
Lignans and Their Role in Cancer Prevention and Gut Health: A Survey

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Abstract

This survey explores the multifaceted health benefits of lignans, a class of polyphenolic compounds predominantly found in plant-based foods, emphasizing their roles in cancer prevention and gut health. Lignans are recognized for their antioxidant properties and ability to modulate hormone activity, contributing to their protective effects against hormone-dependent cancers and cardiovascular diseases. The conversion of dietary lignans into bioactive enterolignans by gut microbiota further enhances their therapeutic potential, underscoring the importance of understanding microbiota-lignan interactions. Despite their promising potential, challenges remain in standardizing analytical methodologies and understanding the mechanisms of action of lignans. This survey highlights the need for interdisciplinary collaboration and innovative research strategies to refine extraction, purification, and characterization techniques, facilitating the development of comprehensive dietary recommendations and therapeutic applications. By advancing our understanding of lignans and their interactions with gut microbiota, targeted dietary strategies can be developed to maximize their health benefits, ultimately contributing to improved public health outcomes.

1 Introduction

1.1 Significance of Lignans

Lignans, polyphenolic compounds primarily found in plant-based foods, are recognized for their potential health benefits and disease prevention roles. Their antioxidant properties help mitigate oxidative stress, a key factor in chronic diseases such as cancer and cardiovascular disorders, by neutralizing free radicals and reducing cellular damage [1].

Additionally, lignans exhibit phytoestrogenic properties that modulate hormone activity, particularly beneficial in hormone-dependent cancers like breast and prostate cancer. By acting as weak estrogen agonists or antagonists, lignans can influence estrogen metabolism and balance hormonal levels, potentially lowering cancer risk [2].

Lignans also play a significant role in gut health through their interaction with gut microbiota, converting into enterolignans. This conversion enhances their bioavailability and therapeutic potential, promoting a balanced microbiome and maintaining intestinal integrity [3, 4].

Research highlights additional bioactive properties of lignans, including antiviral [5] and ethnopharmacological potentials [6]. Their diverse biological activities underscore their significance as multifunctional compounds with applications in nutraceuticals and pharmaceuticals, addressing the urgent need for effective agents in chronic disorder prevention and treatment [7].

1.2 Health Benefits Overview

Lignans have been extensively studied for their health benefits, particularly in chronic disease prevention. Their antioxidant activity is well-documented, providing protective effects against

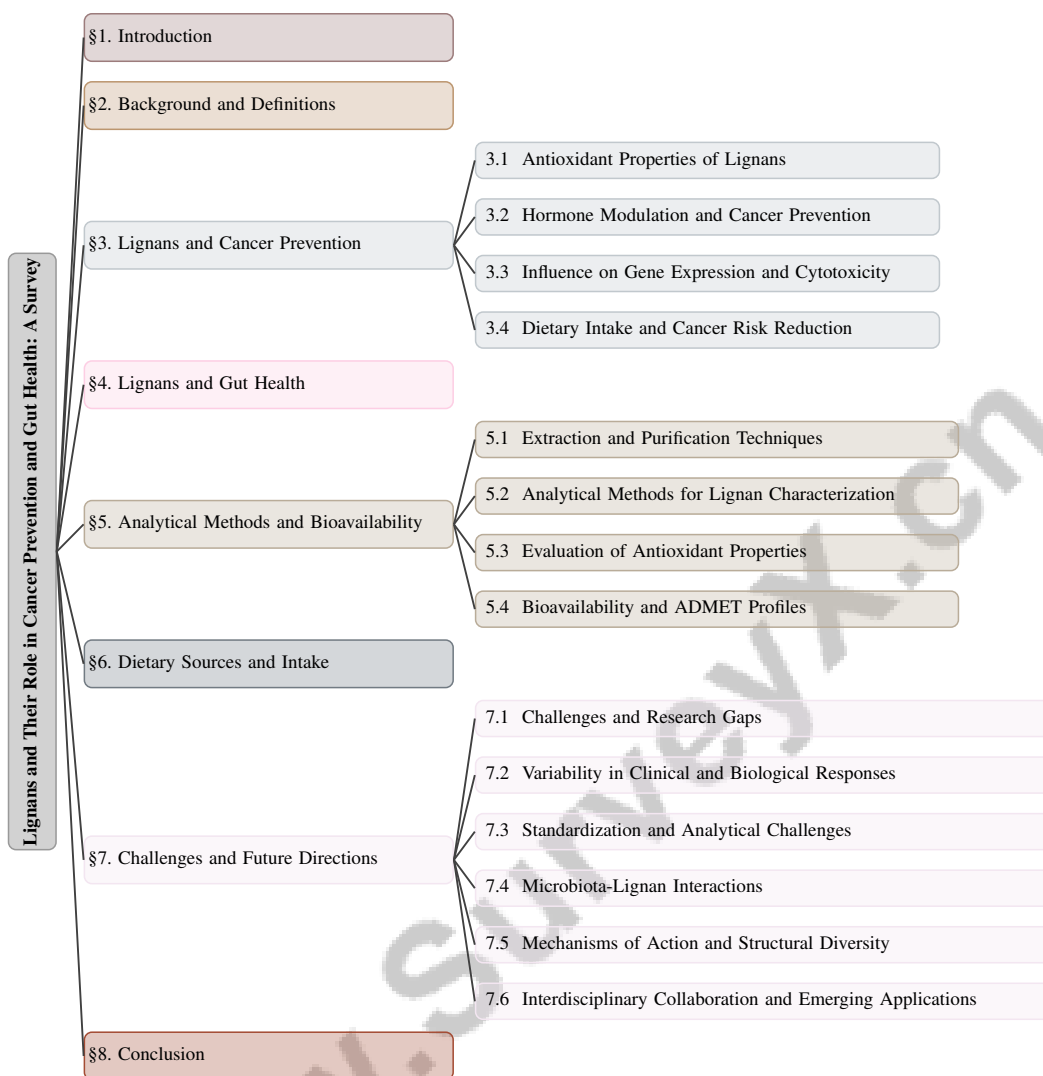


Figure 1: chapter structure

cellular damage and lowering the risk of cancer and cardiovascular diseases. The conversion of lignans into enterolignans by gut microbiota further enhances their health benefits, significantly reducing the risk of hormone-dependent cancers and cardiovascular disorders [3].

Sesame lignans, in particular, have demonstrated promising potential in disease prevention, emphasizing the importance of optimizing breeding strategies to enhance lignan content in plants [8]. This optimization is crucial, as lignans contribute to hormone modulation, offering protective effects against hormone-dependent cancers such as breast and prostate cancer [2]. Their phytoestrogenic properties, allowing them to act as weak estrogen agonists or antagonists, are vital for maintaining hormonal balance and reducing cancer risk.

Beyond antioxidant and phytoestrogenic properties, lignans exhibit pharmacological significance in various therapeutic applications. Their antiviral and ethnopharmacological potentials further highlight their versatility as bioactive compounds with applications in nutraceuticals and pharmaceuticals [2]. Ongoing research continues to reveal insights into their mechanisms of action and therapeutic potential, underscoring the need for further studies to fully exploit their health benefits.

1.3 Structure of the Survey

This survey is meticulously structured to comprehensively explore lignans, emphasizing their health benefits, particularly in cancer prevention and gut health. The introduction highlights the significance

of lignans as polyphenolic compounds and their potential health benefits, setting the stage for subsequent discussions.

The second section provides background and definitions, detailing lignans' chemical structure, classification, and occurrence in various plant sources. Key terms related to lignans, such as polyphenols, antioxidants, and hormone modulation, are defined to establish a foundational understanding.

The third section focuses on lignans and cancer prevention, examining the mechanisms by which lignans reduce cancer risk, including their antioxidant properties, hormone modulation, influence on gene expression, and dietary lignan intake.

The fourth section addresses the role of lignans in gut health, discussing their interaction with gut microbiota, conversion to enterolignans, and impact on the gut-brain axis. It reviews the benefits of lignans in managing gut-related disorders, highlighting their therapeutic potential.

The fifth section covers analytical methods and bioavailability of lignans, describing extraction, purification, and characterization techniques, as well as evaluating antioxidant properties and bioavailability.

The sixth section identifies major dietary sources of lignans and discusses dietary patterns for optimizing lignan intake, providing recommendations for maximizing their health benefits through diet.

The seventh section highlights challenges and future directions in lignan research, identifying gaps and suggesting areas for further investigation, including the need for standardization, understanding microbiota-lignan interactions, and exploring the mechanisms of action and structural diversity of lignans.

The conclusion synthesizes the primary results of the survey, emphasizing the significant health benefits associated with lignans, particularly their anticancer properties, and the necessity for ongoing research to explore and harness their therapeutic potential, including the development of novel lignan compounds with enhanced pharmacological activities [9, 10, 2, 11]. The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Chemical Structure and Classification of Lignans

Lignans are polyphenolic compounds distinguished by two phenylpropanoid units connected via a carbon-carbon bond, essential for their biological functions and therapeutic potential [9]. Their classification, based on carbon skeletons and cyclization patterns, includes lignans, cyclolignans, neolignans, cycloneolignans, and oxyneolignans [9]. Further categorization into acyclic lignan derivatives, dibenzocyclooctadiene derivatives, and aryl-naphthalene derivatives highlights structural variations critical to their bioactivity [9]. Understanding these classifications aids in exploring lignans' chemical diversity and informs the development of therapeutic strategies.

2.2 Biosynthesis and Distribution

Lignan biosynthesis involves complex enzymatic pathways, primarily the phenylpropanoid pathway, converting phenylalanine to p-coumaroyl-CoA via key enzymes like PAL, C4H, and 4CL [8]. This process leads to lignan precursors such as pinoresinol, secoisolariciresinol, and matairesinol [12]. Distribution varies across plant species, influenced by genetic and environmental factors, with linseed and sesame seeds being prominent sources [4, 2]. Gut microbiota metabolizes lignans into enterolignans, enhancing their antioxidant and hormone-modulating benefits [3]. Understanding lignan biosynthesis and distribution is vital for advancing their application in nutraceuticals and pharmaceuticals.

2.3 Role as Phytoestrogens

Lignans act as phytoestrogens due to their structural similarity to estrogens, allowing them to bind to estrogen receptors and modulate hormonal activity. This is beneficial in hormone-dependent cancers, such as breast and prostate cancer, by balancing hormonal levels and potentially reducing cancer risk

[2]. Their conversion into enterolignans by gut microbiota further enhances these effects, contributing to protective activities against hormone-related disorders [3]. A lignan-rich diet is associated with a reduced risk of hormone-dependent cancers, emphasizing their importance in hormone modulation and health support [2].

2.4 Occurrence in Plant Sources

Lignans are abundant in seeds, grains, fruits, vegetables, and some beverages. Flaxseeds, with high secoisolariciresinol diglucoside (SDG) content, and sesame seeds, rich in sesamin and sesamol, are notable for their health benefits [1]. Whole grains like rye and barley, along with fruits and vegetables, diversify dietary lignan sources [11]. Beverages such as tea and coffee also contribute significantly to lignan intake [11]. This diversity underscores the importance of a varied diet for optimal lignan consumption, supporting health maintenance and therapeutic applications [1].

2.5 Key Terms: Polyphenols, Antioxidants, and Hormone Modulation

Polyphenols, including lignans, are plant-derived compounds with multiple phenol units, contributing to their biological activities like antioxidant and hormone-modulating effects [7]. Lignans' antioxidant properties neutralize free radicals, reducing oxidative stress and mitigating chronic diseases such as cancer and cardiovascular disorders [7]. Their conversion into mammalian lignans by gut microbiota enhances these effects [13]. As phytoestrogens, lignans modulate hormone activity by binding to estrogen receptors, beneficial in reducing hormone-dependent cancer risks [7]. These properties highlight lignans' potential as therapeutic agents in disease prevention and management.

3 Lignans and Cancer Prevention

The exploration of lignans' role in cancer prevention necessitates a detailed analysis of their biological activities and health benefits. Lignans, as significant phytonutrients, exhibit properties that contribute to their protective effects against various cancers. This section delves into the mechanisms through which lignans influence cancer prevention, emphasizing their antioxidant capabilities, which are pivotal in mitigating oxidative stress and cellular damage, key contributors to cancer development.

Figure 2 illustrates the hierarchical structure of lignans' role in cancer prevention, highlighting their antioxidant properties, hormone modulation, influence on gene expression and cytotoxicity, and the impact of dietary intake. Each category is further divided into specific mechanisms and health benefits, emphasizing the complex interactions and therapeutic potential of lignans in cancer prevention strategies. By integrating this visual representation, we can better appreciate the multifaceted nature of lignans and their contributions to health, thereby enhancing our understanding of their preventive roles in cancer.

3.1 Antioxidant Properties of Lignans

Lignans, as prominent polyphenolic compounds, are acclaimed for their potent antioxidant properties essential in cancer prevention. Their ability to scavenge free radicals and reduce oxidative stress is crucial in lowering the risk of chronic diseases such as cancer and cardiovascular disorders [2]. The transformation of dietary lignans into enterolignans by gut microbiota augments their antioxidant potential, enhancing their anti-inflammatory and anticancer effects [3].

As illustrated in Figure 3, the antioxidant properties of lignans emphasize their potential in scavenging free radicals, which is vital for health benefits in chronic disease prevention. Specific lignans, such as orleralignan, have demonstrated superior antioxidant activities compared to traditional antioxidants like BHA, underscoring their potential as bioactive compounds in disease prevention [14]. Comprehensive assessments using multiple assays have solidified the understanding of lignans' health benefits, distinguishing them from earlier research focused on isolated methods [13]. Lignans from sesame seeds also exhibit significant health-promoting properties, including antioxidant activities beneficial for managing chronic diseases [8]. The diverse pharmacological attributes of lignans, particularly from the Lauraceae family, highlight their therapeutic applications and chemotaxonomic relevance [7].

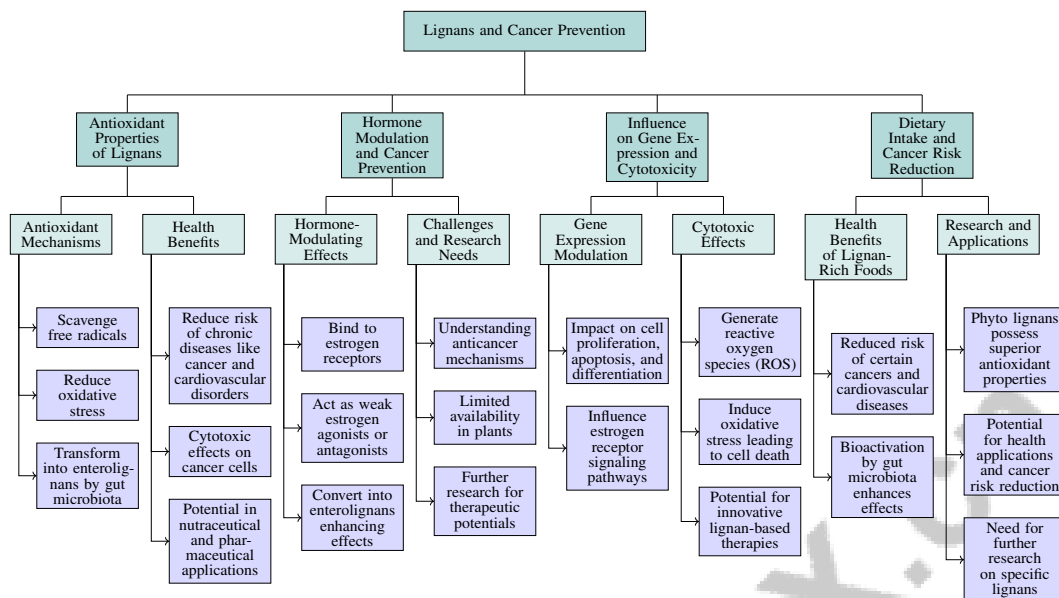


Figure 2: This figure illustrates the hierarchical structure of lignans' role in cancer prevention, highlighting their antioxidant properties, hormone modulation, influence on gene expression and cytotoxicity, and the impact of dietary intake. Each category is further divided into specific mechanisms and health benefits, emphasizing the complex interactions and therapeutic potential of lignans in cancer prevention strategies.

Lignans' cytotoxic effects on cancer cells further underscore their anticancer potential, with evidence of significant cytotoxicity against various cancer cell lines [5]. These findings advocate for lignans' inclusion in nutraceutical and pharmaceutical applications to harness their health benefits [4].

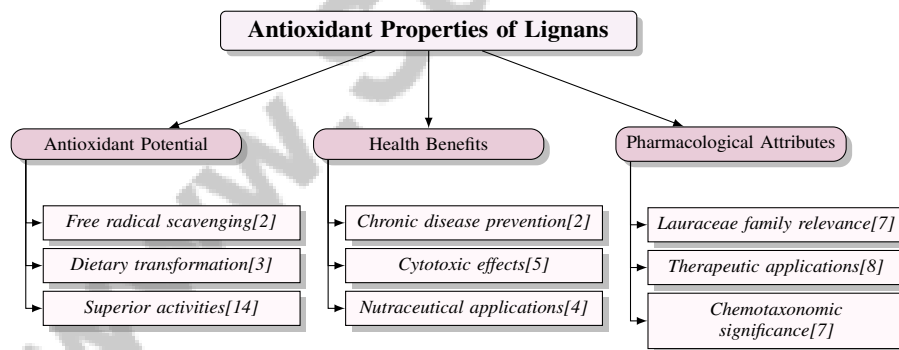


Figure 3: This figure illustrates the antioxidant properties of lignans, emphasizing their potential in scavenging free radicals, health benefits in chronic disease prevention, and pharmacological attributes, including their significance in the Lauraceae family.

3.2 Hormone Modulation and Cancer Prevention

Lignans are notable for their hormone-modulating capabilities, crucial in preventing hormone-dependent cancers such as breast and prostate cancer. Acting as phytoestrogens, lignans bind to estrogen receptors, functioning as weak estrogen agonists or antagonists, thereby influencing estrogen metabolism and maintaining hormonal balance [2]. This modulation is particularly beneficial in hormone-dependent cancers, where estrogen significantly impacts cancer progression.

The conversion of lignans into enterolignans, such as enterodiols and enterolactone, by gut microbiota enhances their hormone-modulating effects. These enterolignans exhibit both estrogenic and anti-estrogenic activities, contributing to their protective effects against hormone-related disorders [9].

The interaction between lignans and estrogen receptors regulates physiological processes critical in cancer prevention, including cell proliferation and differentiation.

Despite their promising potential, challenges persist in fully understanding lignans' anticancer mechanisms and clinical efficacy. The limited availability of lignans in plants necessitates further research to explore their therapeutic potentials and optimize their use in cancer prevention strategies [9]. Continued investigation into lignans' hormone-modulating properties is essential for developing effective interventions for hormone-dependent cancers, emphasizing their significance as multifunctional compounds in nutraceuticals and pharmaceuticals [15].

3.3 Influence on Gene Expression and Cytotoxicity

Lignans' influence on gene expression and their cytotoxic effects on cancer cells are pivotal to their anticancer properties. They can modulate gene expression involved in cell proliferation, apoptosis, and differentiation, particularly in hormone-dependent cancers by impacting estrogen receptor signaling pathways [6].

Comparative studies have highlighted lignans' superior cytotoxic activities against various cancer cell lines, underscoring their therapeutic potential. Some lignans also demonstrate enhanced anti-inflammatory activities, contributing to their overall anticancer efficacy [6]. The cytotoxicity of lignans is linked to their capacity to generate reactive oxygen species (ROS) and induce oxidative stress, leading to cell death and tumor growth inhibition.

Despite promising results, questions remain regarding the precise mechanisms of lignans and their interactions with gut microbiota, which play a pivotal role in bioactivating lignans into biologically active enterolignans [4]. This interaction may also influence the expression of genes related to inflammation and immune response, further enhancing their cytotoxic effects.

The exploration of lignans' influence on gene expression and cytotoxicity continues to yield insights into their mechanisms of action and therapeutic potential. Ongoing research is vital for uncovering the intricate biological mechanisms through which lignans, as diverse secondary metabolites found in various plants, exert their anticancer effects. This deeper understanding may facilitate the development of innovative lignan-based therapies, effectively integrated into comprehensive cancer prevention and treatment strategies. Current studies demonstrate that lignans possess a range of beneficial properties, including antioxidant and estrogenic activities, and show promise in reducing cancer risk, particularly through compounds like secoisolariciresinol diglucoside (SDG). However, significant gaps remain regarding their pharmacological mechanisms and the potential for modifying or synthesizing new lignans with enhanced efficacy, necessitating extensive research into both well-studied and novel lignan sources for effective anticancer drug development [2, 11, 9, 10, 4].

3.4 Dietary Intake and Cancer Risk Reduction

Dietary intake of lignan-rich foods is associated with a reduced risk of certain cancers and cardiovascular diseases, highlighting the health benefits of these polyphenolic compounds. The bioactivation of dietary lignans by gut microbiota plays a crucial role in determining their health effects, influencing the concentrations of enterolignans, the bioactive forms of lignans with enhanced biological activities [3]. This variability in bioactivation affects the overall efficacy of lignans in cancer prevention, emphasizing the need to understand the interactions between dietary lignans and gut microbiota to optimize their health benefits.

Research indicates that phyto lignans possess superior antioxidant properties compared to mammalian lignans, supporting their potential for health applications, including cancer risk reduction [13]. The antioxidant capacity of lignans is pivotal in mitigating oxidative stress, a key factor in cancer development, by neutralizing free radicals and reducing cellular damage [1]. This protective effect is further enhanced by the conversion of lignans into enterolignans, which exhibit potent antioxidant and hormone-modulating activities.

Key findings suggest that the consumption of lignan-rich foods, such as flaxseeds and sesame seeds, may lower the risk of hormone-dependent cancers, including breast and prostate cancer, by modulating hormone activity and maintaining hormonal balance [1]. However, the limited knowledge about the biological functions and potential applications of specific lignans, particularly those derived

from sesame, underscores the need for further research to fully exploit their therapeutic potential in health and agriculture [8].

Evaluations of lignans' cytotoxic effects on various cancer cell lines, including HepG-2 human liver cancer cells, BGC-823 human gastric cancer cells, and HCT-116 human colon cancer cells, have provided insights into their anticancer mechanisms and effectiveness [15]. These findings underscore the importance of dietary lignans in cancer prevention strategies and advocate for their inclusion in dietary recommendations to maximize health benefits. Continued research is essential to better understand the role of dietary lignans in reducing cancer risk and to develop effective interventions for cancer prevention.

4 Lignans and Gut Health

4.1 Interaction with Gut Microbiota

The interaction between lignans and gut microbiota is pivotal in converting dietary lignans into bioactive enterolignans, such as enterodiol and enterolactone, which exhibit enhanced antioxidant and hormone-modulating effects beneficial for chronic disease prevention [16]. Variability in enterolignan production due to differences in gut microbiota composition impacts lignans' bioavailability and therapeutic efficacy [17]. This variability suggests that distinct microbiota profiles may result in varied health outcomes from lignan consumption. Despite recognized benefits, the precise mechanisms and bioavailability of specific lignans like secoisolariciresinol diglucoside (SDG) remain inadequately understood [4]. Further research is essential to elucidate lignan-microbiota interactions and identify microbial species involved in lignan metabolism. A deeper understanding of these interactions can inform dietary strategies to optimize lignan intake, enhancing gut health and reducing chronic disease risks [1, 17, 11, 16, 3].

4.2 Conversion to Enterolignans

The conversion of lignans into enterolignans by gut microbiota significantly enhances their bioactivity, contributing to antioxidant, anti-inflammatory, and hormone-modulating effects that protect against chronic diseases [16]. This transformation depends on individual gut microbiome composition, influencing plasma enterolactone levels and metabolic risk [16]. Enterolignans, such as enterolactone and enterodiol, demonstrate superior bioactivity by activating estrogen receptors and influencing gene expression, offering protection against diseases like colorectal and breast cancer, and cardiovascular conditions [17, 3, 2, 4]. The conversion to enterolignans is crucial for maximizing lignans' therapeutic potential, advocating for dietary strategies that support this biotransformation.

4.3 Impact on Gut-Brain Axis

Lignans' influence on the gut-brain axis highlights their potential as nutraceuticals in managing chronic diseases. This axis, a communication network between the gut and the central nervous system, is modulated by gut microbiota [17]. Lignans, converted into bioactive enterolignans by gut microbiota, exhibit antioxidant and anti-inflammatory properties that may mitigate oxidative stress and inflammation, factors implicated in neurodegenerative diseases [16]. By affecting neurotransmitter production, lignans may impact brain health and cognitive functions [16]. Continued exploration of lignans' effects on the gut-brain axis is essential for understanding their mechanisms and therapeutic potential, facilitating the development of dietary interventions to optimize cognitive health and mitigate metabolic risks [2, 17, 11, 16, 3].

4.4 Benefits in Gut-Related Disorders

Lignans show promise in managing gut-related disorders through their conversion into bioactive enterolignans, which possess antioxidant and anti-inflammatory properties crucial for gut health [17]. The modulation of gut microbiota by lignans influences gut health and metabolic risk [16]. The biotransformation of lignans into active forms enhances their therapeutic potential in reducing inflammation and oxidative stress, key factors in gut-related disorders [16]. Despite promising benefits, current studies often lack comprehensive *in vivo* data, necessitating further research to optimize lignan-based interventions [17]. Understanding lignan-microbiota interactions will enable

targeted dietary strategies to enhance health benefits and address gut-related disorders, with potential implications for preventing chronic diseases like colorectal cancer and cardiovascular conditions [17, 3, 11].

5 Analytical Methods and Bioavailability

Category	Feature	Method
Extraction and Purification Techniques	Chromatographic Methods	LiganIsolation[14]

Table 1: This table provides a summary of the extraction and purification techniques used for isolating lignans, focusing on chromatographic methods. The method LiganIsolation is highlighted, as referenced in the literature, demonstrating its application in lignan research.

Exploring analytical methods and bioavailability is crucial for understanding lignans, recognized for their health benefits. Table 3 offers a comprehensive comparison of the methodologies utilized in lignan research, emphasizing the techniques for extraction and purification, the analytical methods for characterization, and the evaluation of antioxidant properties. Table 1 presents an overview of the extraction and purification techniques employed in lignan research, with a specific emphasis on chromatographic methods. This section examines the extraction and purification techniques essential for isolating lignans from plant sources, ensuring their integrity and efficacy in subsequent analyses. Establishing robust methodologies enhances our comprehension of lignans' bioavailability and therapeutic applications.

5.1 Extraction and Purification Techniques

Extracting and purifying lignans from plants are fundamental for their study and application, requiring efficient methodologies due to lignans' structural complexity and variable content across sources [2, 11]. Techniques like solvent extraction, supercritical fluid extraction, and pressurized liquid extraction are employed. Solvent extraction, using methanol, ethanol, and acetone, is common but requires optimization for yield and selectivity [11]. Supercritical fluid extraction with carbon dioxide offers an eco-friendly alternative.

Chromatographic techniques, such as HPLC and preparative TLC, are used for lignan purification, enabling compound separation based on chemical properties. NMR and mass spectrometry provide structural information essential for understanding lignan bioactivity [14]. Despite advancements, standardizing these techniques across studies remains challenging, complicating comparisons of lignan content and bioactivity [11]. Benchmark studies evaluate antioxidant and antiradical properties, ensuring consistency in research [13]. Enhancing extraction and purification techniques is vital for incorporating lignans into nutraceuticals and pharmaceuticals, unlocking their full health benefits, including anticancer and antioxidant properties [2, 11, 9, 10, 4].

As illustrated in Figure 4, lignan analysis involves understanding their complex structures and molecular interactions. The first subfigure presents the diverse chemical structures of dietary lignans, such as secoisolariciresinol and mataresinol. The second subfigure details the phenylpropane unit and C6-C3 dimerization via -' bonding, emphasizing the importance of molecular interactions in extraction and purification processes, crucial for enhancing lignan bioavailability in dietary applications [11, 9].

5.2 Analytical Methods for Lignan Characterization

Characterizing lignans provides insights into their chemical structure and biological activity. Chromatography and mass spectrometry are fundamental for precise identification and quantification [11]. HPLC is widely used for lignan separation and analysis, offering high resolution and sensitivity, particularly in distinguishing isomers. Coupling HPLC with MS enhances capabilities by providing molecular weight and structural information [11].

MS, often used with HPLC, detects lignans at low concentrations. Tandem MS (MS/MS) fragments lignan molecules, offering structural insights [11]. NMR spectroscopy complements these methods, elucidating complex structural details and providing critical insights into lignans' molecular configurations and interactions [2, 18, 11]. Robust analytical methods are crucial for advancing lignan research, facilitating accurate dietary source assessments, and supporting health implication

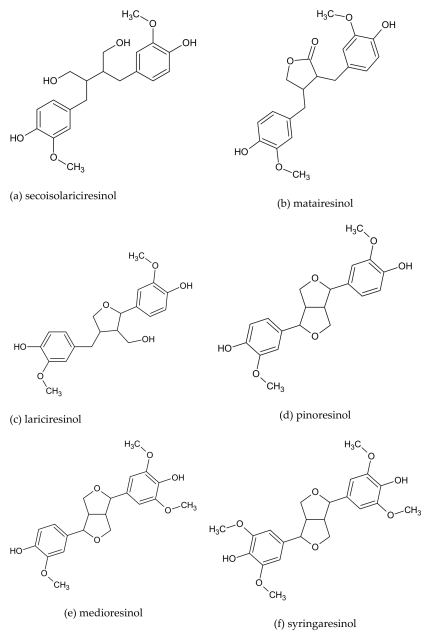


Figure 1. The chemical structure of main dietary lignans, (a) secoisolariciresinol, (b) matairesinol, (c) lariciresinol, (d) pinoresinol, (e) medioresinol, and (f) syringaresinol.
Plant lignans give rise to metabolites, enterodiol, and enterolactone [12], generally called enterolignans due to their colonic origin (named also mammalian lignans) (shown in Figure 2).

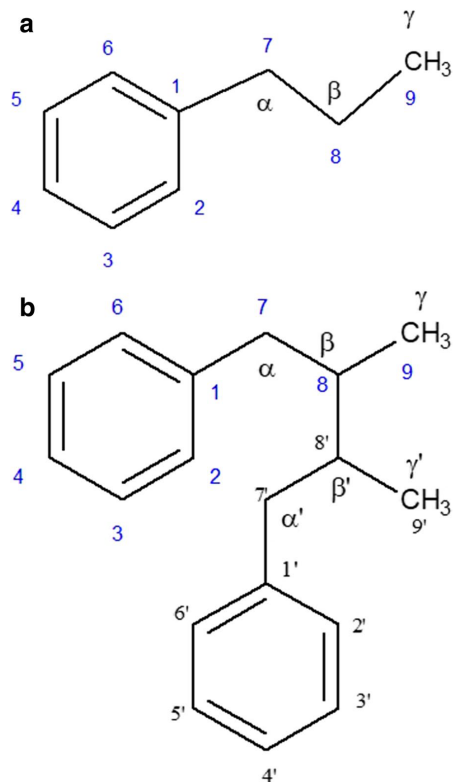


Fig. 2 a Phenylpropane unit. b Dimer of C6-C3 unit via β - β' bonding

(a) The Chemical Structure of Main Dietary Lignans[11]

(b) Phenylpropane unit and Dimer of C6-C3 unit via β - β' bonding[9]

Figure 4: Examples of Extraction and Purification Techniques

investigations. Future research should improve methods, expand food databases, and explore health implications [11]. Integrating analytical techniques enhances lignan study reliability, contributing to a deeper understanding of their therapeutic potential.

5.3 Evaluation of Antioxidant Properties

Benchmark	Size	Domain	Task Format	Metric
Lignans-AO[13]	1,000	Biochemistry	Antioxidant Activity Evaluation	IC50, DPPH Scavenging
LCA[18]	160	Pharmaceutical Chemistry	Property Assessment	Molecular Weight, LogP
MLVS[16]	911	Nutrition	Correlation Analysis	Plasma enterolactone levels, Microbiome species score

Table 2: Table of presents a comparative overview of three representative benchmarks used in the evaluation of lignan antioxidant properties. It details the size, domain, task format, and metrics employed in each benchmark, highlighting the diversity and scope of methodologies applied in this field of research.

Evaluating lignan antioxidant properties is vital for understanding their health benefits in chronic disease prevention. Antioxidant capacity is assessed through various in vitro assays, providing insights into lignans' ability to neutralize free radicals [13]. The DPPH assay measures hydrogen atom or electron donation to neutralize radicals, reducing oxidative stress [13]. The ABTS assay evaluates lignans' capacity to quench radicals, indicating antioxidant potential [13].

The FRAP assay assesses lignans' reducing power, reflecting antioxidant activity by converting ferric to ferrous ions. The ORAC assay measures lignans' ability to inhibit fluorescein oxidation by

peroxyl radicals, offering a comprehensive antioxidant efficacy evaluation [13]. Table 2 provides a comprehensive summary of the benchmarks utilized in assessing the antioxidant properties of lignans, emphasizing the varied approaches and metrics that contribute to a robust evaluation framework. Using multiple assays allows a robust antioxidant property assessment, crucial for distinguishing lignan activities and understanding health benefits [13]. Standardizing methods across studies is challenging but necessary for consistent and reliable research [13]. Continued refinement and standardization efforts enhance study reproducibility, deepening our understanding of lignans' therapeutic potential in disease prevention.

5.4 Bioavailability and ADMET Profiles

Lignan bioavailability is crucial for determining therapeutic efficacy, influencing health benefits post-ingestion. A primary research challenge is the lack of comprehensive bioavailability studies and inconsistent health effect results [1]. Bioavailability variability arises from individual gut microbiota composition differences, affecting dietary lignans' conversion into bioactive enterolignans like enterodiol and enterolactone [3].

Precise, validated analytical methods are needed to quantify enterolignans and understand inter-individual variability [3]. Developing such methodologies is essential for accurate bioavailability assessments and pharmacokinetic profile elucidation. ADMET profiles highlight lignans' therapeutic potential. Pilkington et al. categorized lignans as drug-like, emphasizing pharmaceutical application potential [18]. Understanding metabolic pathways and excretion processes optimizes therapeutic use.

Despite promising health benefits, limited ADMET profile understanding hinders lignans' full therapeutic application. Further research is needed to elucidate these profiles and overcome purification, metabolism, and delivery barriers [9, 4, 2, 11]. Continued research refines bioavailability studies and develops comprehensive ADMET profiles, enhancing lignans' application in nutraceuticals and pharmaceuticals. Advancing our understanding maximizes lignans' therapeutic potential.

Feature	Extraction and Purification Techniques	Analytical Methods for Lignan Characterization	Evaluation of Antioxidant Properties
Extraction Method	Solvent Extraction	Not Specified	Not Specified
Analytical Technique	Chromatographic Purification	Hplc And MS	IN Vitro Assays
Evaluation Focus	Yield And Selectivity	Structure And Bioactivity	Antioxidant Capacity

Table 3: This table provides a comparative analysis of various methods involved in the extraction, purification, and characterization of lignans, as well as the evaluation of their antioxidant properties. It highlights the techniques used, including solvent extraction and chromatographic purification, alongside the analytical methods such as HPLC and mass spectrometry, and the focus areas such as yield, structure, bioactivity, and antioxidant capacity.

6 Dietary Sources and Intake

6.1 Major Dietary Sources of Lignans

Lignans are abundant in plant-based foods, with seeds, whole grains, fruits, and vegetables being significant sources. Flaxseeds (*Linum usitatissimum*) are particularly rich in lignans, especially secoisolariciresinol diglucoside (SDG), renowned for its health benefits [1]. Sesame seeds also contribute substantially to lignan intake, offering sesamin and sesamolin, known for their antioxidant and phytoestrogenic properties [1]. Whole grains such as rye and barley are vital for cardiovascular health and may reduce hormone-dependent cancer risks [11]. Fruits and vegetables, especially berries and cruciferous types, diversify lignan sources [1]. Beverages like tea and coffee further enhance lignan intake, with regular consumption linked to increased dietary lignan levels [11]. The extensive presence of lignans in various plants underscores the importance of a diverse diet for optimal lignan intake, highlighting their potential as functional foods with therapeutic applications [1].

6.2 Variability in Lignan Content

Lignan content varies widely among foods due to plant species, growth conditions, and processing methods, complicating dietary lignan intake assessments and health benefit evaluations. Flaxseeds consistently show high SDG levels, while sesame seeds provide sesamin and sesamolin [11]. Whole

grains like rye and barley are influenced by cultivation and processing, affecting lignan intake and health benefits. Factors such as soil, climate, and agricultural practices impact lignan biosynthesis, contributing to dietary diversity and potential health benefits [1, 2, 11, 17, 4]. The lack of standardized analytical methods complicates lignan content comparisons across foods, necessitating unified methodologies to accurately evaluate lignan levels for health implications [11].

6.3 Dietary Patterns and Lignan Intake

Dietary patterns critically influence lignan intake and related health benefits. Incorporating lignan-rich foods into daily diets is crucial for maximizing their therapeutic potential, particularly against chronic diseases like cancer and cardiovascular disorders [11]. Flaxseeds and sesame seeds are key lignan sources, with whole grains like rye and barley playing significant roles in reducing hormone-dependent cancer risks and promoting cardiovascular health [1, 11]. The Mediterranean diet, rich in plant-based foods, optimizes lignan intake, offering numerous health benefits including reduced inflammation and chronic disease risk [11]. Regular consumption of lignan-rich beverages like tea and coffee supports health-promoting diets [11]. Emphasizing lignan-rich foods and beverages in dietary patterns enhances health benefits, supporting evidence-based dietary guidelines and interventions to exploit lignans' health-promoting properties [1, 2, 4, 11].

6.4 Recommendations for Optimizing Lignan Intake

To optimize lignan intake and harness health benefits, a diet rich in lignan-containing foods like flaxseeds, whole grains, fruits, and vegetables is essential. These foods are associated with reduced risks of chronic diseases due to their bioactive and antioxidant properties [1, 2, 4, 11]. Prioritizing seeds, especially flaxseeds and sesame seeds, is crucial as they are rich in SDG, sesamin, and sesamol, contributing to their antioxidant and phytoestrogenic effects. Whole grains such as rye and barley should also be included for cardiovascular benefits and cancer risk reduction [11]. A variety of fruits and vegetables, particularly berries and cruciferous types, further enhance lignan intake and support a balanced diet [1]. Adopting the Mediterranean diet, emphasizing plant-based foods, can optimize lignan intake, offering numerous health benefits [11]. Regular consumption of lignan-rich beverages like tea and coffee can also increase lignan intake [11]. A diverse diet rich in lignan-containing foods and beverages promotes health maintenance, highlighting lignans' role as functional food components with therapeutic applications in disease prevention and treatment [9, 2, 11]. Continued research into dietary sources and patterns maximizing lignan consumption will aid in developing effective dietary recommendations to improve public health.

7 Challenges and Future Directions

7.1 Challenges and Research Gaps

Lignan research is impeded by several challenges, notably the scarcity of large-scale human studies, which complicates dietary recommendations due to the variability in lignan content across foods [1]. This variability necessitates standardized classification and nomenclature for comprehensive research comparisons [7]. A thorough understanding of lignans' mechanisms, especially newly identified dibenzocyclooctadiene lignans, remains incomplete [15]. Current methodologies fall short in isolating and evaluating lignans' antioxidant potential from specific sources like **Portulaca oleracea* L.* [14]. The absence of extensive genetic analyses and molecular markers for high lignan content limits breeding efforts [8]. Moreover, the limited evaluation of plant species and the scarcity of comprehensive *in vivo* studies hinder progress [9]. Challenges in extraction, purification, metabolism, and toxicity further restrict lignans' therapeutic applications [4]. Understanding bacterial strains involved in lignan metabolism and enterolignans' mechanisms is also lacking [17]. Future initiatives must prioritize clinical trials, standardized analytical methods for enterolignans, and investigations into lignan-gut microbiota interactions to enhance therapeutic potential against chronic diseases like cancer and cardiovascular conditions, considering individual variability in metabolism and bioavailability [2, 17, 11, 16, 3].

7.2 Variability in Clinical and Biological Responses

Variability in clinical and biological responses to lignan intake affects their efficacy and health outcomes. Differences in gut microbiota composition play a crucial role in metabolizing dietary lignans into bioactive enterolignans, such as enterodiols and enterolactones [16]. This metabolic variability results in differing plasma enterolactone levels, impacting metabolic risks and health benefits [17]. Genetic factors also contribute, influencing enzyme expression in lignan biosynthesis and metabolism, thereby affecting bioavailability and efficacy [8]. The interaction of genetic differences with environmental factors complicates lignan intake's health impact. Other dietary components may interact with lignans, affecting absorption and metabolism, modulating health benefits [11]. Despite recognized variability, comprehensive studies considering these differences are lacking. Future research should elucidate factors contributing to variability, including gut microbiota, genetic variations, and dietary interactions, to formulate personalized dietary recommendations and maximize lignans' health benefits in disease prevention and management [1, 2, 11].

7.3 Standardization and Analytical Challenges

Standardization and analytical challenges significantly hinder lignan research, particularly due to variability in lignan content across plant sources and inconsistent methodologies for extraction, purification, and analysis. The lack of standardized techniques complicates comparisons of lignan content and biological activities, impeding comprehensive dietary recommendations and therapeutic applications [11]. The diverse chemical nature of lignans requires robust extraction and purification techniques to accommodate their structural complexity [14]. Variability in lignan content, influenced by genetic and environmental factors, complicates dietary intake assessments and health benefit evaluations, highlighting the need for standardized classification and nomenclature [7]. The absence of standardized methods for evaluating lignan bioavailability and ADME profiles further complicates therapeutic potential assessments, emphasizing the need for precise analytical techniques [3]. Addressing these challenges involves developing unified methodologies for lignan extraction and characterization, establishing benchmark studies for antioxidant properties, and exploring lignan-gut microbiota interactions to enhance reproducibility and comparability of studies.

7.4 Microbiota-Lignan Interactions

Interactions between lignans and gut microbiota are crucial for determining lignans' bioactivity and therapeutic potential. Gut microbiota metabolize lignans into bioactive enterolignans, such as enterodiols and enterolactones, enhancing biological activities like antioxidant and hormone-modulating effects [16]. This metabolic conversion is vital for lignans' health benefits, as enterolignans are more readily absorbed and utilized. The composition and diversity of gut microbiota significantly influence lignan metabolism, leading to variability in enterolignan production and distinct health outcomes [16]. Understanding these interactions is essential for optimizing lignan intake and maximizing therapeutic potential. Future research should explore microbiome-lignan interactions, considering genetic, dietary, and environmental factors influencing gut microbiota composition and function, to develop targeted dietary strategies enhancing lignan bioavailability and efficacy.

7.5 Mechanisms of Action and Structural Diversity

Lignans exhibit diverse biological activities due to their structural diversity and complex mechanisms of action. Their chemical structure, characterized by two phenylpropanoid units linked by a central carbon-carbon bond, determines bioactivity and therapeutic potential [9]. This configuration enables various biochemical interactions, influencing antioxidant, anti-inflammatory, and hormone-modulating properties. Lignans scavenge free radicals and reduce oxidative stress, key factors in chronic diseases like cancer and cardiovascular disorders [2]. Gut microbiota convert lignans into enterolignans, enhancing bioactivity and protective roles against hormone-dependent cancers and other chronic diseases [3]. Structural diversity is reflected in lignan subgroups, each demonstrating distinct biological activities [9]. Despite lignans' potential, precise mechanisms remain incompletely understood. Further research is needed to clarify lignan bioactivity, particularly interactions with gut microbiota producing bioactive metabolites, influencing gene expression, and cellular signaling pathways, with implications for health outcomes. Understanding variability in lignan metabolism

among individuals, influenced by diet and gut microbiome, is crucial for optimizing health benefits [16, 17, 3].

7.6 Interdisciplinary Collaboration and Emerging Applications

Advancing lignan research requires interdisciplinary collaboration among chemists, biologists, nutritionists, and medical researchers to unravel lignans' complex bioactivities and therapeutic potentials. Future research should focus on developing novel extraction methods and optimizing existing techniques to enhance lignan yield and purity from plant sources [8]. Leveraging advanced molecular and genetic techniques will enable exploration of lignan biosynthetic pathways, allowing targeted manipulation of lignan content in plants and enhancing therapeutic applications [2]. Synthesizing novel lignan derivatives and exploring their molecular mechanisms represent promising avenues for expanding lignans' therapeutic landscape. Detailed mechanism studies and clinical trials are crucial to evaluate these derivatives against resistant viral strains and other health challenges. Investigating biotechnological lignan production should ensure sustainable supply chains [6]. The interplay between dietary lignans and gut microbiota is another critical research area. Developing standardized protocols for enterolignan analysis and exploring lignan metabolic pathways in diverse populations can provide insights into health impacts and facilitate microbiota-targeted therapies [9]. Emerging lignan applications extend beyond traditional health benefits, with potential implications in nutraceuticals, pharmaceuticals, and functional foods. Expanding molecular descriptor datasets and conducting biological assays can validate lignans' therapeutic potential, paving the way for innovative health solutions [18]. Comprehensive epidemiological studies are needed to clarify lignans' health effects and explore dietary trends influencing intake [1].

8 Conclusion

Lignans emerge as pivotal bioactive compounds with substantial health benefits, notably in mitigating hormone-dependent cancers and cardiovascular ailments. Predominantly sourced from seeds, whole grains, fruits, and vegetables, these compounds exhibit robust antioxidant and hormone-modulating properties, contributing significantly to chronic disease prevention. Their transformation into bioactive enterolignans by gut microbiota underscores the importance of understanding microbiota-lignan interactions to optimize health outcomes.

Although lignans show promising anticancer potential, further exploration is necessary to unravel their mechanisms of action and to innovate lignan derivatives with enhanced pharmacological efficacy. The variation in lignan content among food sources and the complexities in standardizing analytical methods highlight the need for continuous refinement of extraction, purification, and characterization techniques. Such advancements are critical for developing comprehensive dietary guidelines and therapeutic applications.

Interdisciplinary collaborations and forward-thinking research strategies are imperative to fully exploit lignans' potential, paving the way for their integration into nutraceuticals, pharmaceuticals, and functional foods. By advancing our understanding of lignans and their synergy with gut microbiota, researchers can formulate targeted dietary approaches to amplify health benefits, thereby improving public health outcomes.

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