Journal Pre-proof

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PII: S0924-2244(20)30638-5

DOI: https://doi.org/10.1016/j.tifs.2020.10.015

Reference: TIFS 2992

To appear in: *Trends in Food Science & Technology*

Received Date: 24 December 2019

Revised Date: 26 July 2020

Accepted Date: 4 October 2020

Please cite this article as: Soleymani, S., Habtemariam, S., Rahimi, R., Nabavi, S.M., The what and who of dietary lignans in human health: Special focus on prooxidant and antioxidant effects, *Trends in Food Science & Technology* (2020), doi: https://doi.org/10.1016/j.tifs.2020.10.015.

The what and who of dietary lignans in human health: Special focus on prooxidant and antioxidant effects

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Abstract

Background:

Lignans are large group of polyphenols that are formed by the coupling of two coniferyl alcohol residues. Based on their origin, lignans are broadly grouped into plant lignans such as isolariciresinol, secoisolariciresinol diglucoside, lariciresinol, and matairesinol; and mammalian lignans such as enterodiol and enterolactone. Based on the oxidation level of the lignan skeleton, they are also categorized into numerous groups such as dibenzylfuran, dibenzylbutyrolactol, dihydroxybenzylbutane, arylnaphtalene and aryltetraline lactone derivatives. Depending on structural type and concentration, numerous dietary lignans have been shown to possess biological activities including protective effect against diseases such as hormone-dependent tumors and cardiovascular diseases. Also, they display antioxidant properties in tissues and organs including the liver and the brain, lignans are found in most fiber-rich seeds such as sesame and pumpkin, and grains including barley, wheat, oats and rye.

Scope and approach:

This paper focus on the metabolism in humans, and recent studies on the antioxidant and possible prooxidant effects of lignans at three levels: *in vitro*, *in vivo* in animals and clinical studies.

Key Findings and Conclusions:

Most of the studies investigating the antioxidant effect of lignans were *in vitro* and animal models and only five clinical trials were found; one evaluating the effect of enterolactone on Low-density lipoprotein (LDL) peroxidation and four investigating the effects of plant lignans including flaxseed lignan components, secoisolariciresinol and sesamin on lipid peroxidation. So, lignans seem to be a valuable source for identifying new molecules for

preventing various diseases especially cardiovascular disorders. Since most of studies are preclinical, however, further clinical trials are required to achieve more conclusive results.

Keywords: Prooxidant, antioxidant, enterolignan, oxidative stress, free radicals, medicinal herb, herbal medicine, phytochemical

Abbreviations

AAPH, 2,20-azo-bis(2-amidinopropane) dihydrochloride; ALP, alkaline phosphatase; AMPK, Adenosine monophosphate-activated protein kinase; AP-1, activator protein-1; CAT, catalase; CCl4, Carbon tetrachloride; COX-2, cyclooxygenase-2; CUPRAC, cupric reducing antioxidant capacity; CYP, cytochrome P450; DPPH, 1,1-diphenyl-2-picrylhydrazyl; ER, endoplasmic reticulum ERK, Extracellular signal-regulated kinase; eNOS, endothelial nitric oxide synthase; GR, glutathione reductase; GSH, glutathione; GSH-px, glutathione peroxidase; GSSG, oxidized glutathione; HO-1, heme oxygenase-1; H2O2, hydrogen peroxide; HSP, heat shock protein; IFN-γ, interferon-gamma; IL, interleukin; iNOS, nitric oxide synthase; JNK, Jun N-terminal kinases; LDL, Low-density lipoprotein; LPS, Lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDA, Malondialdehyde; MMP, mitochondrial membrane potential; NF-κB, nuclear factor-kappa B; NO, nitric oxide; NOX, NADPH oxidase; Nqo1, quinone oxidoreductase-1; Nrf2, nuclear factor erythroid 2-related factor-2; ORAC, oxygen radical absorbance capacity; oxLDL, oxidized low-density lipoprotein; PPARa, peroxisome proliferator–activated receptor; ROS, reactive oxygen species; RT-PCR, Real-time reverse transcription–polymerase chain reaction; SIRT3, Sirtuin-3; PPARalpha, peroxisome proliferator-activated receptor alpha; RAGE, Receptor for advanced glycation end products; ROS, reactive oxygen species; SDG, secoisolariciresinol diglucoside; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SIRT3, Sirtuin-3; SOD, superoxide dismutase; SOD2, manganese

superoxide dismutase; SREBP-1c, Sterol regulatory element binding protein-1c; STAT3, signal transducer and activator of transcription 3; TBARS, Thiobarbituric acid reactive substances t-BHP, tert-butyl hydroperoxide; TNF-α, Tumor necrosis factor-α

1. Introduction

Lignans are structurally complex bioactive polyphenolic compounds that are formed by the coupling of two coniferyl alcohol residues through the shikimic acid or the phenylpropanoid pathway. Based on their origin, they are broadly grouped into plant lignans and mammalian lignans (Imran et al., 2015). Plant lignans have the oxygenated substituents principally in the para positions while the mammalian lignans possess the hydroxyl groups in the meta position (Imran et al., 2015). On the basis of their structure, they are also categorized into several groups such as dibenzylfuran, dibenzylbutyrolactol, dihydroxybenzylbutane, arylnaphtalene and aryltetraline lactone derivatives (Alcorn et al., 2017). Monolignols are lignans derived from the dimerization of hydroxycinnamic acids such as sinapic, p-coumaric and ferulic acids. In this case, the dimers are called neolignans. These lignans are not commonly found in nature in their free form, but linked to other molecules, mainly as glycosylated derivatives. Moreover, they present not only as dimers but also as complex oligomers, such as dilignans and sesquilignans (Pilar et al., 2017). The mammalian lignans, first recognized in animals and humans in the 1980's, are produced through the action of diverse phylogenetically bacterial strains in the human body dominated by *Peptostreptococcus sp* (Setchell et al., 2014). Furfuran-type lignans from edible plants, including lariciresinol, secoisolariciresinol, matairesinol and pinoresinol, are known to be converted to mammalian lignans, enterodiol or enterolactone by the gut microflora. These bacterial byproducts display more useful properties on human health when compared to their lignin precursors. The enterolignans (mammalian lignans) are also food lignans' metabolites which are products of the human

intestinal bacteria. They have been routinely detected in human plasma and urine (Mukker et al., 2015).

As food ingredients, lignans are found in most fiber-rich plants such as sesame seed, pumpkin seed, grains including barley, wheat, oats and rye; legumes such as lentils, beans, and soybeans and vegetables including asparagus, garlic, carrots, and broccoli (Imran et al., 2015). The lignan content of foods is commonly low and generally does not exceed 2 mg/100 g. The exceptions are sesame seeds and flaxseed which have lignan contents of several times higher than other dietary sources (Pilkington, 2018).

The flaxseeds are sourced from *Linum usitatissimum* L. which belongs to the Linaceae family and have potential health benefits associated with the biologically active components such as α-linolenic acid (50–55 % of total fatty acids composition), dietary fiber (25–28 %) and phenolic compounds (Alcorn et al., 2017). Flaxseeds are principally the richest known source of lignans (9–30 mg/g (approximately 301 mg/100 g), with lignan production at 75–800 times that of cereals, legumes, other oil seeds, vegetables and fruit. The principal dietary lignan present in flaxseeds is secoisolariciresinol (2,3-bis (3-methoxy-4-hydroxybenzyl) butane-1,4-diol) which is stored as the conjugate SDG that occurs as a component of a linear ester-linked complex in the plant (Pilar et al., 2017).

Sesame (*Sesamum indicum* L.) is a flowering plant which belongs to the Pedaliaceae family. The lignan concentrations in sesame seeds (almost 29 mg/100 g, principally pinoresinol and lariciresinol) are relatively high. Sesamin as a furofuran-type lignan, one of the main lignan compositions in sesame, is present in the seeds in amounts of 0.1-0.5% (Baluchnejadmojarad et al., 2017). Sesamin, can also be converted by intestinal microbiota to the mammalian lignans which may have protective effects against hormone-related diseases such as breast cancer (Khamphio et al., 2016).

Various epidemiological studies have demonstrated a strong protective effect of a lignan-rich diet or of the enterolignans against several diseases principally cardiovascular diseases and hormone-dependent tumors (Witkowska et al., 2018). They also display some anti-inflammatory and antioxidant properties. Hence, lignans have demonstrated to ameliorate oxidative stress in organs including the liver or brain. The biological activities of dietary lignans may depend on the type or amount of lignans contained in the diet (Michalak et al., 2018). Enterolactone and enterodiol, which are commonly called enterolignans because of their colonic origin, may also have estrogenic/anti-estrogenic effects due to their similar structure to the human hormone, estrogen (Witkowska et al., 2018). The present paper outlines metabolism in humans, and recent studies on the beneficial effects of lignans with special emphasis on their prooxidant/antioxidant effects. For this, data from *in vitro*, *in vivo* in animals and clinical studies are scrutinized.

2. Lignan intake and Bioavailability

Lignan intake does not commonly exceed 1 mg/day in most Western populations. Estimates of lignan intakes differ from about 150 μg/day (matairesinol and secoisolariciresinol) to about 1600 μg/day (pinoresinol, syringaresinol, secoisolariciresinol, medioresinol, matairesinol, lariciresinol, enterolactone, enterodiol) (Tomimori et al., 2013).

Intakes of the two most usually measured lignans differ from 2 to 74 μg/day for matairesinol and from 70 to 1000 μg/day for secoisolariciresinol. Pinoresinol varies from 73 to 423 μg/day while lariciresinol varies in the diet from 74 to 500 μg/day. In the study on lignanas including, matairesinol, lariciresinol, pinoresinol, secoisolariciresinol, syringaresinol and medioresinol found a median total lignin intake of the Swedish women as 1632 μg/day. On the other hand, another study has shown that lignans (lariciresinol, secoisolariciresinol,

pinoresinol, and matairesinol) median total intake for the Dutch as 979 μg/day. Also, measuring only secoisolariciresinol and matairesinol found the mean total lignan intake of Finns as 434 μg/day (Probst, Guan, & Kent, 2018).

In addition to diet, many factors including smoking, antibiotics, intestinal microflora, and obesity may affect the level of circulating lignans in the body. Several ingested plant lignans are deglycosylated and partially converted to the mammalian lignans enterolactone and enterodiol by colonic bacteria. Enterodiol is easily oxidized to enterolactone (Durazzo, Zaccaria, Polito, Maiani & Carcea, 2013). Then, these metabolites are absorbed in the colon. Further, lignans containing phenolic hydroxyl groups are targets of phase II metabolic reactions, and conjugate with glutathione (GSH), sulfate or glucuronic acid, which result in the reduction of pharmacological activity of lignans. Also, some of the metabolites may undergo enterohepatic circulation. Lignans are excreted in urine and bile in the form of conjugated glucuronides and in feces in the unconjugated form (Michalak et al., 2018).

2.1. Lignan metabolism

Absorption and bioconversion of plant lignans to mammalian lignans and their subsequent absorption differs significantly from person to person. Lignans exist in plants both as glycosides (with sugars) and as aglycones (without sugars). At present, only secoisolariciresinol has been found as a lignan oligomer in flaxseed. After metabolism by intestinal bacteria to the enterolignans (enterodiol and enterolactone) and lignin aglycones, lignan glycosides are absorbed in the gastrointestinal tract. The amount of hydrolysis to release the lignans from the sugars and from the oligomer in flax as well as the formation of enterolignans and their bioavailability significantly differ on individual basis (Setchell et al., 2014).

2.2. Bacterial metabolism in the gut

Lignan glycosides, such as the sesame seed sesamolin triglucoside and the flax SDG ester-linked complex are hydrolyzed to lignan aglycones by the anaerobic microbes in the gut. Then, the free lignans are transformed to enterolignans via metabolic reactions by several gut bacteria (Setchell et al., 2014). The efficiency of transformation depends on various factors and varies significantly from person to person. The lignans metabolism in the tissues is affected by genetic factors, but these are not well understood as yet (Jan, Ku, Chu, Hwang & Ho, 2010). In an *in vitro* fecal microflora metabolism system, lariciresinol was entirely converted in 24 hours into the enterolignans, enterodiol (54%) and enterolactone (46%); while other plant lignans such as pinoresinol diglucoside (55%) matairesinol (62%), and SDG (72%) were incompletely converted (Peterson, et al., 2010).

2.3. Systemic metabolism

The enterolignans enterolactone and enterodiol are absorbed in the colon and most of them are conjugated to glucuronides in colonic tissues. They generally appear in the blood 8 to 10 hours after dietary intake. In another study, some plant lignans (e.g., cyclolariciresinol, anhydrosecoisolariciresinol, 7′-hydroxymatairesinol, pinoresinol, matairesinol, lariciresinol, secoisolariciresinol, and sesamin) were shown to be quickly absorbed in the small intestine and detected in the systemic circulation, one hour after ingestion of sesame seeds. The enterohepatic recirculation of enterolignans, secoisolariciresinol and sesame lignans is significant. Sulfates and glucuronides of enterolactone, enterodiol and secoisolariciresinol may simply be eliminated in the bile, urine or undergo enterohepatic recirculation (Brito & Zang, 2019).

2.4. The effect of food processing on lignans content and stability

Plant foods or oils are used principally in processed form like chips, bakery products, blanched and cooked vegetables. Therefore, it is important to consider the variations of the lignan content during processing. Processing technologies including baking, milling, heating, drying, boiling and extraction may influence lignan content and therefore may affect the bioavailability of lignans because of disruption the natural food matrix or the microstructure prior to consumption (Gerstenmeyer et al., 2013).

Numerous studies demonstrated that processing could reduce the amount of special lignans in grains, while others including SDG are stable in various bakery products. Other processes like drying and cooking have mixed effects on lignan levels depending on the lignan structure, lignan profile, type of conjugation, and the nature of the food matrix (Manikantan et al., 2015).

Processing barley to swelled barley could reduce the levels of pinoresinol, matairesinol secoisolariciresinol, and while lariciresinol level enhances.

Drying the refined wheat flour had an overall positive influence on the total concentration of lignans and enhances the levels of secoisolariciresinol, pinoresinol and lariciresinol concentration. While whole grain oat had a positive influence on pinoresinol level, it has lower level of secoisolariciresinol, matairesinol, and lariciresinol (Gerstenmeyer et al., 2013).

Treatment of grains, rye flour and sesame seeds with steam (or 100° C) could degrade lignans while higher roasting temperatures (e.g. 250° C) degrade glycosides and aglycones in sesame seeds and rye. In flaxseeds, pinoresinol, lariciresinol, secoisolariciresinol and isolariciresinol which are principally present as esterified compounds were shown to be stable when heated up to 250° C for 3.5 min.

In sesame oil, heating conditions hardly affect the content of sesamin whereas the content of sesamol is enhanced while sesamolin is slightly reduced. Also, sesamolin is degraded when the temperature of the oil is maintained at 200° C for 20 min (Simbalista et al., 2012).

Palermo et al. (2014) reported that boiling Brassicaceae samples could decrease lignan content while no significant changes were observed in the lignan content of carrot. The lignan content of numerous vegetables (particularly tubers) was shown to be enhanced after cooking (Palermo et al., 2014).

3. Applications of lignans in the human health and food industry

Most of the plant lignans in foods are transformed via the intestinal microflora in the upper part of the large bowel to enterolignans. Low plasma enterolactone may enhance risk of breast cancer, principally for estrogen negative breast cancer. Evidence demonstrates that pure lignans, flaxseed and SDG, prevent several diseases like prostate, colon, ovarian cancer and metastasis by inhibiting the tumor formation and also decreasing blood vessel cell progression, cardiovascular diseases, diabetes, obesity, renal and bone disorders (Grosso et al., 2017).

Functional food or nutraceuticals are foods that claimed to have disease-prevention or health-promoting properties in addition to providing basic nutrients in the food. Many functional foods or nutraceuticals have been made by flax meal, whole flax seed and milled flax. Moreover, value added products are made for increasing the value of food items via the addition of ingredient such as lignans, processing or packaging. These products are more acceptable and preferred by the consumers than their main original sources. Some examples of value-added products are extruded snacks, yogurt, skim milk, ice cream, cheeses, breakfast cereals, etc. (Kaur et al., 2018). Lignans are used commercially in products such as bakery,

dairy, extruded, snack, fermented, traditional (chapatti, khakhra, vegetable chilla and manchurian) products. For example, flax seed can be combined into baked product as whole, roasted, ground, milled and in the form of oil. Also, flaxseed lignans have been supplemented with various dairy products including milk, yogurt, cheese, ice cream, butter and whey drinks. SDG added to milk, yogurt, and cheese is found to well tolerate fermentation, high temperature pasteurization and milk renneting processes (Kaur et al., 2018).

4. Possible prooxidant activity

Natural antioxidants anthocyanins, flavonoids carotenoids and polyphenols, play major role in the prevention and treatment of many different diseases. Although, in recent years, several studies have demonstrated that natural antioxidants can have a prooxidant activity predominantly in the presence of transition metal ions principally Cu and Fe. Phenolic compounds under some conditions, such as high phenolic concentrations, high pH and presence of metals ions, can induce prooxidant activity and generate free radicals. This ultimately leads to mutagenesis and DNA damage (Eghbaliferiz & Iranshahi, 2016). The prooxidant activity of antioxidant composites is not essentially destructive for biological systems and can be applied therapeutically to cure cancer, for instance, using high doses of vitamin C for several cancers. The prooxidant activities of polyphenols from apple, citrus, grape, and other natural sources were specified via a cyclic voltammetry method *in vitro*. In the presence of copper ions, a polyphenol, resveratrol, extracted from grapes displays prooxidant activity (Cotoras et al., 2014). Resveratrol can catalyse the reduction of Cu (II) to Cu (I), that from this way produces highly reactive oxygen species (ROS) and cause DNA damage, mutagenesis, oncogenesis and aging (Eghbaliferiz & Iranshahi, 2016).

Khamphio et al. (Khamphio, Barusrux & Weerapreeyakul, 2016) reported the paradoxical effect of sesame lignan sesamol. In this study, sesamol displayed a prooxidant activity at high concentrations (0.5, 1, 2, and 5 mM) and an antioxidant activity at low concentrations (< 0.05 mM) in human colorectal carcinoma (HCT116) cells. Sesamol based on its prooxidant effect induced the mitochondrial apoptosis pathway through intracellular $O_2^{\cdot -}$ generation in HCT116 cells (Khamphio et al., 2016).

5. Antioxidant activity

Reactive oxygen species (ROS) are an inevitable consequence of aerobic metabolism, that produces free radicals including hydroxyl radicals (·OH), superoxide anions (O_2^-) and also, nonradical molecules such as H_2O_2 and singlet oxygen (Huang et al., 2018). ROS made either exogenously or endogenously, may contribute to several pathological factors, such as cellular degeneration and DNA damage. If the cellular antioxidant capacity that prohibits oxidative injury cannot neutralize ROS production, cells exhibits a condition called oxidative stress. Oxidative stress is directly or indirectly responsible for causing several diseases. The accumulation of ROS in organelle or cytoplasm can interrupt the cells' balance through break in the structure and function of nucleic acids, activation of apoptotic pathways, oxidative modification of proteins, causing peroxidation of lipids, inhibition of antioxidant enzymes, and finally cell dysfunction (Zheng, J., 2014).

Antioxidant activity of lignans can be achieved through several mechanisms including attenuation of ROS generation and MDA and increasing tissues antioxidant enzyme capacity by enhancing SOD, CAT, GSH-Px, and GSH activities (Yu et al., 2010). They also inhibit lipid peroxidation, protein and DNA oxidation. Antioxidants activate the JAK2/STAT3 signaling pathway (Huang et al., 2018), upregulate PI3K/AKT signaling and HO-1 through the P38 MAPK phosphorylation and Nrf2/ARE pathways (Jeong et al., 2010). Through these

diverse mechanisms, antioxidants can regulate key molecules involved in oxidative stress and inflammation by decreasing the production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and mediators (COX-2, iNOS and ROS) primarily through downregulating the activity of I-κB kinase and the DNA binding activity of NF-κB (Lee, Choi & Kim, 2015).

6. Assessing the antioxidant effect of lignans: evidences from in vitro, animal and human studies

The general antioxidant effects of lignans documented through *in vitro*, animal and human studies is shown in Table1, 2 and 3 respectively. It seems that among lignans, SDG, sesamin, honokiol, schisandrin, sauchinone and gomisin N, to have been the most studied.

Honokiol, sauchinone, and gomisin N in two levels of *in vitro* and animal, sesamin and SDG have been also evaluated in human studies.

Honokiol is a lignan isolated from *Magnolia* spp. that exhibits, antithrombotic, antidepressant, anxiolytic, antimicrobial antitumorigenic, antioxidant, analgesic antispasmodic, neuroprotective and cardioprotective properties (Woodbury, Yu, Wei & García, 2013). Honokiol ameliorated oxidative damage by activating SIRT3 in hepatocytes (Liu, Shen, Tong, Wang & Lin, 2018), ROS inhibition via Nrf2/ARE pathway and improves pancreatic β-cell function of type 2 diabetes mellitus rats (Li et al., 2018). It also significantly increased SIRT3 expression, decreased ROS generation, lipid peroxidation, increased antioxidant activities and mitochondrial function in Chinese Hamster Ovarian (CHO) cells (Ramesh et al., 2018).

Gomisin N is a lignan derived from *Schisandra chinensis* (Turcz.) Baill. fruits that has been shown antimelanogenic, anticancer, anti-inflammatory, and hepatoprotective properties and also protect against nonalcoholic fatty liver disease by inhibiting endoplasmic stress (ER) and activating the AMP-activated protein kinase (AMPK). On the other hand, gomisin N has been

shown to suppress the expression and enzymatic activity of CYP2E1 while enhancing antioxidant genes and GSH level and reducing hepatic malondialdehyde (MDA) levels in hepatic tissues of mice and promoted hepatic sirtuin1(SIRT1)-AMPK signaling in mice (Nagappan, Jung, Kim, Lee & Jung, 2018).

Sauchinone is a unique lignan extracted from the roots of *Saururus chinensis* (Lour.) Baill. It has various biological activities, including hepatoprotective, cytoprotective, immunosuppressive, anti-inflammatory and hepatoprotective effects. Under *t*-butyl hydroperoxide-induced oxidative injury conditions in HepG2 cells, treatment with sauchinone upregulated HO-1 through the P38 MAPK and Nrf2/ARE pathways in a concentration- and time-dependent manner (Jeong et al., 2010). Sauchinone protected hepatocytes from oxidative stress induced by fat accumulation via inhibition of LXRα-mediated SREBP-1c induction and AMPK activation (Kim et al., 2010b). Furthermore, another study demonstrated that sauchinone prevents the iron-induced oxidative stress and liver injury through mechanism of LKB1-dependent AMPK activation (Park et al., 2013).

The antioxidant effect of sesamin in twenty-six postmenopausal women was examined. Cross over and randomized double-blinded trial with sesamin 50 g, and 50 g rice powder as placebo were performed with five weeks interval. After sesame treatment, LDL-C, plasma total cholesterol (TC), the ratio of LDL-C to HDL-C, serum dehydroepiandrosterone sulfate, and TBARS in ox-LDL, reduced significantly by 10, 5, 6, 18 and 23%, respectively. The ratio of tocopherol to TC and serum sex hormone increased significantly. These results demonstrated that sesame ingestion benefits postmenopausal women by improving antioxidant status, blood lipids, and sex hormone status (Wu et al., 2006). The second study is about SDG. Results from chronic intervention trial of community-dwelling healthy older adults revealed that SDG supplementation reduced oxidative stress (MDA level) and inflammation (IL-6, TNF-α levels) in community-dwelling healthy older adults compared to the placebo group. These

findings demonstrated that this lignan might help in improving and maintaining functionality markers including muscle strength, cognition, and aging (Alcorn et al., 2017). In another study that was done by Hallund et al, daily consumption for 6 weeks of SDG significantly enhanced urinary enterolactone excretion and serum enterolactone concentrations in healthy postmenopausal women but had no effect on plasma antioxidant capacity, serum lipoprotein oxidation resistance, plasma lipid concentrations (Hallund, Ravn-Haren, Bügel, Tholstrup & Tetens, 2006).

Findings of this study demonstrate that the most antioxidant effects of lignans are through the reduction of ROS, lipid peroxidation, DNA damage, and increasing tissues antioxidant enzyme capacity by enhancing SOD, GSH, GSH-Px activities and attenuation MDA, respectively. Nrf2/ARE, Nrf2/HO-1, SIRT/AMPK signaling pathways are the most antioxidant pathways that are affected by lignans.

It seems that honokiol, sauchinone, gomisin N and schisandrin in addition to sesamin and SDG among lignans more appropriate to be investigated during clinical trials to establish a more comprehensive conclusion on the antioxidant effects of lignans.

7. Conclusion

Lignans are a large group of polyphenols that are divided based on their origin into plant lignans and mammalian lignans. In this paper, recent studies on possible prooxidant and antioxidant effects of lignans at three levels (*in vitro*, animal and human) and their molecular mechanisms were discussed. Few studies have been done on the prooxidant effect of lignans, for instance, paradoxical effect of sesamol displayed an antioxidant activity at low concentrations and a prooxidant activity at high concentrations and induced mitochondrial apoptosis pathway in HCT116 cells (Khamphio et al., 2016). Most of the lignans investigated in oxidative stress include secoisolariciresinol diglucoside, sesamin, honokiol,

gomisin N and schisandrin in animal and *in vitro* models and there were only five clinical trials evaluating the effects of lignans such as enterolactone (Vanharanta et al., 2002), flaxseed lignan components (Almario & Karakas, 2013), SDG (Alcorn et al., 2017; Hallund et al., 2006) and sesamin (Wu et al., 2006).

Antioxidant activity of lignans can be achieved through several mechanisms including attenuating ROS generation, MDA, lipid peroxidation, protein and DNA oxidation, increasing tissues antioxidant enzyme capacity by enhancing SOD, CAT, GSH-Px, GSH activities, activation of the JAK2/STAT3 signaling pathway, upregulation of PI3K/AKT signaling, upregulating HO-1 through the P38 MAPK phosphorylation and Nrf2/ARE pathways, regulating key molecules involved in oxidative stress and inflammation by decreasing the production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and mediators (COX-2, iNOS and ROS) primarily through downregulating the activity of I-κB kinase and the DNA binding activity of NF-κB.

On the basis of the numerous mechanisms of lignans discussed at cellular and molecular levels, well-designed clinical trials are necessary to establish a more comprehensive conclusion on the antioxidant and/or prooxidant effects of lignans.

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630 **Table 1**. ***In vitro*** **studies assessing the antioxidant effect of lignans**

Lignan	Scientific name	Part	Model/Cell line	Results	Reference
Americanin B (dibenzylbutyrolactone lignan)	*Centaurea Americana* Nutt. (Family: Asteraceae)	Seed	Human keratinocytes cell line	↓ROS, ↓level of DPPH radicals, ↓superoxide anions, ↓hydroxyl radicals, ↓ DNA damage, ↓ protein oxidation, ↓lipid peroxidation	(Zheng et al., 2014)
Bisdemethylpinoresinol (furofuran lignans)	*Opuntia ficus-indica* (L.) Mill. (Cactaceae)	Seed	Rat primary hepatocytes (ethanol-induced oxidative stress) and HepG2	↓ROS, preserving antioxidative defense enzyme	(Kim et al., 2017)

			cells	activities, maintaining the GSH content	
Ribesin D & Ribesin G (7,7'-epoxylignans)	*Ribes nigrum* L. (Family: Grossulariaceae)	Leaves	Superoxide anion scavenging assay, DPPH free radical scavenging assay	Potent superoxide anion scavenging activity	(Sasaki et al., 2013)
Gomisin A	*Schisandra chinensis* (Turcz.) Baill (Family: Schisandraceae)	Fruit	Human diploid fibroblast (HDF) cells	↓ROS, ↑SOD, ↑HO-1 expression by MAPK pathway and the translocation of NF-κB	(Kim et al., 2018)
Gomisin N	*Schisandra*	Fruit	Ethanol-induced liver	↓Lipogenesis	(Nagappan et

	chinensis (Turcz.) Baill (Family: Schisandraceae)		injury using *in vivo* (ethanol-fed mice) + *In vitro* (HepG2 cells)	gene expression, ↑fatty acid oxidation gene expression, ↑antioxidant genes, ↑GSH, ↓MDA, promoted hepatic SIRT1-AMPK signaling, ↓ROS by downregulating CYP2E1 ↑SIRT1, ↑phosphorylated	al., 2018)

				AMPK	
Gomisin T	*Schisandra chinensis (Turcz.) Baill* (Family: Schisandraceae)	Fruit	PLB-985 cell-based NOX2 assay	Inhibit NOX2	(Park et al., 2018)
Hinokinin, (dibenzylbutyrolactone lignin)	*Piper cubeba* L.f. (Family: Piperaceae)	Seed	Quantification of the oxidation product of H2DCFDA, a dichlorofluorescein compound	↓H2O2 & other peroxides	(Lima et al., 2017)
Honokiol (polyphenolic lignan)	*Magnolia* spp. (Family: Magnoliaceae)	Bark & seed cone	Chinese Hamster ovarian cells	↑SIRT3 expression, ↓ROS, ↓lipid peroxidation,	(Ramesh et al., 2018)

				↑antioxidant activities, ↑mitochondrial function, ↑ AMPK expression	
Hydroxymatairesinol			Vascular endothelial cells	↓ROS, Blocking the MAPK/ NF-κB, activating Nrf2/HO-1	(Yang et al., 2017)
Icariside E5	*Capsicum annuum* L. (red pepper) (Family: Solanaceae)	Fruit	DPPH radical scavenging assay	Strong scavenging effect on DPPH	(Lee et al., 2011)

4-Ketopinoresinol			Western blot analysis, measurement of ROS, Histone H2AX phosphorylation, Immunofluorescence, RT-PCR	Nrf2/ARE-mediated transcription activator, activates the Nrf2/HO-1 axis, activation of PI3K/AKT signaling, ↑AKT phosphorylation, ↑ GSH, ↓ROS	(Chen et al., 2012)
Lariciresinol	*Rubia philippinensis* Elmer. (Family: Rubiaceae)	Root	Murine macrophage (RAW 264.7) cells, DPPH radical scavenging assay, RT-PCR	Upregulation of Nrf2-mediated HO-1 expression, through the	(Bajpai et al., 2017)

				activation of p38, ↓ROS	
Lyciumamide K (lignanamide)	*Lycium yunnanense* Kuang. (Family: Solanaceae)	Root	Oxygen radical absorption capacity (ORAC) assay	Antioxidant activities	(Zheng et al., 2018)
Sauchinone	*Saururus chinensis* (Lour.) Baill. (Family: Saururaceae)	Root	HepG2 cells	Upregulating HO-1 via the P38 MAPK and Nrf2/ARE pathways	(Jeong et al., 2010)
Saururin A (diarylbutane lignan)	*Saururus chinensis* (Lour.) Baill.	Underground parts	TBARS assay	LDL antioxidant activity	(Ahn et al., 2010)

	(Family: Saururaceae)				
SDG	*Linum usitatissimum* L. (Family: Linaceae)	Seed	H9C2 rat cardiomyocytes.	Activation of the JAK2/STAT3 signaling pathway, ↓H2O2	(Huang et al., 2018)
SDG	*Linum usitatissimum* L. (Family: Linaceae)	Seed	AAPH-induced liposome lipid peroxidation	Strong scavenging effect on DPPH, protecting DNA against AAPH peroxyl	(Velalopoulou et al., 2015)

				radical-induced damage	
Sesamin	*Sesamun indicum* L. (Family: Pedaliaceae)	Seed	Neuronal PC12 cells and microglial BV-2 cells	↓MDA, ↑SOD, ↓ROS, ↓COX-2 expression, ↓ERK1/2, p38 mitogen-activated protein kinases, inhibition of MAPK	(Hsieh et al., 2011)
Sesamin	*Sesamun indicum* L. (Family: Pedaliaceae)	Seed	Human neuroblastoma (SH-SY5Y) cell	↓ROS, ↓H2O2, activating SIRT1-SIRT3-FOXO3a signaling	(Ruankham et al., 2019)

				pathway	
Sesaminol	*Sesamun indicum* L. (Family: Pedaliaceae)	Seed	Pheochromocytoma (PC12) cells oxidative damaged by H2 O2	↑SOD, CAT and GSH-Px activity, ↓ROS	(Cao et al., 2013)
Sesamol	*Sesamun indicum* L. (Family: Pedaliaceae)	Seed	HCT116 human colon cancer cells	Pro-oxidant effect, ↓ FRAP reagent, DPPH scavengener, ↓ROS, ↓cell viability	(Khamphio et al., 2016)
Zanthoxyloside C, Zanthoxyloside D	*Zanthoxylum piperitum* Benn. (Family: Rutaceae)	Stems	ORAC, CUPRAC assays	Peroxyl radical-scavenging activity	(Yang et al., 2018b)

AAPH, 2,20-azo-bis(2-amidinopropane) dihydrochloride; AP-1, activator protein-1; CYP, cytochrome P450; CUPRAC, cupric reducing antioxidant capacity; DPPH, 1,1-diphenyl-2-picrylhydrazyl; GSH, glutathione; GSH-px, glutathione peroxidase; HO-1, heme oxygenase-1; H2O2, hydrogen peroxide; IFN-γ, interferon-gamma; iNOS, nitric oxide synthase; JAK2, Janus kinase 2; LDL, Low-density lipoprotein; LPS, Lipopolysaccharide; MDA, malondialdehyde; MPP, 1-methyl-4-phenyl-pyridine; NF-κB, nuclear factor-kappa B, NO, nitric oxide; NOX, NADPH oxidase; Nqo1, quinone oxidoreductase-1; Nrf2, nuclear factor-E2-related factor 2, ORAC, oxygen radical absorbance capacity; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; RT-PCR, Real-time reverse transcription–polymerase chain reaction; SDG, secoisolariciresinol diglucoside; SIRT3, Sirtuin-3; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TBARS, Thiobarbituric acid reactive substances

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641 **Table 2. Animal studies assessing the antioxidant effect of lignans**

Lignan	Scientific name	Part	Model	Results	Reference
Arctigenin	*Arctium lappa* L. (Family: Compositae)	Fruit	Unilateral ureteral obstruction in rats	↓Oxidative stress by ↑activity of renal manganese SOD_2, ↓levels of lipid peroxidation	(Li et al., 2017)
Arctigenin	*Arctium lappa* L. (Family: Compositae)	Fruit	Ischemia/reperfusion injured rat heart model	↓Oxidative stress by Nrf2 signaling pathway, ↑SOD, ↑GSH-Px, ↓MDA	(Yang et al., 2018a)
Cubebin (dibenzylbutyrolactone lignan)	*Piper cubeba* L.f.	Dried fruits	Scopolamine-induced amnesia in mice	↓MDA	(Somani et al., 2017)
Dehydrodiconiferyl alcohol	*Cucurbita moschata* Duchesne. (Family: Cucurbitaceae)	Stem	Mouse dextran sodium sulfate induced colitis model + *In vitro*: murine macrophage cell	↓ROS by down-regulating the activity of I-κB kinase	(Lee et al., 2015)
3,3′-bisdemethylpinor	*Opuntia ficus-indica* (L.)	Seed	Ethanol-induced hepatotoxicity in	↓ROS, , maintaining the GSH content, induced the HO-1 expression	(Kim et al.,

esinol (furofuran lignans)	Mill. (Family: Cactaceae)		rat		2017)
Gomisin N	*Schisandra chinensis* (Turcz.) Baill. (Family: Schisandraceae)	Fruit	Ethanol-induced hepatic steatosis in mice	↓ROS generation by ↓CYP2E1 & ↑antioxidant genes, ↑GSH level, ↓hepatic malondialdehyde levels, promotion hepatic SIRT1- AMPK signaling	(Nagappan et al., 2018)
Honokiol	*Magnolia* spp. (Family: Magnoliaceae)	Bark & seed cone	CCl4-stimulated liver damaged mice + t-BHP-injured AML12 hepatocytes *in vitro*	Activating SIRT3, ↓SOD2 acetylation, ↑antioxidative capacity, ↓ROS accumulation, promote mitochondrial biogenesis by ↑the deacetylated peroxisome proliferator-activated receptor γ coactivator 1-α level, ↓mitochondrial fragmentation through Ku70-dynamin-related protein 1 axis	(Liu et al., 2018)
Honokiol	*Magnolia* spp. (Family: Magnoliaceae)	Bark & seed cone	Rat (fed with a high-fat diet for 4 weeks and administered streptozocin) +	Potent ROS scavenger via Nrf2/ARE pathway	(Li et al., 2018)

			In vitro (Rat pancreatic β cells)		
Isochaihulactone	*Bupleurum scorzonerifolium* Willd. (Family: Apiaceae)	Root	H_2O_2 induced oxidative stress in D-galactose aging mouse model	↑Cell viability & ↓membrane damage, ↓ROS generation, ↓COX-2 expression, via downregulation of NF-κB, ↓lipid peroxidation, ↑SOD, ↑GSH-px activities and ↓MDA level	(Yu et al., 2010)
Nectandrin B (tetrahydrofuran-type)	*Myristica fragrans* Houtt. (Nutmeg) (Family: Myristicaceae)	Dried kernel	t-BHP-induced oxidative injury in primary mouse hepatocytes	Nrf2 activation through ERK phosphorylation & AMPK-dependent inhibition of GSK-3beta, ↓ROS production, ↑GSH	(Song et al., 2016)
Nordihydroguaiaretic acid	*Larrea tridentata* (Sessé & Moc. ex DC.) Coville (Creosote) (Family: Zygophyllace	Bush	Ischemia-reperfusion - induced renal oxidant damage in kidneys of rats	Induce Nrf2 translocation	(Zúñiga-Toalá et al., 2013)

	ae)				
Nordihydroguaiaretic acid	*Larrea tridentata* (Sessé & Moc. ex DC.) Coville (Creosote) (Family: Zygophyllaceae)	Bush	Mice with American lifestyle-induced obesity syndrome (ALIOS) diet for 8 weeks	↑Hepatic expression of antioxidant enzymes, ↑GSH-px4, ↑peroxiredoxin 3 proteins, modulating the PPARalpha transcription factor (the master regulator of fatty acid oxidation) & mRNA levels of carnitine palmitoyltransferases Cpt1c and Cpt2	(Chan et al., 2018)
Pinoresinol	*Forsythiae Fructus* (Family: Oleaceae)		CCl4-induced liver injury in mice	↓Lipid peroxidation, ↓MDA, ↑GSH	(Kim et al., 2010a)
Piperkadsin A (neolignans)	*Piper attenuatum* Buch. -Ham. ex Miq. (Family: Piperaceae)	Fruit	Oral glucose tolerance test in rats	Potent free radical scavenging activity	(Reddy et al., 2015)
Sauchinone	*Saururus chinensis*(Lour.) Baill. (Family:	Root	SREBP-1c-mediated hepatic steatosis in rat	AMPK-activating, inhibit oxidative stress	(Kim et al., 2010b)

	Saururaceae)				
Sauchinone	*Saururus chinensis* (Lour.) Baill. (Family: Saururaceae)	Root	Iron-induced liver injury in mice	AMPK-activating	(Kim et al., 2017)
SDG	*Linum usitatissimum* L. (Family: Saururaceae)	Seed	Rats received 30% fructose in drinking water for induction metabolic syndrome	↓Lipid peroxidation	(Pilar et al., 2017)
SDG	*Linum usitatissimum* L. (Family: Saururaceae)	Seed	Mice to diabetes by a single intraperitoneal injection of streptozotocin	↓ROS, ↓lipid peroxidation, ↑catalase activity, ↑GSH	(Hu et al., 2015)
Schisandrin A (dibenzocyclooctadiene lignan)	*Schisandra chinensis* (Turcz.) Baill (Family: Schisandraceae)	Fruit	Aβ-induced neurodegeneration with cognitive decline in mice	↑SOD, ↑GSH-Px, ↑GSH	(Li et al., 2014)
Schisandrin A	*Schisandra*	Fruit	Hepatic ischemia	↓Oxidative/nitrosative stress by	(Zhen

	chinensis (Turcz.) Baill (Family: Schisandraceae)		& reperfusion model in C57BL/6 male mice	inhibition of MAPK signaling pathway	g et al., 2017)
Schisandrin B	*Schisandra chinensis* (Turcz.) Baill (Family: Schisandraceae)	Fruit	Scopolamine- and cisplatin-induced neuronal dysfunction in mouse brain	↓Oxidative and nitrosative stresses through inhibiting RAGE/NF-κB/MAPK, up-regulating HSP/beclin expression	(Giridharan et al., 2015)
Schisandrin C	*Schisandra chinensis* (Trucz.) Baill (Family: Schisandraceae)	Fruit	Aβ1-42 -induced Alzheimer's disease mice	↑SOD, ↑GSH-px activity, ↑GSH levels	(Mao et al., 2015)
Sesamin	*Sesamun indicum* L. (Family: Pedaliaceae)	Seed	CCl4 induced injury in mice liver	↓ROS, ↓lipid peroxidation, antioxidant activity, modulate the JNK signaling pathway.	(Ma et al., 2014)
Sesamin	*Sesamun indicum* L. (Family: Pedaliaceae)		Liver injury induced by carbon tetrachloride in	↓Lipid peroxidation, ↑liver antioxidant enzymes	(Lv et al., 2015)

			rat		
Sesamin	*Sesamun indicum* L. (Family: Pedaliaceae)	Seed	Unilateral striatal 6-hydroxydopamine (6-OHDA) model of parkinson's disease in rats	↓MDA, ↓ROS, improved SOD activity	(Baluchnejadmojarad et al., 2017)

642 AMPK, Adenosine monophosphate-activated protein kinase; CCl4, Carbon tetrachloride;
643 COX-2, cyclooxygenase-2; CYP2E1, cytochrome P450 2E1; ERK, Extracellular signal-
644 regulated kinase; GR, glutathione reductase; GSH, glutathione; GSH-px, glutathione
645 peroxidase; GSSG, oxidized glutathione; HO-1, heme oxygenase-1; H2O2, hydrogen
646 peroxide; HSP, heat shock protein; JNK, Jun N-terminal kinases; MAPK, mitogen-activated
647 protein kinase; MDA, Malondialdehyde; MMP, mitochondrial membrane potential; NF-κB,
648 nuclear factor-kappa B; Nrf2, nuclear factor erythroid 2-related factor-2; SIRT3, Sirtuin-3;
649 PPARalpha, peroxisome proliferator-activated receptor alpha; RAGE, Receptor for advanced
650 glycation end products; ROS, reactive oxygen species; SOD, superoxide dismutase; SOD2,
651 manganese superoxide dismutase; SREBP-1c, Sterol regulatory element binding protein-1c;
652 t-BHP, tert-butyl hydroperoxide
653

654 **Table 3. Clinical studies assessing the antioxidant effect of lignans**

Lignan	Scientific name	Intervention	Duration	Outcomes	Reference
Enterolactone (formed by intestinal bacteria from precursors in plant foods)		Cross-sectional study, 256 males		High serum enterolactone concentration is associated with decreased lipid peroxidation	(Vanharanta et al., 2002)
Flaxseed lignan components	*Linum usitatissimum* L. (Family: Linaceae)	Randomized, double-blinded, placebo-controlled study, 37 healthy men and women 54+/-7 years	6-weeks	Decreasing Ox-LDL, which is an independent risk factor for cardiovascular disease	(Almario & Karakas, 2013)
SDG	*Linum usitatissimum* L. (Family: Linaceae)	Randomized, double-blinded, clinical study, healthy community-dwelling adults 60-80 years, 600mg/day oral	24-weeks	↓Oxidative stress (MDA), ↓inflammation (IL-6, TNF-α)	(Alcorn et al., 2017)

		dose			
SDG	*Linum usitatissimum* L. (Family: Linaceae)	Randomized, double-blinded, placebo-controlled, crossover study, 22 healthy postmenopausal women, 500 mg/day	6-weeks	↑Serum enterolactone concentrations, ↑urinary enterolactone excretion, no effect on plasma lipid concentrations, serum lipoprotein oxidation resistance & plasma antioxidant capacity	(Hallund et al., 2006)
Sesamin	*Sesamun indicum* L. (Family: Pedaliaceae)	Randomized, placebo-controlled, crossover study, 26 healthy postmenopausal women 50–70 years, 50g/day sesame seed powder, 50g/day rice powder placebo period	5-weeks	Benefits on postmenopausal women by improving blood lipids, antioxidant status, and possibly sex hormone status, ↓LDL oxidation	(Wu et al., 2006)

655 MDA, malondialdehyde; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen

656 species; SDG, secoisolariciresinol diglucoside

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- Lignans are important class of bioactive natural compounds
- Dietary lignans possess multiple therapeutic effects
- Lignans are commonly found in different fiber-rich seeds
- We reviewed the antioxidant and prooxidant activities of lignans