Stigmasterol as a Multifunctional Phytosterol: Pharmacological Activities, Therapeutic Potential, and Future Perspectives

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Abstract

Stigmasterol is a naturally occurring phytosterol widely distributed in plant-based foods, medicinal plants, and vegetable oils and has attracted increasing scientific interest because of its diverse pharmacological properties and therapeutic potential. This review provides a comprehensive overview of the biological activities, molecular mechanisms, therapeutic applications, safety profile, and future prospects of stigmasterol. Available evidence indicates that stigmasterol exhibits antioxidant, anti-inflammatory, anticancer, antidiabetic, hypocholesterolemic, cardioprotective, hepatoprotective, neuroprotective, antimicrobial, immunomodulatory, anti-arthritic, and bone-protective effects. These activities are associated with its ability to modulate oxidative stress, inflammatory mediators, lipid metabolism, apoptosis, mitochondrial function, and signaling pathways such as NF-κB, MAPK, PI3K/Akt/mTOR, and other cellular regulatory networks. Potential applications of stigmasterol have been explored in metabolic disorders, cardiovascular diseases, cancer, neurodegenerative conditions, liver diseases, inflammatory disorders, dermatological conditions, and women's health. Despite its promising pharmacological profile, clinical translation remains challenging because of its poor aqueous solubility, limited oral bioavailability, variable pharmacokinetic behavior, and the predominance of preclinical evidence. Advanced drug-delivery systems, standardized formulations, rigorous toxicological evaluation, and well-designed clinical trials are required to establish its therapeutic efficacy and safety. Overall, stigmasterol represents a promising multifunctional phytosterol and a potential lead molecule for the development of novel preventive and therapeutic strategies against chronic and multifactorial diseases.

Keywords: Stigmasterol; Phytosterols; Pharmacological activities; Therapeutic potential; Antioxidant; Anti-inflammatory; Anticancer; Metabolic disorders; Neuroprotection; Bioavailability; Drug delivery; Clinical translation.

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1. Introduction

Phytosterols are a diverse group of naturally occurring plant-derived sterols that share structural similarities with cholesterol and constitute important components of plant cell membranes. More than 250 phytosterol molecules have been identified in plants, although β-sitosterol, campesterol, and stigmasterol are among the most abundant and extensively investigated members of this group. By influencing membrane fluidity, permeability, organization, and signaling, phytosterols contribute to fundamental physiological processes in plants, including growth, development, reproduction, and adaptation to environmental stress. Their structural resemblance to cholesterol has also generated considerable interest in human nutrition and medicine, as dietary phytosterols can interfere with intestinal cholesterol absorption and consequently contribute to the regulation of circulating cholesterol concentrations. Beyond their lipid-modulating effects, increasing experimental evidence suggests that phytosterols possess a broad spectrum of biological activities, including antioxidant, anti-inflammatory, immunomodulatory, anticancer, metabolic, and neuroprotective effects, thereby establishing them as promising nutraceutical and pharmacologically relevant compounds (Choudhary & Tran, 2011; Feng et al., 2020; Shen et al., 2024; Tan & Men, 2026).

Among the naturally occurring phytosterols, stigmasterol has emerged as a particularly interesting multifunctional bioactive molecule. Stigmasterol is an unsaturated phytosterol with the molecular formula $C_{29}H_{48}O$ and the systematic designation stigmasta-5,22-dien-3β-ol. It possesses the characteristic four-ring steroid nucleus of phytosterols, a hydroxyl group at the C-3 position, and an additional trans-oriented double bond in its side chain, particularly distinguishing it structurally from β-sitosterol. This structural feature contributes to differences in its physicochemical characteristics and biological activities. Stigmasterol is generally described as a white crystalline or powder-like lipophilic compound with very low water solubility, while showing greater solubility in organic solvents and alcohols. Its hydrophobic nature and limited aqueous solubility are important

considerations for its absorption, bioavailability, formulation, and eventual therapeutic development (Bakrim et al., 2022; Yoon et al., 2025). The structural similarity of stigmasterol to cholesterol is also pharmacologically relevant because it facilitates interactions with lipid membranes and pathways involved in cholesterol and lipid homeostasis. Recent research has further emphasized that structural differences among individual phytosterols can substantially influence their physicochemical behavior, metabolism, and biological functions, highlighting the importance of understanding stigmasterol as a distinct bioactive sterol rather than merely as a member of the broader phytosterol family (Liu et al., 2026; Tan & Men, 2026).

Stigmasterol is widely distributed throughout the plant kingdom and occurs in a variety of edible and medicinal plant sources. It has been detected in vegetable oils, particularly soybean and rapeseed oils, as well as in cereals, seeds, nuts, legumes, vegetables, and several medicinal plants. It has also been isolated from diverse botanical species and has been reported as a major or significant phytosterol component in certain plant extracts. The distribution and concentration of stigmasterol vary considerably depending on plant species, tissue type, geographical origin, cultivation conditions, processing methods, and extraction procedures. In plants, stigmasterol is synthesized through the mevalonate-dependent sterol biosynthetic pathway, with β-sitosterol serving as an important precursor that undergoes C22 desaturation to generate stigmasterol. Interestingly, stigmasterol is increasingly recognized not only as a structural component of plant membranes but also as a sterol associated with plant responses to environmental stress, suggesting that its biological importance extends beyond membrane organization (Bakrim et al., 2022; Shulaev et al., 2024).

From a dietary perspective, stigmasterol is consumed as part of plant-based foods and edible oils, although its intestinal absorption is considerably lower than that of cholesterol. Phytosterols are able to compete with cholesterol during intestinal absorption, partly by influencing the incorporation of cholesterol into mixed micelles, thereby reducing the amount of cholesterol available for uptake. This property has contributed to the growing interest in phytosterols as functional food ingredients and nutraceutical agents for maintaining healthy lipid profiles. However, the biological relevance of individual phytosterols, including stigmasterol, extends beyond cholesterol lowering. Experimental studies have demonstrated that stigmasterol may influence several physiological and pathological processes associated with oxidative stress, chronic inflammation, abnormal cell proliferation, glucose metabolism, lipid homeostasis, neuronal dysfunction, and immune responses. Consequently, stigmasterol has attracted increasing attention as a potential multifunctional molecule with applications extending from dietary health promotion to pharmaceutical and cosmeceutical development (Choudhary & Tran, 2011; Feng et al., 2020; Shen et al., 2024).

The growing pharmacological interest in stigmasterol is largely attributable to its diverse biological effects observed in cellular, animal, and, to a more limited extent, translational studies. Available evidence indicates that stigmasterol may exert antioxidant activity by modulating oxidative stress and reducing the consequences of excessive reactive oxygen species generation. Its anti-inflammatory effects have been associated with the regulation of inflammatory mediators and signaling pathways, including pathways related to cyclooxygenase-2, inducible nitric oxide synthase, nuclear factor-κB, and inflammatory cytokine production. In cancer research, stigmasterol has demonstrated potential to influence multiple processes involved in tumor development, including cell proliferation, apoptosis, angiogenesis, migration, and survival signaling. Studies have also linked its biological actions to pathways such as PI3K/Akt/mTOR and JAK/STAT, although the precise molecular mechanisms may differ according to the cancer type and experimental model. In addition, preclinical investigations have reported antidiabetic, hypolipidemic, hepatoprotective, neuroprotective, antimicrobial, immunomodulatory, and anti-arthritic effects, suggesting that stigmasterol may act through multiple molecular targets rather than a single pharmacological pathway (Bakrim et al., 2022; Li et al., 2025).

The multifunctional nature of stigmasterol may be explained by its capacity to interact with biological membranes and influence several interconnected cellular processes. As a lipophilic sterol, it can participate in membrane organization and potentially modify membrane-associated signaling events. Its structural relationship with cholesterol may also enable interactions with lipid metabolic pathways, while its effects on oxidative stress and inflammatory signaling can indirectly influence apoptosis, cellular proliferation, mitochondrial function, and tissue homeostasis. Importantly, many pathological conditions—including cancer, diabetes, cardiovascular disease, neurodegeneration, and chronic inflammatory disorders—share common biological mechanisms such as oxidative stress, inflammation, dysregulated metabolism, and abnormal cellular signaling. Therefore, the ability of stigmasterol to modulate several of these mechanisms simultaneously provides a plausible basis for its broad pharmacological profile. Nevertheless, the

majority of evidence remains derived from in vitro and preclinical studies, and the relationship between experimental concentrations and achievable human exposure requires careful consideration. Furthermore, low aqueous solubility, limited bioavailability, rapid metabolism, and incomplete understanding of pharmacokinetic behavior remain important challenges in translating the promising biological properties of stigmasterol into clinically useful therapeutic interventions (Bakrim et al., 2022; Feng et al., 2020; Liu et al., 2026).

In recent years, the scientific literature on stigmasterol has expanded considerably, encompassing investigations of its natural occurrence, biosynthesis, physicochemical characteristics, pharmacological activities, molecular mechanisms, and therapeutic applications (Racette et al., 2010). However, the available evidence remains fragmented across different disease models and biological systems, and several aspects of its pharmacodynamics, pharmacokinetics, safety, bioavailability, and clinical relevance remain insufficiently characterized. In particular, although multiple studies have reported promising antioxidant, anti-inflammatory, anticancer, metabolic, neuroprotective, antimicrobial, and immunomodulatory properties, the extent to which these findings can be translated into effective human therapies requires systematic evaluation. A comprehensive understanding of the molecular mechanisms underlying these effects is also essential for identifying appropriate therapeutic targets and developing suitable delivery systems capable of overcoming the intrinsic physicochemical limitations of stigmasterol (Bakrim et al., 2022; Yoon et al., 2025).

Against this background, the present review provides a comprehensive overview of stigmasterol as a multifunctional phytosterol, with particular emphasis on its chemical and physicochemical characteristics, dietary and natural sources, biological significance, and diverse pharmacological activities. The review further examines the molecular and cellular mechanisms proposed to underlie its antioxidant, anti-inflammatory, anticancer, metabolic, cardiovascular, neuroprotective, antimicrobial, immunomodulatory, and other therapeutic effects. In addition, the emerging therapeutic potential of stigmasterol, current limitations related to bioavailability and clinical translation, and the need for advanced formulation strategies and rigorous clinical investigations are discussed. By integrating current knowledge from mechanistic, preclinical, and translational research, this review aims to clarify the therapeutic significance of stigmasterol, identify existing research gaps, and highlight future directions for its development as a potential nutraceutical, pharmaceutical, and multifunctional therapeutic agent.

2. Pharmacokinetics, Bioavailability, and Molecular Mechanisms of Stigmasterol

2.1 Absorption, Distribution, Metabolism, and Elimination

Stigmasterol is a plant-derived sterol with a chemical structure closely related to cholesterol. Its intestinal absorption is generally low compared with cholesterol, and only a small fraction of orally administered phytosterols is absorbed into the systemic circulation. Following ingestion, stigmasterol enters the gastrointestinal tract together with dietary lipids and undergoes incorporation into mixed micelles in the intestinal lumen. This process is influenced by the physicochemical properties of stigmasterol, including its high lipophilicity and poor aqueous solubility. Micellar incorporation facilitates the interaction of stigmasterol with the intestinal brush border and its subsequent uptake by enterocytes (Ras et al., 2013). However, intestinal absorption is restricted by the activity of ATP-binding cassette (ABC) transporters, particularly ABCG5 and ABCG8, which promote the efflux of absorbed plant sterols back into the intestinal lumen. Consequently, most dietary stigmasterol is eliminated through the fecal route rather than reaching systemic circulation (Feng et al., 2020; Bakrim et al., 2022).

The fraction of stigmasterol that escapes intestinal efflux can be incorporated into chylomicrons and transported through the lymphatic system before entering the systemic circulation. Similar to other sterols, its distribution is influenced by its affinity for lipoproteins and biological membranes. Circulating stigmasterol may be transported predominantly in association with plasma lipoproteins and subsequently distributed to tissues. However, compared with cholesterol, stigmasterol generally occurs at substantially lower concentrations in human tissues because of its limited intestinal absorption and efficient elimination mechanisms. The liver represents an important organ in the handling of absorbed phytosterols, where sterol transport and metabolism contribute to their eventual clearance (Trautwein et al., 2003; Feng et al., 2020).

Once absorbed, stigmasterol can undergo metabolic transformation involving oxidation, hydroxylation, and other enzymatic reactions. The liver plays a major role in sterol metabolism, while intestinal and hepatic transporters contribute substantially to the regulation of circulating phytosterol concentrations. ABCG5/ABCG8-mediated biliary secretion represents an important mechanism for removing absorbed plant sterols from the body. Consequently, the overall pharmacokinetic profile of stigmasterol is characterized by limited absorption, extensive transporter-mediated efflux,

hepatic processing, and predominantly fecal elimination. These features distinguish stigmasterol from many conventional small-molecule drugs and represent a major consideration when evaluating its systemic pharmacological effects (Feng et al., 2020; Silbernagel et al., 2013).

2.2 Bioavailability and Factors Influencing Systemic Exposure

The bioavailability of stigmasterol is influenced by several interrelated physiological, dietary, and formulation-dependent factors. The first major limitation is its low water solubility. As a highly lipophilic molecule, stigmasterol requires dietary lipids and bile salts for efficient incorporation into mixed micelles. The amount and composition of dietary fat can therefore influence its intestinal solubilization and absorption. In addition, the presence of other sterols, including cholesterol and other phytosterols, may influence intestinal competition for micellar incorporation and transporter-mediated uptake (Feng et al., 2020; Yoon et al., 2025).

The expression and activity of intestinal ABCG5 and ABCG8 transporters are among the most important determinants of phytosterol bioavailability. These transporters actively limit systemic exposure by transporting plant sterols from enterocytes back into the intestinal lumen. Genetic or functional alterations in these transporters can markedly modify phytosterol absorption and plasma concentrations. The efficiency of hepatic clearance and biliary secretion also contributes to the relatively low systemic levels of stigmasterol observed under normal physiological conditions (Feng et al., 2020).

Food processing and extraction techniques can further affect stigmasterol availability. The concentration of stigmasterol varies among plant species and plant tissues, and processing conditions may alter its recovery and chemical stability. Moreover, the administration matrix, particle size, formulation, and presence of lipid-based excipients can influence dissolution and intestinal absorption. Advanced delivery systems—including nanoemulsions, lipid-based formulations, liposomes, phytosomes, and other nanocarriers—have therefore been proposed as strategies to enhance the solubility and bioavailability of poorly water-soluble phytosterols. However, the clinical relevance of these approaches for stigmasterol requires further validation through pharmacokinetic and clinical studies (Yoon et al., 2025; Bakrim et al., 2022).

Table 2.1. Major pharmacokinetic characteristics of stigmasterol

Pharmacokinetic parameter	Major characteristics of stigmasterol	Principal determinants
Absorption	Relatively low intestinal absorption	Lipophilicity, poor aqueous solubility, micellar incorporation
Intestinal uptake	Occurs mainly following incorporation into mixed micelles	Bile salts, dietary lipids, intestinal sterol transport
Efflux	Significant efflux from enterocytes	ABCG5/ABCG8 transporters
Distribution	Associated with circulating lipoproteins and biological membranes	Lipophilicity and sterol-binding environment
Metabolism	Predominantly involves hepatic and intestinal sterol-processing pathways	Enzymatic transformation and sterol transport
Elimination	Mainly through fecal and biliary pathways	ABCG5/ABCG8-mediated secretion and hepatic clearance
Systemic exposure	Generally low compared with cholesterol	Limited absorption and efficient elimination
Major bioavailability limitation	Poor aqueous solubility and low absorption	Physicochemical and physiological barriers

Note. The table summarizes the major pharmacokinetic features reported for phytosterols and stigmasterol based primarily on experimental and mechanistic literature (Bakrim et al., 2022; Feng et al., 2020; Yoon et al., 2025).

2.3 Interaction with Cellular Membranes and Lipid Metabolism

The biological activity of stigmasterol is closely related to its structural similarity to cholesterol and its ability to interact with lipid bilayers. Sterols are important regulators of membrane organization and fluidity, and the incorporation of phytosterols into biological membranes may modify membrane packing, permeability, and the organization of membrane-associated proteins. Although the precise effects of stigmasterol vary according to membrane composition and cellular context, its presence may influence lipid domains and membrane-dependent signaling processes. These

interactions provide a possible mechanistic explanation for some of the diverse cellular effects attributed to stigmasterol (Bakrim et al., 2022; Yoon et al., 2025).

In the context of lipid metabolism, stigmasterol and other phytosterols can interfere with intestinal cholesterol absorption by competing with cholesterol for incorporation into mixed micelles. This contributes to decreased cholesterol availability for enterocyte uptake and may ultimately influence hepatic cholesterol homeostasis. Phytosterols can also affect the expression or activity of genes involved in cholesterol transport and metabolism, although the magnitude and clinical relevance of these effects may differ among individual phytosterols (Feng et al., 2020).

The structural similarity between stigmasterol and cholesterol also enables it to participate in pathways regulating cellular sterol sensing. Changes in intracellular sterol availability can influence sterol regulatory element-binding proteins (SREBPs), liver X receptors (LXRs), and other components of lipid homeostasis. Through these pathways, phytosterols may indirectly affect cholesterol biosynthesis, uptake, transport, and efflux. However, the precise molecular effects of stigmasterol remain incompletely characterized and may differ from those of β-sitosterol and campesterol (Feng et al., 2020; Shen et al., 2024).

2.4 Modulation of Molecular Targets, Receptors, and Signaling Pathways

The pharmacological effects of stigmasterol are increasingly understood as the result of interactions with multiple molecular pathways rather than a single pharmacological target. One of the best-characterized mechanisms involves the regulation of inflammatory signaling. Experimental studies have associated stigmasterol exposure with reduced activation of nuclear factor-κB (NF-κB), a central transcriptional regulator of inflammatory gene expression. Inhibition of NF-κB-associated signaling may reduce the production of pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and nitric oxide (NO) under specific experimental conditions (Bakrim et al., 2022).

Stigmasterol has also been investigated for its potential effects on mitogen-activated protein kinase (MAPK) pathways, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. These pathways regulate cellular proliferation, differentiation, inflammation, stress responses, and apoptosis. Modulation of MAPK signaling may contribute to the anti-inflammatory and anticancer properties reported for stigmasterol in experimental models. In cancer-related studies, stigmasterol has additionally been associated with modulation of PI3K/Akt/mTOR signaling, which plays a central role in cell survival, proliferation, metabolism, and tumor progression (Bakrim et al., 2022).

The potential interaction of stigmasterol with nuclear receptors and lipid-regulating transcription factors is another area of increasing interest. Phytosterols can influence pathways involving LXRs and other sterol-sensitive regulatory mechanisms, thereby affecting lipid metabolism and inflammatory responses. In addition, stigmasterol has been reported in experimental studies to influence apoptotic signaling, mitochondrial function, and oxidative stress-related pathways. However, many of these findings remain dependent on experimental systems, and the direct molecular targets responsible for individual effects have not always been definitively established (Shen et al., 2024; Yoon et al., 2025).

2.5 Role in Oxidative Stress, Inflammation, Apoptosis, and Cellular Homeostasis

Oxidative stress is characterized by an imbalance between reactive oxygen species (ROS) generation and endogenous antioxidant defense mechanisms. Excessive ROS can cause lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, and activation of stress-responsive signaling pathways(Plat et al., 2019). Stigmasterol has demonstrated antioxidant-related effects in several experimental models, although its mechanisms may extend beyond direct radical scavenging. It may influence endogenous antioxidant defense systems, including enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thereby contributing to the maintenance of cellular redox balance (Bakrim et al., 2022).

The relationship between oxidative stress and inflammation is highly interconnected. Excess ROS can activate NF-κB and MAPK pathways, promoting the expression of inflammatory cytokines and enzymes. By attenuating oxidative stress and inflammatory signaling simultaneously, stigmasterol may help interrupt this pathological cycle. This dual antioxidant and anti-inflammatory activity may partly explain its reported protective effects in experimental models of metabolic, cardiovascular, hepatic, neurological, and inflammatory diseases (Bakrim et al., 2022; Feng et al., 2020).

Stigmasterol has also attracted considerable attention for its potential ability to regulate apoptosis. Apoptosis is a highly controlled form of programmed cell death that maintains tissue homeostasis by eliminating damaged or unwanted cells. In cancer models, stigmasterol has been reported to promote apoptotic mechanisms through alterations in mitochondrial membrane potential, activation of caspases, and regulation of pro- and anti-apoptotic proteins. Such effects may contribute to inhibition of tumor cell proliferation and

survival. However, the mechanisms appear to be cell-type dependent, and further studies are required to determine whether these effects occur at physiologically achievable concentrations in humans (Bakrim et al., 2022).

Overall, the biological actions of stigmasterol can be conceptualized as an interconnected network involving sterol transport, lipid metabolism, membrane organization, oxidative stress, inflammation, apoptosis, and cellular signaling. Rather than acting through a single pathway, stigmasterol may exert pleiotropic effects by simultaneously influencing multiple molecular processes. This multifunctionality represents a major strength of stigmasterol as a potential therapeutic molecule, but it also presents challenges in defining its primary molecular targets and translating preclinical findings into clinically meaningful outcomes.

Table 2.2. Major molecular mechanisms associated with the biological effects of stigmasterol

Biological process	Potential molecular targets/pathways	Proposed effects
Cholesterol metabolism	ABCG5/ABCG8, SREBP, LXR-related pathways	Reduced sterol absorption and modulation of lipid homeostasis
Membrane organization	Sterol-rich membrane domains, lipid bilayers	Alteration of membrane fluidity and signaling
Inflammation	NF-κB, MAPK, COX-2, iNOS	Reduction of inflammatory mediator production
Oxidative stress	ROS, SOD, CAT, GPx, glutathione system	Improvement of cellular antioxidant defense
Apoptosis	Caspases, Bax/Bcl-2, mitochondrial pathways	Promotion of programmed cell death in susceptible cells
Cancer signaling	PI3K/Akt/mTOR, MAPK	Inhibition of proliferation and enhancement of apoptosis
Cellular homeostasis	Mitochondrial and redox signaling	Maintenance of cellular integrity and stress adaptation

Note. The molecular mechanisms listed represent pathways proposed or observed in experimental studies and should not be interpreted as definitively established direct molecular targets in humans (Bakrim et al., 2022; Feng et al., 2020; Shen et al., 2024).

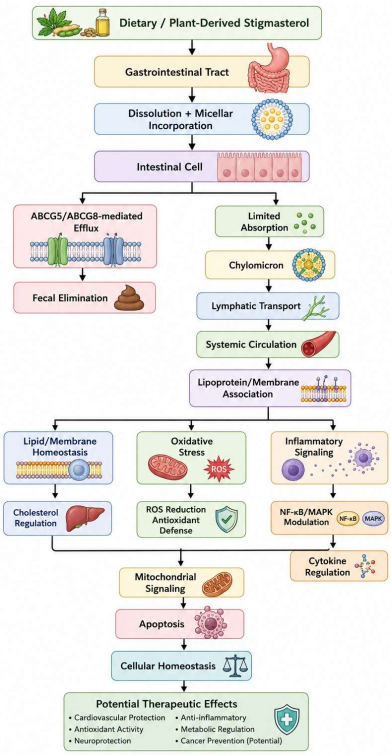

Figure 1. Proposed pharmacokinetic and molecular mechanism pathway of stigmasterol

Figure 1. *Schematic representation of the proposed pharmacokinetic fate and major molecular mechanisms of stigmasterol. Following dietary intake, stigmasterol undergoes limited intestinal absorption because of poor aqueous solubility and active ABCG5/ABCG8-mediated efflux. The absorbed fraction enters systemic circulation and interacts with lipid membranes and metabolic pathways. Subsequent modulation of lipid homeostasis, oxidative stress, inflammatory signaling, mitochondrial function, and apoptosis may contribute to its diverse pharmacological effects. The pathways shown represent a conceptual model based primarily on experimental evidence and should be further validated in human pharmacokinetic and mechanistic studies.*

2.6 Integrated Molecular Perspective

Collectively, the pharmacokinetic properties of stigmasterol are characterized by low intestinal absorption, active transporter-mediated efflux, extensive sterol homeostasis mechanisms, and predominantly fecal elimination. These characteristics explain why systemic concentrations of stigmasterol are generally low despite its widespread dietary exposure. At the same time, its ability to interact with intestinal lipid metabolism

and cellular membranes means that biological activity may occur both locally in the gastrointestinal tract and systemically following absorption (Feng et al., 2020; Bakrim et al., 2022).

The therapeutic potential of stigmasterol is therefore closely connected to the relationship between its pharmacokinetic limitations and its pleiotropic molecular effects. Its poor aqueous solubility and limited bioavailability represent important barriers to drug development, whereas its ability to modulate lipid metabolism, oxidative stress, inflammation, apoptosis, and cellular signaling provides a strong rationale for further investigation (Patel & Thompson, 2006). Future research should prioritize the development of validated pharmacokinetic models, identification of direct molecular targets, evaluation of tissue distribution, and optimization of advanced drug-delivery systems. Such investigations will be essential for determining whether the promising biological activities of stigmasterol observed in preclinical research can be translated into clinically relevant therapeutic applications (Salen et al., 1970).

3. Pharmacological Activities of Stigmasterol

Stigmasterol has attracted substantial scientific interest because of its broad spectrum of pharmacological activities demonstrated in various **in vitro, in vivo, and computational studies**. Its biological effects encompass antioxidant, anti-inflammatory, anticancer, antidiabetic, hypolipidemic, hepatoprotective, neuroprotective, antimicrobial, immunomodulatory, anti-arthritic, and bone-protective properties (Ostlund, 2002). The multifunctional nature of stigmasterol is believed to arise from its ability to interact with several cellular and molecular pathways involved in oxidative stress, inflammation, lipid metabolism, apoptosis, mitochondrial function, and cellular signaling. Nevertheless, it is important to recognize that much of the available evidence remains preclinical, and further pharmacokinetic and clinical investigations are required to establish its efficacy and safety in humans (Bakrim et al., 2022; Zhang et al., 2022; Li et al., 2025).

3.1 Antioxidant and Free-Radical Scavenging Activity

Oxidative stress is a major contributor to the development and progression of numerous chronic diseases, including cancer, diabetes, cardiovascular disorders, neurodegenerative diseases, and inflammatory conditions. Stigmasterol has demonstrated antioxidant activity in several experimental models, where it has been associated with attenuation of oxidative damage and regulation of endogenous antioxidant defense mechanisms. Its antioxidant effects may involve modulation of reactive oxygen species (ROS), lipid peroxidation, and cellular antioxidant enzymes rather than direct free-radical scavenging alone. Experimental evidence indicates that stigmasterol can influence antioxidant systems involving catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase, and related enzymatic defenses (Bakrim et al., 2022).

In experimental models of oxidative stress, stigmasterol has been associated with increased antioxidant enzyme activity and reduced oxidative injury. Such effects may protect cellular membranes, proteins, and nucleic acids from ROS-mediated damage. In diabetic experimental models, stigmasterol-containing fractions have also been associated with attenuation of oxidative stress and improvement of antioxidant defense. These findings suggest that stigmasterol may contribute to cellular protection by restoring redox balance and limiting oxidative damage. However, the precise contribution of direct radical scavenging versus indirect modulation of endogenous antioxidant systems remains to be clearly established (Bakrim et al., 2022).

3.2 Anti-Inflammatory Effects

Chronic inflammation is a common pathological feature of metabolic, cardiovascular, autoimmune, musculoskeletal, and neurodegenerative disorders. Stigmasterol has demonstrated anti-inflammatory effects in both cellular and animal models. Its activity has been linked to suppression of inflammatory mediators and modulation of important signaling pathways, including nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways. In experimental inflammatory models, stigmasterol has been reported to reduce the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), while potentially increasing anti-inflammatory mediators such as interleukin-10 (IL-10) (Bakrim et al., 2022).

Stigmasterol may additionally influence inflammatory enzymes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), thereby reducing the production of nitric oxide and other inflammatory mediators. In arthritis-related experimental models, suppression of NF-κB/p65 and p38 MAPK signaling has been associated with reduced inflammatory responses. These findings indicate that stigmasterol may act at multiple levels of the inflammatory cascade, making it a potentially valuable natural compound for the management of chronic inflammatory conditions. However, clinical studies are needed to determine whether these preclinical effects translate into meaningful anti-inflammatory activity in humans (Bakrim et al., 2022).

3.3 Anticancer and Antitumor Potential

Among the pharmacological properties of stigmasterol, its anticancer potential has received considerable attention. Experimental studies have reported inhibitory effects against several types of

cancer, including breast, ovarian, gastric, hepatic, pulmonary, and other malignancies. The antitumor effects of stigmasterol appear to be multifactorial and may involve inhibition of cancer-cell proliferation, induction of apoptosis, cell-cycle arrest, suppression of migration and invasion, inhibition of angiogenesis, and modulation of autophagy (Zhang et al., 2022).

At the molecular level, stigmasterol has been associated with modulation of PI3K/Akt signaling and other pathways involved in tumor-cell survival. In certain cancer models, it has also been linked to regulation of cyclins and cyclin-dependent kinases, thereby interfering with cell-cycle progression. Furthermore, stigmasterol may promote mitochondrial dysfunction and ROS generation in susceptible tumor cells, ultimately facilitating apoptotic cell death (Miettinen et al., 2000). Studies have also suggested effects on Akt/mTOR and JAK/STAT signaling in selected cancers. In cholangiocarcinoma models, stigmasterol has been associated with inhibition of angiogenic signaling involving TNF-α and VEGFR-2, while combination studies with conventional agents such as sorafenib have indicated possible enhancement of apoptotic mechanisms (Bakrim et al., 2022; Zhang et al., 2022).

Despite these promising observations, the anticancer evidence for stigmasterol remains predominantly preclinical. Differences in experimental concentrations, cancer-cell types, extraction methods, and formulations make direct comparison difficult. Moreover, the low systemic bioavailability of stigmasterol represents an important challenge for translating in vitro anticancer activity into clinical applications. Therefore, future investigations should focus on pharmacologically relevant concentrations, tumor-targeted delivery, combination therapy, and well-designed clinical studies (Zhang et al., 2022).

3.4 Antidiabetic and Metabolic Effects

Metabolic disorders, particularly diabetes mellitus and associated insulin resistance, are important targets for natural-product research. Stigmasterol has demonstrated potential antidiabetic effects in experimental models, with reported reductions in fasting blood glucose, serum insulin levels, and abnormalities in glucose tolerance. These findings suggest that stigmasterol may influence glucose homeostasis and insulin-related metabolic processes (Bakrim et al., 2022).

The antidiabetic activity of stigmasterol may also be connected with its antioxidant and anti-inflammatory properties. Oxidative stress and chronic low-grade inflammation contribute significantly to insulin resistance and β-cell dysfunction; therefore, attenuation of these processes may indirectly improve metabolic control. In addition, stigmasterol may influence lipid metabolism and reduce metabolic abnormalities associated with diabetes. Nevertheless, the exact molecular targets responsible for these effects remain incompletely characterized, and further studies are required to clarify its influence on insulin signaling, glucose transport, pancreatic β-cell function, and hepatic glucose metabolism (Bakrim et al., 2022; Li et al., 2025).

3.5 Hypocholesterolemic and Cardioprotective Activity

The structural similarity of stigmasterol to cholesterol provides a biological basis for its potential hypocholesterolemic effects. Phytosterols can compete with cholesterol during intestinal absorption, reducing the incorporation of cholesterol into mixed micelles and consequently limiting its uptake by intestinal enterocytes. This mechanism may contribute to improved cholesterol homeostasis and reduced circulating cholesterol levels (Feng et al., 2020).

Stigmasterol may also influence broader aspects of lipid metabolism and cardiovascular health. By modulating cholesterol absorption and lipid homeostasis, it may potentially contribute to the reduction of cardiovascular risk associated with dyslipidemia. In addition, its antioxidant and anti-inflammatory properties could provide complementary cardioprotective effects because oxidative stress and chronic inflammation play important roles in endothelial dysfunction and atherosclerotic progression. However, the extent to which stigmasterol itself, as opposed to the broader phytosterol mixture commonly consumed in the diet, contributes to cardiovascular protection requires further investigation (Feng et al., 2020; Bakrim et al., 2022).

3.6 Hepatoprotective Effects

The liver is a major organ involved in lipid metabolism, detoxification, and maintenance of metabolic homeostasis. Stigmasterol has demonstrated hepatoprotective potential in experimental models, which may be associated with its antioxidant and anti-inflammatory activities. By reducing oxidative stress and inflammatory signaling, stigmasterol may help protect hepatocytes from injury caused by metabolic stress and toxic insults.

The hepatoprotective effects of stigmasterol may also be linked to modulation of lipid metabolism and prevention of excessive lipid accumulation in the liver. Since oxidative stress, inflammation, and lipid dysregulation are closely associated with the development of hepatic injury and metabolic liver disease, the multifunctional nature of stigmasterol could provide a mechanistic basis for hepatoprotection. Nevertheless, direct evidence specific to purified stigmasterol remains comparatively limited, and additional studies using standardized preparations are needed to establish

its efficacy and mechanism of action (Bakrim et al., 2022; Li et al., 2025).

3.7 Neuroprotective and Cognitive Benefits

The potential neuroprotective properties of stigmasterol have emerged as another important area of investigation. Neuronal damage is frequently associated with oxidative stress, mitochondrial dysfunction, neuroinflammation, neurotransmitter imbalance, and abnormal protein aggregation. Stigmasterol may exert neuroprotective effects by regulating ROS generation and improving cellular antioxidant defenses.

Experimental studies have suggested that stigmasterol may influence dopaminergic signaling and acetylcholinesterase activity, mechanisms that are relevant to neurological disorders and cognitive dysfunction. Its ability to modulate oxidative stress may further protect neuronal membranes and mitochondria from damage (Moreau et al., 2002). These findings raise the possibility that stigmasterol could have applications in neurodegenerative disorders and cognitive impairment. However, most evidence remains preclinical, and its ability to cross the blood–brain barrier, achieve therapeutically relevant concentrations in the brain, and produce clinically meaningful cognitive benefits requires further investigation (Bakrim et al., 2022; Li et al., 2025).

3.8 Antimicrobial, Antibacterial, and Antifungal Activity

Stigmasterol has demonstrated antimicrobial potential against selected bacterial, fungal, and parasitic organisms. The antibacterial effects reported for stigmasterol and stigmasterol-containing plant extracts may involve disruption of microbial membranes, alteration of membrane-associated processes, or interference with essential cellular functions. However, the specific antimicrobial mechanisms of purified stigmasterol remain less well defined than those of many conventional antimicrobial phytochemicals (Bakrim et al., 2022).

Antifungal activity has also been reported against selected *Candida* species and other fungal organisms. In addition, stigmasterol has demonstrated antiparasitic activity against certain parasites, including experimental models involving *Trypanosoma* and *Leishmania*. These findings suggest that stigmasterol may possess broad anti-infective potential. Nevertheless, the observed activity can vary substantially according to microbial species, compound concentration, extraction method, and experimental conditions. Further research should establish minimum inhibitory concentrations, mechanisms of action, potential synergism with established antimicrobial agents, and in vivo efficacy before therapeutic applications can be considered (Bakrim et al., 2022).

3.9 Immunomodulatory Effects

The immune system is closely interconnected with inflammatory and metabolic pathways, and stigmasterol appears capable of modulating immune responses under experimental conditions. Its immunomodulatory activity may involve regulation of cytokine production, inflammatory signaling, and immune-cell activation. Rather than producing a simple immunostimulatory or immunosuppressive effect, stigmasterol may exert context-dependent immunomodulation by influencing pathways that regulate the balance between pro-inflammatory and anti-inflammatory responses (Bakrim et al., 2022).

The ability of stigmasterol to reduce inflammatory cytokines while promoting anti-inflammatory mediators may be relevant to chronic inflammatory and immune-mediated diseases. In addition, its effects on NF-κB and MAPK signaling could indirectly regulate immune-cell function. However, the precise cellular targets and immune pathways involved remain insufficiently characterized. Further investigations involving macrophages, T cells, dendritic cells, and other immune-cell populations are needed to clarify the immunological effects of stigmasterol and determine whether these properties can be therapeutically exploited (Bakrim et al., 2022; Li et al., 2025).

3.10 Anti-Arthritic and Bone-Protective Activity

Stigmasterol has demonstrated potential in the management of arthritis and other musculoskeletal disorders, particularly through its anti-inflammatory effects. In experimental models of collagen-induced arthritis, stigmasterol has been associated with reduced expression of TNF-α, IL-6, IL-1β, iNOS, and COX-2, together with modulation of NF-κB and p38 MAPK signaling. These effects may reduce inflammatory responses within joint tissues and potentially attenuate cartilage damage (Bakrim et al., 2022).

The anti-arthritic potential of stigmasterol may also be related to its effects on chondrocytes. Experimental studies have indicated that stigmasterol can reduce inflammatory mediators such as iNOS and IL-6 in interleukin-1β-stimulated chondrocytes. These findings suggest that stigmasterol may influence both systemic inflammatory responses and local joint pathology. Its potential bone-protective effects are also of interest because oxidative stress and inflammation contribute to bone loss and skeletal degeneration (Klingberg et al., 2008). However, evidence specifically demonstrating direct effects on bone formation, osteoblast activity, osteoclast differentiation, or bone mineral density remains less extensive than evidence for its anti-inflammatory and anti-arthritic properties. Consequently, additional animal and clinical studies are required to establish its potential role in

osteoporosis and other bone-related disorders (Bakrim et al., 2022).

Table 3.1. Summary of the major pharmacological activities of stigmasterol

Pharmacological activity	Major proposed mechanisms	Potential therapeutic relevance	Evidence status
Antioxidant	Regulation of ROS, lipid peroxidation, CAT, GSH, GPx, and other antioxidant systems	Protection against oxidative cellular injury	Mainly preclinical
Anti-inflammatory	Modulation of NF-κB, MAPK, COX-2, iNOS, TNF-α, IL-1β, and IL-6	Chronic inflammatory and inflammatory-mediated diseases	In vitro and in vivo
Anticancer	Apoptosis, cell-cycle arrest, PI3K/Akt/mTOR modulation, autophagy, inhibition of migration and angiogenesis	Potential adjunct or lead compound for cancer therapy	Mainly preclinical
Antidiabetic	Improvement of glucose homeostasis, reduction of oxidative stress and inflammation	Diabetes and metabolic dysfunction	Mainly animal studies
Hypocholesterolemic	Competition with cholesterol for intestinal absorption; modulation of lipid metabolism	Dyslipidemia and cardiovascular risk reduction	Strong phytosterol evidence; stigmasterol-specific evidence requires further study
Cardioprotective	Lipid regulation, antioxidant and anti-inflammatory effects	Cardiovascular disease prevention	Mainly preclinical/indirect
Hepatoprotective	Antioxidant, anti-inflammatory, and lipid-regulating effects	Protection against metabolic and toxic liver injury	Mainly preclinical
Neuroprotective	ROS regulation, antioxidant defense, dopaminergic and cholinergic modulation	Neurodegeneration and cognitive dysfunction	Mainly preclinical
Antimicrobial	Potential microbial membrane and cellular disruption	Bacterial and fungal infections	In vitro and preliminary in vivo
Immunomodulatory	Regulation of cytokines and inflammatory signaling	Immune-mediated and inflammatory disorders	Mainly preclinical
Anti-arthritic	Suppression of NF-κB/MAPK signaling and	Arthritis and joint inflammation	Animal and cellular evidence

	inflammatory cytokines		
Bone-protective	Potential reduction of oxidative stress and inflammation affecting bone homeostasis	Osteoporosis and skeletal disorders	Emerging evidence; requires further validation

4. Therapeutic Potential and Applications of Stigmasterol

Stigmasterol has emerged as a promising multifunctional phytosterol with potential applications across a broad range of therapeutic areas. Its structural similarity to cholesterol, together with its reported antioxidant, anti-inflammatory, hypolipidemic, anticancer, antimicrobial, immunomodulatory, and metabolic effects, provides a biological basis for investigating its use in chronic and multifactorial diseases (Katan et al., 2003). Experimental studies have demonstrated that stigmasterol can influence several interconnected pathways, including oxidative stress, inflammatory signaling, lipid metabolism, apoptosis, mitochondrial function, and cellular survival. These pleiotropic effects are particularly relevant to diseases in which multiple pathological mechanisms coexist, such as diabetes, cardiovascular disease, cancer, neurodegeneration, and chronic inflammatory disorders. Nevertheless, most evidence remains preclinical, and the clinical translation of stigmasterol requires further investigation regarding pharmacokinetics, bioavailability, dose optimization, safety, and therapeutic efficacy in humans (Bakrim et al., 2022; Feng et al., 2020; Shen et al., 2024).

4.1 Role in Metabolic Disorders and Diabetes

Metabolic disorders, including diabetes mellitus, obesity, insulin resistance, and dyslipidemia, represent important areas for the potential therapeutic application of stigmasterol. The development and progression of metabolic diseases are strongly associated with oxidative stress, chronic low-grade inflammation, abnormal lipid metabolism, and impaired glucose homeostasis. Because stigmasterol possesses antioxidant, anti-inflammatory, and lipid-modulating properties, it may influence several of these pathological processes simultaneously (Bakrim et al., 2022).

Experimental studies have suggested that stigmasterol may improve glucose metabolism and reduce hyperglycemia in animal models. Its potential antidiabetic effects have been associated with improvements in insulin sensitivity, glucose utilization, and oxidative stress. In addition, stigmasterol may influence lipid metabolism, which is particularly relevant because diabetes is frequently accompanied by hypertriglyceridemia, elevated low-density lipoprotein cholesterol, and other metabolic abnormalities. By simultaneously affecting glucose and lipid homeostasis, stigmasterol may have potential as a multifunctional metabolic therapeutic agent (Bakrim et al., 2022; Feng et al., 2020).

The antioxidant and anti-inflammatory properties of stigmasterol may provide additional benefits in diabetes. Persistent hyperglycemia promotes ROS generation, oxidative damage, endothelial dysfunction, and inflammatory responses, all of which contribute to diabetic complications. Stigmasterol-mediated modulation of oxidative and inflammatory pathways may therefore help protect tissues against metabolic stress. However, the majority of evidence has been obtained from experimental models, and clinical studies specifically evaluating purified stigmasterol in patients with diabetes remain limited. Future research should investigate its effects on insulin signaling, pancreatic β-cell function, glucose transporters, hepatic gluconeogenesis, and diabetic complications (Jiménez-Escrig et al., 2006).

4.2 Potential Applications in Cardiovascular Diseases

Cardiovascular disease is closely associated with dyslipidemia, oxidative stress, inflammation, endothelial dysfunction, and atherosclerosis. The lipid-lowering properties of phytosterols are well established, and stigmasterol may contribute to this activity by interfering with intestinal cholesterol absorption. Because phytosterols structurally resemble cholesterol, they can compete for incorporation into intestinal mixed micelles, thereby reducing cholesterol absorption and promoting favorable changes in lipid metabolism (Feng et al., 2020).

Stigmasterol may also provide cardiovascular benefits through mechanisms extending beyond cholesterol regulation. Oxidative stress and inflammation are central contributors to endothelial dysfunction and atherosclerotic plaque development. The antioxidant and anti-inflammatory activities attributed to stigmasterol may therefore help reduce oxidative damage and inflammatory signaling within the cardiovascular system. In addition, modulation of lipid metabolism may contribute to improved plasma lipid profiles and reduced cardiovascular risk (Bakrim et al., 2022).

However, an important distinction should be made between the cardiovascular benefits demonstrated for phytosterol mixtures and those specifically attributable to stigmasterol. Much of the clinical evidence for cholesterol reduction involves combinations of plant sterols or stanols rather than

purified stigmasterol. Therefore, while stigmasterol represents a biologically plausible cardiovascular therapeutic candidate, further controlled clinical investigations are necessary to establish its independent contribution to cardiovascular risk reduction (Sanclemente et al., 2020).

4.3 Therapeutic Relevance in Cancer Management

Cancer is one of the most extensively investigated therapeutic areas for stigmasterol. Experimental studies have reported anticancer effects against several tumor types, including breast, ovarian, gastric, hepatic, pulmonary, and other cancers. These effects appear to involve multiple mechanisms, including inhibition of cancer-cell proliferation, induction of apoptosis, cell-cycle arrest, suppression of migration and invasion, inhibition of angiogenesis, and modulation of autophagy (Zhang et al., 2022).

Stigmasterol may influence important oncogenic signaling pathways such as PI3K/Akt/mTOR, MAPK, and JAK/STAT, which regulate tumor-cell survival, proliferation, metabolism, and resistance to apoptosis. In certain experimental models, stigmasterol has been reported to promote mitochondrial dysfunction and activate caspase-dependent apoptotic pathways. It may also alter the balance between pro-apoptotic and anti-apoptotic proteins, thereby facilitating programmed cell death in susceptible cancer cells (Bakrim et al., 2022; Zhang et al., 2022).

Another potentially important application is the use of stigmasterol as an adjunct to conventional anticancer therapy. Experimental evidence suggests that stigmasterol may enhance apoptosis or alter survival pathways in combination with established chemotherapeutic agents. Such combination strategies could potentially allow improved therapeutic efficacy or reduced drug doses. However, these possibilities remain experimental, and rigorous pharmacokinetic, toxicological, and clinical investigations are necessary before stigmasterol can be considered a clinically established anticancer agent (Zhang et al., 2022).

4.4 Neurodegenerative Disorders and Brain Health

The potential role of stigmasterol in maintaining brain health and preventing neurodegenerative disorders has gained increasing attention. Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and related cognitive disorders, are characterized by complex interactions among oxidative stress, mitochondrial dysfunction, neuroinflammation, abnormal protein aggregation, and neuronal loss. Stigmasterol may potentially influence several of these pathological mechanisms through its antioxidant and anti-inflammatory activities (Bakrim et al., 2022).

Experimental studies have suggested that stigmasterol may influence neurotransmitter-related pathways and enzymes involved in cognitive function. Its potential effects on acetylcholinesterase activity may be relevant to cholinergic neurotransmission, while modulation of oxidative stress may protect neuronal membranes and mitochondria from oxidative injury. In addition, suppression of neuroinflammatory signaling could potentially reduce the chronic inflammatory environment associated with neurodegenerative disease progression.

Despite these promising observations, important limitations remain. The low systemic bioavailability of stigmasterol raises questions regarding the extent to which sufficient concentrations can reach the central nervous system. Furthermore, the ability of stigmasterol to cross the blood–brain barrier and its pharmacokinetic behavior within neural tissues require detailed investigation. Advanced delivery systems, including lipid-based nanoparticles and targeted nanocarriers, may therefore represent future strategies for improving brain delivery and therapeutic efficacy (Sesso et al., 2008).

4.5 Liver Diseases and Gastrointestinal Disorders

The liver plays a central role in lipid metabolism, detoxification, and systemic metabolic regulation. Stigmasterol may have hepatoprotective potential through its ability to regulate oxidative stress, inflammation, and lipid metabolism. These properties may be relevant to metabolic dysfunction-associated steatotic liver disease, drug-induced liver injury, and other hepatic disorders characterized by oxidative and inflammatory damage (Bakrim et al., 2022).

Stigmasterol may potentially reduce hepatic lipid accumulation and improve disturbances in lipid metabolism. Its antioxidant properties could additionally protect hepatocytes against ROS-induced injury, while anti-inflammatory effects may reduce the production of inflammatory cytokines and mediators. However, direct evidence from well-controlled studies using purified stigmasterol remains relatively limited, and its effects should be distinguished from those of complex plant extracts containing multiple bioactive constituents.

The gastrointestinal tract represents another potentially important site of action. Because stigmasterol interacts with intestinal cholesterol absorption and lipid micelle formation, it may exert local metabolic effects within the intestine even when systemic absorption is limited (Sudhop et al., 2002). Its interaction with intestinal lipid metabolism and potential influence on gut-associated inflammatory processes provide opportunities for further research. Future studies should investigate whether stigmasterol can influence intestinal barrier integrity, gut microbiota

composition, bile acid metabolism, and metabolic signaling within the gut–liver axis.

4.6 Inflammatory and Autoimmune Conditions

Chronic inflammation contributes to numerous pathological conditions, including rheumatoid arthritis, inflammatory bowel disorders, metabolic diseases, and autoimmune diseases. Stigmasterol's ability to modulate inflammatory pathways provides a rationale for exploring its potential application in these disorders. Experimental evidence suggests that stigmasterol can influence NF-κB and MAPK signaling and reduce the expression of inflammatory mediators such as TNF-α, IL-1β, IL-6, COX-2, and iNOS (Bakrim et al., 2022).

In arthritis models, these effects have been associated with reduced joint inflammation and tissue damage. Similar mechanisms could theoretically be relevant to other chronic inflammatory disorders. The potential immunomodulatory activity of stigmasterol may also be beneficial in diseases characterized by dysregulated immune responses (Huang et al., 2022). However, autoimmune diseases involve highly complex and disease-specific immune mechanisms, and the distinction between beneficial immunomodulation and undesirable immunosuppression must be carefully considered.

Consequently, future studies should evaluate stigmasterol in disease-specific models of autoimmune and inflammatory disorders, with particular emphasis on immune-cell populations, cytokine networks, and long-term safety.

4.7 Skin Health, Dermatological Applications, and Cosmeceutical Potential

The antioxidant and anti-inflammatory properties of stigmasterol provide a potential basis for dermatological and cosmeceutical applications. Oxidative stress, inflammation, ultraviolet radiation, and environmental exposure contribute to skin aging, barrier disruption, pigmentation abnormalities, and inflammatory skin disorders. As a plant-derived sterol, stigmasterol may potentially support skin health by influencing membrane organization and reducing oxidative and inflammatory damage.

Phytosterols have also been investigated for their potential effects on skin barrier function and moisturization. The structural similarity between plant sterols and cholesterol may facilitate their incorporation into lipid-rich skin structures, potentially contributing to barrier maintenance. In addition, stigmasterol-containing botanical preparations may possess anti-inflammatory properties relevant to irritated or inflamed skin (Bakrim et al., 2022).

The cosmeceutical potential of stigmasterol may therefore extend to anti-aging formulations, skin-barrier products, antioxidant preparations, and formulations designed to reduce inflammation. However, the development of stigmasterol-based dermatological products requires systematic evaluation of topical penetration, formulation stability, skin tolerability, photostability, and long-term safety. Liposomes, nanoemulsions, and other advanced topical delivery systems may improve its incorporation into dermatological formulations (Han et al., 2021).

4.8 Potential Role in Women's Health and Reproductive Disorders

Stigmasterol has attracted interest in reproductive biology because plant sterols may participate in steroid-related metabolic pathways and may serve as precursors or substrates in steroid hormone biosynthesis in plants and microorganisms. However, the direct clinical role of stigmasterol in human reproductive health remains insufficiently established. The potential relevance of stigmasterol to women's health should therefore be considered an emerging research area rather than an established therapeutic application.

Experimental research has investigated phytosterols and plant-derived sterols in relation to hormonal regulation, reproductive physiology, and disorders associated with metabolic dysfunction. Because conditions such as polycystic ovary syndrome (PCOS) involve insulin resistance, chronic inflammation, oxidative stress, and abnormal lipid metabolism, the antioxidant, anti-inflammatory, and metabolic properties of stigmasterol could theoretically provide a rationale for further investigation. However, direct evidence demonstrating that purified stigmasterol improves PCOS, fertility, endometriosis, or other reproductive disorders is currently limited (Gylling et al., 2014).

Accordingly, future research should investigate the effects of stigmasterol on ovarian function, steroidogenesis, insulin sensitivity, inflammatory signaling, and reproductive outcomes using validated experimental models. Particular attention should be given to potential endocrine effects and safety during pregnancy, as the biological activity of plant sterols in reproductive tissues requires careful evaluation.

4.9 Synergistic Potential with Conventional Therapeutic Agents

One of the most promising future applications of stigmasterol is its potential use in combination with conventional pharmacological agents. Multifactorial diseases often require combination therapy because single-target interventions may be insufficient to control complex pathological networks. Since stigmasterol can influence oxidative stress, inflammation, apoptosis, lipid metabolism, and cellular survival pathways, it may theoretically complement drugs that act on related or distinct mechanisms *(He et al., 2020)*.

In oncology, stigmasterol has been investigated in combination with conventional anticancer drugs,

with experimental findings suggesting that it may enhance apoptotic signaling or suppress survival pathways. Such combinations may potentially increase anticancer efficacy, although rigorous studies are required to determine whether stigmasterol produces true pharmacodynamic synergy or merely additive effects (Zhang et al., 2022).

Similar approaches may be relevant to metabolic and inflammatory diseases. For example, stigmasterol could potentially be investigated as an adjunct to lipid-lowering, antidiabetic, anti-inflammatory, or neuroprotective therapies. Its antioxidant and anti-inflammatory effects may complement conventional drugs by targeting disease mechanisms that are not directly addressed by standard pharmacotherapy.

However, combination therapy also introduces potential risks. Stigmasterol may alter drug absorption, metabolism, transport, or pharmacodynamic responses. Therefore, systematic drug–phytochemical interaction studies are essential before clinical use. Future research should employ combination-index analysis, pharmacokinetic interaction studies, and mechanistic investigations to distinguish genuine synergistic effects from simple additive activity (Yang et al., 2025) .

Table 4.1. Therapeutic potential and emerging applications of stigmasterol

Therapeutic area	Proposed mechanisms of action	Potential applications	Current evidence and research needs
Metabolic disorders and diabetes	Antioxidant, anti-inflammatory, lipid and glucose metabolism modulation	Diabetes, insulin resistance, metabolic syndrome	Mainly preclinical; clinical trials needed
Cardiovascular diseases	Reduced cholesterol absorption, lipid regulation, antioxidant and anti-inflammatory effects	Dyslipidemia, atherosclerosis, cardiovascular risk reduction	Strong phytosterol rationale; stigmasterol-specific clinical evidence limited
Cancer	Apoptosis, cell-cycle arrest, PI3K/Akt/mTOR and MAPK modulation, anti-angiogenic effects	Potential anticancer and adjunctive therapy	Extensive preclinical research; clinical validation required
Neurodegenerative disorders	Antioxidant, anti-inflammatory, mitochondrial and neurotransmitter modulation	Alzheimer's disease, Parkinson's disease, cognitive impairment	Emerging preclinical evidence; brain delivery and BBB penetration require study
Liver diseases	Antioxidant, anti-inflammatory and lipid-regulating effects	Metabolic liver disease and hepatotoxicity	Mainly experimental; purified stigmasterol requires further evaluation
Gastrointestinal disorders	Modulation of intestinal lipid metabolism and possible gut–liver interactions	Intestinal metabolic health and inflammatory conditions	Emerging research area
Inflammatory/ autoimmune diseases	NF-κB and MAPK modulation; cytokine regulation	Arthritis and chronic inflammatory disorders	Preclinical evidence; disease-specific studies needed
Dermatology and cosmeceuticals	Antioxidant, anti-inflammatory and membrane/barrier effects	Skin aging, barrier support, inflammatory skin conditio	Promising; topical formulation and clinical studies

		ns	required
Women's health	Potential metabolic, antioxidant and anti-inflammatory effects	PCOS and reproductive metabolic disorders	Preliminary hypothesis; direct clinical evidence insufficient
Combination therapy	Complementary effects on apoptosis, oxidative stress, inflammation and metabolism	Adjunct to anticancer, metabolic and anti-inflammatory drugs	Experimental; drug-interaction and clinical synergy studies required

5. Safety, Toxicological Profile, and Challenges in Clinical Translation

The growing interest in stigmasterol as a multifunctional phytosterol has generated substantial research into its pharmacological properties; however, its successful development as a therapeutic agent requires a comprehensive assessment of safety, toxicity, pharmacokinetics, formulation characteristics, clinical evidence, and regulatory requirements. Although stigmasterol is naturally present in numerous edible plants and vegetable oils and is generally considered to have a favorable safety profile at dietary exposure levels, its pharmacological use at concentrated doses presents different considerations. Importantly, the majority of available evidence concerning stigmasterol safety is derived from phytosterol-rich foods, plant extracts, experimental models, or short-term studies rather than long-term clinical trials specifically evaluating purified stigmasterol. Therefore, its potential therapeutic benefits must be considered alongside uncertainties regarding chronic exposure, dose optimization, systemic bioavailability, drug interactions, and product standardization (Bakrim et al., 2022; Feng et al., 2020).

5.1 Safety and Toxicity Considerations

Stigmasterol is a naturally occurring phytosterol that is widely consumed through plant-based foods and edible oils. Compared with many synthetic pharmacological compounds, its long history of dietary exposure provides an initial basis for considering it a relatively well-tolerated bioactive compound. However, dietary exposure and therapeutic administration are fundamentally different situations. A therapeutic formulation may deliver substantially higher or more sustained concentrations than those obtained through conventional food consumption, potentially producing biological effects that are not apparent at normal dietary intake levels (Feng et al., 2020).

The available experimental evidence generally suggests that stigmasterol has a relatively favorable toxicity profile, but comprehensive toxicological characterization remains incomplete. Acute toxicity studies of stigmasterol-containing preparations have generally not indicated severe toxicity at experimentally administered doses; however, the available evidence is heterogeneous and often concerns plant extracts or phytosterol mixtures rather than highly purified stigmasterol. Consequently, it is difficult to extrapolate the safety findings of one preparation directly to another. Differences in purity, route of administration, formulation, dose, and coexisting phytochemicals can substantially influence toxicological outcomes (Bakrim et al., 2022).

Another important consideration is the potential accumulation of plant sterols under conditions of impaired sterol metabolism. Individuals with rare genetic disorders affecting ABCG5 or ABCG8 transporter function can develop markedly elevated circulating phytosterol concentrations, as observed in sitosterolemia. Although this condition is distinct from normal dietary exposure to stigmasterol, it demonstrates that altered phytosterol transport and clearance can have pathological consequences. Therefore, the safety of concentrated stigmasterol administration should be evaluated in relation to individual differences in sterol metabolism and transporter activity (Feng et al., 2020).

Potential drug–phytochemical interactions should also be considered. Because stigmasterol may influence lipid metabolism, membrane organization, and transporter-mediated processes, interactions with lipid-lowering drugs, metabolic agents, or other medications cannot be excluded. However, direct evidence regarding clinically relevant drug interactions involving purified stigmasterol remains limited. Dedicated pharmacokinetic and pharmacodynamic interaction studies are therefore necessary before widespread therapeutic application.

5.2 Dose-Dependent Effects and Long-Term Administration

The pharmacological effects of stigmasterol are likely to be dose dependent. In experimental studies, biological responses are frequently observed at concentrations that may be substantially higher than those achievable through normal dietary intake. Consequently, a critical issue in therapeutic development is determining whether effective concentrations observed in cell culture and animal models can be achieved safely in humans (Bakrim et al., 2022).

Dose-response relationships may not always be linear. At relatively low exposure levels, stigmasterol may exert beneficial effects through

modulation of lipid metabolism, oxidative stress, or inflammatory pathways, whereas higher concentrations may produce altered membrane interactions or unexpected biological effects. Therefore, the therapeutic window of stigmasterol must be clearly established through systematic dose-escalation studies.

Long-term administration represents another important area of uncertainty. Most available studies have evaluated stigmasterol over relatively short experimental periods, whereas chronic diseases such as diabetes, cardiovascular disease, neurodegenerative disorders, and cancer may require prolonged treatment. Long-term exposure studies should therefore investigate potential effects on hepatic and renal function, lipid profiles, endocrine pathways, reproductive health, immune function, and tissue accumulation (Zhao et al., 2023).

Particular attention should also be given to vulnerable populations, including pregnant and lactating women, children, elderly individuals, and patients with hepatic or renal impairment. At present, insufficient evidence is available to establish the safety of pharmacological doses of stigmasterol in these populations. Thus, therapeutic recommendations should not be extrapolated solely from dietary exposure data.

5.3 Pharmacokinetic and Bioavailability Limitations

One of the major barriers to the therapeutic development of stigmasterol is its limited systemic bioavailability. Stigmasterol is a highly lipophilic compound with poor aqueous solubility, resulting in limited dissolution in gastrointestinal fluids. Its intestinal absorption is also restricted by physiological sterol transport mechanisms, including the activity of ABCG5 and ABCG8 transporters, which promote the efflux of plant sterols from enterocytes back into the intestinal lumen (Feng et al., 2020).

Consequently, the majority of orally administered stigmasterol is not absorbed into systemic circulation and is eliminated through fecal and biliary pathways. Although low systemic exposure may reduce the likelihood of systemic toxicity, it simultaneously presents a major challenge when systemic pharmacological effects are desired. For example, therapeutic applications targeting the brain, liver, or other distant organs may require adequate systemic concentrations, which may be difficult to achieve using conventional oral formulations (Chan et al., 2020).

Another limitation is the incomplete characterization of stigmasterol pharmacokinetics in humans. Compared with conventional pharmaceutical compounds, detailed information regarding its absorption rate, distribution volume, plasma half-life, tissue distribution, metabolic pathways, and elimination kinetics remains limited. This lack of pharmacokinetic information complicates the selection of optimal dosing regimens and makes it difficult to establish exposure–response relationships.

Future pharmacokinetic investigations should therefore incorporate sensitive analytical techniques such as liquid chromatography–mass spectrometry (LC–MS/MS) to accurately quantify stigmasterol and its metabolites in plasma and tissues. Such studies are essential for determining the relationship between administered dose, systemic exposure, tissue distribution, and pharmacological response.

5.4 Poor Aqueous Solubility and Formulation Challenges

The poor aqueous solubility of stigmasterol represents a major pharmaceutical development challenge. As a highly lipophilic sterol, stigmasterol has limited dissolution in aqueous biological environments, which can reduce its oral absorption and result in variable systemic exposure. This physicochemical limitation may contribute to inconsistent pharmacological effects and make conventional tablet or capsule formulations less effective for achieving predictable bioavailability (Yoon et al., 2025).

Several advanced drug-delivery strategies may help overcome these limitations. Lipid-based formulations, self-emulsifying drug delivery systems, nanoemulsions, liposomes, phytosomes, polymeric nanoparticles, and solid lipid nanoparticles have the potential to enhance stigmasterol solubilization and improve intestinal absorption. Nanotechnology-based approaches may additionally facilitate targeted delivery to specific tissues and potentially reduce the dose required to achieve therapeutic effects.

However, formulation development introduces new challenges, including physical stability, particle-size control, drug loading, encapsulation efficiency, scalability, manufacturing reproducibility, and long-term storage stability. Furthermore, the safety of nanocarriers must be evaluated independently because the toxicity profile of a stigmasterol formulation may differ from that of the free compound.

An ideal stigmasterol formulation should therefore provide enhanced solubility and bioavailability while maintaining chemical stability, minimizing toxicity, and allowing reproducible dose delivery. Future formulation research should integrate pharmacokinetic studies with pharmacodynamic assessments to demonstrate whether improved bioavailability actually translates into superior therapeutic outcomes (De Smet et al., 2012).

5.5 Evidence from Preclinical Versus Clinical Studies

The therapeutic potential of stigmasterol is currently supported primarily by preclinical research. In vitro studies have demonstrated

antioxidant, anti-inflammatory, anticancer, antimicrobial, and metabolic effects, while animal studies have provided additional evidence for its potential in diabetes, inflammation, arthritis, cancer, and other disease models (Bakrim et al., 2022; Zhang et al., 2022).

However, there is a substantial gap between preclinical evidence and clinical validation. Biological activity demonstrated in cultured cells does not necessarily predict therapeutic efficacy in humans. In vitro studies often use stigmasterol concentrations that may not be achievable in human plasma or tissues following oral administration. Similarly, animal models may differ from humans in terms of metabolism, transporter expression, pharmacokinetics, and disease biology.

The lack of large-scale randomized controlled trials specifically evaluating purified stigmasterol is therefore a major limitation. Some clinical evidence exists for phytosterol-containing foods and preparations, particularly in relation to cholesterol metabolism, but such findings cannot automatically be attributed exclusively to stigmasterol because these products often contain mixtures of β-sitosterol, campesterol, stigmasterol, and other sterols (Feng et al., 2020).

Future clinical development should therefore progress through carefully designed Phase I studies assessing safety, tolerability, pharmacokinetics, and dose escalation, followed by Phase II studies evaluating preliminary efficacy in specific therapeutic indications. Larger Phase III trials would subsequently be necessary to confirm clinical efficacy and establish long-term safety. Such a stepwise approach is essential for distinguishing promising experimental activity from clinically meaningful therapeutic benefit.

5.6 Standardization and Quality Control of Stigmasterol-Containing Extracts

The therapeutic development of stigmasterol is further complicated when it is administered as part of a plant extract rather than as a purified compound. Plant extracts may contain multiple phytosterols, flavonoids, terpenoids, phenolics, and other constituents that can contribute to or modify the biological activity of the preparation (Calpe-Berdiel et al., 2009). Consequently, variations in plant species, geographic origin, cultivation conditions, harvesting time, extraction solvent, and processing procedures can significantly alter stigmasterol content and overall pharmacological activity.

Standardization is therefore essential for ensuring reproducibility and quality. Quantitative determination of stigmasterol should ideally be performed using validated chromatographic techniques, including high-performance liquid chromatography (HPLC), gas chromatography (GC), or LC–MS-based methods. Analytical characterization should also evaluate the presence of related phytosterols, degradation products, residual solvents, and potential contaminants (Yoon et al., 2025).

Quality control should include authentication of botanical raw materials, assessment of stigmasterol concentration, evaluation of purity, and monitoring of batch-to-batch consistency. Where stigmasterol is incorporated into pharmaceutical or nutraceutical products, stability studies should determine whether storage conditions, temperature, oxygen exposure, and light influence its chemical integrity.

For clinical research, the use of highly characterized and standardized stigmasterol preparations is particularly important. Without rigorous quality control, differences between studies may reflect variations in product composition rather than genuine differences in biological response. Standardized preparations would therefore improve the reproducibility of pharmacological and clinical investigations.

5.7 Regulatory Considerations and Barriers to Therapeutic Development

The regulatory pathway for stigmasterol depends substantially on its intended use and product classification. A stigmasterol-containing food supplement, nutraceutical, cosmetic, or pharmaceutical product may be subject to different regulatory requirements. Products marketed as dietary supplements or functional foods generally require evidence of safety and quality, whereas therapeutic claims typically require substantially more extensive evidence demonstrating efficacy, safety, pharmacokinetics, and manufacturing consistency.

One major regulatory challenge is the distinction between stigmasterol as a naturally occurring dietary constituent and stigmasterol as an active pharmaceutical ingredient. Although its presence in commonly consumed foods supports a history of exposure, this does not automatically establish the safety of concentrated pharmacological doses or novel delivery systems. Regulatory authorities may therefore require detailed toxicological and clinical evidence before approving stigmasterol for therapeutic indications.

Another challenge involves defining the appropriate quality specifications for stigmasterol-based products. For purified stigmasterol, specifications may include identity, purity, impurity profile, particle characteristics, and stability. For botanical extracts, additional requirements concerning botanical authentication, marker compounds, contaminant limits, and batch consistency may apply.

The absence of well-established clinical endpoints for several proposed applications represents another barrier. While stigmasterol has shown potential in cancer, neurodegenerative diseases, diabetes, inflammatory disorders, and other

conditions, the evidence is insufficient to support therapeutic claims in most of these areas. Consequently, the most realistic path toward clinical translation may involve prioritizing indications with strong mechanistic evidence, favorable preclinical efficacy, and measurable clinical outcomes.

Overall, the regulatory development of stigmasterol will require a multidisciplinary approach integrating pharmacology, toxicology, pharmaceutical formulation, analytical chemistry, pharmacokinetics, and clinical medicine. The development of standardized pharmaceutical-grade stigmasterol preparations and well-defined clinical indications will be particularly important for overcoming regulatory uncertainties.

5.8 Major Challenges in the Clinical Translation of Stigmasterol

Despite its broad pharmacological potential, several challenges must be addressed before stigmasterol can be considered a clinically established therapeutic agent. First, the low oral bioavailability of stigmasterol makes it difficult to relate administered doses to systemic pharmacological exposure. Second, many reported biological activities originate from in vitro studies using concentrations that may not be physiologically relevant. Third, the lack of comprehensive human pharmacokinetic and long-term toxicity data limits confidence in therapeutic dosing.

Additional challenges include the need for standardized formulations, validated analytical methods, well-controlled clinical trials, and comprehensive assessment of potential drug interactions. The heterogeneity of experimental preparations is another significant problem, as studies involving purified stigmasterol cannot always be directly compared with those involving complex plant extracts.

Future research should therefore adopt a translational framework in which mechanistic studies are directly linked to pharmacokinetic exposure and clinically relevant concentrations. Advanced delivery systems should be developed alongside pharmacokinetic studies rather than independently, ensuring that improvements in formulation produce measurable improvements in therapeutic outcomes. Furthermore, clinical trials should prioritize clearly defined disease populations and validated biomarkers to determine whether stigmasterol produces clinically meaningful effects (Cabral & Klein, 2017).

5.9 Future Strategies to Overcome Translational Barriers

Several strategies may accelerate the development of stigmasterol as a therapeutic molecule. First, systematic pharmacokinetic studies should establish absorption, distribution, metabolism, and elimination profiles in humans. Second, formulation technologies such as nanoemulsions, liposomes, phytosomes, and targeted nanoparticles should be investigated to overcome poor solubility and limited bioavailability. Third, standardized pharmaceutical-grade stigmasterol should be used in clinical studies to eliminate variability associated with botanical extracts.

Mechanistic research should also focus on identifying direct molecular targets and distinguishing primary pharmacological effects from secondary consequences of antioxidant or anti-inflammatory activity. High-throughput screening, transcriptomics, proteomics, metabolomics, and molecular docking may help identify novel stigmasterol-responsive pathways, although computational predictions should ultimately be validated experimentally.

Finally, clinical development should focus on therapeutic areas where the preclinical evidence is strongest and where the pharmacological mechanisms are most plausible. Carefully designed early-phase clinical studies should first establish safety and pharmacokinetic characteristics before efficacy is evaluated in larger trials. Such an evidence-based strategy may help bridge the gap between the extensive preclinical literature and the limited clinical evidence currently available for stigmasterol.

Conclusion

Stigmasterol possesses considerable therapeutic potential, but its transition from a promising phytochemical to a clinically useful therapeutic agent is constrained by several important challenges. Although available evidence generally supports a favorable safety profile at dietary exposure levels, comprehensive data concerning high-dose administration, long-term use, tissue accumulation, drug interactions, and vulnerable populations remain inadequate. Its poor aqueous solubility, limited intestinal absorption, and low systemic bioavailability further restrict its therapeutic application. At the same time, the majority of evidence supporting its pharmacological activities originates from preclinical studies, and direct clinical validation remains limited.

Addressing these challenges will require integrated research combining pharmacokinetic characterization, toxicological assessment, formulation optimization, molecular pharmacology, analytical standardization, and clinical investigation. Advanced delivery systems may overcome bioavailability limitations, while standardized pharmaceutical-grade preparations can improve reproducibility and regulatory acceptance. Ultimately, well-designed randomized clinical trials will be essential to determine whether the diverse pharmacological activities of stigmasterol observed in experimental systems translate into safe, effective, and clinically

meaningful therapeutic benefits. The future development of stigmasterol should therefore focus not only on demonstrating additional biological activities but also on establishing exposure–response relationships, therapeutic windows, long-term safety, and robust clinical efficacy.

6. Future Perspectives and Conclusion

Stigmasterol has emerged as a promising multifunctional phytosterol with a broad range of pharmacological activities and potential therapeutic applications. The evidence discussed throughout this review indicates that stigmasterol can influence multiple biological processes, including oxidative stress, inflammation, lipid metabolism, apoptosis, mitochondrial function, and cellular signaling. These pleiotropic properties provide a strong scientific rationale for investigating stigmasterol in the prevention and management of complex diseases such as metabolic disorders, cardiovascular diseases, cancer, neurodegenerative conditions, inflammatory disorders, liver diseases, and musculoskeletal diseases (Bakrim et al., 2022; Feng et al., 2020).

The pharmacological profile of stigmasterol is particularly attractive because many chronic diseases are multifactorial in nature and involve simultaneous dysregulation of several molecular pathways. Its antioxidant and anti-inflammatory properties may contribute to protection against cellular damage, while its effects on lipid metabolism may support cardiovascular and metabolic health. Similarly, its ability to modulate apoptosis, cell-cycle progression, and survival pathways has generated considerable interest in cancer research. However, the therapeutic significance of these activities should be interpreted cautiously because most available evidence is derived from in vitro and animal studies rather than well-controlled human clinical trials (Bakrim et al., 2022; Zhang et al., 2022).

One of the most important priorities for future research is the improvement of the pharmacokinetic profile and bioavailability of stigmasterol. Its high lipophilicity, poor aqueous solubility, limited intestinal absorption, and active efflux by intestinal transport mechanisms represent significant barriers to achieving predictable systemic exposure. Advanced pharmaceutical technologies, including nanoemulsions, liposomes, phytosomes, polymeric nanoparticles, solid lipid nanoparticles, and self-emulsifying drug delivery systems, may provide effective approaches for overcoming these limitations. Future investigations should determine whether improvements in bioavailability translate into enhanced pharmacological efficacy and whether targeted delivery can improve tissue-specific therapeutic effects.

The development of standardized stigmasterol formulations is another critical area for future investigation. Considerable variability exists among studies involving purified stigmasterol, phytosterol mixtures, and plant extracts. Differences in purity, extraction procedures, phytochemical composition, dose, and experimental conditions can substantially influence biological outcomes. Therefore, validated analytical methods based on HPLC, GC, LC–MS, and other advanced techniques should be employed to establish the identity, purity, stability, and concentration of stigmasterol in research and commercial preparations. Standardization will be essential for reproducibility, quality control, and regulatory approval.

Future research should also focus on clarifying the precise molecular mechanisms underlying the pharmacological effects of stigmasterol. Although pathways such as NF-κB, MAPK, PI3K/Akt/mTOR, oxidative stress networks, and apoptotic signaling have been implicated, the direct molecular targets of stigmasterol remain incompletely defined. Integration of molecular biology, omics technologies, systems pharmacology, molecular docking, artificial intelligence-assisted drug discovery, and experimental validation may help identify new targets and clarify the complex biological interactions of stigmasterol.

The potential synergistic interaction between stigmasterol and conventional therapeutic agents represents another promising research direction. Combination approaches may be particularly relevant in oncology, metabolic diseases, inflammatory disorders, and cardiovascular conditions. Stigmasterol could potentially complement existing drugs by simultaneously targeting oxidative stress, inflammation, lipid dysregulation, and cell-survival pathways. Nevertheless, combination therapy should be investigated systematically to distinguish true synergistic effects from additive or antagonistic interactions. Pharmacokinetic drug–phytochemical interaction studies will also be necessary to ensure that stigmasterol does not adversely affect the absorption, metabolism, or elimination of co-administered medications.

Clinical translation remains the most significant unmet need in stigmasterol research. Although extensive preclinical evidence supports its pharmacological potential, clinical evidence involving purified stigmasterol remains comparatively limited. Future studies should therefore progress through appropriately designed Phase I, II, and III clinical trials. Initial investigations should establish safety, tolerability, pharmacokinetic behavior, and optimal dosage, followed by controlled clinical studies evaluating efficacy in specific disease populations. Clinical research should prioritize therapeutic indications supported by strong mechanistic and preclinical

evidence and should use validated biomarkers and clinically meaningful endpoints.

Safety assessment also requires greater attention. Although stigmasterol is naturally consumed through the diet and is generally considered to have a favorable safety profile, the safety of concentrated pharmacological doses and long-term administration remains insufficiently characterized. Future toxicological investigations should examine chronic exposure, reproductive and developmental safety, hepatic and renal effects, endocrine interactions, immunological consequences, tissue distribution, and potential drug interactions. Particular attention should be given to populations with altered phytosterol metabolism or conditions affecting sterol transport and clearance (Feng et al., 2020).

The role of stigmasterol in women's health, neurodegenerative diseases, dermatology, gastrointestinal disorders, and other emerging therapeutic areas also deserves further investigation. However, these applications should be approached with appropriate scientific caution. The presence of a plausible mechanism or positive experimental result does not necessarily establish clinical efficacy. Rigorous disease-specific studies are required to determine whether stigmasterol can produce meaningful therapeutic outcomes in humans.

From a regulatory perspective, the future development of stigmasterol will depend on establishing clear distinctions between dietary, nutraceutical, cosmetic, and pharmaceutical applications. Products intended to make therapeutic claims will require robust evidence of quality, safety, efficacy, and reproducibility *(*Awad et al., 1996). The development of pharmaceutical-grade stigmasterol with well-defined specifications, validated manufacturing processes, and consistent batch-to-batch composition will be essential for successful regulatory translation.

Overall, stigmasterol represents a promising natural bioactive compound with considerable potential as a multifunctional therapeutic candidate. Its broad pharmacological profile, combined with its ability to influence multiple pathological pathways, makes it an attractive molecule for future drug discovery and development. Nevertheless, the current evidence base is characterized by a substantial gap between experimental findings and clinical validation. Addressing limitations related to bioavailability, formulation, pharmacokinetics, toxicology, standardization, and clinical evidence will be essential for converting the promising biological properties of stigmasterol into clinically meaningful applications.

In conclusion, stigmasterol should be viewed not simply as a dietary phytosterol but as a potential lead molecule for the development of innovative therapeutic strategies. Its future may lie in optimized formulations, targeted delivery systems, combination therapies, and personalized approaches based on disease-specific molecular mechanisms. Continued multidisciplinary research involving pharmacognosy, pharmaceutical technology, molecular pharmacology, toxicology, analytical science, and clinical medicine will be necessary to fully realize its therapeutic potential. If the existing preclinical evidence can be successfully translated through rigorous pharmacokinetic, toxicological, and clinical research, stigmasterol may ultimately contribute to the development of novel preventive and therapeutic interventions for a range of chronic and multifactorial diseases (Bakrim et al., 2022; Feng et al., 2020; Zhang et al., 2022).

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