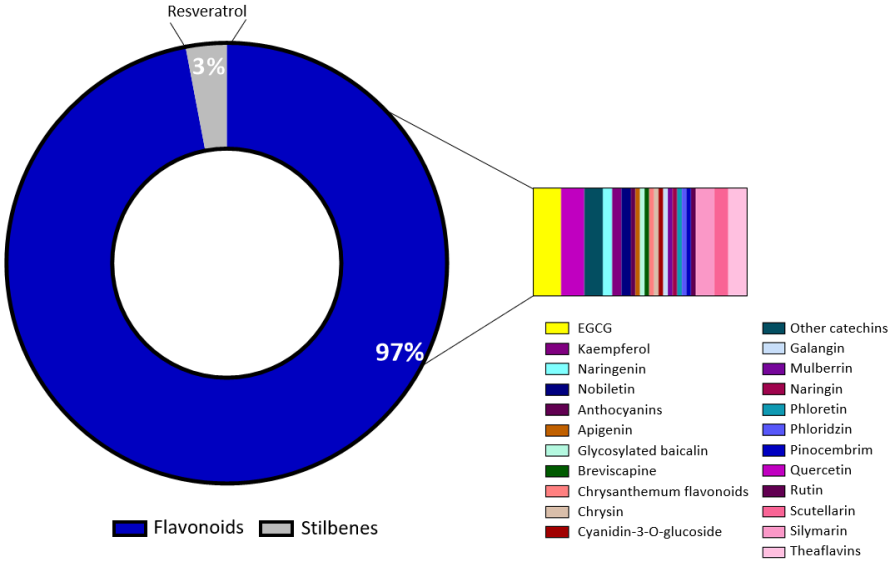

Figure 8. Distribution of polyphenols reported in the included studies according to flavonoid and stilbene classes.

4.3. Type of studies enrolled in the literature search

The experimental and quasi-experimental studies that met the inclusion criteria for this scoping review were categorized into three major types: non-clinical (*in vitro, in vivo*), and clinical studies. The majority of studies were primarily non-clinical, with 31 *in vitro* studies, 19 *in vivo* animal studies, and only 6 clinical studies, as shown in Figure 9.

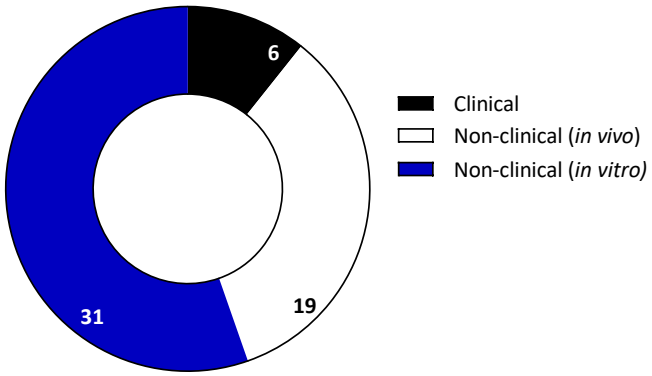

Figure 9. Types of studies included in the enrolled articles.

4.4. Characterization of statin-polyphenol interactions

Out of the 38 studies analyzed, 32 (84.2%) reported significant pharmacodynamic and/or pharmacokinetic outcomes upon statin-polyphenol interactions, while 6 (15.8%) did not, as depicted in Figure 10.

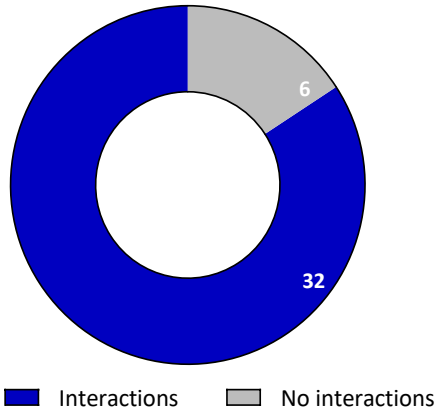

Figure 10. Proportion of studies reporting statin-polyphenol interactions.

To deepen the understanding of the pharmacodynamic and pharmacokinetic effects resulting from statin-polyphenol interactions, data extraction focused on the key biological targets putatively involved. As shown in Figure 11, OATPs inhibition is the most commonly reported biological target responsible for statin-polyphenol interactions (16 studies), followed by the inhibition of CYP enzymes (9 studies), P-gp (3 studies), HMG-CoA reductase (2 studies) and intestinal esterases (1 study).

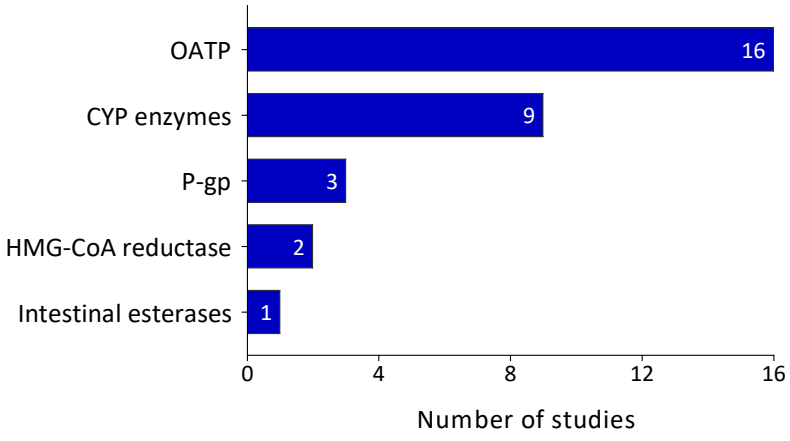

Figure 11. Proportion of studies reporting the biological targets mediating statin-polyphenol interactions.

Flavonoids such as EGCG, phloretin and theaflavins were shown to inhibit intestinal OATP1A2 and OATP2B1 transporters when co-administered with rosuvastatin (Takahashi et al., 2021) (Table 1). Silymarin**,** scutellarin and glycosylated baicalein were found to inhibit hepatic OATP1B1 transporter upon rosuvastatin co-treatment (Fan et al., 2008; Kock, Xie, Hawke, Oberlies, & Brouwer, 2013; Liu, Guo, Xu, Yuan, & Zhu, 2020). Similarly, EGCG, apigenin, kaempferol, and quercetin inhibited OATP1B1-mediated transport of simvastatin, atorvastatin, and pravastatin (Kim et al., 2017; Mandery et al., 2012; Wu et al., 2012). Moreover, OATP1B3 was also inhibited upon flavonoids (EGCG, silymarin, scutellarin, apigenin, kaempferol, quercetin, naringenin, naringin and rutin) and statins (atorvastatin, simvastatin, and rosuvastatin) simultaneous dosing (Kock et al., 2013).

While the inhibitory effects of polyphenols on OATPs-mediated transport are well-documented, the translation of *in vitro* findings to *in vivo* outcomes has been inconsistent. Studies have shown that polyphenols like phloretin and phloridzin, both polyphenols derived from apples, potently inhibit OATP2B1 in the intestine, reducing the uptake of rosuvastatin and other statins into enterocytes (Takahashi et al., 2021). However, when administered in animals, the systemic exposure of rosuvastatin was not significantly impacted despite the clear inhibitory effect in the intestinal loop model. This discrepancy raises questions about the translation of *in vitro* findings to *in vivo* contexts, suggesting that factors such as drug metabolism, polyphenol stability, and compensatory transport mechanisms might mitigate the expected effects in living organisms (Takahashi et al., 2021).

Table 1. Statin-polyphenol interactions: Main biological targets.

Statin	Polyphenol component	Type of study	Main biological targets					References
			Inhibition of OATP-mediated uptake	Inhibition of P-gp efflux transporter	Inhibition of CYPs activity	Inhibition of HMG-CoAR	Inhibition of intestinal esterases	
Rosuvastatin	Chrysin, galangin, and pinocembrim	Non-clinical (*In vitro*)	X					(Navratilova, Ramos Mandikova, Pavek, Mladenka, & Trejtnar, 2018)
Rosuvastatin	EGCG	Clinical	X					(Kim et al., 2017)
Rosuvastatin	Glycosylated baicalein	Clinical	X					(Fan et al., 2008)
Rosuvastatin	Phloretin and phloridzin	Non-clinical (*In vitro; In vivo*)	X					(Takahashi et al., 2021)
Rosuvastatin	Scutellarin	Non-clinical (*In vitro; In vivo*)	X					(Liu, Guo, Liu, et al., 2020)
Rosuvastatin	Silymarin	Non-clinical (*In vitro*)	X					(Kock et al., 2013)
Rosuvastatin	Silymarin	Non-clinical (*In vitro*)	X					(Kock et al., 2013)
Rosuvastatin	Silymarin	Non-clinical (*In vitro*)	X	X				(Deng et al., 2008)
Rosuvastatin	Theaflavin, theaflavin-3-gallate, theaflavin-3´gallate; theaflavin-3,3-digallate	Non-clinical (*In vitro; In vivo*)	X					(Kondo et al., 2019)
Simvastatin	Baicalein	Non-clinical (*In vivo*)			X			(Meng, Li, Zhang, & Sun, 2021)
Simvastatin	Breviscapine	Non-clinical (*In vivo*)			X			(Ju, Li, Qu, & Li, 2017)
Simvastatin	EGCG	Non-clinical (*In vitro; In vivo*)	X		X			(Yang et al., 2017)
Simvastatin	Naringenin	Non-clinical (*In vitro*)			X			(Ubeaud, Hagenbach, Vandenschrieck, Jung, & Koffel, 1999)
Simvastatin	Naringenin	Non-clinical (*In vitro; In vivo*)			X			(Motawi, Teleb, El-Boghdady, & Ibrahim, 2014)
Simvastatin	Naringenin	Non-clinical (*In vitro*)			X			(Le Goff-Klein, Koffel, Jung, & Ubeaud, 2003)

Abreviations: EGCG, Epigallocatechin-3-gallate; HMG-CoAR, Hydroxymethylglutaryl-CoA (HMG-CoA) reductase; OATP, Organic Anion-Transporting Polypeptide; P-gp, P-glycoprotein.

Table 1. Statin-polyphenol interactions: Main biological targets (continued).

Statin	Polyphenol component	Type of study	Main biological targets					References
			Inhibition of OATP-mediated uptake	Inhibition of P-gp efflux transporter	Inhibition of CYPs activity	Inhibition of HMG-CoAR	Inhibition of intestinal esterases	
Simvastatin	Quercetin	Non-clinical (*In vivo*)			X			(Cermak, Wein, Wolffram, & Langguth, 2009)
Simvastatin	Resveratrol	Non-clinical (*In vitro*)				X		(Wong et al., 2011)
Simvastatin	Resveratrol	Non-clinical (*In vitro*)				X		(Villanueva et al., 2013)
Atorvastatin	Apigenin, kaempferol, quercetin; naringenin, naringin, and rutin	Non-clinical (*In vitro*)	X					(Mandery et al., 2012)
Atorvastatin	EGCG	Clinical	X					(Abdelkawy, Abdelaziz, Abdelmageed, Donia, & El-Khodary, 2020)
Atorvastatin	EGCG and other catechins (epicatechin-3-gallate, epigallocatechin, epicatechin, and gallocatechin gallate)	Non-clinical (*In vitro*, *In vivo*)				X		(Lu et al., 2008)
Atorvastatin, Fluvastatin, Rosuvastatin	Mulberrin, scutellarin, chrysanthemum flavonoids and quercetin	Non-clinical (*In vitro*)	X					(Wen, Shi, Bian, Zhang, & Gui, 2016)
Lovastatin	Kaempferol and narigenin	Non-clinical (*In vitro; In vivo*)					X	(P. Li, Callery, Gan, & Balani, 2007)
Fluvastatin	EGCG	Non-clinical (*In vitro*)			X			(Misaka et al., 2018)
Pitavastatin	Naringin	Non-clinical (*In vitro*)	X	X				(Shirasaka, Suzuki, Shichiri, Nakanishi, & Tamai, 2011)
Pravastatin	Quercetin	Non-clinical (*In vitro*); Clinica	X					(Wu et al., 2012)
Pravastatin Pitavastatin	Naringin	Non-clinical (*In vitro; In vivo*)	X	X				(Shirasaka, Suzuki, Nakanishi, & Tamai, 2011)

Abreviations: EGCG, Epigallocatechin-3-gallate; HMG-CoAR, Hydroxymethylglutaryl-CoA (HMG-CoA) reductase; OATP, Organic Anion-Transporting Polypeptide; P-gp, P-glycoprotein.

Statin-polyphenol interactions are also mediated by CYP450 enzymes (9 studies), particularly the CYP3A4 isoform, a key enzyme in statin metabolism. This inhibition was most frequently observed in non-clinical studies (8) and mainly involved simvastatin. Polyphenols such as baicalein, breviscapine, and EGCG inhibited CYP3A4 activity upon statin co-administration (Ju et al., 2017; Lu et al., 2008; Meng et al., 2021). Breviscapine also reduced the expression of CYP3A4 mRNA, suggesting that the polyphenol affects both the enzyme's activity and its production at the transcriptional level. Such dual mechanisms of inhibition could exacerbate the risk of adverse reactions when simvastatin is co-administered with breviscapine.

P-glycoprotein is a cellular defense mechanism by effluxing its substrates. Although less common (3 studies), polyphenols inhibit the efflux transporter P-gp. Naringin and silymarin inhibited the efflux of rosuvastatin and pitavastatin, respectively (Deng et al., 2008; Shirasaka, Suzuki, Nakanishi, et al., 2011; Shirasaka, Suzuki, Shichiri, et al., 2011). Accordingly, while this effect may enhance drug absorption in some cases, it could also lead to higher drug retention in the intestinal compartment, raising concerns about localized toxicity.

A concurrent biological target of statin-polyphenol interactions is the HMG-CoA reductase, the enzyme targeted by statins to reduce cholesterol synthesis (2 studies). Studies by Wong et al. (2011) and Villanueva et al. (2013) demonstrated that resveratrol not only decreased HMG-CoA reductase activity but also amplified the cholesterol-lowering effects of simvastatin, suggesting that polyphenols may enhance the therapeutic benefits of statins by targeting multiple steps of cholesterol biosynthesis (Villanueva et al., 2013; Wong et al., 2011).

Lastly, the inhibition of intestinal esterases by polyphenols like kaempferol and naringenin was also found to mediate statin-polyphenol interactions, potentially impacting drug pharmacodynamics and pharmacokinetics (P. Li et al., 2007). By inhibiting esterase activity, they prevented the rapid degradation of statins in the intestine, highlighting the potential of these polyphenols to enhance the bioavailability of ester prodrugs like lovastatin by limiting their esterase-dependent degradation.

Collectively, our results reinforce existing knowledge on the significant roles of OATP transport, CYP450 metabolism, and mevalonate synthesis in mediating statin-polyphenol interactions, with important clinical outcomes (myopathy). Notably, this work advances understanding by unveiling two key factors in drug transport and metabolism - P-gp and intestinal esterases - through which additional interactions between statins and polyphenols may occur.

The range of biological mechanisms through which statins interact with polyphenols suggests significant changes in drug pharmacokinetics. Studies analyzing the pharmacokinetic behavior of statins have shown a wide variety of results (Table 2). Nine studies reported an increase in AUC, indicating greater systemic exposure to statins when co-administered with polyphenols, while five studies observed a decrease in area under the curve (AUC), and another five found no significant changes. In terms of half-life ($T_{1/2}$), the majority of studies (7) did not observe a reduction in the time required for the statin to reach half of its initial concentration, with 5 studies reporting increases and only 1 reporting a decrease. Clearance adjusted for bioavailability (CL/F), a parameter that reflects the efficiency with which the drug is eliminated from the body after accounting for its absorption, was found to be reduced in most studies (9), though 5 studies reported increases and 3 found no significant differences. Results are summarized in Figure 12.

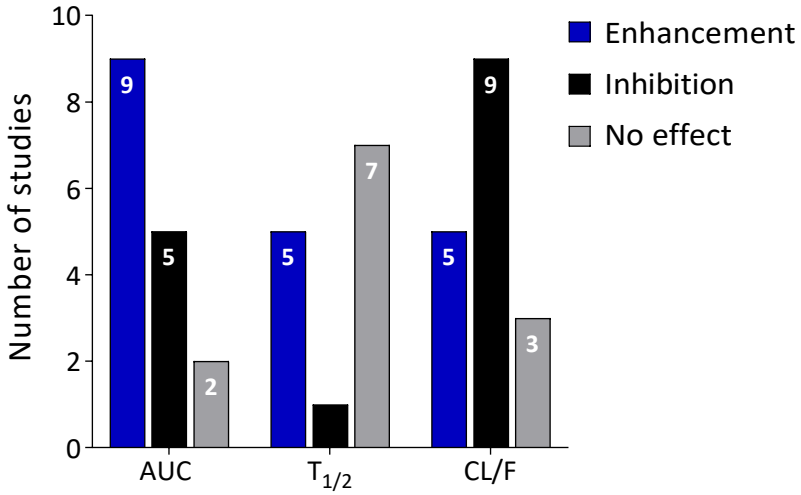

Figure 12. Proportion of studies reporting alterations in chief pharmacokinetic parameters upon statin-polyphenol interaction (AUC, area under the curve; $T_{1/2}$, half-life; CL/F, clearance adjusted for bioavailability).

Table 2. Statin-polyphenol interactions: Pharmacokinetic outcomes.

Statin	Polyphenol component	Type of study	Pharmacokinetic parameters					References
			AUC	C_{max}	T_{max}	$T_{1/2}$	CL/F	
Rosuvastatin	EGCG	Clinical	↓	↓	N.D.	N.D.	N.D.	(Kim et al., 2017)
Rosuvastatin	Glycosylated baicalein	Clinical	↓	=	=	↓	↑	(Fan et al., 2008)
Rosuvastatin	Naringin	Non-clinical (*In vivo*)	=	=	=	=	=	(Zeng et al., 2018)
Rosuvastatin	Phloretin and phloridzin	Non-clinical (*In vitro; In vivo*)	=	N.D.	N.D.	N.D.	N.D.	(Takahashi et al., 2021)
Rosuvastatin	Silymarin	Clinical	=	=	=	=	=	(Deng et al., 2008)
Rosuvastatin	Scutellarin	Non-clinical (*In vitro; In vivo*)	↑	↑	=	=	↓	(Liu, Guo, Xu, et al., 2020)
Rosuvastatin	Scutellarin	Non-clinical (*In vitro; In vivo*)	↑	↑	=	=	↓	(Liu, Guo, Liu, et al., 2020)
Rosuvastatin	Theaflavin, theaflavin-3-gallate, theaflavin-3´gallate and theaflavin-3,3-digallate)	Non-clinical (*In vitro; In vivo*)	↓	↓	=	N.D.	N.D.	(Kondo et al., 2019)
Simvastatin	Baicalein	Non-clinical (*In vivo*)	↑	↑	↓	↑	↓	(Meng et al., 2021)
Simvastatin	Breviscapine	Non-clinical (*In vivo*)	↑	↑	↑	↑	↓	(Ju et al., 2017)
Simvastatin	EGCG	Non-clinical (*In vitro; In vivo*)	↑	N.D.	N.D.	↑	↓	(Yang et al., 2017)
Simvastatin	Quercetin	Non-clinical (*In vivo*)	↓	↓	=	=	N.D.	(Cermak et al., 2009)
Simvastatin metabolite	Silymarin	Non-clinical (*In vitro*)	↑	↑	=	=	N.D.	(Y. Li et al., 2019)
Atorvastatin	EGCG	Clinical	↓	↓	=	=	↑	(Abdelkawy et al., 2020)
Atorvastatin	Quercetin	Non-clinical (*In vivo*)	=	=	=	=	=	(Koritala et al., 2015)
Atorvastatin	Silymarin	Non-clinical (*In vitro; In vivo*)	↑	↑	↑	↑	↓	(Malekinejad et al., 2014)
Lovastatin	Kaempferol and narigenin	Non-clinical (*In vitro; In vivo*)	↑	=	=	N.D.	N.D.	(P. Li et al., 2007)
Fluvastatin	EGCG	Clinical	=	=	=	=	N.D.	(Misaka et al., 2018)
Pravastatin	Quercetin	Non-clinical (*In vitro*); Clinical	↑	↑	=	↑	↓	(Wu et al., 2012)

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; CL/F, clearance/fraction of dose available in the systemic circulation: clearance adjusted for bioavailability; EGCG, Epigallocatechin-3-gallate; $T_{1/2}$, elimination half-life; T_{max}, time to C_{max}.

Baicalein, a flavonoid found in *Scutellariae radix*, was found to significantly alter the pharmacokinetic profiles of simvastatin by inhibiting CYP3A4. Baicalein co-administration significantly increased the systemic exposure of simvastatin, prolonging its half-life and reducing its clearance through the inhibition of CYP3A4 activity. This interaction raises concerns about the potential for increased side effects, such as myopathy, due to higher systemic concentrations of the drug (Meng et al., 2021). In the study by Ju et al., pre-treatment with breviscapine increased the AUC and Cmax of simvastatin by 57% and 31%, respectively, while reducing its total clearance by 36%. These results align with those observed with baicalein, further emphasizing the role of CYP3A4 inhibition in modulating the pharmacokinetics of simvastatin (Ju et al., 2017).

Theaflavins, a group of polyphenol compounds contained in black tea extracts have been shown to significantly inhibit OATP2B1, leading to a reduction in the maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) of rosuvastatin by 48% and 37%, respectively. These findings indicate that the presence of polyphenols derived from black tea reduces the plasma concentrations of rosuvastatin by inhibiting the intestinal OATP2B1-mediated transport of rosuvastatin and thus could interfere with the effective absorption of rosuvastatin (Kondo et al., 2019).

Wu et al. (2012) investigated the effect of quercetin on the pharmacokinetics of pravastatin, another OATP1B1 substrate, and found quercetin can inhibit OATP1B1-mediated transport of pravastatin in vitro, and also has a modest inhibitory effect on pravastatin systemic exposures, with a 24% increase in AUC and a 31% increase in Cmax, suggesting that quercetin inhibits OATP1B1-mediated transport of pravastatin, leading to prolonged systemic exposure (Wu et al., 2012). Atorvastatin, another widely prescribed statin, is similarly affected by polyphenol-mediated OATP inhibition. Abdelkawy et al. (2020) explored the effect of green tea extract (EGCG) on atorvastatin pharmacokinetics and found that co-administration significantly reduced the AUC and Cmax of atorvastatin by 24% and 25%, respectively. This decrease in atorvastatin absorption can substantially diminish its cholesterol-lowering efficacy, particularly in individuals consuming large quantities of green tea or EGCG supplements (Abdelkawy et al., 2020).

Interestingly, not all polyphenols have the same impact on statin pharmacokinetics. In a study involving fluvastatin, green tea extract and brewed green tea were found to have minimal effects on the pharmacokinetics of fluvastatin, despite significant CYP2C9 inhibition observed in vitro (Misaka et al., 2018). This suggests that the degree of interaction may vary depending on the specific statin and polyphenol involved, as well as the transporter or enzyme involved. The observed variability in pharmacokinetics can be attributed to several factors, including the type of statin and polyphenol, the doses administered, co-administration with other drugs, a lack of standardization in experimental conditions, genomic differences, to name a few. Further non-clinical and clinical *in vivo* studies are necessary to investigate the impact of statin-polyphenol interactions on pharmacokinetic parameters mediated by other biological targets, namely the P-gp, HMG-CoA reductase and intestinal esterases.

Chapter V | **Conclusion**

Conclusion

This comprehensive scoping review highlights the key biological targets mediating statin-polyphenol interactions, which may alter pharmacokinetic responses and, ultimately, the success of lipid-lowering therapy. These interactions not only influence drug transport (OATP, P-gp) and metabolism (CYP450, esterases) but also impact critical biochemical pathways involved in lipid metabolism, such as the mevalonate pathway (HMG-CoA-R), essential for cholesterol biosynthesis. Figure 13 illustrates the primary biological mechanisms driving the changes in statin pharmacodynamics and pharmacokinetics during polyphenol co-administration:

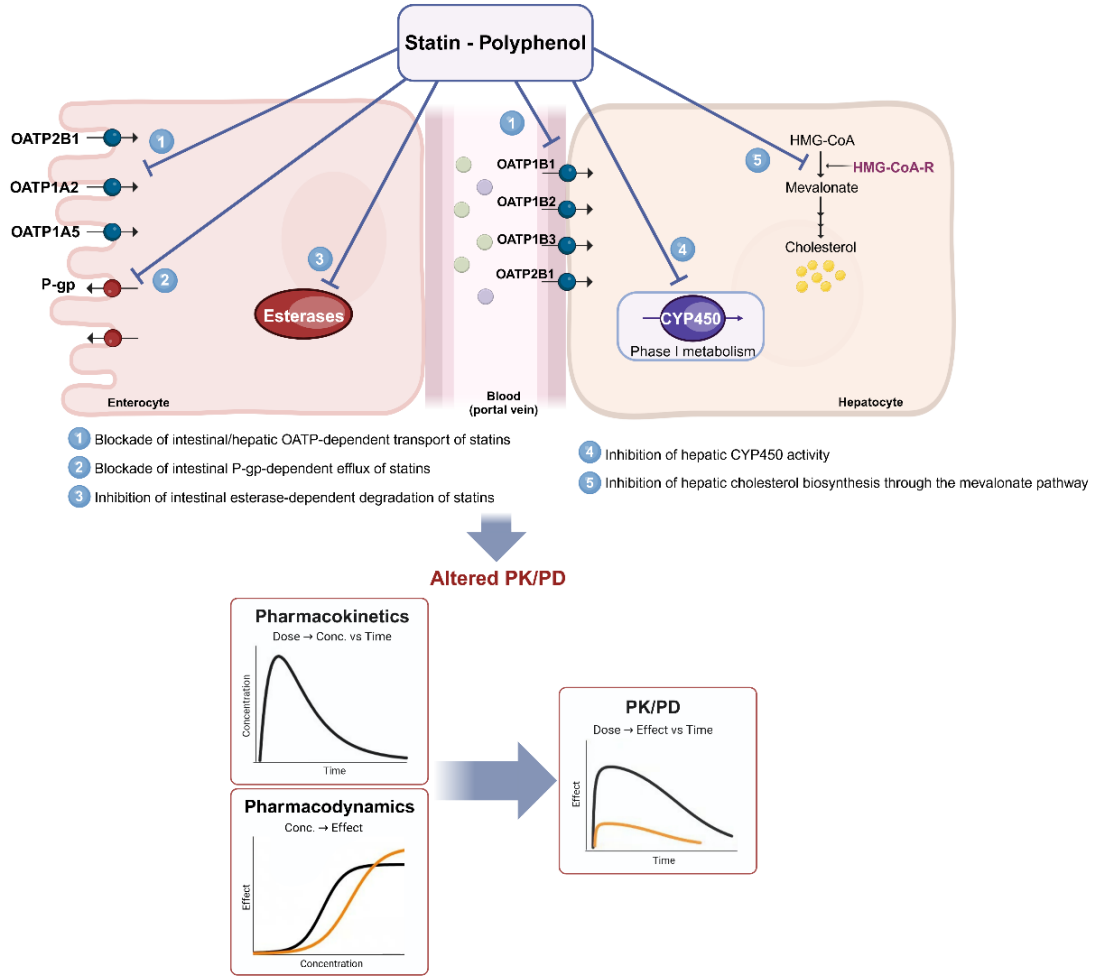

Figure 13. Key biological targets mediating statin-polyphenol interactions. (Image created in BioRender.com).

1. Blockade of OATP-dependent transport of statins: Polyphenols inhibit intestinal OATPs transporters (OATP2B1, OATP1A2, and OATP1A5), reducing the uptake of statins by enterocytes and thereby limiting their absorption and systemic bioavailability, which may lead to suboptimal therapeutic efficacy. In the liver, polyphenols block the uptake of statins into hepatocytes by inhibiting OATP transporters (OATP1B1, OATP1B3, and OATP2B1), impairing statins' ability to restrain HMG-CoA reductase activity, thereby reducing their cholesterol-lowering effectiveness.

2. Blockade of intestinal P-gp-dependent efflux of statins: Polyphenols inhibit P-glycoprotein (P-gp) activity, which may alter the efflux of statins, potentially resulting in increased intestinal retention of these drugs. This change could either enhance or diminish statin absorption, depending on the specific dynamics of the interaction.

3. Inhibition of intestinal esterase dependent degradation: Certain polyphenols inhibit intestinal esterase activity, potentially preventing the early degradation of statins, which are prodrugs, thus enhancing the systemic exposure to their active metabolites.

4. Inhibition of hepatic CYP450 activity: Polyphenols inhibit CYP450 enzymes, particularly CYP3A4 and CYP2C9, which are crucial for the metabolism of various statins. This inhibition can slow drug clearance and prolong systemic exposure, potentially increasing the risk of statin-related side effects or enhancing therapeutic efficacy at lower doses.

5. Inhibition of hepatic cholesterol biosynthesis via the mevalonate pathway: Polyphenols can directly impact cholesterol biosynthesis by inhibiting the rate-limiting enzyme HMG-CoA reductase. This effect may complement or enhance the action of statins, potentially providing therapeutic benefits beyond the effects of statins alone. However, it may also increase the risk of side effects.

The pharmacokinetic outcomes of statin-polyphenol interactions exhibit considerable variability and inconsistency across the studies analyzed, indicating both potential enhancement and inhibition of therapeutic effects. A key challenge in the coming decade will be advancing knowledge through studies that evaluate both pharmacodynamic and pharmacokinetic parameters. This will help determine whether statin-polyphenol

interactions are confined to *in vitro* or *in silico* models or have real-world clinical significance. This information is essential for optimizing the therapeutic efficacy of statins, potentially through adjustments in dosing or closer monitoring of plasma statin concentrations, to avoid both suboptimal treatment outcomes and an increased risk of adverse effects. Evidence-based guidelines are also needed to manage the dietary intake of polyphenol-rich foods and nutraceuticals in patients on statin therapy.

Chapter VI | **References**

References

Abdelkawy, K. S., Abdelaziz, R. M., Abdelmageed, A. M., Donia, A. M., & El-Khodary, N. M. (2020). Effects of Green Tea Extract on Atorvastatin Pharmacokinetics in Healthy Volunteers. *Eur J Drug Metab Pharmacokinet, 45*(3), 351-360. doi:10.1007/s13318-020-00608-6

Alqarni, S., Alsebai, M., Alsaigh, B. A., Alrashedy, A. S., Albahrani, I. T., Aljohar, A. Y., & Alazmi, A. O. (2024). Do polyphenols affect body fat and/or glucose metabolism? *Front Nutr, 11*, 1376508. doi:10.3389/fnut.2024.1376508

Antony, A., & Farid, M. (2022). Effect of Temperatures on Polyphenols during Extraction. *12*(4), 2107.

Attardo, S., Musumeci, O., Velardo, D., & Toscano, A. (2022). Statins Neuromuscular Adverse Effects. *Int J Mol Sci, 23*(15). doi:10.3390/ijms23158364

Bacle, A., Kadri, L., Khoury, S., Ferru-Clement, R., Faivre, J. F., Cognard, C., Bescond, J., Krzesiak, A., Contzler, H., Delpech, N., Colas, J., Vandebrouck, C., Sebille, S., & Ferreira, T. (2020). A comprehensive study of phospholipid fatty acid rearrangements in metabolic syndrome: correlations with organ dysfunction. *Dis Model Mech, 13*(6). doi:10.1242/dmm.043927

Bolat, E., Saritas, S., Duman, H., Eker, F., Akdasci, E., Karav, S., & Witkowska, A. M. (2024). Polyphenols: Secondary Metabolites with a Biological Impression. *Nutrients, 16*(15). doi:10.3390/nu16152550

Cermak, R., Wein, S., Wolffram, S., & Langguth, P. (2009). Effects of the flavonol quercetin on the bioavailability of simvastatin in pigs. *Eur J Pharm Sci, 38*(5), 519-524. doi:10.1016/j.ejps.2009.09.018

Cilla, D. D., Jr., Gibson, D. M., Whitfield, L. R., & Sedman, A. J. (1996). Pharmacodynamic effects and pharmacokinetics of atorvastatin after administration to normocholesterolemic subjects in the morning and evening. *J Clin Pharmacol, 36*(7), 604-609. doi:10.1002/j.1552-4604.1996.tb04224.x

Ciuta, A. D., Nosol, K., Kowal, J., Mukherjee, S., Ramirez, A. S., Stieger, B., Kossiakoff, A. A., & Locher, K. P. (2023). Structure of human drug transporters OATP1B1 and OATP1B3. *Nat Commun, 14*(1), 5774. doi:10.1038/s41467-023-41552-8

Climent, E., Benaiges, D., & Pedro-Botet, J. (2021). Hydrophilic or Lipophilic Statins? *Front Cardiovasc Med, 8*, 687585. doi:10.3389/fcvm.2021.687585

D'Archivio, M., Filesi, C., Vari, R., Scazzocchio, B., & Masella, R. (2010). Bioavailability of the polyphenols: status and controversies. *Int J Mol Sci, 11*(4), 1321-1342. doi:10.3390/ijms11041321

Davies, J. T., Delfino, S. F., Feinberg, C. E., Johnson, M. F., Nappi, V. L., Olinger, J. T., Schwab, A. P., & Swanson, H. I. (2016). Current and Emerging Uses of Statins in Clinical Therapeutics: A Review. *Lipid Insights, 9*, 13-29. doi:10.4137/LPI.S37450

Deng, J. W., Shon, J. H., Shin, H. J., Park, S. J., Yeo, C. W., Zhou, H. H., Song, I. S., & Shin, J. G. (2008). Effect of silymarin supplement on the pharmacokinetics of rosuvastatin. *Pharm Res, 25*(8), 1807-1814. doi:10.1007/s11095-007-9492-0

Dias, R. (2020). From chemistry to biological implications of polyphenols in Celiac Disease.

Duranton, F., Laget, J., Gayrard, N., Saulnier-Blache, J. S., Lundin, U., Schanstra, J. P., Mischak, H., Weinberger, K. M., Servel, M. F., & Argiles, A. (2019). The CKD plasma lipidome varies with disease severity and outcome. *J Clin Lipidol, 13*(1), 176-185 e178. doi:10.1016/j.jacl.2018.07.010

Fan, L., Zhang, W., Guo, D., Tan, Z. R., Xu, P., Li, Q., Liu, Y. Z., Zhang, L., He, T. Y., Hu, D. L., Wang, D., & Zhou, H. H. (2008). The effect of herbal medicine baicalin on pharmacokinetics of rosuvastatin, substrate of organic anion-transporting polypeptide 1B1. *Clin Pharmacol Ther, 83*(3), 471-476. doi:10.1038/sj.clpt.6100318

Ferreira, C., Vieira, P., Sa, H., Malva, J., Castelo-Branco, M., Reis, F., & Viana, S. (2024). Polyphenols: immunonutrients tipping the balance of immunometabolism in chronic diseases. *Front Immunol, 15*, 1360065. doi:10.3389/fimmu.2024.1360065

Filppula, A. M., Hirvensalo, P., Parviainen, H., Ivaska, V. E., Lonnberg, K. I., Deng, F., Viinamaki, J., Kurkela, M., Neuvonen, M., & Niemi, M. (2021). Comparative Hepatic and Intestinal Metabolism and Pharmacodynamics of Statins. *Drug Metab Dispos, 49*(8), 658-667. doi:10.1124/dmd.121.000406

Freese, R., & Lysne, V. (2023). Niacin - a scoping review for Nordic Nutrition Recommendations 2023. *Food Nutr Res, 67*. doi:10.29219/fnr.v67.10299

Golonko, A., Olichwier, A. J., Swislocka, R., Szczerbinski, L., & Lewandowski, W. (2022). Why Do Dietary Flavonoids Have a Promising Effect as Enhancers of Anthracyclines? Hydroxyl Substituents, Bioavailability and Biological Activity. *Int J Mol Sci, 24*(1). doi:10.3390/ijms24010391

Goszcz, K., Duthie, G. G., Stewart, D., Leslie, S. J., & Megson, I. L. (2017). Bioactive polyphenols and cardiovascular disease: chemical antagonists, pharmacological agents or xenobiotics that drive an adaptive response? *Br J Pharmacol, 174*(11), 1209-1225. doi:10.1111/bph.13708

Guo, X., Tresserra-Rimbau, A., Estruch, R., Martinez-Gonzalez, M. A., Medina-Remon, A., Fito, M., Corella, D., Salas-Salvado, J., Portillo, M. P., Moreno, J. J., Pi-Sunyer, X., & Lamuela-Raventos, R. M. (2017). Polyphenol Levels Are Inversely Correlated with Body Weight and Obesity in an Elderly Population after 5 Years of Follow Up (The Randomised PREDIMED Study). *Nutrients, 9*(5). doi:10.3390/nu9050452

Hemmerlin, A., Huchelmann, A., Tritsch, D., Schaller, H., & Bach, T. J. (2019). The specific molecular architecture of plant 3-hydroxy-3-methylglutaryl-CoA lyase. *J Biol Chem, 294*(44), 16186-16197. doi:10.1074/jbc.RA119.008839

Hughes, L. A., Arts, I. C., Ambergen, T., Brants, H. A., Dagnelie, P. C., Goldbohm, R. A., van den Brandt, P. A., Weijenberg, M. P., & Netherlands Cohort, S. (2008). Higher dietary flavone, flavonol, and catechin intakes are associated with less of an increase in BMI over time in women: a longitudinal analysis from the Netherlands Cohort Study. *Am J Clin Nutr, 88*(5), 1341-1352. doi:10.3945/ajcn.2008.26058

Jiang, Y. R., Liu, R. J., Tang, J., Li, M. Q., Zhang, D. K., Pei, Z. Q., Fan, S. H., Xu, R. C., Huang, H. Z., & Lin, J. Z. (2024). The health benefits of dietary polyphenols on pediatric intestinal diseases: Mechanism of action, clinical evidence and future research progress. *Phytother Res, 38*(7), 3782-3800. doi:10.1002/ptr.8218

Jin, L., Hua, H., Ji, Y., Jia, Z., Peng, M., & Huang, S. (2023). Anti-inflammatory role of fenofibrate in treating diseases. *Biomol Biomed, 23*(3), 376-391. doi:10.17305/bb.2022.8534

Ju, A., Li, Y. Y., Qu, Z., & Li, Q. (2017). Impact of the Herbal Breviscapine on the Pharmacokinetics of Simvastatin in Rats: The Involvement of CYP3A4. *Drug Res (Stuttg), 67*(5), 271-274. doi:10.1055/s-0042-118170

Kaneko, H., Itoh, H., Kiriyama, H., Kamon, T., Fujiu, K., Morita, K., Michihata, N., Jo, T., Takeda, N., Morita, H., Yasunaga, H., & Komuro, I. (2021). Possible association between eating behaviors and cardiovascular disease in the general population: Analysis of a nationwide epidemiological database. *Atherosclerosis, 320*, 79-85. doi:10.1016/j.atherosclerosis.2021.01.022

Kempegowda, S. N., Sugur, K., & Thimmulappa, R. K. (2024). Dysfunctional HDL Diagnostic Metrics for Cardiovascular Disease Risk Stratification: Are we Ready to Implement in Clinics? *J Cardiovasc Transl Res*. doi:10.1007/s12265-024-10559-x

Kim, T. E., Ha, N., Kim, Y., Kim, H., Lee, J. W., Jeon, J. Y., & Kim, M. G. (2017). Effect of epigallocatechin-3-gallate, major ingredient of green tea, on the pharmacokinetics of rosuvastatin in healthy volunteers. *Drug Des Devel Ther, 11*, 1409-1416. doi:10.2147/DDDT.S130050

Kimura, Y., Ito, H., Ohnishi, R., & Hatano, T. (2010). Inhibitory effects of polyphenols on human cytochrome P450 3A4 and 2C9 activity. *Food Chem Toxicol, 48*(1), 429-435. doi:10.1016/j.fct.2009.10.041

Kock, K., Xie, Y., Hawke, R. L., Oberlies, N. H., & Brouwer, K. L. (2013). Interaction of silymarin flavonolignans with organic anion-transporting polypeptides. *Drug Metab Dispos, 41*(5), 958-965. doi:10.1124/dmd.112.048272

Kondo, A., Narumi, K., Okuhara, K., Takahashi, Y., Furugen, A., Kobayashi, M., & Iseki, K. (2019). Black tea extract and theaflavin derivatives affect the pharmacokinetics of rosuvastatin by modulating organic anion transporting polypeptide (OATP) 2B1 activity. *Biopharm Drug Dispos, 40*(8), 302-306. doi:10.1002/bdd.2202

Koritala, R., Challa, S. R., Ragam, S. K., Geddam, L. B., Venkatesh Reddy Challa, V. R., Devi, R., Sattenapalli, S., & Babu, N. (2015). Quercetin does not alter the oral bioavailability of Atorvastatin in rats. *Pak J Pharm Sci, 28*(5), 1607-1612.

Kounatidis, D., Tentolouris, N., Vallianou, N. G., Mourouzis, I., Karampela, I., Stratigou, T., Rebelos, E., Kouveletsou, M., Stamatopoulos, V., Tsaroucha, E., & Dalamaga, M. (2024). The Pleiotropic Effects of Lipid-Modifying Interventions: Exploring Traditional and Emerging Hypolipidemic Therapies. *Metabolites, 14*(7). doi:10.3390/metabo14070388

Lagunas-Rangel, F. A., Liepinsh, E., Fredriksson, R., Alsehli, A. M., Williams, M. J., Dambrova, M., Jonsson, J., & Schioth, H. B. (2024). Off-target effects of statins: molecular mechanisms, side effects and the emerging role of kinases. *Br J Pharmacol*. doi:10.1111/bph.17309

Le Goff-Klein, N., Koffel, J. C., Jung, L., & Ubeaud, G. (2003). In vitro inhibition of simvastatin metabolism, a HMG-CoA reductase inhibitor in human and rat liver by bergamottin, a component of grapefruit juice. *Eur J Pharm Sci, 18*(1), 31-35. doi:10.1016/s0928-0987(02)00222-1

Li, P., Callery, P. S., Gan, L. S., & Balani, S. K. (2007). Esterase inhibition by grapefruit juice flavonoids leading to a new drug interaction. *Drug Metab Dispos, 35*(7), 1203-1208. doi:10.1124/dmd.106.013904

Li, Y., Wu, Y., Li, Y. J., Meng, L., Ding, C. Y., & Dong, Z. J. (2019). Effects of Silymarin on the In Vivo Pharmacokinetics of Simvastatin and Its Active Metabolite in Rats. *Molecules, 24*(9). doi:10.3390/molecules24091666

Lippolis, T., Cofano, M., Caponio, G. R., De Nunzio, V., & Notarnicola, M. (2023). Bioaccessibility and Bioavailability of Diet Polyphenols and Their Modulation of Gut Microbiota. *Int J Mol Sci, 24*(4). doi:10.3390/ijms24043813

Liu, J., Guo, Y., Liu, K., Ye, X., Wang, F., Xu, Y., & Xia, C. (2020). Scutellarin inhibition of the rosuvastatin uptake in rat hepatocytes and the competition for organic anion transporting polypeptide 1B1 in HEK293T cells. *Sci Rep, 10*(1), 1308. doi:10.1038/s41598-020-58303-0

Liu, J., Guo, Y., Xu, Y., Yuan, L., & Zhu, H. (2020). Scutellarin is Highly Likely to be Responsible for Drug-Drug Interactions Mediated by Hepatic Organic Anion-Transporting Polypeptide1B3. *Pharm Res, 37*(12), 232. doi:10.1007/s11095-020-02950-5

Loeffen, R., Winckers, K., Ford, I., Jukema, J. W., Robertson, M., Stott, D. J., Spronk, H. M., ten Cate, H., Lowe, G. D., & Group, P. S. (2015). Associations Between Thrombin Generation and the Risk of Cardiovascular Disease in Elderly Patients: Results From the PROSPER Study. *J Gerontol A Biol Sci Med Sci, 70*(8), 982-988. doi:10.1093/gerona/glu228

Loos, N. H. C., Beijnen, J. H., & Schinkel, A. H. (2022). The Mechanism-Based Inactivation of CYP3A4 by Ritonavir: What Mechanism? *Int J Mol Sci, 23*(17). doi:10.3390/ijms23179866

Lu, G., Xiao, H., You, H., Lin, Y., Jin, H., Snagaski, B., & Yang, C. S. (2008). Synergistic inhibition of lung tumorigenesis by a combination of green tea polyphenols and atorvastatin. *Clin Cancer Res, 14*(15), 4981-4988. doi:10.1158/1078-0432.CCR-07-1860

Luo, X., Zhou, L., Wang, S., Yuan, J., Chang, Z., Hu, Q., Chen, Y., Liu, Y., Huang, Y., Wang, B., Gao, Y., Wang, Z., Cui, Y., Liu, Y., & Zhang, L. (2022). The Therapeutic Effect and the Potential Mechanism of Flavonoids and Phenolics of Moringa oleifera Lam. Leaves against Hyperuricemia Mice. *Molecules, 27*(23). doi:10.3390/molecules27238237

Malekinejad, H., Rokhsartalab-Azar, S., Hassani-Dizaj, S., Alizadeh-Fanalou, S., Rezabakhsh, A., & Amniattalab, A. (2014). Effects of silymarin on the pharmacokinetics of atorvastatin in diabetic rats. *Eur J Drug Metab Pharmacokinet, 39*(4), 311-320. doi:10.1007/s13318-013-0166-5

Mandery, K., Balk, B., Bujok, K., Schmidt, I., Fromm, M. F., & Glaeser, H. (2012). Inhibition of hepatic uptake transporters by flavonoids. *Eur J Pharm Sci, 46*(1-2), 79-85. doi:10.1016/j.ejps.2012.02.014

Martin, K. R., & Appel, C. L. (2009). Polyphenols as dietary supplements: A double-edged sword. *Nutrition and Dietary Supplements, 2*(null), 1-12. doi:10.2147/NDS.S6422

McPherson, R., Adreak, N., & Sharma, A. (2024). Medications for Lipid Control: Statins vs Newer Drugs. *Can J Cardiol, 40*(8S), S26-S34. doi:10.1016/j.cjca.2024.05.004

Meng, M., Li, X., Zhang, X., & Sun, B. (2021). Baicalein inhibits the pharmacokinetics of simvastatin in rats via regulating the activity of CYP3A4. *Pharm Biol, 59*(1), 880-883. doi:10.1080/13880209.2021.1942927

Misaka, S., Abe, O., Sato, H., Ono, T., Shikama, Y., Onoue, S., Yabe, H., & Kimura, J. (2018). Lack of pharmacokinetic interaction between fluvastatin and green tea in healthy volunteers. *Eur J Clin Pharmacol, 74*(5), 601-609. doi:10.1007/s00228-018-2420-x

Mollazadeh, H., Tavana, E., Fanni, G., Bo, S., Banach, M., Pirro, M., von Haehling, S., Jamialahmadi, T., & Sahebkar, A. (2021). Effects of statins on mitochondrial pathways. *J Cachexia Sarcopenia Muscle, 12*(2), 237-251. doi:10.1002/jcsm.12654

Motawi, T. K., Teleb, Z. A., El-Boghdady, N. A., & Ibrahim, S. A. (2014). Effect of simvastatin and naringenin coadministration on rat liver DNA fragmentation and cytochrome P450 activity: an in vivo and in vitro study. *J Physiol Biochem, 70*(1), 225-237. doi:10.1007/s13105-013-0296-x

Mutlu, A. S., Duffy, J., & Wang, M. C. (2021). Lipid metabolism and lipid signals in aging and longevity. *Dev Cell, 56*(10), 1394-1407. doi:10.1016/j.devcel.2021.03.034

Nagao, T., Hase, T., & Tokimitsu, I. (2007). A green tea extract high in catechins reduces body fat and cardiovascular risks in humans. *Obesity (Silver Spring), 15*(6), 1473-1483. doi:10.1038/oby.2007.176

Natesan, V., & Kim, S. J. (2021). Lipid Metabolism, Disorders and Therapeutic Drugs - Review. *Biomol Ther (Seoul), 29*(6), 596-604. doi:10.4062/biomolther.2021.122

Navratilova, L., Ramos Mandikova, J., Pavek, P., Mladenka, P., & Trejtnar, F. (2018). Honey flavonoids inhibit hOATP2B1 and hOATP1A2 transporters and hOATP-mediated rosuvastatin cell uptake in vitro. *Xenobiotica, 48*(7), 745-755. doi:10.1080/00498254.2017.1358469

Nigam, S. K., & Granados, J. C. (2023). OAT, OATP, and MRP Drug Transporters and the Remote Sensing and Signaling Theory. *Annu Rev Pharmacol Toxicol, 63*, 637-660. doi:10.1146/annurev-pharmtox-030322-084058

Othman, R. A., Myrie, S. B., & Jones, P. J. (2013). Non-cholesterol sterols and cholesterol metabolism in sitosterolemia. *Atherosclerosis, 231*(2), 291-299. doi:10.1016/j.atherosclerosis.2013.09.038

Pan, T., Shi, Y., Yu, G., Mamtimin, A., & Zhu, W. (2023). Intracranial Aneurysms and Lipid Metabolism Disorders: From Molecular Mechanisms to Clinical Implications. *Biomolecules, 13*(11). doi:10.3390/biom13111652

Pawelec, G., & Gouttefangeas, C. (2006). T-cell dysregulation caused by chronic antigenic stress: the role of CMV in immunosenescence? *Aging Clin Exp Res, 18*(2), 171-173. doi:10.1007/BF03327436

Pollicino, F., Veronese, N., Dominguez, L. J., & Barbagallo, M. (2023). Mediterranean diet and mitochondria: New findings. *Exp Gerontol, 176*, 112165. doi:10.1016/j.exger.2023.112165

Poznyak, A., Grechko, A. V., Poggio, P., Myasoedova, V. A., Alfieri, V., & Orekhov, A. N. (2020). The Diabetes Mellitus-Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. *Int J Mol Sci, 21*(5). doi:10.3390/ijms21051835

Rastegar, T. F., Khan, I. A., & Christopher-Stine, L. (2024). Decoding the Intricacies of Statin-Associated Muscle Symptoms. *Curr Rheumatol Rep, 26*(7), 260-268. doi:10.1007/s11926-024-01143-y

Rastogi, H., & Jana, S. (2014). Evaluation of inhibitory effects of caffeic acid and quercetin on human liver cytochrome p450 activities. *Phytother Res, 28*(12), 1873-1878. doi:10.1002/ptr.5220

Saboori, S., Yousefi Rad, E., Tammam, J., Thondre, P. S., & Coe, S. (2024). Effects of niacin on apo A1 and B levels: a systematic review and meta-analysis of randomised controlled trials. *Br J Nutr, 131*(7), 1225-1235. doi:10.1017/S000711452300288X

Schachter, M. (2005). Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol, 19*(1), 117-125. doi:10.1111/j.1472-8206.2004.00299.x

Sever, P. S., Chang, C. L., Prescott, M. F., Gupta, A., Poulter, N. R., Whitehouse, A., & Scanlon, M. (2012). Is plasma renin activity a biomarker for the prediction of renal and cardiovascular outcomes in treated hypertensive patients? Observations from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). *Eur Heart J, 33*(23), 2970-2979. doi:10.1093/eurheartj/ehs241

Shirasaka, Y., Suzuki, K., Nakanishi, T., & Tamai, I. (2011). Differential effect of grapefruit juice on intestinal absorption of statins due to inhibition of organic anion transporting polypeptide and/or P-glycoprotein. *J Pharm Sci, 100*(9), 3843-3853. doi:10.1002/jps.22586

Shirasaka, Y., Suzuki, K., Shichiri, M., Nakanishi, T., & Tamai, I. (2011). Intestinal absorption of HMG-CoA reductase inhibitor pitavastatin mediated by organic anion transporting polypeptide and P-glycoprotein/multidrug resistance 1. *Drug Metab Pharmacokinet, 26*(2), 171-179. doi:10.2133/dmpk.dmpk-10-rg-073

Shitara, Y., & Sugiyama, Y. (2006). Pharmacokinetic and pharmacodynamic alterations of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors: drug-drug interactions and interindividual differences in transporter and metabolic enzyme functions. *Pharmacol Ther, 112*(1), 71-105. doi:10.1016/j.pharmthera.2006.03.003

Sirtori, C. R. (2014). The pharmacology of statins. *Pharmacol Res, 88*, 3-11. doi:10.1016/j.phrs.2014.03.002

Soleimani, H., Mousavi, A., Shojaei, S., Tavakoli, K., Salabat, D., Farahani Rad, F., Askari, M. K., Nelson, J., Ruzieh, M., & Hosseini, K. (2024). Safety and Effectiveness of High-Intensity Statins Versus Low/Moderate-Intensity Statins Plus Ezetimibe in Patients With Atherosclerotic Cardiovascular Disease for Reaching LDL-C Goals: A Systematic Review and Meta-Analysis. *Clin Cardiol, 47*(8), e24334. doi:10.1002/clc.24334

Somers, T., Siddiqi, S., Morshuis, W. J., Russel, F. G. M., & Schirris, T. J. J. (2023). Statins and Cardiomyocyte Metabolism, Friend or Foe? *J Cardiovasc Dev Dis, 10*(10). doi:10.3390/jcdd10100417

Tabrizi, R., Tamtaji, O. R., Lankarani, K. B., Akbari, M., Dadgostar, E., Dabbaghmanesh, M. H., Kolahdooz, F., Shamshirian, A., Momen-Heravi, M., & Asemi, Z. (2020). The effects of resveratrol intake on weight loss: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr, 60*(3), 375-390. doi:10.1080/10408398.2018.1529654

Takahashi, Y., Narumi, K., Nadai, T., Ueda, H., Yamamura, T., Furugen, A., & Kobayashi, M. (2021). In vitro and in vivo evaluation of organic anion-transporting polypeptide 2B1-mediated pharmacokinetic interactions by apple polyphenols. *Xenobiotica, 51*(11), 1318-1325. doi:10.1080/00498254.2021.1969480

Ubeaud, G., Hagenbach, J., Vandenschrieck, S., Jung, L., & Koffel, J. C. (1999). In vitro inhibition of simvastatin metabolism in rat and human liver by naringenin. *Life Sci, 65*(13), 1403-1412. doi:10.1016/s0024-3205(99)00380-x

Villanueva, J. A., Sokalska, A., Cress, A. B., Ortega, I., Bruner-Tran, K. L., Osteen, K. G., & Duleba, A. J. (2013). Resveratrol potentiates effect of simvastatin on inhibition of mevalonate pathway in human endometrial stromal cells. *J Clin Endocrinol Metab, 98*(3), E455-462. doi:10.1210/jc.2012-3387

Wang, S., Moustaid-Moussa, N., Chen, L., Mo, H., Shastri, A., Su, R., Bapat, P., Kwun, I., & Shen, C. L. (2014). Novel insights of dietary polyphenols and obesity. *J Nutr Biochem, 25*(1), 1-18. doi:10.1016/j.jnutbio.2013.09.001

Wen, F., Shi, M., Bian, J., Zhang, H., & Gui, C. (2016). Identification of natural products as modulators of OATP2B1 using LC-MS/MS to quantify OATP-mediated uptake. *Pharm Biol, 54*(2), 293-302. doi:10.3109/13880209.2015.1034326

Wessler, J. D., Grip, L. T., Mendell, J., & Giugliano, R. P. (2013). The P-glycoprotein transport system and cardiovascular drugs. *J Am Coll Cardiol, 61*(25), 2495-2502. doi:10.1016/j.jacc.2013.02.058

Wiggins, B. S., Saseen, J. J., Page, R. L., 2nd, Reed, B. N., Sneed, K., Kostis, J. B., Lanfear, D., Virani, S., Morris, P. B., American Heart Association Clinical Pharmacology Committee of the Council on Clinical, C., Council on, H., Council on Quality of, C., Outcomes, R., Council on Functional, G., & Translational, B. (2016). Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation, 134*(21), e468-e495. doi:10.1161/CIR.0000000000000456

Wong, D. H., Villanueva, J. A., Cress, A. B., Sokalska, A., Ortega, I., & Duleba, A. J. (2011). Resveratrol inhibits the mevalonate pathway and potentiates the antiproliferative effects of simvastatin in rat theca-interstitial cells. *Fertil Steril, 96*(5), 1252-1258. doi:10.1016/j.fertnstert.2011.08.010

Wu, L. X., Guo, C. X., Chen, W. Q., Yu, J., Qu, Q., Chen, Y., Tan, Z. R., Wang, G., Fan, L., Li, Q., Zhang, W., & Zhou, H. H. (2012). Inhibition of the organic anion-transporting polypeptide 1B1 by quercetin: an in vitro and in vivo assessment. *Br J Clin Pharmacol, 73*(5), 750-757. doi:10.1111/j.1365-2125.2011.04150.x

Yang, W., Zhang, Q., Yang, Y., Xu, J., Fan, A., Yang, C. S., Li, N., Lu, Y., Chen, J., Zhao, D., Aa, J., & Chen, X. (2017). Epigallocatechin-3-gallate decreases the transport and metabolism of simvastatin in rats. *Xenobiotica, 47*(1), 86-92. doi:10.3109/00498254.2016.1159747

Zechner, J., Britza, S. M., Farrington, R., Byard, R. W., & Musgrave, I. F. (2022). Flavonoid-statin interactions causing myopathy and the possible significance of OATP transport, CYP450 metabolism and mevalonate synthesis. *Life Sci, 291*, 119975. doi:10.1016/j.lfs.2021.119975

Zeng, X., Su, W., Liu, H., Zheng, Y., Chen, T., Zhang, W., Yan, Z., Bai, Y., & Yao, H. (2018). Simultaneous determination of rosuvastatin, naringin and naringenin in rat plasma by RRLC-MS/MS and its application to a pharmacokinetic drug interaction study. *J Chromatogr Sci, 56*(7), 611-618. doi:10.1093/chromsci/bmy034

Zodda, D., Giammona, R., & Schifilliti, S. (2018). Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. *Pharmacy (Basel), 6*(1). doi:10.3390/pharmacy6010010