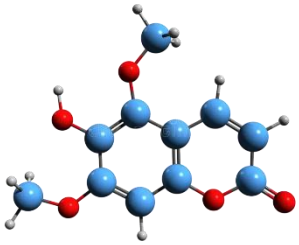
CHAPTER 10



Lignans and stilbenes: phytochemicals with anticancer and cardioprotective properties

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ABSTRACT: Polyphenols, particularly lignans and stilbenes, are widely explored for their varied therapeutic characteristics, including anticancer, cardioprotective, and antioxidant activities. These compounds are classified one the basis of the number of phenolic rings in their structure. They are biosynthesized through precisely regulated phenylpropanoid pathway, derived from L-phenylalanine or L-tyrosine. These natural phenolic compounds counteract oxidative stress, apoptosis and inflammation from an excess of reactive nitrogen and oxygen species (RNS, ROS), which have a dual function in biological systems. They do this by modifying important pathways like Nrf2 and NF-κB, which mediate the body's antioxidant defense system and inflammatory responses. They exhibit significant therapeutic potential as they may alter autophagy, apoptosis, and signaling pathways, as well as affect estrogen receptor function, to provide anti-cancer and general protection against many diseases. These phenolic compounds, such as resveratrol (RES) and enterolactone, produce significant cardioprotective effects by lowering cardiovascular risk factors, influencing lipid profiles, blood pressure, and aggregation of platelets. The gut microbiota metabolism, which transforms plant lignans into bioactive mammalian lignans, has a major impact on the health benefits of these polyphenols. There is an extensive amount of clinical evidence supporting the diverse therapeutic effects of these polyphenols in different health conditions, i.e., cardiovascular diseases, cancer, anxiety and menopausal symptoms, but further study on these compounds is required. Here we will discuss the therapeutic properties of stilbenes and lignans and their interaction with different pathways.

Polyphenolic phytochemicals found in tea, fruits, and vegetables are widely used in medicine. These plant compounds have a dual effect: they can either hinder or promote processes like apoptosis, inflammation, cell proliferation, and differentiation. Based on the number of phenolic rings, these are divided into polyphenolic acids, flavonoids, lignans and stilbene (Yi et al., 2019). These phytochemicals exhibit antioxidant, anti-inflammatory, antitumor and cardioprotective effects (Sun et al., 2019).

Numerous plant families such as Fabaceae (e.g., peanut), Pinaceae (e.g., pine), Vitaceae (e.g., grapes) and Leguminosae (e.g., beans) contain stilbene. Stilbenes are also produced by the *Yucca periculosa* tree. Stilbenes are categorized as Resveratrol (RES), piceatannol (PIC), and Pterostilbene (PTS). They defend against fungus, microbes, nematodes, and herbivores as they have antiseptic properties. Lignans are diphenolic plant products that are produced when two cinnamic acid residues dimerize. The International Union of Pure and Applied Chemistry (IUPAC) define lignans as the dimer C6-C3 coupled motifs connected at carbon 8 and 8'. Lignans are extracted out of the bark of plants and the coat of the seeds. Lignans are

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commonly found in plant kingdom (seeds, grains and vegetables) and they are also present in *Cannabis sativa* (Hazafa et al., 2022). Lignans can be classified into plant and mammalian lignans. Plant lignans, including are present in high carb food items, including grains, vegetables, and various fruits.

The highest concentration of lignans is found in the bran and outer layers of cereals. In rye, these lignans exist in a glycosidic form within the bran portion. Some lignans include whole-grain cereals, nuts, vegetables, fruits, and legumes (Landete, 2012). Over the past 20 years, the use of plant-based medicines has increased significantly due to their beneficial effects on the body, high affinity for a variety of cellular targets, and reduced harm to normal cells (Seca and Pinto, 2018).

Phytochemicals like stilbenes and lignans are some of the polyphenols that are readily available and have the potential to be used to inhibit different types of cancers such as prostate, liver, breast, colorectal, and lung cancer. These polyphenolic phytochemicals are water-soluble and contain more than two hydroxyl (OH) groups in an aromatic ring (Hazafa et al., 2020; Manach et al., 2004).

Some studies indicated that stilbenes and lignans have anticancer effects, they can induce apoptotic effects, stop cell cycle (S/G1/G2 phase), eliminate toxins, and prevent from oxidation. Moreover, they are involved in the activation of different pathways like MAPKs (mitogen-activated protein kinases), activation of protein 1, inhibition/activation of signal transmission and transcription factors (Nrf2 and NF-κB) and division of cell (Fantini, 2015; Niedzwiecki et al., 2016). This chapter discusses the different health advantages of lignans and stilbenes, as well as their derivatives. Their impact on cholesterol, molecular structure, biosynthesis, antioxidant mechanisms, PI3K, NF-kB, and MAPK pathways, and cancer, along with estrogenic and cardioprotective roles and gut microbiota metabolism, are all covered in this chapter.

STRUCTURE AND BIOSYNTHESIS

Structural characteristics

Over 8000 phenolic structures have been identified. Polyphenols are classified according to the number and presence of the phenol rings. Aromatic ring with at least two hydroxyl (OH) groups are present in polyphenols. Stilbenoids are hydroxylated stilbene derivatives. Stilbene's basic structural framework consists of two aromatic rings connected by a methylene bridge. The structure contains double bond that does not permit free rotation, and and only two configurations, *cis* and *trans*, exist (Fig. 1) (Valletta et al., 2021). The *trans* isomers tend to be more stable, more prevalent and more biologically active than the *cis* ones. Nature has manufactured a intricate arrangement of hydroxyl groups from these simple structures through which these groups are able to form dimers, trimmers and bigger polymers, when replaced with methyl, methoxy, sugar or other residues (Xiao et al., 2008).

Lignans are a vast non-flavonoid class of dimeric phenylpropanoids. They are broadly distributed in vascular plants. Lignans are two monomers of phenylpropanoid connected by a C8-C8’ bond. Classical lignans exhibited dimeric forms where two propenylphenyl units were linked through a

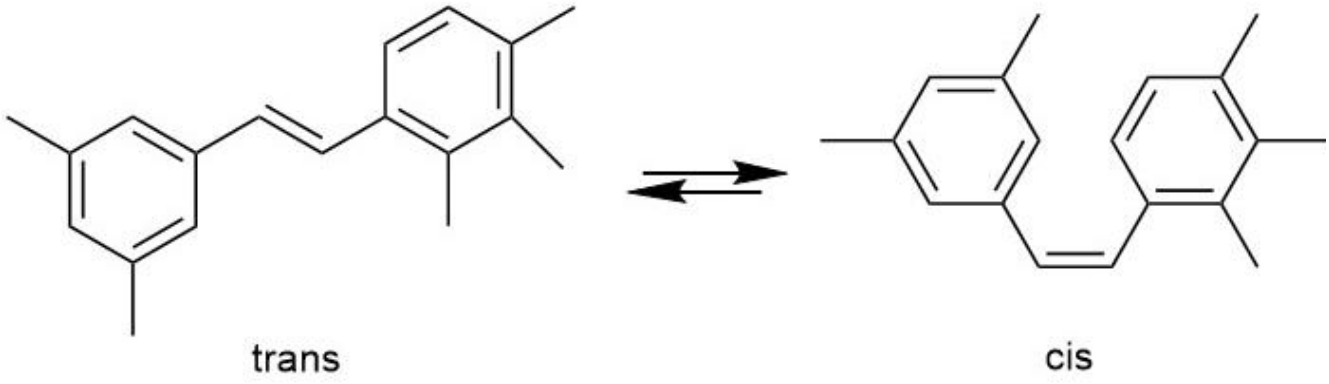

Fig 1. *trans* and *cis* forms of stilbene

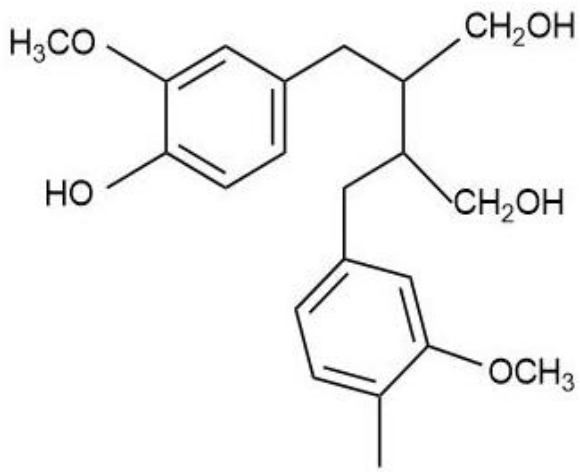

Fig 1. General structure of lignans

beta β, β' (otherwise 8-8') linkage having a different pattern of substitution in the aromatic moieties and a different level of oxidation in the side-chain (Teponno, 2016). General structure of lignans has been illustrated in Fig. 2.

KEY BIOSYNTHETIC PATHWAYS: SHIKIMATE AND PHENYLPROPANOID ROUTES

The biosynthesis of stilbenes and stilbenoids occurs in the phenylpropanoid pathway that also biosynthesizes many primary and secondary metabolites such as flavonoids, lignans, coumarins, hydrolyzable tannins, monolignols, and lignins (Sharma et al., 2019). The aromatic amino acid L-phenylalanine is the most important starting molecule of the phenylpropanoid pathway and is produced by the shikimate pathway. The carbon channeling of the primary metabolism into the phenylpropanoid secondary metabolism starts with the nonoxidative deamination of L-phenylalanine to trans-cinnamic acid by phenylalanine ammonia-lyase (PAL). PAL is rich in plants (Emiliani et al., 2009), and it is certainly the most investigated enzyme of secondary metabolism in plants (Lv et al., 2017).

Cinnamate-CoA ligase can attach cinnamic acid to a molecule of coenzyme A to produce cinnamoyl-CoA. Alternatively, cinnamic acid may be converted to p-coumaric acid by cinnamate 4-hydroxylase (C4H), a cytochrome P450 enzyme (EC). A few plants (primarily monocots, but also dicots) also have a bifunctional phenylalanine / tyrosine ammonia-lyase (PTAL) that effectively deaminates both L-phenylalanine (PAL activity) and L-tyrosine (TAL activity) (Barros & Dixon, 2020). These plants have the ability to make p-coumaric acid directly with L-tyrosine as a substrate without the need of L-phenylalanine and C4H. The enzyme 4-coumarate-CoA ligase (4CL) couples p-coumaric acid to a molecule of CoA to form p-coumaroyl-CoA, an active intermediate in many general phenylpropanoid pathways (Ferrer et al., 2008).

Examples of Lignans and Stilbenes

Stilbenes possess metabolites with a general structure and exhibit a similar biological property. Each stilbene exhibits a unique behavior, as pharmacokinetic studies have shown with the absorption, distribution, metabolism and excretion processes. Some plant lignans are indispensable which are converted into mammalian lignans by gut microflora like matairesinol and secoisolariciresinol transformed into enterolactone and enterodiol. Lignans have been found to have anticancer properties due to their pro-apoptotic, mild estrogenic, and anti-angiogenic effects.

ANTIOXIDANT AND CYTOPROTECTIVE MECHANISMS

In the past decades, the studies on free radicals and their effect on living things have acquired much interest. The reactive oxygen species (ROS) and reactive nitrogen species (RNS) are very vital for the defense and cell signaling processes. Nevertheless, reactive species overproduction may induce oxidative damage that may damage lipids, and proteins, and start a chain reaction that lead to DNA damage. Substances like antioxidants that safeguard living things against excess oxidation via ensuring that the levels of ROS remain non-toxic. Natural phenolic compounds represent a significant group of antioxidants, vastly used in industries like biopharmaceutical and nutritional, and are regarded as health-friendly phytochemicals (Hamadouche et al., 2021).

Antioxidant enzymes can be activated by stilbenes, which is a form of defense against oxidative stress (Reinisalo et al., 2015). MAPK, NF-kB and activator protein 1, are transcription

factors that contribute to inflammation, are inhibited by stilbenes that have anti-inflammatory properties (Dvorakova & Landa, 2017). Flaxseeds have a high level of stilbene. Stilbenes are also reported to prevent cancer (Wu et al., 2021). The medicinal properties of stilbenes are explained by the unique features of their chemical structure. For instance, their ability to oligomerize leads to increased contact with elements of the immune system. Additionally, the presence of two methoxy groups (PTS) allows for a potent antioxidant mechanism, while an oxidizable catechol group (PIC) may also enhance their anti-inflammatory effects (Zhan et al., 2021; Al-Khayri et al., 2023).

Research has explored how the molecular action of stilbenes affects nuclear factor pathways, which in turn regulates the expression of pro-inflammatory cytokines and reactive oxygen species (ROS) (Reinisalo et al., 2015; Farkhondeh et al., 2020). Humans have adaptable bodies that react to external and internal stress. NF-κB and Nrf2 are the major components of the protective system of our body, which triggers the antioxidants to counteract the ROS. The NF-κB pathway is initiated when the IκB kinase complex connects with the NF-κB transcription factor. This connection activates NF-κB, which then regulates genes involved in inflammation and immune responses. When this signaling pathway is activated, it increases proinflammatory cytokines, adipokines, and others, along with the increase in the level of ROS; therefore, it is related to some severe and long-lasting disorders (Bhandari et al., 2021; De Mendonca et al., 2022).

Lignans are also capable of reducing the growth of inflammatory cells and the generation of nitric oxide. Lignans are the compounds that have ability to block the NF-κB, which results in a decrease of pro-inflammatory cytokine numbers. According to a study, the lignan's consumption is negatively associated with blood vessel inflammation and impaired vessel function. In short, human bodies have complex mechanisms to deal with stress; NF-κB is the driver of inflammation and Nrf2 is a leading target in the for various innovative treatments against a diversity of syndromes (Mendonca et al., 2024). Lignans and stilbenes have the ability to regulate these pathways.

ANTICANCER ACTIVITIES AND MECHANISTIC INSIGHTS

Autophagy is vital for cell life and aid cells to survive under stressful circumstances like oxygen deprivation, energy scarcity and nutritional constraint. It directs cytoplasmic components for lysosome breakdown or recycling, such as damaged proteins and organelles. Autophagy assists in maintaining energy homeostasis, cellular metabolism, as well as cell protection, and is vital in development, differentiation, and regulation of immunity (Eskelinen, 2019; Siedlecka-Kroplewska et al., 2025). Apoptosis refers to a form of controlled cell death that is an essential process for homeostasis (Yuan & Ofengeim, 2024). Apoptosis is a process that is induced by a number of factors such as UV radiation, oxidative stress, and cell type. It consists of initiation, effector and destruction stages. Initiation stage indicates the death of cell, effector initiates the execution and destruction phase destroys cellular structures (Moyer et al., 2025).

Autophagy has a dual role in carcinogenesis, either preventing or promoting it. Defects in the autophagy genes can also predispose tumors. Autophagy is known to contribute to homeostasis between healthy cells and malignant cells. The autophagy in cell death is contextual and may be characterized as autophagy-dependent, autophagy-mediated or autophagy-associated cell death (Denton & Kumar, 2019). Cell death that depends on autophagy as a controlled routine that does not rely on apoptosis or necrosis and is initiated by autophagic machinery (according to Nomenclature Committee). Biological and pharmacological restriction of macro-autophagy can slow down this process and prevent cell death (Galluzzi et al., 2017; Galluzzi et al., 2018).

The PAM (P13k/AKT/mTOR) path is the main network of transmission within larger cells of eukaryotes. It contributing to cell growth, cell survival or cell division in response to outside factors. It is regulated by PI3K and AKT, with external factors in the growth of transcribable transcription factors. Dysregulation of this pathway stimulates cancer development and progression, and PAM related abnormalities are known to occur in 50% of tumors (Glaviano et al., 2023). MAPK

signaling is responsible for orthodontic motions, basic cellular homeostasis, and cellular responses during innate immune response regulation (Yong et al., 2021). This is important for bone/cement mineralization and modulation of orthodontic ligaments in periodontal ligaments (Li et al., 2012). The Wnt/β-catenin signaling pathway involves important molecular cascades for cell metabolism and bone remodeling (Clevers & Nusse, 2012; Yong et al., 2022).

The anticancer properties of stilbenes appear to depend on their ability to obstruct various signaling pathways involved in cancer development. Stilbenes also inhibit the metabolic activation of pro-carcinogens by affecting some isoforms of cytochrome P450. RES modulates signaling pathways such as MAPK, which facilitates apoptosis and halts the cell cycle of cancer cells. In the context of skin cancer, it reduces factors linked to cell proliferation and survival. Conversely, in gastric cancer, it halts the cell cycle during G1 stage rather than triggering apoptosis. Additionally, RES curbs cell proliferation by enhancing MIC-1 expression while diminishing NF-κB expression. It has shown efficacy in the treatment of epidermoid carcinoma and gastric adenocarcinoma cells by halting the cell cycle during G1 stage (Yang et al., 2013; Hazafa et al., 2022).

RES has demonstrated anti-proliferative properties and the ability to initiate apoptosis in various cancerous cells, related to ovarian cancer, prostate cancer and breast cancer and others (Qin et al., 2022; Dong et al., 2024). The substance exhibits immune system regulatory effects which could prove useful for cancer immunotherapy treatments (Deng et al., 2020). RES activates natural killer cells, which are essential immune system components. The treatment helps produce more interferon-gamma (IFN-γ) which serves as a vital cytokine for cancer cell destruction. The research shows that RES stops breast cancer cell growth (MDA-MB-231) through its effect on macrophage polarization and STAT3 pathway inhibition. The results suggest that RES might function as a useful component for cancer immunotherapy treatments (Morvan & Lanier, 2016). The treatment with RES prevented colon cancer cells (HT-29) from undergoing division which eventually led to cell death.

RES triggered oxidative stress, which played a role in regulating apoptosis and autophagy. The application of RES can induce autophagy that promotes cell survival. Furthermore, in ovarian cancer cells, RES can initiate cell death (autophagy or apoptosis), which can result in the buildup of cells during the S phase. The pan-caspase inhibitor Z-VAD-FMK blocked the cytochrome c that was released from mitochondria. Additionally, inhibitors like chloroquine (CQ), along with the suppression of autophagy-related gene 5 (ATG5) expression have been shown to safeguard cells from the cell death triggered by RES (Siedlecka-Kroplewska et al., 2025).

Lignans are structurally related to estradiol, which is the active form of estrogen. Such lignans are able to interact with estrogen receptors and possess moderate estrogenic or anti-estrogenic activities (Plaha et al., 2022). *In vivo* studies have shown that lignans possess the ability to modulate estrogen receptor signaling (Penttinen-Damdimopoulou et al., 2009) and inhibit aromatase which is a potential aid in breast cancer (Adams and Chen, 2009). The lignans occupy the same sites on the cells as estrogen potentially decreasing the impact of estrogen by removing it from the cells (Dhirhi et al., 2016). Lignans can also prevent malignancies that are dependent on estrogen like breast cancer. A study revealed that flaxseed diets elevated the urine 2-OH estrogen and urine 2/16-OHE1 ratio. Comparative analyses revealed a positive relationship between urinary lignan defecation and estrogen metabolites in flaxseed and soya diet (Haggans et al., 1999; Brooks et al., 2004).

A higher intake of lignans can lower the risk of hormone-based cancers, including breast, colon, prostate gland, and esophageal cancers. Other studies have also revealed cancer-protective benefits. According to research based on an animal model, secoisolariciresinol diglucoside can delay the development of mammary cancer, encourage cell differentiation in mammary glands, and result in advantageous changes to the mammary gland during breastfeeding or pregnancy, including tissue remodeling (Adolphe et al., 2010). Anticarcinogenic effects may be present in postmenopausal breast cancer patients, as they have reduced levels of enterolactone compared to healthy cases. Overall survival rates have improved in postmenopausal breast cancer cases with high

serum enterolactone levels (Buck et al., 2011). A critical review conducted by Velentzis et al., (2009) found that post-menopausal women who consume a lot of plant lignans had a decreased possibility of breast carcinoma. This suggests that eating plant lignans may help women by lowering their danger of cancer like breast cancer.

CARDIOPROTECTIVE EFFECTS

A group of chronic illnesses that affect the heart and blood vessels are called cardiovascular diseases (CVDs). They are frequently caused by a combination of variables, including age, genetic history, obesity, asthma, and metabolic syndrome (Pourbagher-Shahri et al., 2021). Peripheral arterial disorder, cardiac arrest, coronary heart disorders, cerebrovascular disease, cardiomyopathies, as well as other cardiovascular disorders are CVD's examples (Gal et al., 2021). Globally, CVDs are the primary cause of death for people (Di Cesare et al., 2024). However, Cardiomyopathy and other cardiovascular problems can be alleviated by phenolic acids.

In streptozotocin-induced diabetic rats, ellagic acid, a derivative of lignans, showed cardioprotective benefits. It lowers the cardiac oxidative stress and dyslipidemia, enhances glycaemia management, and boosts insulin secretion. Ellagic acid inhibits lipid peroxidation and lowers plasma lipid levels (Saibabu et al., 2015). Supplementing with lignan likely lowers blood pressure and cholesterol.

An animal study states that fat-rich food that contains secoisolariciresinol diglucoside can lower the overall triglycerides content of liver and serum, cholesterol, insulin and leptin levels that decreases the fat gain compared to control group (Fukumitsu et al., 2008). Higher intake of lignans drops the danger of cardiovascular or other chronic illnesses. Consumption of lignans is negatively associated with the onset of cardiovascular disease and hypertension, particularly in menopausal women and aged men. Additionally, via altering the processes of glucose metabolism and triacylglyceride and secoisolariciresinol diglucoside has been demonstrated to have cardioprotective properties (Zhang et al., 2008). Enterolactone levels in the blood are associated with a reduced risk of CVDs as they can regulate the vascular endothelial growth component, production of hemoglobin oxygenase-1 and endothelial nitric oxide synthase, which promote cardiac ischemia (Adolphe et al., 2010). According to Milder et al., (2006), there was a substantial and negative correlation between matairesinol (a lignan) intake and cardiovascular illnesses, mortality from all causes and coronary cardiac disorders. Moreover, men in top quartile of plasma enterolactone were shown to have a considerably decreased possibility of incidental cardiac disruption (Vanharanta et al., 2003).

The equilibrium between vasoconstrictors (nitric oxide and endothelin) and vasodilators helps RES in enhancing thrombus resistance and stopping plaque formation in human vascular endothelial cells (Colica et al., 2018). Blood cells called platelets aid in the maintenance of blood vessels, however excessive platelet activity can result in thrombosis, which is a cause of cardiovascular disorders. A serine protease thrombin controls blood coagulation and platelet aggregation. Protease-activated receptors (PARs) function as a specific group of platelet G protein-coupled receptors (GPCRs) which trigger platelet activation and thrombus formation (Peng et al., 2025). Scientists created new RES compounds during 2023 to test their anti-platelet action. The research demonstrates that RES could operate as an antiplatelet drug because methylation of RES molecules seems to enhance their antiplatelet effects (Fragopoulou et al., 2023).

Trans-3,3′,4,5′-tetramethoxystilbene (3,3′,4,5′-TMS) and trans-3,4′,5-trimetoxystilbene (3,4′,5-TMS) were studied in 2021 for their anti-inflammatory effects in lipopolysaccharide-induced (LPS) macrophages as an in vitro model. The findings indicated that LPS stimulation dramatically increases the release of nitric acid, whereas 3,3′,4,5′-TMS and 3,4′,5-TMS dose-dependently inhibit the release of nitric oxide in LPS cells. It is possible that 3,3′,4,5′ TMS and 3,4′,5 TMS could reduce swelling initiated by LPS via deactivating the NF-κB and MAPK signaling pathways. Accordingly, these two substances can treat atherosclerosis by acting on the nitric oxide and anti-inflammatory pathways (Zhou et al., 2021).

Studies have shown that, depending on the quantity of methoxy groups and the particular substituent location, methoxylated derivatives of RES are useful in treating cardiovascular disorders

(CVD). The compounds contain anti-inflammatory properties and antioxidant effects which also enable them to manage signaling pathways and stop platelets. These compounds show potential as candidates for additional research because they possess basic structures along with enhanced performance characteristics. According to Peng et al., (2025), RES activity levels will increase when additional methoxy groups are introduced which leads to unexpected results.

CLINICAL EVIDENCE

Scientists have conducted extensive research on Stilbenes during the past two decades. The scientific community has devoted extensive research to RES which stands as the most thoroughly examined Stilbene compound. The scientific community has established through 240 clinical trials and essential fundamental research that RES (*trans*) exhibits multiple pharmacological activities, including anti-inflammatory (Banez et al., 2020), anti-oxidant (Gülçin, 2010), anti-carcinoma (Vervandier-Fasseur & Latruffe, 2019; Ahmadi & Ebrahimzadeh, 2020), estrogenic (Yang et al., 2020), neuroprotective (Sun et al., 2010), cardioprotective (Cheng et al., 2020), anti-atherosclerotic (Seo et al., 2019) and anti-obesity properties. Other monomeric stilbenes have also gained a lot of interest recently. PIC has demonstrated health-promoting qualities that are comparable to or even stronger than those of RES (Piotrowska et al., 2012).

Production of stilbenes on a large scale by using different techniques is of great importance because of their potential usage in pharmaceutical, cosmetics, and nutraceutical industries. RES (*trans*) in global market, is predicted to nearly double over the following six years, from 58 million USD to 99.4 million USD, between 2020-2026. One study found that menopausal women with anxiety and depression who were treated with RES (25mg for 12 weeks) experienced a decrease in both physical and psychological anxiety (Davinelli et al., 2017). RES showed anxiolytic effects in treating stress/anxiety in 70 patients with mild hepatic encephalopathy (Malaguarnera et al., 2018). RES also decreased harmful signs of schizophrenia in clinical settings. Clinical evidence is likewise insufficient to support RES's potential therapeutic benefit in neurodegenerative diseases (Yadav et al., 2022).

Another study found that after consuming 30 mg flaxseed/day for a month, there was an opposite relationship among tumor tissues, enterolactones and enterolignans in 147 participants with prostate cancer (Azrad et al., 2013). According to a study performed on 58,049 postmenopausal French women with breast cancer, consuming more than 1,395 µg of flaxseed per day for six weeks successfully decreased the incidence of breast cancer by 18–24% (Touillaud et al., 2007).

In a study, forty-five women with menopause who took 50 milligrams of lignan per day for a year saw an 80% decrease in the possibility of breast cancer (Fabian et al., 2010). The curative potential of stilbenes in neurological and neuropsychiatric disorders, including their safety, tolerability, pharmacokinetic profile, and interactions with gut microbiota, requires further investigation. Research should also evaluate their potential to lessen side effects and their effectiveness as an adjuvant therapy to traditional central nervous system (CNS) medications. To confirm the effects of stilbenes in CNS diseases, more multidirectional research and extensive clinical studies are required (Socała et al., 2024).

CONCLUSION

Polyphenolic phytochemicals, particularly lignans and stilbenes, possess anti-oxidant, anti-inflammatory, and anti-cancer abilities, that make them useful in treating various illnesses. These phytochemicals, which are classified by their number and presence of phenol rings, are produced by the phenylpropanoid pathway, which protects biological systems from excessive oxidation. Lignans attach to estrogen receptors and have a mild estrogenic action, which may decrease the risk of hormone-based carcinoma. Stilbenes, such as RES, exhibit anticancer properties through cell cycle arrest, apoptosis, immunomodulatory action, and inhibiting signaling pathways like MAPK. Stilbenes, most notably resveratrol (RES), are well-documented to modulate oxidative stress and autophagy to inhibit cancer cells. Potential cardiovascular advantages are demonstrated by these via a number of pathways, like antioxidant activity, anti-inflammatory actions, and modification of glucose or lipid metabolism. Therefore, lignans and stilbenes possess significant

anti-cancer and cardioprotective properties and may provide many health benefits to humans and animals.

REFERENCES

Adams LS & S Chen 2009. Phytochemicals for breast cancer prevention by targeting aromatase. Frontiers in Bioscience 14:3846-63.

Adolphe JL, SJ Whiting, BHJ Juurlink, et al., 2010. Health effects with consumption of the flax lignin Secoisolariciresinol Diglucoside. British Journal of Nutrition 103:929-38.

Ahmadi R & MA Ebrahimzadeh, 2020. Resveratrol-A comprehensive review of recent advances in anticancer drug design and development. European Journal of Medicinal Chemistry 200:112356.

Al-Khayri JM, R Mascarenhas, HM Harish, et al., 2023. Stilbenes, a Versatile Class of Natural Metabolites for Inflammation. An Overview. Molecules 28:3786.

Azrad M, RT Vollmer, J Madden, et al., 2013. Flaxseed-derived enterolactone is inversely associated with tumor cell proliferation in men with localized prostate cancer. Journal of Medicinal Food 16:357-60.

Banez MJ, MI Geluz, A Chandra, et al., 2020. A systemic review on the antioxidant and anti-inflammatory effects of resveratrol, curcumin, and dietary nitric oxide supplementation on human cardiovascular health. Nutrition Research 78:11-26.

Barros J & RA Dixon, 2020. Plant phenylalanine/tyrosine ammonia-lyases. Trends in Plant Science 25:66-79.

Bhandari R, G Khanna, D Kaushik, et al., 2021. Divulging the intricacies of crosstalk between NF-Kb and Nrf2-Keap1 pathway in neurological complications of COVID-19. Molecular Neurobiology 58:3347-61.

Brooks JD, WE Ward, JE Lewis, et al., 2004. Supplementationwith faxseed alters estrogen metabolism in postmenopausal women to a greater extent than does supplementation with an equal amount of soy. The American Journal of Clinical Nutrition 79:318-25.

Buck K, A Vrieling, AK Zaineddin, et al., 2011. Serum enterolactone and prognosis of postmenopausal breast cancer. Journal of Clinical Oncology 29:3730-8.

Cheng CK, JY Luo, CW Lau, et al., 2020. Pharmacological basis and new insights of resveratrol action in the cardiovascular system. British Journal of Pharmacology 177:1258-77.

Clevers H & R Nusse, 2012. Wnt/beta-catenin signaling and disease. Cell 149:1192-1205.

Colica, C, M Milanović, N Milić, et al., 2018. A systematic review on natural antioxidant properties of resveratrol. Natural Product Communications 13:1195-1203.

Davinelli S, G Scapagnini, F Marzatico, et al., 2017. Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized, placebo-controlled study. Maturitas 96:77-83.

De Mendonca ELSS, MBT Fragoso, JM de Oliveira, et al., 2022. Gestational diabetes mellitus: the crosslink among inflammation, nitroxidative stress, intestinal microbiota and alternative therapies. Antioxidants 22:115-29.

Deng LJ, M Qi, N Li, et al., 2020. Natural products and their derivatives: Promising modulators of tumor immunotherapy. Journal of Leukocyte Biology 108:493-508.

Denton D & S Kumar, 2019. Autophagy-dependent cell death. Cell Death Differentiation 26:605-16.

Dhirhi N, R Shukla, NB Patel, et al., 2016. "Lignan"-antioxidant of linseed. Plant Archive 6:12-7.

Di Cesare M, P Perel, S Taylor, et al., 2024.The heart of the world. Global Heart 19:11.

Dong Q, A Zheng, H Zhai, et al., 2024. Resveratrol mediated the proliferation and apoptosis of gastric cancer cells by modulating the PI3K/Akt/P53 signaling pathway. Biochemical and Biophysical Research Communications 723:150186.

Dvorakova M & P Landa, 2017. Anti-inflammatory activity of natural stilbenoids: a review. Pharmacological Research 124:126-45.

Emiliani G, M Fondi, R Fani, et al., 2009. A horizontal gene transfer at the origin of phenylpropanoid metabolism: A key adaptation of plants to land. Biology Direct 4:7.

Eskelinen EL, 2019. Autophagy: Supporting cellular and organismal homeostasis by self-eating. International Journal of Biochemistry 111:1-10.

Fabian CJ, BF Kimler, CM Zalles, et al., 2010. Reduction in Ki-67 in benign breast tissue of high-risk women with the lignan secoisolariciresinol diglycoside. Cancer Prevention Research 3:1342-50.

Fantini M, 2015. In vitro and in vivo antitumoral effects of combinations of polyphenols, or polyphenols and anticancer drugs: perspectives on cancer treatment. International Journal of Molecular Sciences 16:9236-82.

Farkhondeh T, SL Folgado, AM Pourbagher-Shahri, et al., 2020. The therapeutic effect of resveratrol: Focusing on the Nrf2 signaling pathway. Biomedicine & Pharmacotherapy 127:110234.

Ferrer JL, MB Austin, C Stewart, et al., 2008. Structure and function of enzymes involved in the biosynthesis of phenylpropanoids Plant Physiology and Biochemistry 46:356-70.

Fragopoulou E, K Gkotsi, F Petsini, et al., 2023. Synthesis and biological evaluation of resveratrol methoxy derivatives. Molecules 28:145547.

Fukumitsu S, K Aida & N Ueno, 2008. Flaxseed lignin attenuates high-fat diet-induced fat accumulation and induces adiponectin expression in mice. British Journal of Nutrition 100:669-76.

Gal R, L Deres, K Toth, et al., 2021. The effect of resveratrol on the cardiovascular system from molecular mechanisms to clinical results. International Journal of Molecular Biology 22:10152.

Galluzzi L, EH Baehrecke, A Ballabio, et al., 2017. Molecular definitions of autophagy and related processes. The EMBO Journal 36:1811-36.

Galluzzi L, I Vitale, SA Aaronson, et al., 2018. Molecular mechanisms of cell death: Recommendations of the Nomenclature Committee on Cell Death. Cell Death Differentiation 25:486-541.

Glaviano A, AS Foo, HY Lam, et al., 2023. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Molecular cancer 22:138.

Gülçin I, 2010. Antioxidant properties of resveratrol: A structure–activity insight. Innovative Food Science & Emerging Technologies 11:210-8.

Haggans CJ, AM Hutchins, BA Olson, et al., 1999. Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. Nutrition and Cancer 33:188-195.

Hamadouche S, A Ounissi, K Baira, et al., 2021. Theoretical evaluation of the antioxidant activity of some stilbenes using the density functional theory. Journal of Molecular Structure 122:129496.

Hazafa A, 2020. The role of polyphenol (Flavonoids) compounds in the treatment of cancer cells. Nutrition and Cancer 72:386-97.

Hazafa A, MO Iqbal, U Javaid, et al., 2022. Inhibitory effect of polyphenols (phenolic acids, lignans, and stilbenes) on cancer by regulating signal transduction pathways: A review. Clinical and Translational Oncology 24:432-45.

Landete JM, 2012. Plant mammalian Lignans: a review of source, intake, metabolism, intestinal bacteria, health. Food Research International 46:410-24.

Li Q, MS Valerio & KL Kirkwood, 2012. MAPK usage in periodontal disease progression. Journal of Signal Transduction 2012:308943.

Lv C, G Zhao & Y Ning, 2017. Interactions between plant proteins/enzymes and other food components, and their effects on food quality. Critical Reviews in Food Science and Nutrition 57:1718-28.

Malaguarnera G, M Pennisi, G Bertino, et al., 2018. Resveratrol in patients with minimal hepatic encephalopathy. Nutrients 10:329.

Manach C, A Scalbert, C Morand, et al., 2004. Polyphenols: food sources and bioavailability. The American Journal of Clinical Nutrition 79:727-47.

Mendonca EL, JA Xavier, MB Fragoso, et al., 2024. E-Stilbenes: General chemical and biological aspects, potential pharmacological activity based on the Nrf2 pathway. Pharmaceuticals 17:22-32.

Milder IEJ, EJM Feskens, ICW Arts, et al., 2006. Intakes of 4 dietary Lignans and cause-specific and all-cause mortality in the Zutphen elderly study. The American Journal of Clinical Nutrition 84:400-5.

Morvan MG & LL Lanier, 2016. NK cells and cancer: You can teach innate cells new tricks. Nature Reviews Cancer 16:7-19.

Moyer A, K Tanaka & EH Cheng, 2025. Apoptosis in cancer biology and therapy. Annual Review of Pathology 20:303-28.

Niedzwiecki A, MW Roomi, T Kalinovsky, et al., 2016. Anticancer Efficacy of Polyphenols and Their Combinations. *Nutrients* 2016:552.

Peng Y, X Zheng, S Zhang, et al., 2025. Advances in the activity of resveratrol and it's derivatives in cardiovascular diseases. Archiv der Pharmazie 358:2400865.

Penttinen-Damdimopoulou PE, KA Power, TT Hurmerinta, et al., 2009. Dietary sources of lignans and isofavones modulate responses to estradiol in estrogen reporter mice. Molecular Nutrition & Food Research 53:996-1006.

Piotrowska H, M Kucinska & M Murias, 2012. Biological activity of piceatannol: Leaving the shadow of resveratrol. Mutation Research 75:60-82.

Plaha, NS, S Awasthi, A Sharma, et al., 2022. Distribution, biosynthesis and therapeutic potential of lignans. 3Biotech 12:255.

Pourbagher-Shahri AM, T Farkhondeh, M Ashrafizadeh, et al., 2021. Curcumin and cardiovascular diseases: focus on cellular targets and cascades. Biomedicine & Pharmacotherapy 136:111214.

Qin X, H Luo, Y Deng, et al., 2022. Resveratrol inhibits proliferation and induces apoptosis via the Hippo/YAP pathway in human colon cancer cells. Biochemical and Biophysical Research Communications 636:197-204.

Reinisalo M, A Karlund, A Koskela, et al., 2015. Polyphenol stilbenes: molecular mechanisms of defence against oxidative stress and aging-related diseases. Oxidative Medicine and Cellular Longevity 2015:340520.

Saibabu V, Z Fatima, LA Khan, & S Hameed, 2015. Therapeutic potential of dietary phenolic acids. Advances in Pharmacological Sciences 82:35-9.

Seca AM & DC Pinto, 2018. Plant secondary metabolites as anticancer agents: successes in clinical trials and therapeutic application. International Journal of Molecular Sciences 19:263.

Seo Y, J Park, W Choi, et al., 2019. Antiatherogenic effect of resveratrol attributed to decreased expression of ICAM-1 (Intercellular adhesion Molecule-1) mechanistic link from focal adhesion to monocyte adhesion. Arteriosclerosis, Thrombosis, and Vascular Biology 39:675-84.

Sharma A, B Shahzad, A Rehman, et al., 2019. Response of phenylpropanoid pathway and the role of polyphenols in plants under abiotic stress. Molecules 24:2452.

Siedlecka-Kroplewska K, Z Kmiec & M A Zmijewski, 2025. The interplay between autophagy and apoptosis in the mechanisms of action of stilbenes in cancer cells. Antioxidants 14:339.

Socała K, E Zmudzka, K Lustyk, et al., 2024. Therapeutic potential of stilbenes in neuropsychiatric and neurological disorders: A comprehensive review of preclinical and clinical evidence. Phytotherapy Research 38:1400-61.

Sun AY, Q Wang, A Simonyi, et al., 2010. Resveratrol as a therapeutic agent for neurodegenerative diseases. Molecular Neurobiology 41:375-83.

Sun L, R Zhou, W Zhang, H M Guo, et al., 2019. Modulation of multiple signaling pathways of the plant-derived natural products. Frontiers in Oncology 9:1153.

Teponno RB, S Kusari & M Spiteller, 2016. Recent advances in research on lignans and neolignan. Natural Products Report 33:1044-92

Touillaud MS, A C Thiébaut, A Fournier, et al., 2007. Dietary lignan intake and postmenopausal breast cancer risk by estrogen and progesterone receptor status. Journal of National Cancer Institute 99:475-86.

Valletta A, LM Iozia & F Leonelli, 2021. Impact of environmental factors on stilbene biosynthesis. Plants 10:61-90.

Vanharanta M, S Voutilainen, T Rissanen, et al., 2003. Risk of cardiovascular disease-related, all-cause death according to serum concentrations of enterolactone: Kuopio ischaemic

heart disease risk factor study. Archives of Internal Medicine 163:1099-1104.
Velentzis LS, MM Cantwell, C Cardwell, et al., 2009. Lignans and breast cancer risk in pre-and post-menopausal women: meta-analyses of observational studies. British Journal of Cancer 100:1492-8.
Vervandier-Fasseur D & N Latruffe, 2019. The potential use of resveratrol for cancer prevention. Molecules 24:4506.
Wu Y, H Wang, Y Wang, 2021. Comparison of lignans and phenolic acids in different varieties of germinated flaxseed (*Linum usitatissimum* L.). International Journal of Food Science and Technology 56:196-204.
Xiao K, H J Zhang, L J Xuan, et al., 2008. Stilbenoids: Chemistry and Bioactivities. Studies in natural products chemistry 34:453-646.
Yadav E, P Yadav, MMU Khan, et al., 2022. Resveratrol: A potential therapeutic natural polyphenol for neurodegenerative diseases associated with mitochondrial dysfunction. Frontiers in Pharmacology 13:922232.
Yang MF, X Yao, LM Chen, et al., 2020. Synthesis and biological evaluation of resveratrol derivatives with anti-breast cancer activity. Archiv der Pharmazie 353:200044.
Yang Q, B Wang, W Zang, et al. 2013. Resveratrol inhibits the growth of gastric cancer by inducing g1 phase arrest and senescence in a sirt1-dependent manner. PLoS ONE 8:70627.
Yi J, S Li, C Wang, et al., 2019. Potential applications of polyphenols on main ncRNAs regulations as novel therapeutic strategy for cancer. Biomedicine and Pharmacotherapy 113:108703.
Yong J, J Bremen, S Groeger, et al., 2021. Hypoxia-inducible factor 1-alpha acts as a bridge factor for crosstalk between ERK1/2 and caspases in hypoxia-induced apoptosis of cementoblasts. Journal of Cellular and Molecular Medicine 25:971-73.
Yong J, S Groeger, J Meyle, et al., 2022. MAPK and β-Catenin signaling: Implication and interplay in orthodontic tooth movement. Frontiers in Bioscience-Landmark 27:54.
Yuan J & DA Ofengeim, 2024. guide to cell death pathways. Nature Reviews Molecular Cell Biology 25:379-95.
Zhan J, T Hu, J Shen, et al., 2021. Pterostilbene is more efficacious than hydroxystilbenes in protecting liver fibrogenesis in a carbon tetracholride-induced rat model. Journal of Functional Foods 84:104604.
Zhang W, X Wang & Y Liu, 2008. Dietary flaxseed lignin extract lowers plasma cholesterol and glucose concentrations in Hypercholesterolaemic subjects. British Journal of Nutrition 99:130-219.
Zhou C, X Zhang, CC Ruan, et al., 2021. Two methoxy derivatives of resveratrol, 3, 3′, 4, 5′-tetramethoxy-trans-stilbene and 3, 4′, 5-trimethoxy-trans-stilbene, suppress lipopolysaccharide-induced inflammation through inactivation of MAPK and NF-κB pathways in RAW 264.7 cells. Chinese Medicine 16:69-78.