Review Article

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Plant Sterols and Metabolic Health: Current Evidence on Insulin Resistance and Type 2 Diabetes Mellitus

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ABSTRACT

Plant sterols are naturally occurring bioactive compounds widely recognized for their cholesterol-lowering effects. This narrative review critically evaluates current evidence regarding the role of phytosterols in insulin resistance, glucose metabolism, and type 2 diabetes mellitus (T2DM). Literature was collected from PubMed, Scopus, and Google Scholar for studies Published between 2000 and 2024 using pre-defined keywords related to phytosterols, insulin resistance, and T2DM. Evidence from in-vitro and animal studies suggests that phytosterols may influence AMPK, PI3/Akt, and GLUT4 signaling pathways and may improve metabolic homeostasis. However, evidence from human clinical trials remains limited and in-consistent. Current findings strongly support the lipid-lowering benefits of phytosterols, where as their role in glycemic control requires further validation through well-designed clinical studies.

Keywords: Type 2 Diabetes, phytosterols, cholesterol-lowering effects, glucose metabolism, lipid profile.

1. Introduction

Type 2 diabetes (T2D) is a growing global health crisis characterized by chronic hyperglycemia and insulin resistance [1]. Diabetes affects roughly 537 million persons aged 20 to 79 years as of 2021. By 2030, the total number of diabetics is predicted to be 643 million, and by 2045, 783 million [2]. India is the capital of diabetes among the other nations [3]. The growing prevalence of T2D is a serious health concern in today's society. Lifestyle factors including high-calorie meals and sedentary behaviour have led to an increase in obesity and diabetes worldwide [4]. T2D is being treated with insulin and oral antidiabetic agents. The role of diet and life style in the prevention and management of this condition has been extensively studied [5]. Among various dietary components, plant sterols, or phytosterols, have emerged as potential therapeutic agents not only for lowering cholesterol levels but also for improving metabolic health [6]. This review delves into the impact of plant sterols on insulin resistance and T2D, offering insights into their mechanisms of action and potential therapeutic applications.

1.1. Selection of phytosterols

A narrative literature review approach was adopted to improve transparency and reproducibility. Electronic databases including PubMed, Scopus, and Google Scholar were searched for studies Published between 2000 and 2024.The keywords used included 'phytosterols',' plantsterols', 'insulin resistance', 'type 2 diabetes mellitus', 'glucose metabolism', and 'dyslipidemia'. Inclusion criteria included preclinical studies, clinical trials, systematic reviews, and mechanistic studies related to metabolic health and T2DM. Studies unrelated to glucose metabolism, insulin resistance, or metabolic disorders, as well as duplicate studies and combination nutraceutical interventions without isolated phytosterol evaluation, were excluded. A PRISMA-style flow chart was included to summarize study selection.

PRISMA-StyleFlowchart

Flowchart1: PRISMA-style flowchart summarizing literature identification, screening, eligibility assessment, and study inclusion.



Structural similarities of plant sterols to cholesterol

Plant sterols are structurally similar to cholesterol but have different side chains, allowing them to compete for absorption in the gut [7]. This competition reduces serum cholesterol levels. Apart from their effects on cholesterol metabolism, plant sterols may have additional advantages in terms of glucose metabolism and insulin sensitivity, both of which are important contributors to the development of type 2 diabetes [8]. Phytosterols are a group of molecules that are structurally similar to cholesterol but have slight variances in their side chain. So far, about 250 phytosterols have been discovered, with β-sitosterol, stigmasterol, and campesterol being the most commonly found in the diet. (Fig.1) [9].

2. Mechanisms of Action of Phytosterols in Metabolic Health

2.1 Cholesterol-lowering effects

These sterols occur naturally in a range of plant-based foods, such as nuts, seeds, vegetables, and

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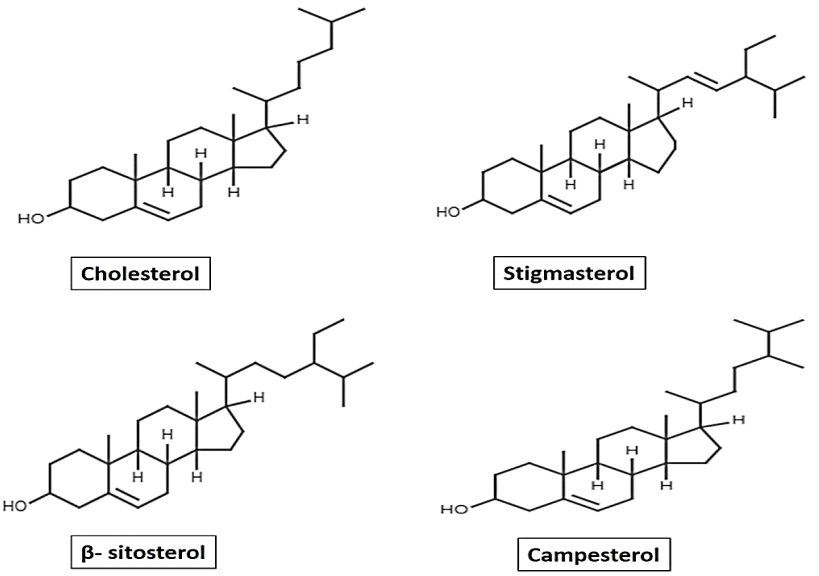


Figure1. Structure of phytosterols.
Showing the structural similarity of cholesterol and phytosterols such as stigmasterol, β-sitosterol, and campesterol.

whole grains [10]. The average daily consumption of plant sterols is quite modest, ranging from 200 to 400 mg, depending on dietary choices [11]. In the small intestine, plant sterols are absorbed and compete with cholesterol for micelle inclusion, blocking the absorption of cholesterol [12]. Plant sterols are frequently included in functional foods and dietary supplements with a cholesterol lowering focus because this method lowers plasma levels of low-density lipoprotein (LDL) cholesterol (Fig.2) [13].

Plant sterols have been demonstrated to lower dyslipidemia, insulin resistance, and β –cell dysfunction, attenuate adipose inflammatory signaling, and improve gut microbiota dysbiosis and barrier function. The major acknowledged advantage of plant sterols is their ability to reduce cholesterol[14]. Plant sterols, which reduce intestinal cholesterol absorption, can lower plasma LDL cholesterol levels by upto 10% [15]. As dyslipidemia is an established risk factor for type 2 diabetes and cardiovascular disease, lowering lipid profiles with plant sterols may have further advantages in decreasing insulin resistance and T2D [16]. Several clinical studies have shown that plant sterols decrease cholesterol, especially when ingested in functional foods such as margarine, dairy products, and supplements [17]. The reduction in LDL cholesterol has been demonstrated to be dose-dependent, with daily consumption of 1.5 to 3 grams of plant sterols advised for the best cholesterol-lowering benefits [18].

2.2. Impact on glucose metabolism

2.2.1. Insulin resistance

Insulin resistance occurs when the body's cells are unable to utilize plasma glucose for energy, despite adequate insulin levels in the blood. To put it another way, the cells are insulin-resistant. Further more, even when glucose is not necessary, the liver may still release it into the circulation. Insulin resistance in peripheral tissues and reduced insulin secretory capacity in pancreatic β-cells contribute to the development of T2D [19]. However, most type 2 diabetes patients maintain normal cell mass and cell proportions. Pancreatic islet amyloid, caused by amylin deposition, affects many T2D [20]. Early signs of altered β-cell function include a delayed and muted response to glucose and aberrant insulin production. Some studies suggest that elevated levels of free fatty acids in serum may contribute to β-cell failure [21]. Although T2D fasting plasma insulin levels may be normal or even higher, glucose-induced insulin production is diminished [22]. When insulin levels are low, insulin-mediated glucose absorption decreases but does not block hepatic glucose production. As a result, the cell's sensitivity to insulin signaling may change, and GLUT4 expression may decrease [23]. As a result, blood glucose levels stay elevated, and the pancreas responds by secreting more insulin,

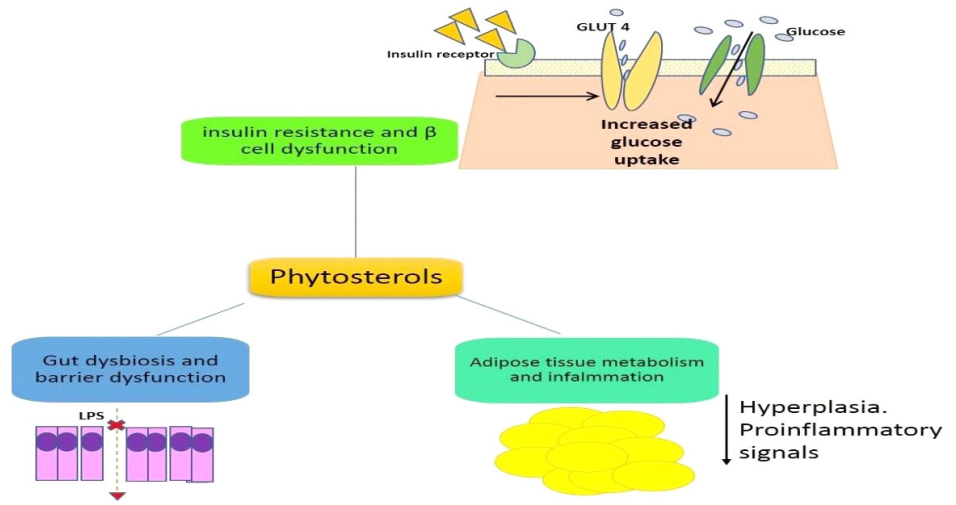


Figure 2. Potential role of phytosterols.
Showing potentially favourable benefits of phytosterols on type 2 diabetes (T2D) prevention and treatment.

resulting in a positive feedback loop that increases intra vascular insulin levels while desensitizing peripheral tissues to insulin. The biomolecular consequence of this cycle is that GLUT4 expression in the cell membrane continues to decrease, exacerbating the problem [24]. Insulin resistance, which can be caused by a variety of factors such as hyperglycemia, obesity, free fatty acids, reactive oxygen species(ROS), and infection, regulates the a fore mentioned insulin signaling (Fig.3a)and causes changes in a variety of genes and protein expression. A high-fat diet, for example, changes glucose and fat oxidation in the body, causing the release of reactive oxygen species (ROS). This results in the production of inflammatory cytokines such as TNF-α, IL-1, and IL-6, as well as changes to insulin signaling genes. Furthermore,the insulin signaling cascade is disrupted, resulting in lower glucose absorption and insulin resistance [25]. Animal models of diabetes and cell lines will be useful in the search for variables that contribute to the development of an inadequate plasma insulin pattern in diabetes, as well as in understanding the processes. Such a study might lead to the identification of particular factors implicated in the pathogenic process, opening the door for new pharmacological therapies that rest or normal plasma insulin levels [26]. Fig.3b depicts the pathophysiology of insulin resistance.

Insulin signaling begins with binding to the insulin receptor, followed by phosphorylation of the Tyr residue of IR S1/2 and activation of PI3K and Akt enzymes (a). Activated Akt activates the GLUT4 translocation proteins, resulting in glucose translocation for oxidation. (b). Insulin resistance occurs when serine residues are phosphorylated instead of Tyr following interaction with the insulin receptor. This results in reduced activation of PI3K and Akt, leading to decreased GLUT4 translocation and glucose absorption. The red arrow indicates that IRS1/2 serine phosphorylation inhibits PI3K /Akt /AS160 signaling, which causes insulin resistance owing to numerous reasons.

According to a new study, plant sterols may alter glucose metabolism and insulin sensitivity via numerous pathways [27]. Animal studies have demonstrated that phytosterols can improve glucose homeostasis, lower fasting blood glucose levels, and increase insulin sensitivity [28]. These effects are assumed to be achieved via the regulation of signaling pathways involved in glucose absorption, including the AMP-activated protein kinase(AMPK) pathway [29]. The activation of AMPK is essential for cellular energy control, and it has been demonstrated to increase insulin sensitivity[30]. In rat models, phytosterol supplementation has been linked to enhanced AMPK activation in liver and muscle tissues, which improves glucose absorption and reduces insulin resistance [31].

Stigmasterol has been found to diminish insulin resistance in KK-Ay mice fed high-fat diets [31]. After 4 weeks of administering this drug at 50 mg/kg/day, mice showed improved glucose tolerance. This sterol's positive impact may be attributed to its capacityto normalize islet forms, inhibit pancreatic is-

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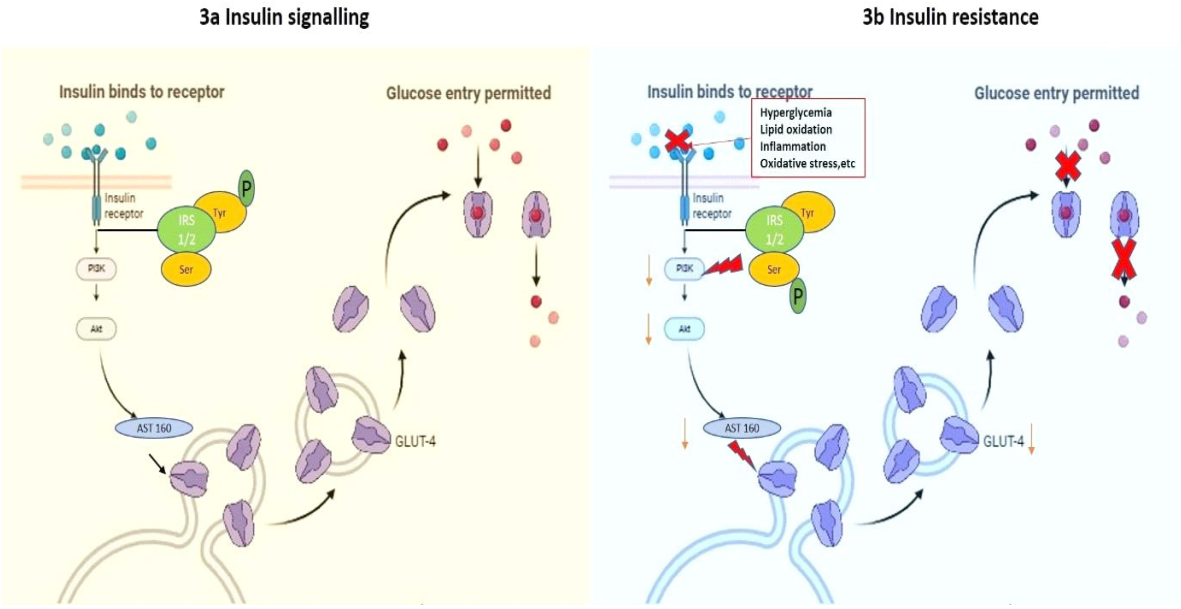


Figure 3. Insulin signaling under physiological and pathophysiological conditions.

let shrinkage, and increase GLUT4 expression levels in skeletal muscle and white adipose tissue. Furthermore, rats given β-sitosterol showed enhanced oral glucose tolerance, lower fasting glucose levels, and higher insulin production from isolated pancreatic islet cells. Additional studies revealed that these effects are mediated via the activation and regulation of PI3K/Akt and GLUT4 [32]. At lower doses, the phyto compound had a substantial lipolytic action, which gradually decreased as concentrations increased. The results of real-time polymerase chain reaction (RT-PCR) showed that GLUT4 gene expression increased whereas PI3KA and AKT genes decreased.

Histological observations suggest that sitosterol treatment can rejuvenate insulin producing β-cells in diabetic rats. This study found that 30 days of oral sitosterol treatment (20 mg/kg) to rats with T2D produced bya high-fat diet and sucrose improved their plasma insulin and blood glucose levels. Several in vitro investigations have shown that phytosterols improve glucose homeostasis [33]. Research indicates that β-sitosterol and stigmasterol can enhance adipocyte glucose uptake, GLUT4 translocation and expression in L6 cells, and immortalized rat skeletal (L6) myoblast cells with GLUT4 expression and high fusion potential in the myotube stage. The favourable impact of phytosterols on glucose metabolism appears to be mediated by AMPK [34].

2.2.2. Anti-inflammatory properties

Chronic inflammation is a major cause of insulin resistance and the development of type 2 diabetes [35]. Plant sterols have been proven to have anti-inflammatory characteristics, which may explain their favourable impact on metabolic health [36]. Research suggests that phytosterols can lower levels of pro-inflammatory cytokines including TNF-α and IL-6 in adipose tissue, whichare linked to insulin resistance [37]. Plant sterols may assist in slowing the progression of insulin resistance by lowering systemic inflammation [38]. This anti-inflammatory activity is especially relevant in obesity, which is associated with persistent low-grade inflammation and is a major risk factor for T2D [39].

2.2.3. Effects on adipose tissue and insulin sensitivity

Adipose tissue regulates insulin sensitivity, and adipose tissue malfunction is a defining feature of insulin resistance [26]. Plant sterols have been demonstrated to increase adipose tissue metabolism by increasing adiponectin release, a hormone that boosts insulin sensitivity and has anti-inflammatory properties [40]. *In-vitro* and animal studies have shown that phytosterols can regulate adipocyte development and function, resulting in better insulin signaling in adipose tissue [41]. These findings indicate that plant

sterols may help restore normal adipose tissue function, improving insulin sensitivity and lowering the risk of T2D [42]. A few of the pre-clinical and clinical research on phytosterols are listed in Table1.

Table1. Summarizes selected preclinical and clinical studies specifically related to metabolic health, insulin resistance, and type 2 diabetes mellitus.

3. Clinical Evidence: Plant Sterols in T2D Management

3.1. Human trials on cholesterol and glucose control

Although some randomized controlled trials have reported modest improvements in fasting

Table1. Pre - clinical and clinical research on phytosterols

S. No.	Phytosterol(s)	Study Type	Study Model	Effect/Mechanism Relevant to Obesity/T2DM	Reference
1	Phytosterols	Preclinical	Diabetic rats	Modulate glucose metabolism through the AMPK signaling pathway and improve glycemic control.	[31]
2	Stigmasterol and β-sitosterol	Clinical	Patients with NAFLD	Reduce hepatic cholesterol accumulation, increase PUFA levels, and decrease inflammatory cytokines.	[49]
3	Phytosterols	Clinical	Patients with cardiovascular disease	Reduce total cholesterol and LDL-C, lowering cardiometabolic risk associated with obesity and T2DM.	[13]
4	β-Sitosterol	Preclinical	High-fat diet-induced obese mice	Reduces body weight gain, adipocyte hypertrophy, and systemic inflammation.	[67]
5	Stigmasterol	Preclinical	Obese mice	Improves insulin sensitivity and regulates lipid metabolism-related genes.	[68]
6	Campesterol	Preclinical	Diabetic rat model	Enhances glucose uptake and improves insulin signaling.	[69]
7	β-Sitosterol	Preclinical	Insulin-resistant adipocyte model	Activates glucose transporter pathways and improves cellular glucose utilization.	[70]
8	Phytosterol mixture	Clinical	Hypercholesterolemic overweight adults	Lowers LDL-C and improves metabolic risk markers.	[71]
9	Phytosterol-enriched diet	Clinical	Adults with metabolic syndrome	Improves lipid profile and reduces cardiovascular risk factors.	[72]
10	β-Sitosterol	Preclinical	High-fat diet-induced NAFLD mice	Reduces hepatic steatosis and improves insulin resistance.	[73]
11	Stigmasterol	Preclinical	Obese diabetic mice	Attenuates oxidative stress and inflammation associated with diabetes.	[74]
12	Phytosterol mixture	Clinical	Subjects with dyslipidemia and obesity	Reduces LDL-C and improves markers of metabolic health.	[75]
13	Campesterol and β-sitosterol	Preclinical	Diabetic rodent model	Enhance antioxidant defenses and improve pancreatic β-cell function.	[76]

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glucose and insulin sensitivity following phytosterol supplementation, the available human

evidence remains inconsistent and insufficient to establish definitive glycemic benefits.

3.2. Potential synergistic effects with other nutraceuticals

Recent studies went further at the possible synergistic effects of plant sterols when paired with other bioactive chemicals such as polyphenols, omega-3 fatty acids, and dietary fibres [56]. These combinations may provide additional advantages for cholesterol-lowering and glucose metabolism. For example,combining plant sterols with omega-3 fatty acids has been proven to improve lipid profiles and insulin sensitivity [57]. Further research is needed to explore the full potential of such combinations in the management of metabolic disorders. Some of the research progress of phytosterols based on the target organs is given in Table 2.

Table 2 indicates the research work carried out using phytosterols on target organs

3.3. Safety and tolerability of plant sterols

Plant sterols are usually considered safe and well-tolerated, with minimal side effects observed at typical dosage [67]. However, large amounts of phytosterols may impair the absorption of fat-soluble vitamins including A, D, E,and K [68]. Long-term studies are required to thoroughly examine the safety of chronic high-dose phytosterol ingestion, especially in those with metabolic problems [69]. One uncommon but

Table 2. Research Progress of Phytosterols based on target organ

S. No.	Target Organ/System	Specific Phytosterol(s) Studied	Mechanism of Action	Study Type	Ref.
1	Intestine	Phytosterols (plant sterols)	Inhibits intestinal cholesterol absorption, reducing plasma LDL cholesterol	Preclinical and Clinical	[58]
2	Liver	Phytosterols (β-sitosterol, campesterol, stigmasterol and related phytosterols)	Suppresses cholesterol synthesis and enhances bile acid secretion, thereby regulating cholesterol metabolism	Preclinical and Clinical Evidence	[59]
3	Heart	Phytosterol supplements	Reduces cardiovascular risk factors, including LDL cholesterol and triglycerides	Clinical	[13]
4	Blood Vessels	Dietary plant sterols	Improves vascular function by increasing nitric oxide production and reducing inflammation	Clinical (Randomized Controlled Trial)	[60]
5	Adipose Tissue	Phytosterols	Modulates adipokine secretion, influencing glucose and lipid metabolism	Preclinical and Clinical Evidence	[61]
6	Pancreas	Phytosterol-enriched spread (mixed phytosterols)	Improves insulin sensitivity and glucose metabolism, reducing the risk of type II diabetes	Clinical (Randomized Double-Blind Placebo-Controlled Trial)	[62]
7	Brain	Phytosterols (including β-sitosterol, campesterol, stigmasterol)	Exerts neuroprotective effects by reducing neuroinflammation and oxidative stress	Primarily Preclinical Evidence	[63]
8	Kidney	β-Sitosterol	Reduces renal inflammation and oxidative stress, improving kidney function	Preclinical (Animal Study)	[64]
9	Immune System	Plant sterols	Exhibits immunomodulatory effects by influencing cytokine production and immune cell function	Preclinical (Cell Culture Study)	[65]
10	Colon	β-Sitosterol	Demonstrates anticancer activity through induction of apoptosis and inhibition of tumor progression	Mainly Preclinical Evidence	[66]

noticeable side effect is phytosterolemia, a hereditary disorder defined by the build-up of plant sterolsin the blood, which leads to early atherosclerosis. People who have this health condition should avoid phytosterol-rich diets and supplements [70].

4. Conclusion

Plant sterols remain promising dietary compounds for improving lipid metabolism and cardiovascular risk factors. Pre-clinical studies suggest potential benefits on insulin signaling, inflammation, and glucose uptake pathways; however, current clinical evidence does not conclusively support phytosterols as established therapies for glycemic control in T2DM. Future well designed randomized clinical trials are needed to determine their therapeutic efficacy and long-term metabolic benefits.

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Conflict of Interest

The author has no conflicts of interest, financial or otherwise,to declare.

Statement of Contribution of Researchers

RV, KR, VG:Concept, Design, Supervision, PDR: Materials; Data Collection and / or Processing, Writing, Analysis and / or Interpretation.TM, RT, PDR: Literature Search, Critical Reviews.

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