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Cereal Lignans, Natural Compounds of Interest for Human Health?

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Cereals are suggested to be the most important sources of lignan in the diets of western populations. Recent epidemiological studies show that European subpopulations in which the major source of lignans are cereals, display lower disease frequency regarding metabolic and cardiovascular diseases. The biological mechanisms of lignan are several. Beyond their antioxidant and anti-inflammatory actions at nutritional doses some lignans regulate the activity of specific nuclear receptors (NRs), such as the estrogen receptors (ERs), and also NRs that are central switches in glucose and fatty acid metabolism such as PPARα, PPARγ and LXRs, highlighting them as selective nuclear receptor modulators (SNRMs). These include enterodiol (END) and enterolactone (ENL), the metabolites produced by the gut microbiota from food lignans. The available knowledge suggests that given some additional research it should be possible to make 'function' claims for a regular intake of lignans-rich foods related to maintaining a healthy metabolism.

Keywords: Lignan, Cereal bran, Obesity, Metabolic syndrome, Health claims.

Introduction: Lignans are a group of compounds found in fiber-rich foods such as cereals, oilseed, nuts, vegetables (brassica), and fruits (berries) typically regarded as components of healthy diets [1-3]. They are expected to have antioxidant, anti-inflammatory and hormone-mimicking effects in humans both as native compounds and after fermentative conversion in the colon [4-7].

Intakes of lignan-rich foods have been shown to be correlated with a lower incidence and progression of diseases / health conditions related to the metabolic syndrome, type 2 diabetes, cardiometabolic risk factors, specific types of cancers and overall mortality [8-12]. The most studied food sources rich in lignans, such as oilseeds (flaxseed and sesame seeds), cereals, and in particular cereal fibers, may contain sufficient concentrations of specific lignans to exert functional effects in humans. Amongst cereals, wheat and rye contain the highest concentration of lignans, mostly in their bran fraction. The most abundant lignans here are 7-hydroxymatairesinol and syringaresinol [14, 15].

Recent studies have highlighted some of the possible mechanisms of action of lignans. Almost all are endowed with antioxidant and anti-inflammatory activities. However, some of these compounds have also shown the ability to bind and activate/inhibit nuclear receptors (NRs) such as the estrogen receptors (ERs) [7], the peroxisome proliferator activate receptor gamma (PPARγ) [16], and the liver X receptor alpha (LXRα) [17]. The regulation of gene expression through these receptors may require the metabolization of most plant lignans to the mammalian lignans enterodiol (END) and enterolactone (ENL) [18], while some lignans like 7-hydroxymatairesinol are shown to engage NRs also in their unmetabolized form [19]. Metabolization of lignans requires gut microbial processes to release them from the food matrix and undergo deglycosylation in the intestine and conversion in the liver to active metabolites. Several of the lignans that have been studied so far have shown interesting roles in promoting human health. Some of them were identified in plants to be of pharmaceutical and cosmetic interest although the diet remains the major route of intake of these chemicals [5, 13, 20, 21]. In particular cereal lignans are present in high amounts in the daily diet of western populations and are likely to be the dietary plants that provide most of the beneficial bioactive lignans in Europe, the US and Canada [5, 13, 20, 21]. Here we review the recent and ongoing research on the characterization of the health effects of cereal lignans and their mechanisms.

Methods: A comprehensive computer literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted to find relevant published articles about the role of lignans in health. No beginning date limit was used; the search was updated until January 2016. Only articles in the English language were selected. To expand our search, references of the retrieved articles were also screened for additional studies.

Lignan chemistry and biochemistry: The chemistry of lignans has been studied for the past 65 years. They possess very different structural composition and can be found in nature in vegetables, mostly in exudates and resins, although they can be present in different parts of the plant. Lignans are polyphenolic substances derived from phenylalanine via dimerization of substituted cinnamic alcohols, known as monolignols, to a dibenzylbutane skeleton and they are found mostly in plants as aglycones, esters or glycosides. These dimeric phenylpropanoids show two C6-C3 units attached to the central carbon C8 while, when two phenylpropanoid units are found coupled in a different manner, like C5-C5', the new term "neolignan" has been adopted (Figure 1) [22].

The lignans can be classified into eight chemical groups and several subgroups based upon the way in which oxygen is incorporated into the skeleton and on the cyclization pattern [22]. Lignan subgroups arise via the shikimic acid pathway from the reduction of cinnamic acid derivatives produced from aromatic aminoacids (L-phenylalanine and L-tyrosine) and subsequently reduced via coenzyme A to alcohols that are the main precursors of all lignans (*p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol) in plants. The enantioselective dimerization of two coniferyl alcohol monomers via intermolecular 8,8' oxidative coupling, generate pinoresinol, a major lignan in food seeds and grains [23].

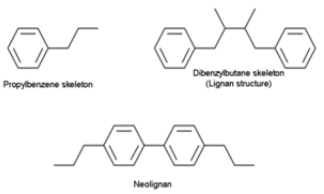

Figure 1: Basic structure of lignans. a and b) The propylbenzene skeleton and the dibenzylbutane skeleton of lignan attached C6-C3 to the central carbon C8. c) Two phenylpropanoid units of a neolignan coupled C5-C5'.

Subsequent metabolization steps generate lariciresinol and secoisolariciresinol through pinoresinol/lariciresinol reductase and secoisolariciresinol dehydrogenase respectively. Secoisolariciresinol is the common precursor of all dibenzylbutyrolactol lignans including matairesinol, yatein and aryltetralin lignans (Figure 2). These subclasses of lignans includes some important bioactive chemicals from which several structural analogues have been derived, studied and employed as pharmaceuticals [24].

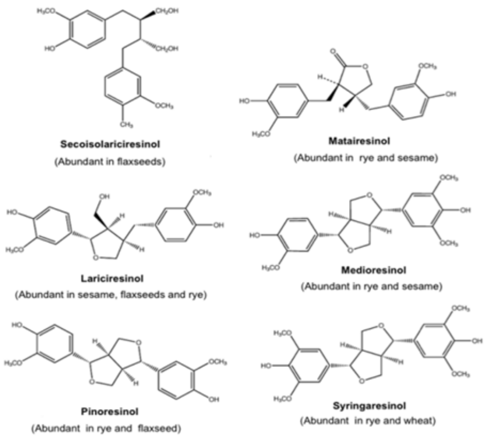

Figure 2: Major lignans in oilseeds and cereals. Secoisolariciresinol is the common precursor of all dibenzylbutyrolactol lignans. These subclasses of lignans include some important bioactive chemicals from which several structural analogues have been derived, studied and employed as pharmaceuticals [24].

Lignans can be converted by intestinal microbiota, under strictly anaerobic condition, to the mammalian lignans, enterodiol (END) and enterolactone (ENL). These compounds, also called enterolignan, following metabolization steps in the gut acquire specific bioactivities and healthy effects, some of which have been shown to occur through the interaction with nuclear receptors [18]. The biotransformation of plant lignans to enterolignan has been extensively studied with secoisolariciresinol (SDG) through the pathway consisting of glycoside hydrolysis, demethylation and dehydroxylation and intermediates [25]. The metabolization steps will be further discussed in the last paragraph of this review in a more detailed manner.

Lignans in nutrition, availability and food sources: Several of the lignans under study are present in plants of a very different kind throughout the whole plant kingdom. Some of them are highly concentrated in plants of medical interest, i.e. *Podophyllum* species containing podophyllotoxin, which is particularly interesting for its anticancer properties [24, 26]. High concentrations of lignans are also found in plants of nutritional interest. The richest are by far oilseeds such as flaxseed and sesame, with concentrations up to 1% of the seed weight. These seeds are consumed in functional amounts in defined geographical regions of the world, in particular the Middle East, North Africa and Asia.

Cereals, nuts, broccoli (*Brassica* species), fruits, berries and beverages (tea, coffee, beer wine) are suggested to be the most important sources of lignans in the diets of Europeans. According to a Dutch lignan database, the average daily intake of lignans in the Netherlands was 1000 to 2000 µg/day and in the Finnish population 1081 µg/day, ranging from 1136 µg/day for men to 1036 µg/day for women) [13]**.** In another study in the Finnish population the average lignan intake based on urinary excretion of lignan was 1224 µg/day [27]**.** Sweden registered the highest intake in Europe with 1773 µg/day total lignans for women and 1947 µg/day for men. Intakes between 1062 and 1188 µg/day have been reported in south Europe (Italy) [13] and 600 µg/day in the USA (Breast Cancer and Environment Research Project Puberty Study) [28]**.** Higher levels of intake (up to 13.5 mg/day) have been reported in previous studies in the USA and Canada [21]**.** In the east, a Chinese study reported intakes measured through the urinary excretion of mammalian lignans giving values in the range of 0.30 and 1.18 nmol/mg creatinine of enterodiol and enterolactone, respectively. The levels of enterodiol were two-fold higher in the Chinese population compared with US women in a similar age range, while enterolactone was observed at similar levels in both populations [29]**.**

Cereal lignans: Up to date, the most investigated lignans have been extracted from food sources such as flaxseed and sesame seeds, the first being known as the richest food source of the lignan secoisolariciresinol and the latter being the most consumed lignan-rich food in the world with a unique lignan composition. However, in the western countries cereals are the major source of lignans (because of their regular daily consumption) with an impact that may influence human health (Table 1).

Wheat: Wheat is the most consumed cereal in the diet in Europe, the USA, and Canada. It is well accepted and has an attractive low price as food, but also as a lignan source. By wheat milling the grain is split into two major parts, the flour (about 70-80%), and the bran fraction, which is approximately 15%. This last fraction contains most of the grain lignans (70-85%), which are mostly situated within the aleurone cells, the single cell layer at the inner site of the bran.

Novel milling and dry-fractionation techniques and new extraction and analytical methods have recently allowed full-scale separation of aleurone cells from the other layers of wheat bran, yielding a fiber rich concentrate which contains many nutrients and well-known bioactive lignans, as well as several new ones with potent bioactivity (Figure 3) [31, 32].

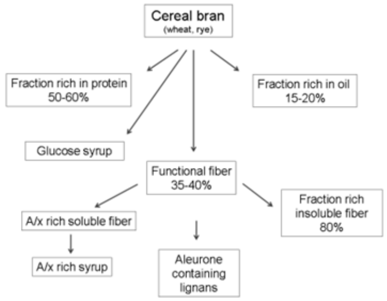

Figure 3: A schematic representation of the fractionation of cereal bran (approximately 15% of the grain). Most of the grain lignan (70-85%) is situated within the aleurone, the single cell layer at the inner site of the bran. Separation of the aleurone cells from the other layers of the cereal bran yields a fiber rich concentrate which, beyond well-known and new lignans, contains many other nutrients.

Table 1: Concentration of main lignan in different food sources.

	Lignan (µg/100 g)						
Food sources	Pinoresinol	Syringaresinol	Lariciresinol	Secoisolariciresinol	Matairesinol	7-Hydroxymatairesinol	Sesamine
Flaxseeds	871	48	1780	165759	529	35	ND
Sesame	47136	205	13060	240	1137	7209	62724
Rye bran	1547	3540	1503	462	729	1017	ND
Wheat bran	138	882	672	868	410	2787	ND
Oat bran	567	297	766	90	440	712	ND
Barley bran	71	140	133	42	42	541	ND

Altogether, wheat grains may contain up to 1 mg lignans/100 g and the large majority of these reside in the bran layer containing up to 20 mg lignans /100 g bran. 7-Hydroxymatairesinol and syringaresinol are the dominant lignans in wheat although secoisolariciresinol, lariciresinol, matairesinol and other less characterized lignans, such as 7-oxomatairesinol are also present in variable concentrations depending on the variety [33, 34] (Table 2).

Table 2: Concentration of total lignans in wheat bran and rye bran.

Wheat bran	Amounts of total lignan 5-20 mg/100 g (*depending on the variety)*
Total lignan	7-hydroxymatairesinol, syringaresinol, secoisolariciresinol, lariciresinol, matairesinol
New lignan	Iso-hydroxymatairesinol, 7-oxomatairesinol
Rye bran	Amounts of total lignan 10-20 mg/100 g *(depending on the variety)*
Total lignan	syringaresinol, pinoresinol, lariciresinol, isolariciresinol, 7-hydroxymatairesinol, matairesinol, secoisolariciresinol.

Different varieties of wheat have been profiled for their content of lignans. In a work by Dinelli *et al.* [35], old and modern Italian wheat varieties cropped in the same location and growing season have been analyzed. The study shows that both free and bound phenols are very variable in content and, on the average, the bound fraction contributed 72.0% to the total phenolic content. The obtained metabolomic fingerprints showed the presence of several classes of compounds which included flavonoids, coumarins, stilbenes, proanthocyanidins and lignans, some of which may have health promoting effects. The HPLC-ESI-TOF-MS analysis identified 104 compounds and also highlighted remarkable differences in the phytochemical fingerprints of old and modern wheat varieties. Six ancient wheat genotypes (Bianco Nostrale, Frassineto, Gentil Rosso, Gentil Rosso Mutico, Marzuolo d'Aqui, Verna) showed phenolic profiles with a number of total compounds and isomer forms including the lignan syringaresinol, with much higher contents than in the modern cultivars, indicating that they might be better sources of phenolic compounds with added value in terms of potential health-promoting components [35].

Rye: Among cereal grains, rye has the highest concentration of lignans, mostly as glycosides which, like in wheat, are concentrated in the outer layers of the kernel [36]. The most abundant are pinoresinol, syringaresinol, 7-hydroxymatairesinol, lariciresinol and isolariciresinol. When considering the whole rye grain, 7-hydroxymatairesinol is the dominant lignin, followed by syringaresinol (Table 2).

In studies aimed at identifying novel urinary biomarkers of wholegrain rye bread intake versus refined wheat bread, the profiling of several metabolites, including END and ENL, allowed the identification of wholegrain rye as a food source providing a higher concentration of urinary phenols [37]. In their study, Bondia-Pons *et al*. experimentally found higher levels of five lignans after intake of wholegrain rye bread than after intake of refined white bread. This was associated with a lower fasting plasma insulin level and lower 24-h urinary C-peptide excretion [37]. The highest concentration of plasma and urinary levels of entrolignans have been measured in subjects traditionally consuming wholegrain rye at the highest amounts in North and East Europe, Russia and China, where the production of rye is mostly concentrated (1 to 4 million tons/year).

Cereal consumption and bioprinciples of accessibility: Regarding the nutritional aspect of cereal grains and bran, studies suggest that whole grains have superior nutritional values compared with foods enriched with fibers. This is because the bioactive components are more abundant in the whole grain and particularly concentrated in the aleurone layer. Moreover, beyond lignans, the bran fraction of cereals contains most of the micronutrients and complex carbohydrates of the grains, in particular beta-glucans and arabinoxylans, which are promising nutraceuticals. Nonetheless, as recently evidenced by an EU study consortia on European cohorts, the consumption of whole seeds or grains supposed to provide health benefits, often does not fulfil the expectations (www.healthgrain.eu). This might be due to the fact that although cereals are good sources of lignans, their bioabsorption from the consumption of the whole grains is limited. This is likely due to their macro- and microstructure and consequently texture of the raw flour which influences their functionality in the gastrointestinal tract, specifically component absorption, bioavailability, and metabolization to enterolignans [38]. The studies carried out by two groups in the Healthgrain consortium working on wholegrain products, including wheat, showed in fact that subjects consuming whole grains did not achieve significant changes in traditional biomarkers of MetS (www.healthgrain.eu). It is now known that this is partially due to the inaccessibility of the bioactive principles contained in the natural matrices because of their insufficient breakdown and digestion but also absorption. The major problem identified by bioavailability studies was the poor bioaccessibility of the active principles. Two studies from Anson *et al.* [39, 40], evidenced that release and conversion of phenolic acids to their microbial metabolites was enhanced by bioprocessing of wheat bran to more bioavailable formulations. In the bioprocessed bread, the bran was processed by yeast fermentation combined with enzyme treatment, consisting of cell-wall-degrading enzymes, mainly xylanase, cellulase, glucanase and feruloyl-esterase [40].

Nutritional impact on health of lignans. The metabolic syndrome (MetS): The high prevalence of MetS and excessive adipose tissue accumulation (in particular, abdominal obesity) is a major threat to public health, being associated with a substantial decrease in health-related quality of life and an increase in economic costs due to disease treatment, as well as lower social productivity.

MetS is a multiplex and life-based risk factor that consists of several correlated risks of metabolic origin. In addition to dyslipidemia, hypertension and hyperglycemia, the syndrome carries a proinflammatory state [41]. Subjects affected by MetS are at increased risk of cardiovascular diseases (2-fold), type-2 diabetes (5-fold), gallbladder disease, certain types of cancer and psychosocial problems (www.lipgene.tcd.ie, www.nutrition.org.uk/lipgene, www.oecd.org.) [42]**.** More than 130 million Europeans are estimated to have MetS and 56 million type-2 diabetes [43] and the numbers are estimated to increase for the next decades**.** Thus, MetS is 'the' major health challenge in Europe and the western countries today but further, the same tendency is also seen in many less developed countries, e.g. India. New strategies and very extensive research and initiatives related to the long-term prevention and reduction of incidence and severity of cardiovascular diseases, type-2 diabetes and obesity have been undertaken by the EU Commission and the WHO for both prevention and cure, to halt the problem [44-46]**.** Amongst the identification of fields of intervention, the better characterization of the bioactive compounds within many foods seems to be a promising area. In fact, although poor diets and physical inactivity are the driving forces behind MetS, appropriate dietary strategies may positively impact on disease predisposition and evolution**.**

For the assessment of the nutritional effects of lignan consumption on human health, different European networks such as the EPIC-Potsdam Study have been particularly suited to serve as epidemiological reference cohorts for results comparison. They have been recently used to investigate the role of lignans on disease occurrence using medically verified data. The analyzed endpoints of chronic diseases following lignan intake were: a) incidence of the metabolic syndrome (NHANES-National Health and Nutrition Examination Survey [47]**;** b) type-2 diabetes (EPIC-InterAct Study) [9]; c) cardiometabolic risk factors (NHANES) [11]; d) specific types of cancers (DietCompLyf Study) [12]**;** (EPIC Study) [10, 48-51], (EPIC-Norfolk) [52-54]**;** and e) overall mortality (EPIC-Spain) [10]**.** From these studies it is apparent that European subpopulations in which the major source of lignans is cereals [9], display considerable lower disease frequency and beneficial effects in the control of metabolic diseases like dyslipidemia and type-2 diabetes**.** Further, other recent observations in different populations report that lignan intake is associated with lower levels of triglycerides, lower fasting glucose, and fasting insulin serum levels in males aged 20-60 years. These data are associated with higher HDL-cholesterol levels [2, 11, 29, 55-58]**.** Some studies have also been conducted in animal models in which partially purified lignan fractions have been shown to improve blood lipids and glycemic control [59, 60]**.** The results from all these studies underline the need to understand better the mechanisms of action of these compounds in maintaining a healthy metabolism.

Mechanisms of lignans on health: Although impressive advances have been seen in the last years as regards the mechanisms of action for the most thoroughly investigated dietary polyphenols (lignans, stilbenes, isoflavones, etc.), most of their health-related effects have been attributed to their activity as antioxidants [61, 62]**.** However, a certain amount of data is now becoming available on the activity of these compounds at doses lower than those required to exert biological antioxidant activities, but sufficient to activate fundamental cell pathways, several of which are regulated by the nuclear receptors (NRs). The availability of data regarding the regulation of different NRs at relatively low doses, stimulated the characterization of the effects of lignans in tissues and cells at doses that are consistent with the doses reached in the blood through the diet (nutritional doses) [7, 18]**.** Among others**,** it has been shown that, at nutritional doses, some lignans can regulate the activity of specific NRs such as the estrogen receptors (ERs) with an efficiency that in some cases approximate to that of the endogenous ligand 17ß-estradiol [18]**.** This highlighted the importance of their actions as hormone mimics suggesting that they are effective on several physiological functions. Based on these observations, molecular and cellular studies are now starting to support the data provided by epidemiological studies and dietary interventions. Significant effects have in fact been shown for regulatory mechanisms related to lipid metabolism, glucose homeostasis, cholesterol biosynthesis and insulin biosynthesis and secretion, [18, 60, 61, 63-65]**.**

Several data on lignans as estrogenic compounds regulating ER-dependent pathways have been published [19, 66]**.** However, recent progress in the area indicate that the term "phytoestrogen" may be poorly representative of the complex activities of lignans when considering as functional targets metabolic functions regulated through the ERs in the liver or adipose tissues, and not representative at all when considering lignan activity through metabolic sensors like the peroxisome proliferator-activated receptors. It is in fact becoming frequent to observe that the same molecules that regulate the ERs, also regulate other NRs that play fundamental actions in metabolic tissues. The engagement and regulation of PPARα, PPARγ, and LXRs that are central regulators of glucose metabolism, fatty acid metabolism and insulin action, evidence the lignans as real SNRMs (Selective Nuclear Receptors Modulators). Known examples are the flaxseed lignan secoisolariciresinol diglucoside (SDG), which can regulate the ERs [6]**,** PPARs [67] and LXRs [17], and unpublished observations. A lignan isolated from medicinal plants, honokiol [68], is a non-adipogenic PPARγ agonist [69] and a ligand of the adipogenic RXRß receptor [70]**.** Meso-dihydroguaiaretic acid (MDGA), a major component of *Myristica fragrans*, a traditionally used food spice in several countries [71], competes with the LXRα agonist T0901317 for binding to the LXRα domain [17]**.** The sesame lignans sesamin and episesamin, can stimulate fatty acid synthesis and oxidation in the liver *via* activation of PPARα, can attenuate nutritional fibrosing steatohepatitis through up-regulation of PPARγ [72], down-regulate PPARγ antiinflammatory effects in 3T3-L1 preadipocytes [16], and can suppress macrophage-derived chemokine expression in human monocytes *via* epigenetic ER- and PPARα–mediated regulation [73]. The mammalian enterolignans, enterodiol (ENL) and enterolactone (END) generated through the metabolization of dietary lignans by the intestinal microbiota bind both the ERs [18] and likely the LXRs, as evidenced by unpublished *in silico* studies (personal communication from Ingemar Pongratz). Activity has also been reported for (+)-pinoresinol through the negative regulation of the human thyroid hormone receptor ß [74], likely interfering with adipose cell differentiation [75]. Negative regulation has also been shown by ENL through the androgen receptor (AR) and by sesamin through the pregnane X receptor (PXR), while secoisolariciresinol and ENL are able to activate PXR in reporter assays suggesting an effect in the metabolism of CYP3A substrates [76]**.** A few cereal lignans have also been tested *in vitro* and found to be effective inhibitors of adipocyte differentiation. Pinoresinol, cycloisolariciresinol, lariciresinol, seicoisolariciresinol in the concentration range of 1-1000 nM, are effective in inhibiting 3T3-L1 cell differentiation [77] and although their fine mechanism of action has still to be clarified, it is likely that it involves the ability to regulate nuclear receptors such as PPARs, ERs and LXRs [65, 78, 79]**.**

Microbial metabolization of lignans: Lignans occur in food in the form of esters, glycoconjugates, and polymers. These compounds are not directly bioavailable and require metabolic steps which involve both mammalian (glucuronidation and to a lesser degree, sulfation) and gut microbial processes [80]. When lignan glycosides are consumed with the diet, they are released from the matrix after mastication, are deglycosylated and are converted in the liver to glucuronidated [81], methylated and sulfated derivatives [82] that can be identified in human urine [83]**,** but also to enterodiol and enterolactone by the intestinal microbiota [20] (Figure 4).

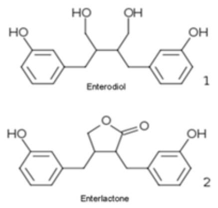

Figure 4: Mammalian lignans. The enterolignans (or mammalian lignan) enterodiol (END) and enterolactone (ENL) are lignan metabolites that are produced in the intestine from plant lignans by the gut microbiota.

Probiotic lactobacilli and bifidobacteria, which have evolved within the colonic ecosystem where indigestible oligo- and polysaccharides are their sole carbon sources, bear several glycosyl-hydrolases and can contribute to the release of the aglycones from glycoconjugated phytochemicals [80]**.** β-Glucosidase-positive probiotic bacteria were proved to release the aglycones of lignans *in vitro* [84]**.** Despite the structural diversity of food lignans and their very different plant origins (i.e. oily matrices versus cereal bran), lignans are converted to enterolignans by the gut microbiota [20]**.** Following metabolization, enterodiol and enterolactone may reach a level high enough for signal pathway regulation in the liver, lung, kidney, heart and brain tissues [83] and pharmacokinetic studies show that these microbial metabolites have high systemic clearance and short half-lives in the blood circulation, before being excreted as hepatic conjugates with the urine [85]. Dietary consumption of probiotics and limited digestible or indigestible food constituents such as oligosaccharides (prebiotics) and polyphenols or both (synbiotics), regulate the numbers and types of microbes which can influence energy utilization from the diet and regulate energy expenditure and storage. However, the genera of the microbiota that contribute to the metabolism of lignans are not yet sufficiently characterized, although investigations are underway and some gut microbiota strands have been identified as major lignan metabolizers in humans [86] and in animals [4, 87] and may thus represent possible beneficial factors for health. Associations are starting to be reported between the composition of the intestinal microbiota, lignan metabolites and the risk of diseases. Recent results suggest that urinary levels of ENL and/or END are associated with a lower risk of type 2-diabetes in US women [5]**,** inflammation [88] and obesity and metabolic alterations in US men [55]**,** and to the inhibition of inflammation and pro-carcinogenic microenvironments in animal tissues [66]**.**

Conclusions: Today, more than 20 different lignans have been identified in seeds and cereals consumed as food worldwide and many others are found in cosmetic and medicinal plants [89]**.** Many of these have not been studied before and may possess potent biological activity, but also, amongst the most studied ones, data are not sufficient to draw definitive considerations for the present. However, the health effects of the most abundant food lignans in ameliorating different chronic diseases and related co-morbidities are being extensively characterized regarding absorption, bioavailability and activity following intake of whole foods, enriched foods, and fractions and extracts. Although so far most of these studies deal mainly with oilseeds lignans, an increasing number of observations indicate that regular intakes of wholegrain cereals and their products may exert a level of protection not observed with the ingestion of refined cereals, and recent research suggests that part of these effects may well be contributed by the lignan components [90]**.**

To conclude, the reviewed body of research suggests that given additional efforts in clinical trials, it may be possible to make ‘function’ claims for lignans related to maintaining a healthy metabolism and the prevention/amelioration of the metabolic syndrome and related pathologies. Importantly, this effect may be elicited through mechanisms that involve their direct agonistic/antagonistic action with different types of nuclear receptors.

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