Phytosterols and Sterol Esters in Cardiovascular Health: Mechanisms, Benefits, and Clinical Perspectives

Congyao Du*

Biosciences, University of Nottingham, Sutton Bonington, Loughborough LE12 5RD, UK

Abstract: Cardiovascular disease (CVD) is one of the leading causes of death worldwide, with high level of low-density lipoprotein cholesterol (LDL-C) being a key risk factor. There is increasing interest in dietary strategies and functional foods as complementary strategies for lowering cholesterol, with a daily intake of 2-3 g phytosterols reducing LDL-C by 8-10% through inhibited intestinal absorption. Although increasing research report that the anti-inflammatory and antioxidative properties of phytosterols could also benefit CVD prevention, how exactly these bioactivities could contribute to CVD intervention requires in-depth exploration. This review explores the role of phytosterols in CVD prevention, focusing on their effects on cholesterol metabolism, inflammation, and oxidative stress. Therefore, this review aims to elucidate the link between phytosterols' bioactivity and CVD prevention by comprehensively examining their effects on cholesterol metabolism, inflammation, and oxidative stress. Furthermore, it highlights key research gaps and future directions, including personalized nutrition strategies to improve absorption and efficacy. Addressing these challenges will help optimize the role of phytosterols in cardiovascular health management.

1. Introduction

Cardiovascular disease (CVD) is a leading cause of mortality worldwide, driven by key risk factors such as high LDL cholesterol (LDL-C), chronic inflammation, and oxidative stress [1]. Lifestyle, diet, and medications are currently well-known ways to improve and prevent CVD, but certain functional food components, such as phytosterols, also show potential to improve cardiovascular health. Phytosterols are plant-derived compounds structurally like cholesterol, allowing them to reduce cholesterol absorption and effectively lower LDL-C levels [2].

Phytosterols are naturally found in vegetable oils, nuts, seeds, legumes, and whole grains. Since these are relatively low in intake in the daily diet, Phytosterols are now being added to fortified foods and supplements to increase daily intake. The European Guidelines for Cardiovascular Disease Prevention [3] clearly recommend that daily intake of 2g of phytosterols can reduce serum LDL-C levels by 10%, which is particularly important for high-risk cardiovascular populations. Beyond their cholesterol-lowering effects, phytosterols also possess anti-inflammatory and antioxidant properties, which may offer additional cardiovascular protection. They regulate key inflammatory pathways, suppress pro-inflammatory cytokines, and reduce oxidative stress by enhancing antioxidant enzyme activity and protecting mitochondrial function [2]. These effects suggest that phytosterols may not only help prevent heart disease but also contribute to overall metabolic health.

Although phytosterols have some cardiovascular health benefits, there are some issues, including changes in absorption, bioavailability, and long-term safety. This review explores the sources, mechanisms, and health benefits of phytosterols, focusing on their role in cholesterol metabolism, inflammation regulation, and antioxidants. It also discusses current applications, research, and future directions, highlighting their potential as a natural, accessible strategy for cardiovascular disease prevention.

2. Source and function of phytosterols and sterol esters

2.1. Source and content distribution of phytosterols

In the natural diet, phytosterols are mainly found in vegetable oils, nuts, seeds, whole grains, and legumes [4].

Vegetable oils and grains are the best natural sources of dietary phytosterols, and three of the most common phytosterols in the diet are canola sterol, sitosterol and stigmasterol. The most common types of steranols are canola sterols and gluconosterols[2]. As shown in Table 1, vegetable oils (e.g., corn oil, canola oil) have the highest content of phytosterols (corn oil 712.1 mg/100g, canola oil 878.6 mg/100g), followed by nuts (e.g., pistachios 255.2 mg/100g) and legumes (soybean 275.6 mg/100g). Grains and vegetables have low phytosterol content, primarily β-sitosterol, followed by campesterol and stigmasterol.

*Corresponding author: ducongyao601@163.com

Table 1. Phytosterols in natural food sources (mg/100g)

Food Source	Total Phytosterols (mg/100g)	Major Phytosterol Type
Canola Oil	878.6	β-Sitosterol, Campesterol
Corn Oil	712.1	β-Sitosterol
Soybean Oil	352.9	β-Sitosterol
Sunflower Oil	280	β-Sitosterol
Olive Oil	150.4	β-Sitosterol
Sweet Potato	140.3	β-Sitosterol
Potato	113.8	β-Sitosterol
Yam	178.5	β-Sitosterol
Soybeans	275.6	β-Sitosterol, Campesterol
Lentils	129.6	β-Sitosterol
Chickpeas	150	β-Sitosterol
Oats	93.8	β-Sitosterol, Campesterol
Wheat	54.7	β-Sitosterol
Barley	34.3	β-Sitosterol
Buckwheat	11.9	β-Sitosterol
Corn Starch	63.4	β-Sitosterol
Almonds	200	β-Sitosterol
Pistachios	255.2	β-Sitosterol
Walnuts	150	β-Sitosterol
Peanuts	100	β-Sitosterol
Chestnuts	15.2	β-Sitosterol
Spinach	80	β-Sitosterol
Cucumber	60	β-Sitosterol
Pumpkin	70	β-Sitosterol

2.2. Structural composition and bioactive structural composition of phytosterols

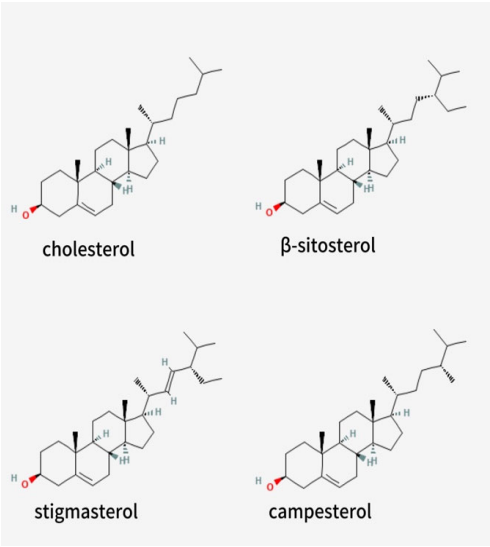

Figure 1. Cholesterol and major phytosterols (β-sitosterol, stigmasterol, and campesterol)

The cholesterol-lowering effect of phytosterols is closely related to their structure. The basic skeleton of phytosterols is similar to cholesterol, but there are significant differences in the side chain structure (Figure 1) [5]. Phytosterols usually have methyl groups (such as canola sterol) or ethyl groups (such as β-sitosterol) at the C24 position, while cholesterol has no substituents at this position. β-Sitosterol, the most abundant phytosterol, has a structure highly similar to cholesterol and exhibits the most effective competence in competing with cholesterol for absorption. In contrast, cholesterol, with additional methyl groups, has a higher intestinal absorption rate than β-sitosterol. Stigmasterol contains double bonds, contributing to its strong antioxidant properties.

2.3. Application of fortified foods and phytosterol supplements

Due to the limited intake of phytosterols in the natural diet (about 150-400 mg per day), fortified foods have become a key strategy to enhance phytosterol consumption and achieve effective levels for cardiovascular benefits. Phytosterols have been widely used in margarine (1.7g /100g), fermented dairy products (1.98g /100g) and cereal beverages (2.5-5g /250ml) [6]. The amount of phytosterols added varies by food type, such as margarine (1.7 g/100g), fermented corn yogurt (1.98 g/100g), skim milk (0.8 - 2.0 g/100g), and milk-based beverages (2.5 - 5 g/250ml)[6]. Phytosterol supplements further enhance the lipid-lowering effect by providing a concentrated high dose of sterols (typically 1.5-3 g daily).

3. Mechanisms of phytosterols in cardiovascular health

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide, and dyslipidemia, chronic inflammation, and the resulting oxidative stress are all key contributors to CVD[1]. Phytosterols, as an important dietary function factor, are similar in structure to cholesterol and can competitively inhibit the absorption of cholesterol and interfere with lipid metabolism. On the other hand, it can reduce the damage of pro-inflammatory response and oxidative stress and thus has the potential to improve cardiovascular diseases[7]. A summary of these mechanistic pathways is illustrated in Figure 2, highlighting their role in cholesterol metabolism, inflammation, and oxidative stress.

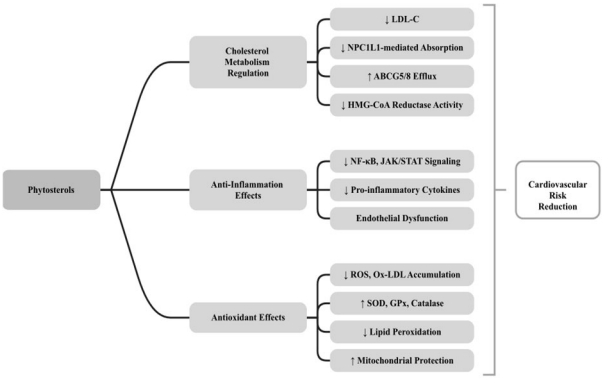

Figure 2. A mechanism diagram

3.1. Cholesterol metabolism regulation

Phytosterols reduce cholesterol by blocking absorption, enhancing cholesterol efflux, and altering bile acid metabolism via FXR signalling, which boosts bile acid excretion and helps balance lipid levels [8].

Numerous preclinical and human clinical trials have demonstrated the cholesterol-lowering effects of phytosterols. A 12-week study in ApoE−/− mice showed that phytosterol-enriched rapeseed oil lowered total and LDL cholesterol by downregulating intestinal cholesterol absorption genes and in vitro, β-sitosterol also suppressed NPC1L1 expression in Caco-2 cells, confirming reduced cholesterol uptake[9]. Similar results were verified in a mouse model of HFWD supplemented with 0.4% Stigmasterol and β-sitosterol[10]. A study in mice further confirmed that β-sitosterol laurate supplementation (2%) significantly reduced serum LDL-C and liver cholesteryl esters, supporting its role in lowering cholesterol by inhibiting both absorption and esterification[11]. In addition, more and more RCT clinical trials and meta-analyses further indicate that PS can effectively regulate the body's cholesterol metabolism. Post hoc analysis of RCTs demonstrated that 0.8–3 g/day phytostanol esters reduced LDL-C by inhibiting absorption and enhancing sterol excretion[12].

3.2. Anti-inflammatory effect

Phytosterols play anti-inflammatory effects by suppressing key signaling pathways[13,14], reducing cytokine production, inhibiting neutrophil recruitment, and promoting immune balance, contributing to cardiovascular protection [15].

Early animal models have shown that phytosterols supplementation reduces inflammation by reducing pro-inflammatory cytokines (IL-12, TNF-α) and regulating the NF-κB and NLRP3 pathways [13]. In vitro studies have confirmed that β-sitosterol inhibits TNF-α-induced VCAM-1 and ICAM-1 expression, reducing endothelial dysfunction and monocyte adhesion [16]. These findings suggest that phytosterols may help reduce vascular inflammation, regulate immune responses, and support joint health.

3.3. Antioxidant

Phytosterols exhibit antioxidant properties by modulating enzyme activity, reducing oxidative stress, and protecting mitochondrial function. Stigmasterol, for example, boosts enzymatic defenses such as SOD and CAT while reducing MDA levels, helping to ease inflammation and cardiac injury associated with oxidative damage [17]. In mouse models, phytosterol compounds such In animal studies, compounds like taraxasterol have been shown to activate the Nrf2/Keap1 pathway, thereby strengthening the body's endogenous antioxidant system and protecting organs from oxidative injury[18]. Similarly, a 14-day dietary intake of 0.25% oxidized stigmasterol was found to elevate glutathione levels and stimulate antioxidant enzymes without causing liver toxicity, indicating its potential in preserving redox homeostasis [19]. In cellular models, schottenol and spinasterol (5 μM) effectively reduced ROS and NO production in LPS-induced BV-2 microglial cells, modulated iNOS and catalase expression, and upregulated PPAR-α and peroxisomal markers, further supporting the antioxidant and anti-inflammatory role of phytosterols at the cellular level[20].

These cholesterol metabolism, inflammation, and antioxidant effects observed in both in vivo and in vitro studies are systematically summarized in Table 2.

Table 2. Effects of phytosterols on cardiovascular health data

Phytosterol Type	Possible mechanism	Pre-/clinical experiment	Treatment	Main effects	Reference
β-sitosterol laurate	Inhibition of cholesterol absorption	Male C57BL/6J mice	2% β-sitosterol laurate diet for 4 weeks	↓ Serum total cholesterol, ↓ LDL-C	[11]
High-phytosterol rapeseed oil	Inhibition of cholesterol absorption	ApoE−/− mice; Caco-2 cells (in vitro)	12-week diet with high-PS rapeseed oil (0.6 g PS/100g), in vitro 50–100 μM sitosterol	↓ plasma TC and LDL-C; ↓ cholesterol absorption genes (NPC1L1, ACAT2); ↑ occludin, ↓ VCAM-1	[9]
Stigmasterol and b-sitosterol	Improve cholesterol metabolism	Male C57BL6 mice	0.4% supplementation with HFWD	↓hepatic TG, total lipids, cholesterol, ↓Intestinal bile acids, ↑fecal lipids	[10]
Phytostanol esters	Reduce cholesterol absorption, increase synthesis and excretion	Human RCTs (post hoc analysis)	Daily intake of 0.8–3 g phytostanol esters	↓ LDL-C, ↓ cholesterol absorption, ↑ cholesterol synthesis, ↑ fecal sterol excretion	[12]
β-sitosterol	Regulate critical signaling pathways	mouse microglia cell line	BS (8–16 μM, 1–2 h) pretreatment before LPS (100 ng/mL) or IFN-γ exposure	↓ mRNA and protein expression of IL-6, TNF-α,	[14]

				iNOS, and COX-2	
β-sitosterol glycoside	immunomodulating activity	BALB/c mice	Daucosterol (200 μg/ml, 200 μl, i.p., twice every 3 days)	↑ expression of IL-2 and IFN-γ levels versus IL-4 and IL-10	[15]
stigmasterol	Regulate critical signaling pathways	APP/PS1 mice	50 mg/kg gavage (1 month)	↓ Neuroinflammation, ↓ Microglial response	[13]
β-sitosterol	Suppression of NF-κB and pro-inflammatory cytokines	HAECs	0.1–100 μM in vitro	↓ TNF-α-induced VCAM-1 and ICAM-1 expression	[16]
Stigmasterol	Inhibits oxidative stress and inflammation via upregulation of antioxidant enzymes and suppression of NF- κ B, TNF- α , IL-1 β , INF- γ , MCP-1; ameliorates myocardial damage	Male Wistar rats (cardiotoxicity model)	Doxorubicin 2.5 mg/kg + Stigmasterol 25 or 50 mg/kg (i.p., 14 days)	↑ SOD, CAT, GPx, GSH, HO-1, NQO1; ↓ TBARS, TNF- α , IL-1 β , INF- γ , MCP-1; ↓ CK-MB, GP-BB, H-FABP; Improved cardiac function and histopathology	[17]
Taraxasterol	Enhances antioxidant defense via Nrf2/Keap1 pathway; reduces ER stress and apoptosis	Mouse model of ZEA-induced kidney damage	5 or 10 mg/kg taraxasterol by gavage for 28 days, with 2 mg/kg ZEA diet	↓ ROS and MDA, ↑ CAT, T-SOD, GSH-Px, ↑ Nrf2, HO-1, NQO1; ↓ kidney damage, ↓ Bax, Caspase-3/12, ↑ Bcl-2	[18]
Phytosterol & α-Tocopherol	Enhances antioxidant defense via GSH/enzymes	ICR mice	0.25% oxidized stigmasterol for 14 days	↑ GSH, ↑ CAT, ↑ GPx, ↑ GR, ↑ SOD activity; no hepatotoxicity .	[19]
Schottenol & Spinasterol	Modulate antioxidant and peroxisomal pathways, suppress ROS and inflammatory mediators	BV-2 microglial cells (in vitro)	5 μ M treatment + LPS (100 ng/mL) for 24h	↓ ROS, ↓ NO, ↓ iNOS expression; ↑ catalase activity; ↑ Pex13, Pex14 and PPAR- α expression	[20]

Notes: ↑, significantly increased; ↓, significantly decreased; PSY - Plant Sterol-Egg Yolk Lipoprotein Complex; SD - Sprague-Dawley; HAECs - human endothelial cells; HFWD - High-Fat Western Diet; RCT - Randomized Controlled Trial; Apo E-KO - Apolipoprotein E Knockout; DPBS - Dulbecco's Phosphate-Buffered Saline; APP/PS1 - Amyloid Precursor Protein / Presenilin 1 (Alzheimer's disease mouse model); HAECs - Human Aortic Endothelial Cells; LDH - Lactate Dehydrogenase; GPx - Glutathione Peroxidase; Mn-SOD - Manganese Superoxide Dismutase; ROS - Reactive Oxygen Species; SOD - Superoxide Dismutase; CAT – Catalase; MDA – Malondialdehyde; POD – Peroxidase; DPPH - 2,2-Diphenyl-1-Picrylhydrazyl (a free radical used in antioxidant assays)

4. Conclusion and future perspectives

Phytosterols and their esters have shown great promise in the prevention of cardiovascular disease (CVD), mainly by inhibiting cholesterol absorption, anti-inflammatory and antioxidant effects, improving lipid levels and vascular function. However, individual responses to phytosterols vary and are influenced by genetic background (such as ABCG8 gene polymorphisms), gut microbiota and basal lipid levels, and the current recommended intake of 2-3 g/ day may not be appropriate for all populations. Therefore, future studies need to focus on personalized interventions to optimize dose and sterol combinations. In addition, existing studies mainly focus on short-term study, and their long-term safety, especially the impact on fat-soluble vitamin absorption, still needs to be evaluated in depth. Meanwhile, it is necessary to explore the synergistic effect of phytosterols with the Mediterranean diet, DASH diet and statins to clarify their comprehensive intervention value.

Improving the stability and bioavailability of phytosterols is gaining increasing interest. New technologies, such as nano-emulsification and microencapsulation, can enhance intestinal absorption while minimizing potential side effects. As phytosterols transition from basic research to clinical and food industry applications, sustainable production methods, including sterol extraction from agricultural by-products (e.g., rice bran, soybean residue) and the use of green technologies

like enzymatic esterification or microbial synthesis, can help lower costs and reduce environmental impact. In the future, continued research on mechanisms, technological advancements, and interdisciplinary collaboration will support the integration of phytosterols into safe and sustainable dietary strategies for high-risk populations.

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