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Phytochemistry, Bioaccessibility, and Bioactivities of Sesame Seeds: An Overview

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ABSTRACT

Sesame (*Sesamum indicum* L.) is a worldwide cultivated oil crop that belongs to the family Pedaliaceae. Sesame seeds possess high nutritional value, enriching fats, proteins, carbohydrates, and vitamins. Various phytochemical constituents are found in sesame seeds and/or oil, such as phenolic acids, flavonoids, phytosterols, tocopherols, phospholipids, and unique class of lignans such as sesamin and sesamolin, showing specific health potential to the human body (antioxidant, antimutagenic, estrogenic, anti-inflammatory, antimicrobial and hypolipidemic). Bioavailability is composed of two components: bioactivity and bioaccessibility. However, because phytochemicals are treated by the body as xenobiotics, their bioavailability is poor, and their presence in the body is temporary. Although specific methods for determining phytochemical bioavailability in sesame are being established using both *in vitro* and *in vivo* approaches, the results are still inconclusive. Several factors will impact bioavailability in the human body, including molecular structure, transport mechanisms, and food-drug interactions. To improve the bioavailability of phytochemicals in sesame and thereby enhance the bioactivities, specific methods such as the application of sesamol solid lipid nanoparticles, the application of colloidal systems, and changing the solubility of phytosterols will be discussed.

KEYWORDS

Sesame seed; phytochemicals; bioaccessibility; bioavailability; bioactivity

Introduction

Sesame (*Sesamum indicum* L., family Pedaliaceae) is regarded as one of the earliest cultivated crops. It is known as the "queen of oilseeds" due to the high quality of oil, sterols, and antioxidative agents such as sesamin, sesamolin, and tocopherols, which function as nutraceuticals and provide physiological and nutritional benefits.[1] Tropical, subtropical, and southern temperate regions support the growth of the sesame plant. Developing countries such as India, China, Myanmar and Sudan are the world's primary sources of sesame exports.[2] Due to its strong aroma and mild flavor, sesame is extensively produced and well-liked. Sesame seeds are frequently used in people's daily lives to prepare a range of dishes, such as sesame oil and paste, or to adorn other cuisines. In addition, the color of the seed coat varies between sesame varieties, the most common being milky white, brown, and charcoal black. In recent years, certain sesame varieties, for example, black and white sesame, have gained popularity for containing high levels of phenolics, such as lignans, flavonoids, and phenolic acids (ferulic, *p*-coumaric, and 4-hydroxybenzoic acids).[2,3] Furthermore, previous research has shown that sesame seeds

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are an excellent source of various nutrients, such as protein, dietary fiber, iron, phosphorous, calcium, copper, manganese, zinc and vitamin B1.[4] Therefore, sesame seeds are thought to possess antioxidant activity, anti-cancer impacts, constipation protection, and anti-diabetes properties, all of which are favorable for human health.[5]

Phytochemicals are nowadays becoming more widely recognized as health-promoting, preservation, and fixing agents in cells, tissues, and the entire human body.[6] Phytochemicals are plant-derived compounds with specific health potential, and they do not always belong to essential nutrients (carbohydrates, proteins, lipids, minerals, or vitamins), medicines, or toxins. Phenolics, carotenoids, organic acids, and distinct bioactive compounds such as saponin, along with sterols, are among the phytochemicals frequently associated with human health.[1] The contributions of phytochemicals in public health cover a wide range of issues around the world. As a result, researchers, industries, the general public, and policymakers see it as a new strategy for monitoring public health.[7]

Lignans are considered the primary phenolic source in sesame seeds. They are responsible for many biological functions, including preventing cardiovascular disease, obesity, and high blood pressure.[8] Moreover, Wang, et al.[9] mentioned that certain bioactive components present in sesame seeds, such as phenolics, vitamins, and phytosterols, exhibit therapeutic benefits. Sesame tannins, for example, have antimicrobial properties which can be used as an antibacterial agent in medical care.[10] Phytosterols, such as β-sitosterol, have been extensively researched for their benefits in reducing cholesterol, boosting immunity, and relieving inflammation.[11] Hence, specific phytochemicals derived from sesame seeds are bioavailable in humans, with beneficial health advantages.

Analyzing the extent of bioavailability and bioaccessibility of health-related components is essential when assessing the link between food and nutrition. Bioavailability, in nutritional terms, refers to the fraction of a provided food that the body can utilize.[12,13] LADME relates to the stages involved in bioavailability, followed by liberation, absorption, distribution, metabolism, and excretion through the food matrix. Bioaccessibility refers to the quantity of a compound which is released from the food matrix in the gastrointestinal tract, becoming available for absorption. *In vivo* and *in vitro* studies often help analyze the bioaccessibility and bioavailability of substances. Pavez-Guajardo, et al.[14] showed that *in vitro* digestion as an essential part of *in vitro* research refers to simulating bodily digestion to determine the bioavailability of specific nutrients. However, *in vivo* research has some ethical limitations and requires a lot of time. Also, careful design and particular resources are needed to control the experiment. Manach, et al.[15] demonstrated that using bioactive food compounds as functional ingredients would be inhibited by limited bioaccessibility and bioavailability. However, studying bioaccessibility and bioavailability shows many limitations, especially the complex nature of biological systems. These limitations mainly include complex mechanistic pathways, the lack of broad representation of human subjects and food materials, and the interaction of specific food components and chemicals to alter their functional properties during a series of processes such as harvesting, storage, and processing. Moreover, understanding the digestion, absorption, metabolism of food-derived substances plays an essential role in improving bioaccessibility and bioavailability of certain bioactive compounds in sesame seeds, thereby expanding health benefits on the human body.

In recent years, among the reviews on sesame, only two reviewed the phytochemistry of sesame in detail.[16,17] There are few reviews on the bioaccessibility and bioavailability of phytochemicals in sesame. The remaining reviews were either on specific chemical constituents and pharmacological effects of sesame,[18] or on the production aspects of sesame and by-products.[19] This current review not only highlights the nutritional composition of sesame seeds, but also phytochemicals along with their bioactivities, bioaccessibility, and bioavailability studying in sesame seeds. Further, general absorption along with metabolism pathways of specific phytochemicals, as well as certain enhancement methods for bioavailability in sesame are illustrated.

Table 1. Nutritional composition in sesame seeds.

Nutrient	Quantity (%)	References
Moisture	6-7	[21–28]
Protein	20-28	
Carbohydrates	14-16	
Minerals	5-7	
Fibers	6-8	
Oil	48-55	
Saturated fatty acids (% in oil)	10-17	
Unsaturated fatty acids (% in oil)	83-90	
Linoleic acid (% in oil)	37-47	
Oleic acid (% in oil)	35-43	
Stearic acid (% in oil)	5-10	
Palmitic acid (% in oil)	9-11	

Phytochemical profile of sesame seeds

Sesame seeds are regarded as a healthy food in the Middle East, which can provide nutritional along with physiological benefits to the human body.[20] Table 1 shows the nutritional composition of sesame seeds.[21–28] Sesame seeds are rich in oil with 83–90% unsaturated fatty acids. Various types of minerals such as iron, phosphorous, calcium, magnesium, and copper are also detected in sesame.[21] More importantly, sesame enriches certain phytochemicals, including lignans, phytosterols, flavonoids, and phospholipids.[24,26,28–33] The contents and structures of various phytochemicals in sesame seeds are presented in Table 2.

Lignans

Lignans refer to compounds originating from C_6C_3 units and possess two β, β0 linkages (8–80 bond). The mixture produced by two *p*-hydroxyphenylpropane molecules is called lignin, and lignans are a type of lignin. There are two types of lignans in sesame seeds, one is the oil-soluble lignans containing sesamin, sesaminol, sesamolin, pinoresinol, and sesamolinol, and the other is glycosylated water-soluble lignans which contain sesaminol monoglucoside, pinoresinol triglucoside, sesaminol triglucoside, pinoresinol monoglucoside as well as two isomers of sesaminol diglucoside and pinoresinol diglucoside.[34] Figure 1 shows the related compounds of sesame lignans.

Brar and Ahuja[35] suggested that a substance called lignans in the oil gives sesame strong antioxidant properties. It was precisely because of the existence of sesamin, sesamolin and other derivatives that provide sesame oil with its antioxidant, high-stability and high-quality characteristics. Yamashita, et al.[36] showed that the activity of vitamin E could be improved because of the coordination between tocopherols and lignans. Namiki[37] proposed that the bioactive compounds found in sesame seeds cannot explain the solid oxidative stability of roasted sesame oil. In contrast, the accumulated effect of all sesame oil components prevents the roasted oil from lipid oxidation.

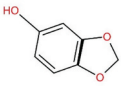
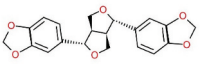
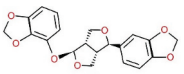
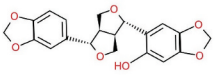
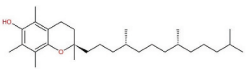
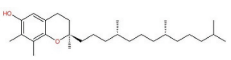
Sesamin, a type of lignan, has now been shown to fight chronic diseases, including breast cancer along with cardiovascular diseases.[38] Episesamin is an isomer of sesamin, mainly from the oil refining process. The presence of functional methylenedioxyphenyl groups in sesamin and sesamolin confers their activity, allowing them to exert their utility by inhibiting liver microsome oxidases.[18,29] The levels of lignans in sesame seeds differ by a significant degree. Several researchers have discovered distinctions in lignan composition in both cultivars and accessions.[2,18] Selected results are shown in Table 2.

Tocopherols

Tocochromanols contain both hydrophilic and hydrophobic components with a lipophilic isoprenoid side chain connected to membrane lipids and a polar chromanol ring pointing towards the membrane surface. Tocochromanols scavenge reactive oxygen species and prevent membrane lipid peroxidation. Tocopherols operate as scavengers of reactive oxygen species, reducing free radical impact and preventing lipid peroxidation. Yoshida, et al.[39] reported that by scavenging free radicals, cell membranes could be protected, and lipids could be replaced and repaired. Heart disease and cancer were also effectively prevented by tocopherols.

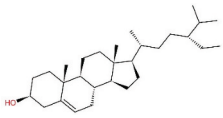
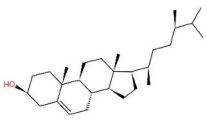
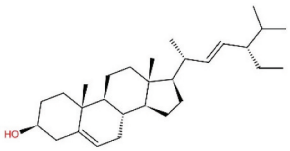
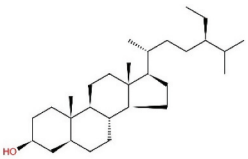
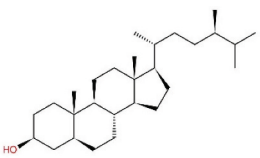
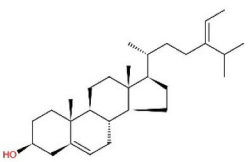
Hofius and Sonnewald[40] demonstrated that tocopherols helped metabolism in plants by transporting sugar from leaves to the phloem. Colombo[41] reported that tocopherol has a chroman ring with one alcoholic hydroxyl group, two methyl groups in the middle of the 12-carbon aliphatic side chain and more than two methyl groups at the end. Further, there are 8 distinct forms of vitamin E synthesized in plants which are α-, β-, γ-, and δ-tocopherols along with α-, β-, γ-, and δ-tocotrienols. A chromanol ring, along with a varied quantity of methyl groups on the chromanol ring, is present in all tocopherols

Table 2. Phytochemicals in sesame seeds.

Bioactive components of sesame	Name of component	Chemical structure	Method of analysis	Findings	Reference
Lignans	Sesamol		High performance liquid chromatography analysis	Sesame seed: 1.20 mg/g	[29] [30]
	Sesamin			Sesame seed: 8.80 mg/g Sesame oil: 6.20 mg/g	
	Sesamolin			Sesame seed: 4.50 mg/g Sesame oil: 2.45 mg/g	
	Sesaminol			Sesame seed: 1.40 mg/g Sesame oil: 0.01 mg/g	
Tocopherols	α-tocopherol		High-performance liquid chromatography diode array detector-fluorescence light detector	Sesame seed: 118.43 mg/kg Sesame press cake: 57.16 mg/kg	[31]
	γ-tocopherol			Sesame seed: 290.37 mg/kg Sesame press cake: 146.16 mg/kg	

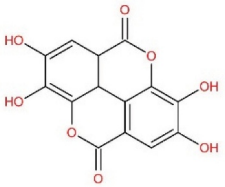
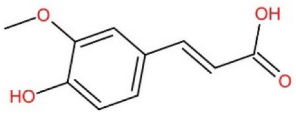
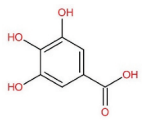
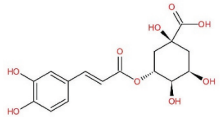
(*Continued*)

Table 2. (Continued).

Bioactive components of sesame	Name of component	Chemical structure	Method of analysis	Findings	Reference
Phytosterols	β-sitosterol		Gas-liquid chromatography analysis	Sesame seed: 3.35 mg/g Sesame oil: 2.63 mg/g	[32]
	Campesterol			Sesame seed: 1.00 mg/g Sesame oil: 1.35 mg/g	
	Stigmasterol			Sesame seed: 0.37 mg/g Sesame oil: 0.47 mg/g	
	Sitostanol			Sesame oil: 0.04 mg/g	
	Campestanol			Sesame oil: 0.02 mg/g	
	Δ5-avenasterol			Sesame oil: 0.82 mg/g	
	Total phytosterols	-		Sesame seed: 4.72 mg/g Sesame oil: 5.33 mg/g	
Phospholipids	Phospholipids	-	High performance liquid chromatography analysis	Unroasted: 3.3% of total lipids Roasted: 0.9–3.2% of total lipids	[28]

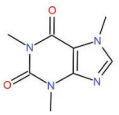
(*Continued*)

Table 2. (Continued).

Bioactive components of sesame	Name of component	Chemical structure	Method of analysis	Findings	Reference
Flavonoids	Procyanidins	-	Reversed-phase high-performance liquid chromatography coupled with diode array detection and electrospray ionization-quadrupole-time-of-flight-mass spectrometry and tandem MS	Sesame oil: 0.03% (area of chromatographic profiles of all characterized metabolites)	[33]
	Catechins	-	Reversed-phase high-performance liquid chromatography coupled with diode array detection and electrospray ionization-quadrupole-time-of-flight-mass spectrometry and tandem MS	Sesame oil: 0.57% (area of chromatographic profiles of all characterized metabolites)	
			High performance liquid chromatography analysis	Raw sesame seed: 280.35 μg/100 g Roasted sesame seed: 173.56 μg/100 g	[24]
	Total flavonoids	-	Spectrophotometric (490 nm)	Sesame seed: 18.03 mg/100 g	[26]
Tannins	Tannins	-	Spectrophotometric (720 nm)	Sesame seed: 3.87 mg/100 g	[26]
Phenolic acids	Ellagic acid		High performance liquid chromatography analysis	Raw sesame seed: 1076.40 μg/100 g Roasted sesame seed: 772.27 μg/100 g	[24]
	Ferulic acid			Raw sesame seed: 14.65 μg/100 g Roasted sesame seed: 9.68 μg/100 g	
	Gallic acid			Raw sesame seed: 3.39 μg/100 g Roasted sesame seed: 4.52 μg/100 g	
	Chlorogenic acid			Raw sesame seed: 75.70 μg/100 g Roasted sesame seed: 68.70 μg/100 g	

(*Continued*)

Table 2. (Continued).

Bioactive components of sesame	Name of component	Chemical structure	Method of analysis	Findings	Reference
Alkaloids	Caffeine		High performance liquid chromatography analysis	Raw sesame seed: 57.60 µg/100 g Roasted sesame seed: 67.58 µg/100 g	[24]
	Total alkaloids	-	Spectrophotometric (568 nm)	Sesame seed: 4.80 mg/100 g	[26]
Saponins	Saponins	-	Spectrophotometric (550 nm)	Sesame seed: 5.60 mg/100 g	[26]

and tocotrienols. Tocopherol's metabolic fate and bioactivities are determined by their morphological characters. Herbers[42] found that the entire isoforms played an essential role in lipid antioxidants, with α-tocopherol possessing the maximum vitamin E activity. Tocotrienols and tocopherols are distinguished by the presence of an unsaturated tail in tocotrienols and a saturated tail in tocopherols.

Moreover, tocopherols were detected in nearly all parts of higher plants, such as in roots, stems, leaves, flowers, fruits, and seeds.[43,44] Nonetheless, different tissues' forms and levels of tocopherols vary greatly. For example, the predominant form of tocopherol in plants' stem and leaf tissues is alpha-tocopherol. DellaPenna[45] showed that γ- and δ-tocopherols were present in relatively high amounts in most seed crops, while the level of α-tocopherol was relatively low. For instance, Pathak, et al.[21] noted an 800 mg/kg of γ-tocopherol content determined in sesame seeds. Besides, Melo, et al.[31] measured the profile of α-tocopherol and γ-tocopherol in sesame, totalizing 218 and 436 mg/kg in sesame cake and seeds, respectively (Table 2).

Phytosterols

Phytosterols, including sterols and stanols, are triterpenoids found in plants, can restrain cancer and other chronic diseases, and exhibit antibacterial, anti-inflammatory, and antioxidant properties.[45–47] Moreau, et al.[48] stated that phytosterols show an extra methyl group at the C-24 position and are structurally similar to cholesterol. Thus, they compete with cholesterol during digestion and reduce blood cholesterol levels. Phytosterols extracted from plant sources are commonly found in functional foods, and processed foods fortified with phytosterols are sometimes labelled as cholesterol-lowering foods. Phytosterols content in sesame seeds is nearly 400 mg/100 g, much higher than that in legumes often used for phytosterols extraction.[21]

β-sitosterol was detected as the principal constituent of phytosterols in sesame seeds, followed by campesterol and stigmasterol.[49] Unlike other phytosterols, β-sitosterol has been significantly explored for its advantages in suppressing inflammation, enhancing immunity, and lowering cholesterol levels.[11] The content of Δ5-avenasterol and stigmasterol present in sesame oil was about 10% and 6.5%, respectively. Δ7-avenasterol and Δ7-stigmasterol were observed in small amounts in total sterols. In addition, the total sterols level in sesame oil was noted at 5.4 mg/g oil.[49]

Phospholipids

Phospholipids, composed of phosphatidic acid and phosphatidylcholine, are known antioxidant enhancers, which help to improve product stability over shelf-life and overall food quality, including smoothness, mouthfeel, etc.[22]

The level of phospholipids in sesame is lower, only accounting for 2.3–3.5% of total lipids, but they are the main components of biological membranes.[34] Phospholipids are widely classified, and different chemical compositions establish other physical properties affecting membrane function.

In sesame seed oil phospholipids studied, the primary fatty acids were palmitic (26.5%), oleic (26.4%) and linoleic (34.0%).[27] Mares, et al.[50] also reported that sesame seeds enriched in unsaturated fatty acids displayed a greater level of unsaturation. Abou-Gharbia, et al.[51] noted that phospholipids in sesame could provide many benefits, including improved memory and learning in mice.

Furthermore, Yoshida, et al.[28] found that phospholipid levels gradually decreased with increasing roasting time, with significant losses followed by phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositol. The breakdown of phospholipids or the formation of complexes with proteins or

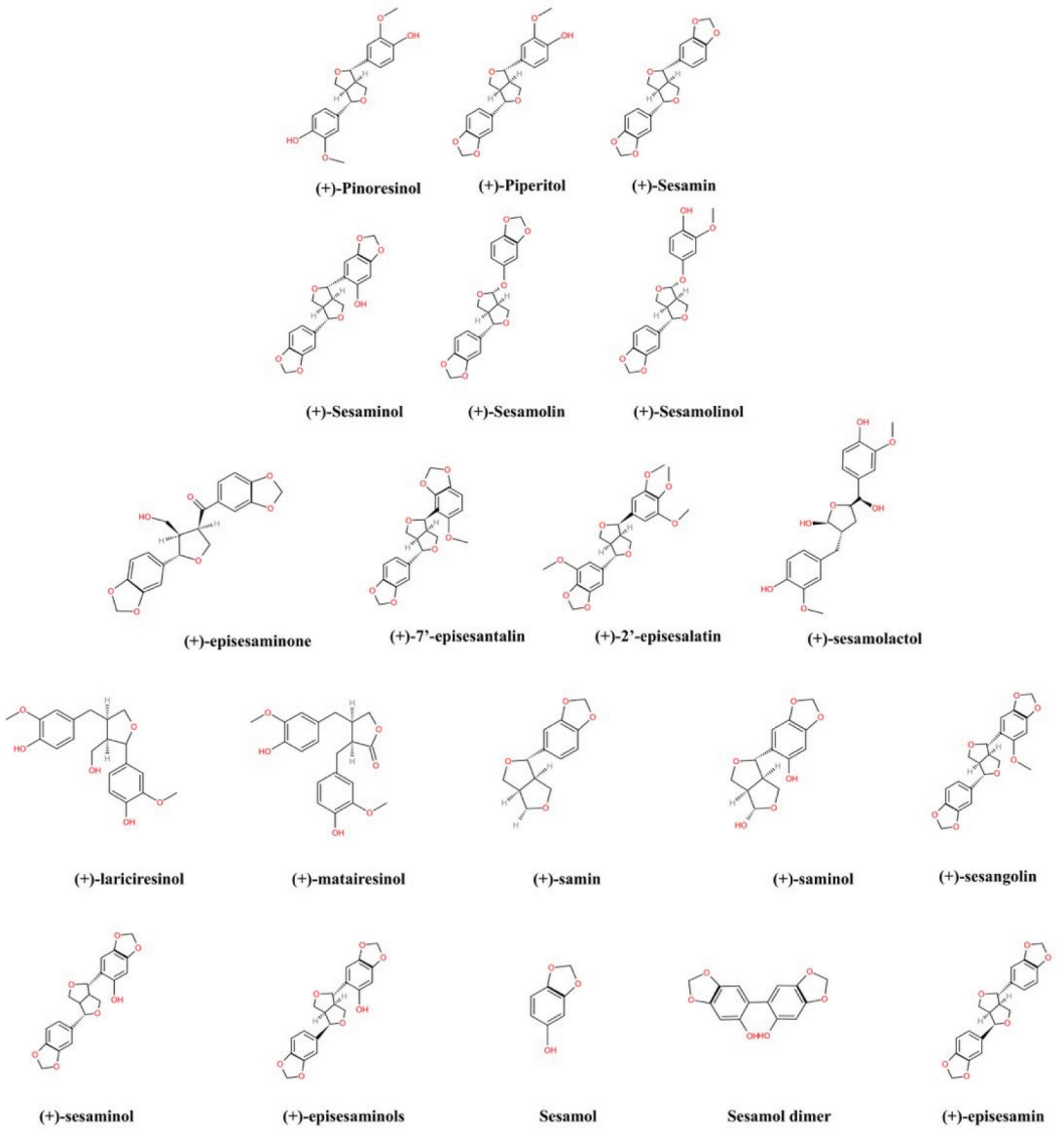


Figure 1. Major (first two rows) and minor (the middle two rows) lignans of sesame and transformation products (bottom row) (adapted from [18]).

carbohydrates causes the phospholipid content to drop during roasting.[52] Phosphatidylethanolamine could significantly enhance the activity of primary antioxidants' activity in vegetable oils by appropriately increasing the roasting temperature.[53]

Flavonoids

Flavonoids, abundant in plants, are classified as phenolic compounds. Asghar, et al.[22] reported that procyanidins, epicatechin, β-catechin, and guercint are at high levels in sesame seeds. Reportedly, C-glycosides are the main flavonoids present in sesame cakes.[33] Samuel and Genevieve[26] reported the phytochemical levels of sesame seeds grown and consumed in Abakaliki, Nigeria, showing a result of 18.03 mg per 100 g of sesame seeds.

Proanthocyanidins, as flavonoid polymers, reportedly have antibacterial, anti-inflammatory, antioxidant, and anti-cancer activities and can reduce cardiovascular disease risk, lower blood sugar levels, and protect from degenerative diseases.[54] Further, Asghar, et al.[22] reported that procyanidins, the subclass of proanthocyanidins, were good scavengers capable of suppressing lipid peroxidation of low-density lipoprotein cholesterol in the human body.

Phenolic acids

Phenolic acids, classified into hydroxybenzoic and hydroxycinnamic acids, participate in several biochemical processes and enrich various vegetal products.[55,56] Laura, et al.[57] noted that, as insoluble substances, phenolic acids are often found to combine with other molecules on the cell wall. Further, phenolic acids have a phenyl group substituted by a carboxylic group and at a minimum of one OH group, which are classified as hydroxycinnamic acids (C_6–C_3 backbone), acetophenones and phenylacetic acids (C_6–C_2 backbones), as well as hydroxybenzoic acids (C_6–C_1 backbone).[56,57]

Gallic, vanillic, salicylic, and protocatechuic acids belong to the group of common hydroxybenzoic acids. While caffeic, *p*-coumaric, and chlorogenic acids will be classified into the group of hydroxycinnamic acids.[57,58] According to Chen, et al,[2] their findings showed that the major phenolics in three processing conditions (raw, roasted, and digested) of sesame were gallic acid, ferulic acid, 4-hydroxybenzoic acid, protocatechuic acid along with quercetin. And these compounds may positively influence the antioxidative activities of sesame products. Furthermore, the level of quercetin, protocatechuic acid, 4-hydroxybenzoic acid, along with gallic acid in sesame would significantly rise after roasting. In another study, Hassan[24] reported that ellagic acid (1076.40 μg/100 g) was the most abundant of the sixteen phenolic acids found in sesame seed samples, and roasting treatment would increase the levels of gallic acid, vanillic acid, and benzoic acid in sesame seeds.

Bioactivities of phytochemicals in sesame seeds

Budowski and Markley[59] reported sesamin and sesamolin as the dominant lignans in sesame seeds. Later, sesaminol was claimed as another dominant lignan in sesame seeds.[60] Shimizu, et al.[61] noted that sesamin, sesamolin, along with sesaminol had the ability to reduce lipids and arachidonic acid levels in humans. They also reported that the lignans from the sesame seed helped lower the level of cholesterol in the blood via suppressing its synthesis and absorption. Other studies noted that these lignans have anti-inflammatory and anticarcinogenic effects and assist in enhancing fatty acid oxidation in the liver.[62,63] In addition, these lignans are neuroprotective and antihypertensive, which can inhibit brain damage or hypoxia.[64,65]

Furthermore, sesame lignans possess tocopherol-sparing as well as antioxidative activities.[66,67] In addition to anti-inflammatory and antihypertensive properties, lignans are reported to influence lipid metabolism where the actions of gene expression and hepatic enzyme are improved, including 3-ketoacyl-CoA-thiolase, bifunctional enzyme, carnitine palmitoyl transferase, and acyl CoA oxidase.[68] Lim, et al.[68] demonstrated that the activity of enzymes that participated in lipogenesis

could be decreased through lignans by altering gene expression, containing fatty acid synthase, glucose-6-phosphate dehydrogenase, acetyl-CoA carboxylase, pyruvate kinase, and ATP citrate cleavage enzymes. Thus, sesame can play an important part in reducing vulnerability and growing protection against cancer, atherosclerosis, and heart disease.[69]

Due to the high amount of lignan and its antioxidative, anticholesterolemic, and antihypertensive effects, sesame possesses both preventive and therapeutic significance in various diseases. After being absorbed by the human body, the sesamin in sesame lignans will undergo enterohepatic circulation and produce potent antioxidant metabolites.[18] Bacteria metabolize this vital antioxidant metabolite in the gut to produce biologically active substances such as mammalian lignan enterolactone and enterodiol compounds. In addition, the effects of such compounds on specific diseases such as breast cancer, colon cancer, bone disease and cardiovascular disease are studied, all illustrating good trends of risk-lowering.[70,71]

In addition to lignans, sesame seeds possess several tocopherol homologues with potential health-promoting effects containing α-tocopherol, γ-tocopherol, δ-tocopherol and tocotrienols. Hemalatha[25] reported that tocopherols and lignans have synergistic effects on the activity of vitamin E and can inhibit the oxidative metabolism of fatty acids in the human body. Lignans are the influencing factors that bring high nutritional value to sesame seeds, and tocopherols play an essential part in promoting the application of sesame seeds in the global daily diet.

Kamal-Eldin[72] noted that α-tocopherol exhibited antioxidant properties by damaging lipoproteins and free radical chains in membranes. At the same time, the incidence of various chronic diseases, including cardiovascular disease, is also reduced because of the antioxidant activity of α-tocopherol and diverse functional properties at the molecular level. Other tocopherols, although possessing low levels, also contain antioxidant biological activity. For example, Li, et al.[73] discovered that γ-tocopherol was more advantageous than α-tocopherol in reducing low-density lipoprotein oxidation, platelet aggregation, and arterial thrombosis. Tocotrienols can inhibit cholesterol synthesis and help lower breast cancer risk.[74,75] Generally, tocopherols have antioxidative, anti-tumor, and cholesterol-lowering effects.[18] In sesame, the most abundant type of tocopherol is γ-tocopherol, while α-tocopherol and δ-tocopherol are in trace levels. Although γ-tocopherol is not the primary form of vitamin E, it has the most potent activities of antioxidants in comparison with other types.[76]

Tocopherols block the cyclic chain reaction of polyunsaturated fatty acid-free radicals, a response that results from lipid oxidation. Subsequently, lipid peroxidation free radicals are converted into tocopherol free radicals under the action of tocopherol. The corresponding tocopherols can be generated under certain antioxidants, such as ascorbic acid.[77] Thus, the tocopherol molecule undergoes multiple fragmentations of the lipid peroxidative chain until final degradation.

It is commonly accepted that the amounts of phytochemicals in nutraceuticals are impacted by manufacturing and storage procedures, affecting their bioactivities. Sesame food and oil are processed mainly through roasting, which imparts a distinctively tasty flavor. Mannan, et al.[20] noted the impact of roasting on total phenolic compounds as well as the γ-tocopherol level of Iranian sesame seeds. They found that with the roasting temperature increasing, the total phenolic content grows considerably. Meanwhile, germinated sesame seeds were illustrated with a higher level of sesamol (4.75 mg/g) along with α-tocopherol (0.32 mg/g), both providing beneficial antioxidative effects to the human body.[50] However, during storage, the total phenolic content, as well as antioxidant activity, was reported to be reduced to a large extent.[29]

Sesame plays a vital role in conventional Chinese and Indian medicinal systems, such as Ayurveda, and has a wide range of medical applications. Sesame oil is applied to treat toothaches and dental problems in China.[69] In India, sesame oil is seen as an antibacterial mouthwash to treat insomnia, anxiety, dizziness, blurry vision, and headache.[25] Additionally, Ang, et al.[78] have reported that sesame oil assists in healing skin burns. A pure herbal formula originating from China, known as moist-exposed burn ointment, is mainly made up of sesame oil, accompanied by small levels of β-sitosterol and other plant extracts, typically utilized to treat burns to the face, neck, as well as hand.[78] Table 3 demonstrates the specific bioactivities of phytochemicals in sesame seeds.[69,79–96]

Table 3. Bioactivities of phytochemicals in sesame seeds.

Compounds	Bioactivity	Model Used	Outcome	Reference
Sesamol	Antioxidative activity	Nanosecond pulse radiolysis technique Cyclic voltammetry	Sesamol effectively scavenges radicals such as hydroxyl, one-electron oxidising, organo-haloperoxyl, lipid peroxyl, and tryptophanyl. Lipid peroxidation, hydroxyl radical-induced deoxyribose degradation, and DNA cleavage are suppressed.	[69]
	Antidepressant activity	Mice using Morris water maze and Y-maze	Chronic unpredictable mild stress (CUMS) triggered loss of memory could be significantly reduced with oral consumption of sesamol (10 mg/kg) and cake extract (600 mg/kg), which increased serum and hippocampus serotonin levels, postsynaptic density protein 95 expression, and hindered oxidative stress.	[79]
	Antimutagenic activity	Ames tester strains TA100 and TA102; Mutagen treatment in many strains of *Salmonella typhimurium*	Sesamol's antimutagenic activity against H_2O_2 and t-BOOH-induced mutagenesis in both TA100 and TA102 strains, particularly TA102, suggests that it works by scavenging oxygen free radicals. Sesamol was observed to be ineffective in suppressing NQNO-induced mutagenicity in *Salmonella typhimurium* TA98 strains, indicating that it does not modulate DNA replication or repair. Sesamol inhibited Na-azide-induced mutagenesis with a maximum inhibition of over 70% in the TA100 strain at 10 µmol/plate.	[80]
	Anti-inflammatory effects and wound healing	C57BL/6 J clean-grade male mice	The composite nanofiber membrane containing high-dose sesamol (5% total polymer concentration, *w/w*) encouraged myofibroblast formation by improving TGF-β signalling pathway transduction and enhanced keratinocyte growth by hindering chronic inflammation in wounds, thereby improving healing of wounds in diabetic mice.	[81]
Sesamin	Antioxidative activity	Male Wistar rats	The rise in vitamin E amounts in rats consumed sesamin, as well as the amounts of vitamin K (menaquinone) in several organs of rats, was demonstrated by supplying a diet containing 0.2% sesamin. Sesamin-fed rats had higher levels of phylloquinone (PK), menaquinone-4 (MK-4), and γ-tocopherol in their livers than control rats. Kidney, heart, lung, testis, and brain PK and brain MK-4 were stronger in rats fed sesame seed than in control rats.	[82]
	Anti-inflammatory effects	Male Wistar rats and male Swiss albino mice	Sesamin (100, 200, or 400 mg/kg) hindered inflammation, decreased edemas caused by carrageenan injections, and sustained pain response, illustrating analgesic effects in a large in *vivo* study on rats and mice.	[83]
	Cardioprotection	Sprague-Dawley rats	Oral administration of sesamin (100 and 200 mg/kg body weight) for 4 weeks slightly enhanced blood sugar levels, body weight, and significantly improved the impacts on heart rate and blood pressure in rats with type 1 diabetes. Sesamin's QT interval was also lowered in comparison to the control group. The results suggested that sesamin may have cardioprotective effects in the STZ-induced diabetes model.	[84]
Episesamin	Antifeedant activity	Flour beetle *Tribolium castaneum*	Among them, asarinin (EC_{50} = 25.64 ppm) demonstrated significantly greater antifeedant activity than the positive control, toosendanin (EC_{50} = 71.69 ppm). As an active chemical group, methylenedioxy may play an important part in antifeedant activities.	[85]

(*Continued*)

Table 3. (Continued).

Compounds	Bioactivity	Model Used	Outcome	Reference
Sesaminol diglucoside	Antiaging activity	Sesaminol diglucoside gel electrophoresis (SDS-PAGE)	Black sesame seed cake was used to extract sesaminol diglucoside. It inhibited collagenase (IC_{50} = 0.26 mg/mL), higher than the standard ascorbic acid inhibitory activity (IC_{50} = 0.44 mg/mL). It has a protective impact on collagen degradation and wrinkle formation Use in cosmetic preparations	[86]
	Anti-inflammatory activity	Sesaminol diglucoside gel electrophoresis (SDS-PAGE)	SDS-PAGE revealed an inhibitory effect on hyaluronidase with an IC_{50} value of 0.70 mg/mL after 48 hours in a concentration-dependent manner.	[86]
	Antioxidative activity	DPPH and FRAP test	Sesaminol diglucoside was found to be a potential DPPH free radical scavenger (IC_{50} = 0.201 ± 0.002 mg/ml) and a strong reducing power (FRAP value: 2.18 ± 0.001 mM Fe (II)/g).	[86]
Sesaminol triglucoside	Anti-inflammatory activity	Sprague-Dawley rats	Sesaminol triglucoside was metabolised by the intestinal flora into catechol metabolites, which were absorbed and distributed to the cardiovascular system and other systems. RAW264.7 murine macrophages stimulated with lipopolysaccharide produced significantly less inflammatory markers such as TNF-α and IL-6.	[87]
	Estrogenic Activity	Sprague-Dawley rats	Beyond sesaminol triglucoside, intestinal flora metabolised sesaminol triglucoside to catechol metabolites that demonstrated ligand-dependent transcriptional activation in oestrogen receptors.	[87]
(+)-Pinoresinol	Hypoglycemic activity	α-glucosidase-guided fractionation	Doses: IC_{50} value of 34.3 μM (+)-pinoresinol inhibits maltose enzymatic hydrolysis in both competitive and noncompetitive ways, and pinoresinol is metabolised to enterolactone in the human digestive tract. A putative hypoglycemic agent.	[88]
Defatted sesame seeds extract	Hypoglycemic activity	Genetically diabetic (type II) KK-Ay mice	Hot water extract (4%) and its methanol-eluent (0.7%) fractions reduced glucose levels in plasma and urine, which was believed to be due to their impact on glucose absorption delay. Good hypoglycemic activity. The methanol extract exhibited α-glucosidase inhibitory in a dose-dependent manner IC_{50} = 375 μg/mL	[89]
Sesame peptides	Antimicrobial activity	Test against two pathogens namely, *Pseudomonas aeruginosa* and *Bacillus subtilis*	Bacteriostatic activity was demonstrated by sesame peptides (smaller than 1 kDa). Sesame peptides inhibit the proliferation of gram negative bacteria (*P. aeruginosa*) more effectively than gram positive bacteria (*B. subtilis*).	[90]
Sesame peptide powder	Antihypertensive activity	Spontaneously hypertensive rats (SHRs)	A reconstituted mixture of the peptides (including Leu-Ser-Ala, Leu-Gln-Pro, Leu-Lys-Tyr, Ile-Val-Tyr, Val-Ile-Tyr, Leu-Val-Tyr, and Met-Leu-Pro-Ala-Tyr) exhibited intensive antihypertensive activity by a drop in the systolic blood pressure (SBP) in spontaneously hypertensive rats (SHRs) (1 and 10 mg/kg). Angiotensin I-converting enzyme (ACE) inhibitory activity	[91]
Sesame seed protein isolate	Antihypertensive activity	Human recombinant renin and angiotensin-converting enzymes (ACE)	The less than 1 kDa peptide fraction was the most efficient inhibitor of angiotensin converting enzyme (81%), while the larger peptides (>3–5 and 5–10 kDa) were the most efficient inhibitors of renin (75–85%).	[92]

(*Continued*)

Table 3. (Continued).

Compounds	Bioactivity	Model Used	Outcome	Reference
Sesame cake bioactive peptides	Antioxidative activity	Transgenic Alzheimer's disease *Caenorhabditis elegans* model	By inhibiting skn-1 downregulation and increasing oxidative stress tolerance via overexpression of essential levels of antioxidant enzyme, dietary supplementation decreases amyloid-induced damage. Reduced risk of Alzheimer's disease.	[93]
		Two transgenic *C. elegans* models (NL5901 and BZ555)	Reduced α-synuclein aggregation in muscle cells, 1-methyl-4-phenylpyridinium ion-induced dopaminergic neurone degeneration, and lowered ROS levels. Lowered risk of Parkinson's disease.	[94]
		Two transgenic *C. elegans* models (AM140 and HA759)	Polyglutamine aggregation was reduced by bioactive peptides, which decreased behavioural impairment and polyglutamine-mediated neuronal death in ASH neurones. Peptides also improved oxidative stress resistance and restored mitochondrial functioning characteristics. Reduced risk of Huntington's disease.	[95]
Defatted sesame seeds powder (fibers and lignans)	Hypocholesterolemic activity	Normal and hypercholesterolemic males Wistar rats	The powder significantly reduced total lipids, cholesterol, and LDL-cholesterol levels in the serum and hepatic tissues while improving HDL-cholesterol levels. There was a considerable rise in hepatic HMG-CoA reductase activity along with bile acid content, as well as a rise in faecal cholesterol and bile acid excretion. The antioxidant enzymes catalase and superoxide dismutase were dramatically increased when defatted sesame powder was consumed orally (fed for four weeks period at dose levels of 5% and 10%).	[96]

Bioaccessibility and bioavailability of phytochemicals in sesame seeds

Bioaccessibility of phytochemicals

Metabolism of polyphenols

Phenolic compounds are associated with organoleptic properties and oxidative stability and are, therefore, important for the quality of plant foods. These phytochemicals have several biological activities that favor the human body. Phenolic compounds have antioxidant, anti-inflammatory, antibacterial, antiallergic, antiarteriosclerotic and antithrombotic effects, with most studies performed as *in vitro* models.[2,97–99] Nonetheless, the physiological activities of polyphenols are not directly related to those substances in the human diet. In fact, those compounds cannot be absorbed or metabolized in the colon and are therefore excreted rapidly. Metabolites of phenolics formed in the digestive tract may no longer have the same biological activity as the original substance after being transferred to the target organ in the blood.[100,101] Antioxidants containing phenolic compounds have different activities in individual organelles than in whole cells. Acting as a barrier, the cell membrane impacts the bioavailability of intracellular antioxidants, potentially reducing genotoxicity or gene protection.[97,101] The comparatively low absorption rate in the upper digestive tract retains the biological effects of polyphenolic compounds on organisms. D'Archivio, et al.[102] noted that the chemical structure is an important factor affecting polyphenols' intestinal absorption and their metabolites circulating in plasma. Molecular weight, esterification, and glycosylation affect the polyphenols' bioavailability. Most phenolic glycans are originally hydrophilic and may be absorbed via biofilms by diffusion, as shown in Fig. 2. Nonetheless, almost all polyphenols present in fruits, as well as vegetables, exist in the form of glycosides, which impacts intestinal absorption.[103]

Flavonoids

Flavonoids are broad polyphenolic compounds diversified according to the oxidation state of heterocyclic compounds. According to different structures, flavonoids are divided into 6 subclasses: flavonols, flavonoids, flavonoid-3-ols, isoflavones, flavonoids, and anthocyanins. Other flavonoids, such as dihydroflavonoids, coumarins, and flavan-3,4-diols, make up a smaller proportion of the diet.[104] So far, over 6,000 flavonoids have been described, and novel substances from this group are still being identified.[105]

Ferreyra, et al.[105] found that except for catechins, most flavonoids exist in plants in close association with β-glycoside sugars. In metabolizing flavonoids, hydrolysis of glycosidic bonds begins first, which may occur directly in enterocytes or the intestinal lumen.[106] The difference in the type of substituted sugar groups will affect the metabolic process. For example, the substrate of human endogenous cellular β-glucosidase is phenolic substances comprising glucose, xylose and arabinose.[44] Since the flora also destroys the released aglycones and generates a variety of simple aromatic acids in the metabolism process, absorption effectiveness is frequently decreased when the flora is present. Some studies demonstrated that phenolics metabolites produced by microflora activity seem to be more active than their precursors.[107,108] Numerous enzymes are responsible for polyphenol metabolism, either endogenous or generated by the micro-flora in the human gastrointestinal system. These contain the previously mentioned cytosolic β-glucosidase, which is found in many tissues but is primarily found in the liver, and lactase, which is found simply in the intestine and may be able to account for the hydrolysis among several polyphenol glycosides, particularly quercetin-3-*O*-glucoside. In the liver and enterocytes, phenolic compounds are conjugated during absorption. Polyphenol methylation is catalyzed by catechol methyltransferase. UDP-glucuronidase catalyzes conjugation with glucuronide conjugates, and aglycones are converted into sulphate derivatives by phenol sulfotransferase. Phenolic compounds are eliminated in the urine or bile after metabolizing them in the body. They are significantly different in the bioavailability, metabolization process, and chemical state than polyphenolic compounds found in plasma.[107] Ferreyra, et al.[105] noted that the degradation of compounds would be prevented if there is a free hydroxy group shown at C-position 4, 5, or 7. The origin of polyphenolic compounds, i.e., the food source, also plays an essential part in

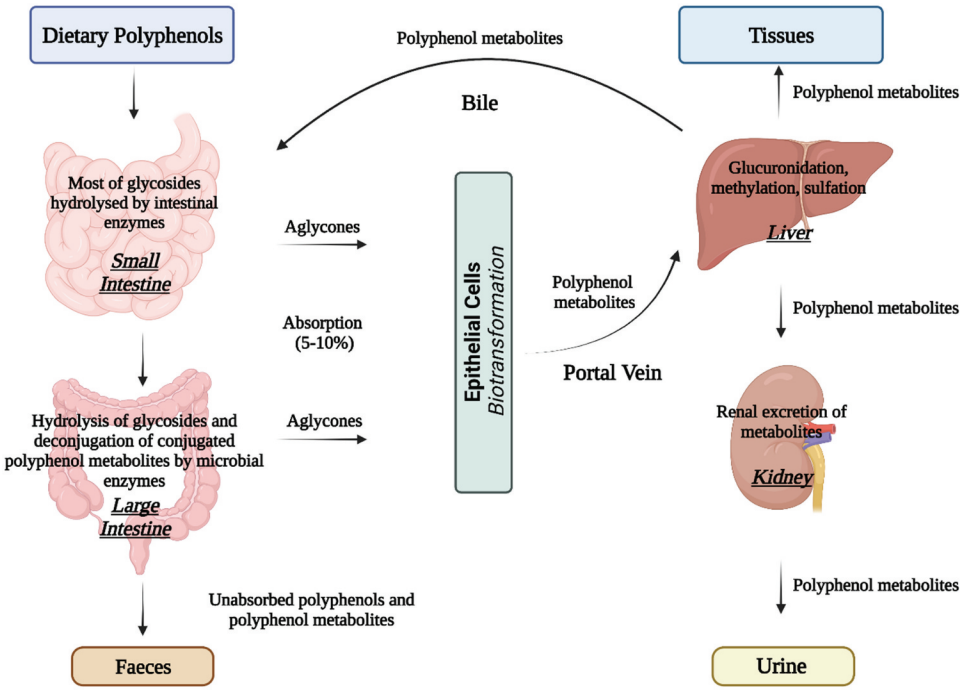


Figure 2. Absorption and metabolism routes for dietary polyphenols in humans (adapted from [103]).

influencing the metabolism, as the molecules can exist in diverse types. In the human digestive system, gallic acid, along with isoflavones, are the main readily absorbed, which are followed by catechin, quercetin glycosides, as well as flavanones.[107]

Phenolic acids

Phenolic acids (C_6-C_3) are non-flavonoids found everywhere in the human diet. Studies on bioavailability show that gallic acid has a very high absorption rate, absorbed by the stomach, small intestine, or both.[109] Gallic acid occurs primarily as 4-*O* methylated and *O*-glucuronic acid conjugates in plasma and urine after ingestion of pure form or food-derived gallic acid.[109] Also, in one *in vitro* study, two phenolic acids were found in all three digestion phases: protocatechuic acid and gallic acid.[110]

Hydroxycinnamic acids, such as ferulic acid, caffeic acid, *p*-coumaric acid, along with caprylic acid, are rarely found in their free form in food. Generally, they undergo esterification with the participation of tartaric acid, quinic acid, or carbohydrate derivatives.[111] However, when such hydroxycinnamic acids are consumed in free form, they will be quickly absorbed in either stomach or small intestine and subsequently combined with intestinal or liver detoxification enzymes.[109,112] Olthof, et al.[113] showed that the colon would be the digestion site for the esterified hydroxycinnamic acids. Comparing the digestion of dextrin-rich and wholemeal bread, one study showed low bioaccessibility for *p*-coumaric acid as well as ferulic acid in both types of bread, while high bioaccessibility for sinapic acid along with caffeic acid.[114]

Lignans

During mammalian digestion, lignan glycosides are altered by the gut bacteria and, thus, deglycosylated, enabling the primary metabolism of lignans. In the laboratory, the total aglycone concentration is measured by deglycosylation, therefore, requiring preparative purification to maximize the yield of aglycones.[115]

Aglycon hydrolysis of pinoresinol diglucoside was successfully achieved via a commercial β-glucosidase.[116] Commercial β-glucosidases cannot hydrolyze the mono- and di-glucosides of sesamol due to steric hindrance inhibiting the enzyme's catalytic action.[117] Katsuzaki, et al.[118] noted that glycosidases could hydrolyze glucosides of lignans successfully, except for sesamolinol. Mixing cellulases and glycosidases could help deglycoylate the lignan glucosides.[119] A study discovered that monoglycosides were the significant sesamin hydrolysates triglycosides, even after combined treatments of β-glucosidase and cellulase.[120] Although Peng, et al.[121] thoroughly optimized the procedure for using the identical combination of enzymes, there was merely a half output of aglycone in pure form.

Glucose will be eliminated from the glucosides of lignans by bacteria in the intestine[122] before the lignan aglycons are transformed into designated enterolignans.[123] Several studies showed that enterolactone and enterodiol were the major types of enterolignans formed by the microbes in the human digestive tract.[124–127] The conversion product of lignans to enteric lignans was found in sterile cultures of microbes separated from the human gut and in cultures inoculated with human fecal inoculum *in vitro*.[71,126] Further, deglycosylation, demethylation, dehydrogenation, along with dihydroxylation are the four conversion steps, while the types of lignans also determine the reduction steps.[126,128]

Bioavailability of phytochemicals in sesame seeds

In vitro gastrointestinal digestion, including oral, gastric and intestinal stages, has been shown to affect defatted sesame meal's antioxidant capacity and lignan bioavailability.[23] In their study, Chen, et al.[23] found that different structures of lignans were influenced distinctly during various stages of *in vitro* gastrointestinal digestion. Specifically, pinoresinol, along with pinoresinol diglucoside contents, significantly increased along the passage of the intestinal track stages. In contrast, the contents of sesamol and pinoresinol diglucosides significantly decreased at the oral stage of digestion. At the same time, the content of sesamol derived from the food matrix was found to reduce after intestinal digestion but increase during gastric digestion. Nonetheless, sesamolin could not be found in all phases of *in vitro* digestion. Meanwhile, analogous trends could be found for sesamolin, sesamol, and pinoresinol levels extracted from 6 distinct varieties of sesame seeds.[2] Chen, et al.[23] found that the antioxidative activity in defatted sesame meal was confirmed to decrease during simulated gastrointestinal digestion using ABTS, DPPH, along with FRAP assays.

The effect of *in vitro* digestion on the content of water-soluble phenolic constituents extracted from six distinct sesame varieties was measured by Chen, et al.[23] Through *in vitro* gastrointestinal digestion, they noted that the mean total phenolic levels were highest in the small intestine, followed by the stomach and oral phases. Further, the existence of several phenolic compounds detected in sesame seeds gradually decreased during upper tract digestion. At the same time, different types of phenolic acids were found to be abundant during gastrointestinal digestion, including chlorogenic acid, protocatechuic acid, gallic acid, as well as 4-hydroxybenzoic acid. Further, Chen, et al.[2] detected the most outstanding amount of chlorogenic acid in roasted sesame seeds in the small intestine (77.3–84.9 mg/100 g dry weight). In contrast, relatively higher levels of protocatechuic acid and gallic acid were found in the gastric and intestinal phases. In addition to the high levels of 4-hydroxybenzoic acid (63.6–91.3 mg/100 g dry weight) detected in the gastric stage, *p*-coumaric acid and quercetin were also manifested during *in vitro* gastrointestinal digestion. Ferulic acid was elevated in the later intestinal phase but was not found in the oral phase. However, Chen, et al.[2] found that the antioxidative activity of sesame was significantly reduced during *in vitro* digestion. The use of a DPPH assay indicated a decrease in the antioxidant capacity of sesame, but FRAP and ABTS assays showed an increase in the antioxidant capacity after digestion.

Luo, et al.[129] measured the antioxidant activities and bioaccessibility of selected phenolic compounds during *in vitro* digestion and colonic fermentation of white, brown, and black sesame seeds. They reported that the bioaccessibility of total phenolic compounds in all varieties peaked at the

colonic stage, followed by the intestinal phase (more significant than the oral and gastric phases). Furthermore, the level of syringic acid was highly bioaccessible in all varieties throughout the digestion and fecal reaction, most likely due to gallic acid metabolism. Nevertheless, kaempferol was noted as the least bioavailable phenolic compound in all three sesame seeds due to its dependence on the action of gut microbiota. After 24 hours of colonic fermentation, all phenolic compounds were wholly bioaccessible and metabolized. In addition, the production of short chain fatty acids was estimated. White sesame seeds produced more individual and total SCFAs than black sesame seeds, which could be favorable for gut health. Nonetheless, because sesame seeds contain a high concentration of lipid and protein fractions, interactions between phenolic compounds and proteins may affect the bioavailability and bioactivity of bioactive compounds, which displays certain limitations.

Factors affecting bioavailability

Bioactive molecule structure

The molecular structure of a bioactive substance considerably affects absorption.[130] For instance, Appeldoorn, et al.[131] indicated that the complex lipids, as well as oligomeric proanthocyanidins (high molecular weight compounds), would only permeate the intestinal cells if they are initially decomposed. In addition, human absorption is also determined by the sugar moiety of flavonoids. As one of the most abundant forms in nature, flavonoids conjugated with β-glucosides are claimed to be less absorbed in the small intestine and are discovered to be absorbed by enzymes, including lactase-phlorizin hydrolase along with β-glucoside hydrolase.[132]

However, Erlund, et al.[133] showed that quercetin, a flavonoid in tea leaves, reaches the large intestine after combining with an additional rhamnose moiety that gut microbiota will break down before being absorbed. Furthermore, the isomeric configuration, along with the chemical structure of bioactive components in food, can influence absorption. In specific drugs, flavonoids with distinct stereochemistry reveal various bioefficacy and bioavailability. The metabolism of hesperidin,[134] (–)-epicatechin and (+)-catechin bioavailability,[135] and the bioactivity of equol,[136] are all the same case.

Mechanisms of transport

One of the most significant elements influencing the bioavailability of consumed food substances and drugs is the multiple transport mechanisms that occur in the intestine's lumen. Facilitated diffusion, passive diffusion, and active transport are examples of these. The initial two mechanisms entail the diffusion of a concentration gradient into the bloodstream via intestinal cells. The final mechanism functions against the gradient of concentration and leads to either increased compound levels in the blood or secretion of the substances back into the gut lumen.[137]

Metabolism and food – drug interactions

After drugs or biologically active food molecules enter the intestinal cells, they may be metabolized by cytochrome 450 enzymes (CYP), changing the biologically foreign bodies through oxidation or reduction. Generally, polyphenols are not substrates for CYP enzymes, while some phase II enzymes affect and act on polyphenols, resulting in polyphenols interacting with sulfotransferases, uridine-5'-bisphosphate glucuronyltransferases, catechol-*O*-methyltransferase and glucuronic acid. As a result, molecular structures that vary from the initial components of the digested food are constituted.[138] Co-administered bioactive compounds or specific drugs could suppress or activate the activity of enzymes belonging to the CYP family. For example, circulating amounts of vitamins that are lipid soluble can be enhanced by inhibiting CYP enzymes, while CYP enzymes could be inhibited by lignans, such as sesamin, thereby assisting in significantly improving the concentration of g-tocopherol in the human body.[139,140]

Bioavailability enhancement method for phytochemicals in sesame seeds

Enhancing the bioavailability of biologically active substances is critical for increasing their bioefficacy. To enhance the bioavailability of bioactive substances, specific methods have been determined. These methods include modifications on chemical and functional aspects of molecules to improve their solubility or absorption sites, the application of nanosystems, and the application of colloidal systems (Table 4).[140–153]

Sesamol possesses various biological activities; however, its low oral bioavailability prevents it from exerting these effects. To increase the bioavailability of sesamol, solid lipid nanoparticles (SLNs), spherical solid lipid particles possessing the ability to disperse in surfactant solutions, are one of the promising alternative drug delivery systems to colloidal drug delivery systems. The generation of SLNs can be achieved by micro-emulsification, a fact shown by many studies. For example, Kakkar, et al.[142] adopted the micro-emulsification technique to make a sesamol solid lipid nanoparticle with materials of Compritol 888, Tween 80, and polysorbate 80. Finding an average particle size of 122 nm for

Table 4. Research works on bioavailability enhancement method for phytochemicals in sesame.

Formulations	Materials	Methodology	Entrapment Efficiency	Loading Capacity	Reference
Solid lipid nanoparticles	Sesamol, polysorbate 80, soy lecithin, Tween 80, compritol 888	Micro-emulsification	75.9%	97.5%	[141]
Solid lipid nanoparticles	Sesamol, soy lecithine, Tween 80, Compritol 888, polysorbate 80	Micro-emulsification	75.9%	86.5%	[142]
Solid lipid nanoparticles	Sesamol, soy lecithine, Tween 80, Compritol 888, polysorbate 80	Micro-emulsification	72.57%	94.26%	[143]
Solid lipid nanoparticles	Sesamol, Tween 80, and egg lecithin	Microemulsion	88.21%	95%	[144]
Solid lipid nanoparticles	Sesamol, polysorbate 80, soy lecithin, Tween 80, compritol 888	Microemulsification	73.92%	75.68%	[145]
Solid lipid nanoparticles	Sesamol, polyethylene glycol, Na2SeO3	Microemulsification	-	84.7%	[146]
Solid lipid nanoparticles	Sesamol, carbon tetrachloride, polysorbate 80, soy lecithin, Tween 80, compritol 888	Microemulsification	73.92%	69.8%	[147]
oleic-acid conjugated nanoparticles	Sesamol, gelatin type A from porcine skin, gluteraldehyde, glycine, 1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide hydrochloride, oleic acid, N-hydroxysuccinimide, and 2-Meracaptoethanol	Micro-emulsification	44.6%	37.16%	[148]
Nano structured lipid carriers	Sesamol, cetyl palmitate and oleic acid, poloxamer 188, Tween 80	High-pressure homogenization	94.3%	82.3%	[149]
Phosphatidyl choline micelles	Sesamol, phosphatidylcholine, deoxysodium cholate, 2,2-diphenyl-1-picrylhydrazyl, pepsin, pancreatin, bile extracts porcine, lucifer yellow dipotassium salt, 20,70-dichlorodihydrofluorescein-diacetate, lipopolysaccharide (LPS) and lipoxygenase.	Microemulsification	96.8%	74.4%	[150]
Casein micelle	Sesamol, sodium caseinate, dibasic potassium phosphate, sodium hydroxide, hydrochloric acid, calcium chloride anhydrous, sodium citrate tribasic dihydrate	Microemulsification	34.9%	-	[151]
Phosphatidyl choline micelles	Sesamol, phosphatidylcholine from soybean, deoxysodium cholate, 2,2-diphenyl-1-picrylhydrazyl, pepsin, pancreatin, bile extracts porcine, lucifer yellow dipotassium salt, 2′,7′-dichlorodihydrofluorescein-diacetate, lipopolysaccharide (LPS) along with lipoxygenase	Microemulsification	97%	74%	[152]
Nano structured lipid carriers	Sesamol, sesame oil, Compritol 888, ATO (glyceryl behenate, tribehenin), a mixture of mono-, di-, and triglycerides of behenic acid (C22), Miglyol 812 (caprylic/capric triglycerides), Lutrol F68 (Poloxamer 188), Sodium polyacrylate	US, HSH	82.5% and 91.2%	-	[153]

sesamol-filled solid lipid nanoparticles, the loading capacity and entrapment efficiency were reported as 86.5% and 75.9%, respectively. Additionally, Kakkar and Kaur[143] later showed a loading capacity and entrapment efficiency of 94.6% and 72.57%, respectively, with a particle size of 106 nm, using soy lecithin, Compritol 888, Tween 80, and polysorbate 80 for preparing the solid lipid nanoparticles. However, in another study by Puglia, et al,[153] sesame oil, sesamol, Compritol 888 ATO, Miglyol 812, Lutrol F68, behenic acid mixture, and sodium polyacrylate were used to produce lipid carriers. The methods of ultrasonication, as well as high shear homogenization, were also adopted. With a particle size of 200 nm, the entrapment efficiency for using the two methods was 91.2% and 82.5%, respectively. Hassanzadeh, et al.[149] prepared the nanostructured sesamol lipid carrier with a particle size of 66.3 nm by utilizing the high-pressure homogenization method, displaying the entrapment efficiency and loading capacity of 94.3% and 82.3%, respectively. In another study, soy lecithin, polysorbate 80, and lipid were added to produce an average particle size of 40 to 70 nm of solid lipid nanoparticles.[141] The loading capacity and entrapment efficiency were noted at 97.5% and 75.9%, respectively.[141] Yashaswini, et al.[152] found an entrapment efficiency of 96.8% by combining phosphatidylcholine-mixed micelles with sesamol, thereby improving its bioavailability.

Another example of improving bioavailability by increasing bioaccessibility is to use of phytosterols. Recrystallization occurs when phytosterols are combined with foodstuff, and product texture changes accordingly. A limited bioavailability is shown in crystalline phytosterols, as they cannot be absorbed in the intestine. To solve this limitation, changing the solubility of phytosterols will be employed to enhance bioaccessibility and bioavailability. Several techniques may be applied, including crystallization retardation, emulsification, and colloidal phytosterol synthesis.[154]

Conclusion

The sesame seed plays the role of a microcapsule containing bioactive components with high variability and medical significance. Sesamin, sesamolin, tocopherols, phytosterols, phospholipids, and other phenolics are among the bioactive and health-promoting phytochemicals found in sesame seeds. Sesamin, sesamol, and other lignan constituents are extremely beneficial to human health and have a wide range of pharmacological impacts. They can be used to treat disorders like anti-inflammatory, antimicrobial, antioxidant, anti-cancer, antimutagenic, antiaging, and anti-cholesterol, as well as to prevent diseases of the heart, breast, and liver.

Generally, when evaluating the relationship between food and nutrition, it is crucial to evaluate the degree of bioaccessibility and bioavailability of health-related components. The results are still ambiguous even though techniques for figuring out phytochemical bioavailability in sesame are being developed using either *in vitro* or *in vivo* methodologies, while eventually leading to the unsustainability of the data. In addition, the use of bioactive compounds in sesame will be inhibited by limited bioaccessibility and bioavailability since most polyphenols are present in food in the form of esters, glycosides, or polymers which cannot be easily absorbed. Meanwhile, other aspects can influence bioavailability, such as the molecular structure of the bioactive compound, transport mechanisms, as well as food-drug interactions.

Specific methods have been developed to enhance the bioavailability of sesame based on the practical level, including changing the solubility of phytosterols by crystallization retardation, the manufacture of sesamol solid lipid nanoparticles by adding lipid matrices, surfactants, and other excipients, along with the application of colloidal systems, such as colloidal phytosterol synthesis. More importantly, a better understanding of the digestion, absorption, and transportation of food-derived compounds is critical in enhancing the bioaccessibility and bioavailability of certain phytochemicals in sesame and will require further research in the future. Possessing various qualities and beneficial nutrients, the sesame crop has enormous potential to improve human health, and it may be one of the most valuable ecological foods over time.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Otles, S.; Bakirci, G. T. Phytochemicals and Health: An Update. In*Phytopharmaceuticals: Potential Therapeutic Applications*, Chauhan, D. N., Shah, K., Eds.,; Beverly: Scrivener Publishing, 2021; pp 437. doi:10.1002/9781119682059.ch22.
[2] Chen, Y.; Lin, H.; Lin, M.; Zheng, Y.; Chen, J. J. F.; Toxicology, C. Effect of Roasting and in vitro Digestion on Phenolic Profiles and Antioxidant Activity of Water-Soluble Extracts from Sesame. *Food Chem. Toxicol.* 2020, *139*, 111239. DOI: 10.1016/j.fct.2020.111239.
[3] Zálešák, F.; Bon, D. J. D.; Pospíšil, J. Lignans and Neolignans: Plant Secondary Metabolites as a Reservoir of Biologically Active Substances. *Pharmacol. Res.* 2019, *146*, 104284. DOI: 10.1016/j.phrs.2019.104284.
[4] Miraj, S.; Kiani, S. Bioactivity of Sesamum Indicum- a Review Study. *Der Pharmacia Lettre*. 2016, *8*(6), 328.
[5] Elleuch, M.; Bedigian, D.; Besbes, S.; Blecker, C.; Attia, H. Dietary Fibre Characteristics and Antioxidant Activity of Sesame Seed Coats (Testae). *Int. J. Food Prop.* 2012, *15*(1), 25. DOI: 10.1080/10942911003687231.
[6] Dillard, C. J.; German, J. B. Phytochemicals: Nutraceuticals and Human Health. *J. Sci. Food Agric.* 2000, *80*(12), 1744. DOI: 10.1002/1097-0010(20000915)80:12<1744:AID-JSFA725>3.0.CO;2-W.
[7] Borges, A.; Abreu, A. C.; Dias, C.; Saavedra, M. J.; Borges, F.; Simões, M. New Perspectives on the Use of Phytochemicals as an Emergent Strategy to Control Bacterial Infections Including Biofilms. *Molecules*. 2016, *21*(7), 877. DOI: 10.3390/molecules21070877.
[8] Mikropoulou, E. V.; Petrakis, E. A.; Argyropoulou, A.; Mitakou, S.; Halabalaki, M.; Skaltsounis, L. A. Quantification of Bioactive Lignans in Sesame Seeds Using HPTLC Densitometry: Comparative Evaluation by HPLC-PDA. *Food Chem.* 2019, *288*, 1. DOI: 10.1016/j.foodchem.2019.02.109.
[9] Wang, D.; Zhang, L.; Huang, X.; Wang, X.; Yang, R.; Mao, J.; Wang, X.; Wang, X.; Zhang, Q.; Li, P. Identification of Nutritional Components in Black Sesame Determined by Widely Targeted Metabolomics and Traditional Chinese Medicines. *Molecules*. 2018, *23*(5), 5. DOI: 10.3390/molecules23051180.
[10] Enemor, V. H. A.; Opara, P. O.; Martins, C. E.; Okafor, C. S.; Mbaka, O. P.; Obayuwana, E. A. Nutritional Composition and in-Vitro Free Radical Scavenging Potentials of Sesamum Indicum Seeds. *IOSR J. Biotechnol. Biochem*. 2020, *6*(3), 52.
[11] Sun, Y.; Gao, L.; Hou, W.; Wu, J. β-Sitosterol Alleviates Inflammatory Response via Inhibiting the Activation of ERK/P38 and NF-κ b Pathways in LPS-Exposed BV2 Cells. *Biomed Res. Int.* 2020, *2020*, 7532306. DOI: 10.1155/2020/7532306.
[12] Benito, P.; Miller, D. Iron Absorption and Bioavailability: An Updated Review. *Nutr. Res.* 1998, *18*(3), 581. DOI: 10.1016/S0271-5317(98)00044-X.
[13] Fernández-García, E.; Carvajal-Lérida, I.; Pérez-Gálvez, A. In vitro Bioaccessibility Assessment as a Prediction Tool of Nutritional Efficiency. *Nutr. Res.* 2009, *29*(11), 751. DOI: 10.1016/j.nutres.2009.09.016.

[14] Pavez-Guajardo, C.; Ferreira, S. R.; Mazzutti, S.; Guerra-Valle, M. E.; Sáez-Trautmann, G.; Moreno, J. Influence of in vitro Digestion on Antioxidant Activity of Enriched Apple Snacks with Grape Juice. *Foods*. 2020, *9*(11), 1681. DOI: 10.3390/foods9111681.
[15] Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C.; Jiménez, L. Polyphenols: Food Sources and Bioavailability. *Am. J. Clin. Nutr*. 2004, *79*(5), 727. DOI: 10.1093/ajcn/79.5.727.
[16] Mili, A.; Das, S.; Nandakumar, K.; Lobo, R. A Comprehensive Review on Sesamum Indicum L.: Botanical, Ethnopharmacological, Phytochemical, and Pharmacological Aspects. *J. Ethnopharmacol*. 2021, *281*, 114503. DOI: 10.1016/j.jep.2021.114503.
[17] Wei, P.; Zhao, F.; Wang, Z.; Wang, Q.; Chai, X.; Hou, G.; Meng, Q. Sesame (Sesamum Indicum L.): A Comprehensive Review of Nutritional Value, Phytochemical Composition, Health Benefits, Development of Food, and Industrial Applications. *Nutrients*. 2022, *14*(19), 4079. DOI: 10.3390/nu14194079.
[18] Andargie, M.; Vinas, M.; Rathgeb, A.; Möller, E.; Karlovsky, P. Lignans of Sesame (Sesamum Indicum L.): A Comprehensive Review. *Molecules*. 2021, *26*(4), 4. DOI: 10.3390/molecules26040883.
[19] Myint, D.; Gilani, S. A.; Kawase, M.; Watanabe, K. N. Sustainable Sesame (Sesamum Indicum L.) Production Through Improved Technology: An Overview of Production, Challenges, and Opportunities in Myanmar. *Sustainability*. 2020, *12*(9), 3515. DOI: 10.3390/su12093515.
[20] Mannan, H.; Oveisi, M. R.; Naficeh, S.; Jannat, B.; Bahaeddin, Z.; Mansouri, S. Gamma Tocopherol Content of Iranian Sesame Seeds. *Iran. J. Pharm. Res. World*. 2008, *7*(2), 135. doi:10.22037/ijpr.2010.756.
[21] Pathak, N.; Rai, A. K.; Kumari, R.; Bhat, K. V. Value Addition in Sesame: A Perspective on Bioactive Components for Enhancing Utility and Profitability. *Pharmacogn. Rev*. 2014, *8*(16), 147. DOI: 10.4103/0973-7847.134249.
[22] Asghar, A.; Majeed, M. N.; Akhtar, M. N. A Review on the Utilization of Sesame as Functional Food. *Am. J. Food Nutr*. 2014, *4*(1), 21.
[23] Chen, Y.; Lin, H.; Lin, M.; Lin, P.; Chen, J. Effects of Thermal Preparation and in vitro Digestion on Lignan Profiles and Antioxidant Activity in Defatted-Sesame Meal. *Food Chem. Toxicol*. 2019, *128*, 89. DOI: 10.1016/j.fct.2019.03.054.
[24] Hassan, M. A. M. Studies on Egyptian Sesame Seeds (Sesamum Indicum L.) and Its Products 1-Physicochemical Analysis and Phenolic Acids of Roasted Egyptian Sesame Seeds (Sesamum Indicum L.). *World J. Dairy Food Sci*. 2012, *7*, 195.
[25] Hemalatha, S. Lignans and Tocopherols in Indian Sesame Cultivars. *J. Am. Oil Chem. Soc*. 2004, *81*(5), 467. DOI: 10.1007/s11746-004-0924-5.
[26] Samuel, N.; Genevieve, A. Proximate Analysis and Phytochemical Properties of Sesame (Sesamum Indicum L.) Seeds Grown and Consumed in Abakaliki, Ebonyi State, Nigeria. *Int. J. Health Med*. 2017, *2*(4), 1. DOI: 10.24178/ijhm.2017.2.4.01.
[27] Vijayalakshmi, B.; Rao, S. V. Fatty Acid Composition of Phospholipids in Seed Oils Containing Unusual Acids. *Chem. Phys. Lipids*. 1972, *9*(1), 82. DOI: 10.1016/0009-3084(72)90035-7.
[28] Yoshida, H.; Abe, S.; Hirakawa, Y.; Takagi, S. Roasting Effects on Fatty Acid Distributions of Triacylglycerols and Phospholipids in Sesame (Sesamum Indicum) Seeds. *J. Sci. Food Agric*. 2001, *81*(7), 620. DOI: 10.1002/jsfa.857.
[29] Ghafoorunissa, S. H.; Rao, M. V. Sesame Lignans Enhance Antioxidant Activity of Vitamin E in Lipid Peroxidation Systems. *Mol. Cell. Biochem*. 2004, *262*(1–2), 195. DOI: 10.1023/B:MCBI.0000038235.01389.a9.
[30] Moazzami, A. A.; Andersson, R. E.; Kamal-Eldin, A. HPLC Analysis of Sesaminol Glucosides in Sesame Seeds. *J. Agric. Food Chem*. 2006, *54*(3), 633. DOI: 10.1021/jf051541g.
[31] Melo, D.; Álvarez-Ortí, M.; Nunes, M. A.; Costa, A. S. G.; Machado, S.; Alves, R. C.; Pardo, J. E.; Oliveira, M. B. P. P. Whole or Defatted Sesame Seeds (Sesamum Indicum L.)? The Effect of Cold Pressing on Oil and Cake Quality. *Foods*. 2021, *10*(9), 2108. DOI: 10.3390/foods10092108.
[32] Normén, L.; Ellegård, L.; Brants, H.; Dutta, P.; Andersson, H. A Phytosterol Database: Fatty Foods Consumed in Sweden and the Netherlands. *J. Food Compost. Anal*. 2007, *20*(3), 193. DOI: 10.1016/j.jfca.2006.06.002.
[33] Mekky, R. H.; Abdel-Sattar, E.; Segura-Carretero, A.; Contreras, M. D. M. Metabolic Profiling of the Oil of Sesame of the Egyptian Cultivar 'Giza 32' Employing LC-MS and Tandem MS-Based Untargeted Method. *Foods*. 2021, *10*(2), 2. DOI: 10.3390/foods10020298.
[34] Kamal-Eldin, A.; Appelqvist, L. A. Variation in Fatty Acid Composition of the Different Acyl Lipids in Seed Oils from Four Sesamum Species. *J. Am. Oil Chem. Soc*. 1994, *71*(2), 135. DOI: 10.1007/BF02541547.
[35] Brar, G. S.; Ahuja, K. L. Sesame: Its Culture, Genetics, Breeding and Biochemistry. *Annual Reviews of Plant Sciences*. 1980, *1*, 245.
[36] Yamashita, K.; Iizuka, Y.; Imai, T.; Namiki, M. Sesame Seed and Its Lignans Produce Marked Enhancement of Vitamin E Activity in Rats Fed a Low α-tocopherol Diet. *Lipids*. 1995, *30*(11), 1019. DOI: 10.1007/BF02536287.
[37] Namiki, M. The Chemistry and Physiological Functions of Sesame. *Food Rev. Int*. 1995, *11*(2), 281. DOI: 10.1080/87559129509541043.
[38] Dalibalta, S.; Majdalawieh, A. F.; Manjikian, H. Health Benefits of Sesamin on Cardiovascular Disease and Its Associated Risk Factors. *Saudi Pharm. J*. 2020, *28*(10), 1276. DOI: 10.1016/j.jsps.2020.08.018.

[39] Yoshida, Y.; Niki, E.; Noguchi, N. Comparative Study on the Action of Tocopherols and Tocotrienols as Antioxidant: Chemical and Physical Effects. *Chem. Phys. Lipids*. 2003, *123*(1), 63. DOI: 10.1016/S0009-3084(02)00164-0.
[40] Hofius, D.; Sonnewald, U. Vitamin E Biosynthesis: Biochemistry Meets Cell Biology. *Trends Plant Sci*. 2003, *8*(1), 6. DOI: 10.1016/S1360-1385(02)00002-X.
[41] Colombo, M. L. An Update on Vitamin E, Tocopherol and Tocotrienol—perspectives. *Molecules*. 2010, *15*(4), 2103. DOI: 10.3390/molecules15042103.
[42] Herbers, K. Vitamin Production in Transgenic Plants. *J. Plant Physiol*. 2003, *160*(7), 821. DOI: 10.1078/0176-1617-01024.
[43] Fritsche, S.; Wang, X.; Jung, C. Recent Advances in Our Understanding of Tocopherol Biosynthesis in Plants: An Overview of Key Genes, Functions, and Breeding of Vitamin E Improved Crops. *Antioxidants (Basel, Switzerland)*. 2017, *6*(4), 99. DOI: 10.3390/antiox6040099.
[44] Panche, A. N.; Diwan, A. D.; Chandra, S. R. Flavonoids: An Overview. *J. Nutr. Sci*. 2016, *5*, e47. DOI: 10.1017/jns.2016.41.
[45] DellaPenna, D. Progress in the Dissection and Manipulation of Vitamin E Synthesis. *Trends Plant Sci*. 2005, *10*(12), 574. DOI: 10.1016/j.tplants.2005.10.007.
[46] Van Rensburg, S.; Daniels, W.; Van Zyl, J.; Taljaard, J. J. M. B. D. A Comparative Study of the Effects of Cholesterol, Beta-Sitosterol, Beta-Sitosterol Glucoside, Dehydro-Epiandrosterone Sulphate and Melatonin on in vitro Lipid Peroxidation. *Metabolic Brain Disease*. 2000, *15*(4), 257. DOI: 10.1023/A:1011167023695.
[47] Zhao, W.; Miao, X.; Jia, S.; Pan, Y.; Huang, Y. J. P. S. Isolation and Characterization of Microsatellite Loci from the Mulberry, Morus L. *J Plant Science*. 2005, *168*(2), 519. DOI: 10.1016/j.plantsci.2004.09.020.
[48] Moreau, R. A.; Whitaker, B. D.; Hicks, K. B. Phytosterols, Phytostanols, and Their Conjugates in Foods: Structural Diversity, Quantitative Analysis, and Health-Promoting Uses. *Prog. lipid res*. 2002, *41*(6), 457. DOI: 10.1016/S0163-7827(02)00006-1.
[49] Gharby, S.; Harhar, H.; Bouzoubaa, Z.; Asdadi, A.; El Yadini, A.; Charrouf, Z. Chemical Characterization and Oxidative Stability of Seeds and Oil of Sesame Grown in Morocco. *J. Saudi Soc. Agric. Sci*. 2017, *16*(2), 105. DOI: 10.1016/j.jssas.2015.03.004.
[50] Mares, L. F. D. M.; Passos, M. C.; Menezes, C. C. Interference of Germination Time on Chemical Composition and Antioxidant Capacity of White Sesame (Sesamum Indicum). *Food Science and Technology/Ciencia e Tecnologia de Alimentos*. 2018, *38*(Suppl. 1), 248. DOI: 10.1590/1678-457x.20217.
[51] Abou-Gharbia, H. A.; Shehata, A. A. Y.; Shahidi, F. Effect of Processing on Oxidative Stability and Lipid Classes of Sesame Oil. *Food Res. Int*. 2000, *33*(5), 331. DOI: 10.1016/S0963-9969(00)00052-1.
[52] Hudson, B. J. F.; Ghavami, M. Phospholipids as Antioxidant Synergists for Tocopherols in the Autoxidation of Edible Oils. *Food Sci. Technol. Int*. 2013, *17*(4), 191.
[53] Cai, Z.; Li, K.; Lee, W. J.; Reaney, M. T. J.; Zhang, N.; Wang, Y. Recent Progress in the Thermal Treatment of Oilseeds and Oil Oxidative Stability: A Review. *Fundam. Res*. 2021, *1*(6), 767. DOI: 10.1016/j.fmre.2021.06.022.
[54] Rue, E. A.; Rush, M. D.; van Breemen, R. B. Procyanidins: A Comprehensive Review Encompassing Structure Elucidation via Mass Spectrometry. *Phytochem. Rev*. 2018, *17*(1), 1. DOI: 10.1007/s11101-017-9507-3.
[55] Vuolo, M. M.; Lima, V. S.; Junior, M. R. M. Phenolic Compounds: Structure, Classification, and Antioxidant Power. In *Bioactive Compounds*, Campos, M. R. S., Ed.; Cambridge: Woodhead Publishing, 2019; pp 33.
[56] Luna-Guevara, M. L.; Luna-Guevara, J. J.; Hernández-Carranza, P.; Ruíz-Espinosa, H.; Ochoa-Velasco, C. E. Phenolic Compounds: A Good Choice Against Chronic Degenerative Diseases. *Stud. Nat. Prod., Elsevier*. 2018, *59*, 79.
[57] Laura, A.; Moreno-Escamilla, J. O.; Rodrigo-García, J.; Alvarez-Parrilla, E. Phenolic Compounds. In *Postharvest Physiology and Biochemistry of Fruits and Vegetables*, Yahia, E. M., Ed.; Cambridge: Woodhead Publishing, 2019; pp 253.
[58] Ferreira, I. C.; Martins, N.; Barros, L. Phenolic Compounds and Its Bioavailability: In vitro Bioactive Compounds or Health Promoters? *Adv. Food Nutr. Res., Elsevier*. 2017, *82*, 1.
[59] Budowski, P.; Markley, K. The Chemical and Physiological Properties of Sesame Oil. *Chem. Rev*. 1951, *48*(1), 125. DOI: 10.1021/cr60149a005.
[60] Osawa, T.; Nagata, M.; Namiki, M.; Fukuda, Y. Sesamolinol, a Novel Antioxidant Isolated from Sesame Seeds. *Agric Biol Chem*. 1985, *49*(11), 3351. DOI: 10.1080/00021369.1985.10867272.
[61] Shimizu, S.; Akimoto, K.; Shinmen, Y.; Kawashima, H.; Sugano, M.; Yamada, H. Sesamin is a Potent and Specific Inhibitor of Δ5 Desaturase in Polyunsaturated Fatty Acid Biosynthesis. *Lipids*. 1991, *26*(7), 512. DOI: 10.1007/BF02536595.
[62] Hsu, D. -Z.; Su, S. -B.; Chien, S. -P.; Chiang, P. -J.; Li, Y. -H.; Lo, Y. -J.; Liu, M. -Y. Effect of Sesame Oil on Oxidative-Stress-Associated Renal Injury in Endotoxemic Rats: Involvement of Nitric Oxide and Proinflammatory Cytokines. *Shock*. 2005, *24*(3), 276. DOI: 10.1097/01.shk.0000172366.73881.c7.
[63] Yokota, T.; Matsuzaki, Y.; Koyama, M.; Hitomi, T.; Kawanaka, M.; Enoki-konishi, M.; Okuyama, Y.; Takayasu, J.; Nishino, H.; Nishikawa, A. Sesamin, a Lignan of Sesame, Down-regulates Cyclin D1 Protein Expression in Human Tumor Cells. *Cancer Sci*. 2007, *98*(9), 1447. DOI: 10.1111/j.1349-7006.2007.00560.x.

[64] Lee, C. -C.; Chen, P. -R.; Lin, S.; Tsai, S. -C.; Wang, B. -W.; Chen, W. -W.; Tsai, C. E.; Shyu, K. -G. Sesamin Induces Nitric Oxide and Decreases Endothelin-1 Production in HUVECs: Possible Implications for Its Antihypertensive Effect. *J. Hypertens.* 2004, *22*(12), 2329. DOI: 10.1097/00004872-200412000-00015.
[65] Nakano, D.; Kurumazuka, D.; Nagai, Y.; Nishiyama, A.; Kiso, Y.; Matsumura, Y. Dietary Sesamin Suppresses Aortic NADPH Oxidase in DOCA Salt Hypertensive Rats. *Clin. Exp. Pharmacol. Physiol.* 2007, *35*(3), 324. DOI: 10.1111/j.1440-1681.2007.04817.x.
[66] Wu, W. -H.; Kang, Y. -P.; Wang, N. -H.; Jou, H. -J.; Wang, T. -A. Sesame Ingestion Affects Sex Hormones, Antioxidant Status, and Blood Lipids in Postmenopausal Women. *J. Nutr.* 2006, *136*(5), 1270. DOI: 10.1093/jn/136.5.1270.
[67] Mak, D.; Chiu, P. Y.; Ko, K. M. Antioxidant and anticarcinogenic potential of sesame lignans. In *Sesame: the genus Sesamum. Medicinal and Aromatic Plants – Industrial Profiles*, Bedigian, D., Ed.; Boca Raton: CRC Press, 2010; pp 111.
[68] Lim, J. S.; Adachi, Y.; Takahashi, Y.; Ide, T. Comparative Analysis of Sesame Lignans (Sesamin and Sesamolin) in Affecting Hepatic Fatty Acid Metabolism in Rats. *Br. J. Nutr.* 2007, *97*(1), 85. DOI: 10.1017/S0007114507252699.
[69] Monteiro, E. M. H.; Chibli, L. A.; Yamamoto, C. H.; Pereira, M. C. S.; Vilela, F. M. P.; Rodarte, M. P.; Pinto, M. A. D. O.; Do Amaral, M. D. P. H.; Silvério, M. S.; Araújo, A. L. S. D. M., et al. Antinociceptive and Anti-Inflammatory Activities of the Sesame Oil and Sesamin. *Nutrients*. 2014, *6*(5), 1931. DOI: 10.3390/nu6051931.
[70] Coulman, K. D.; Liu, Z.; Hum, W. Q.; Michaelides, J.; Thompson, L. U. Whole Sesame Seed is as Rich a Source of Mammalian Lignan Precursors as Whole Flaxseed. *Nutr. Cancer*. 2005, *52*(2), 156. DOI: 10.1207/s15327914nc5202_6.
[71] Liu, Z.; Saarinen, N. M.; Thompson, L. U. Sesamin is One of the Major Precursors of Mammalian Lignans in Sesame Seed (Sesamum Indicum) as Observed in vitro and in Rats. *J. Nutr.* 2006, *136*(4), 906. DOI: 10.1093/jn/136.4.906.
[72] Kamal-eldin, A. The Chemistry and Antioxidant Properties of Tocopherols and Tocotrienols. *Lipids*. 1996, *31*(7), 671. DOI: 10.1007/BF02522884.
[73] Li, D.; Saldeen, T.; Romeo, F.; Mehta, J. L. Relative Effects of α-And γ-Tocopherol on Low-Density Lipoprotein Oxidation and Superoxide Dismutase and Nitric Oxide Synthase Activity and Protein Expression in Rats. *J. Cardiovasc. Pharmacol. Ther.* 1999, *4*(4), 219. DOI: 10.1177/107424849900400403.
[74] Qureshi, A.; Bradlow, B.; Brace, L.; Manganello, J.; Peterson, D.; Pearce, B.; Wright, J.; Gapor, A.; Elson, C. Response of Hypercholesterolemic Subjects to Administration of Tocotrienols. *Lipids*. 1995, *30*(12), 1171. DOI: 10.1007/BF02536620.
[75] Schwenke, D. C. Does Lack of Tocopherols and Tocotrienols Put Women at Increased Risk of Breast Cancer? *J. Nutr. Biochem.* 2002, *13*(1), 2. DOI: 10.1016/S0955-2863(01)00207-8.
[76] Rizvi, S.; Raza, S. T.; Ahmed, F.; Ahmad, A.; Abbas, S.; Mahdi, F. The Role of Vitamin E in Human Health and Some Diseases. *Sultan Qaboos Univ. Med. J.* 2014, *14*(2), e157.
[77] Traber, M. G.; Stevens, J. F. Vitamins C and E: Beneficial Effects from a Mechanistic Perspective. *Free Radic. Biol. Med.* 2011, *51*(5), 1000. DOI: 10.1016/j.freeradbiomed.2011.05.017.
[78] Ang, E.; Lee, S.; Gan, C.; See, P.; Chan, Y.; Ng, L.; Machin, D. Evaluating the Role of Alternative Therapy in Burn Wound Management: Randomized Trial Comparing Moist Exposed Burn Ointment with Conventional Methods in the Management of Patients with Second-Degree Burns. *Medgenmed: Medscape General Medicine*. 2001, *3*(2), 3.
[79] Liu, Z.; Liu, X.; Luo, S.; Chu, C.; Wu, D.; Liu, R.; Wang, L.; Wang, J.; Liu, X. Extract of Sesame Cake and Sesamol Alleviate Chronic Unpredictable Mild Stress-Induced Depressive-Like Behaviors and Memory Deficits. *J. Funct. Foods*. 2018, *42*, 237. DOI: 10.1016/j.jff.2018.01.005.
[80] Joshi, R.; Kumar, M. S.; Satyamoorthy, K.; Unnikrisnan, M. K.; Mukherjee, T. Free Radical Reactions and Antioxidant Activities of Sesamol: Pulse Radiolytic and Biochemical Studies. *J. Agric. Food Chem.* 2005, *53*(7), 2696. DOI: 10.1021/jf0489769.
[81] Kaur, I. P.; Saini, A. Sesamol Exhibits Antimutagenic Activity Against Oxygen Species Mediated Mutagenicity. *Mutat. Res/Genet. Toxicol. Environ. Mutagen.* 2000, *470*(1), 71. DOI: 10.1016/S1383-5718(00)00096-6.
[82] Liu, F.; Li, X.; Wang, L.; Yan, X.; Ma, D.; Liu, Z.; Liu, X. Sesamol Incorporated Cellulose Acetate-Zein Composite Nanofiber Membrane: An Efficient Strategy to Accelerate Diabetic Wound Healing. *Int. J. Biol. Macromol.* 2020, *149*, 627. DOI: 10.1016/j.ijbiomac.2020.01.277.
[83] Hanzawa, F.; Nomura, S.; Sakuma, E.; Uchida, T.; Ikeda, S. Dietary Sesame Seed and Its Lignan, Sesamin, Increase Tocopherol and Phylloquinone Concentrations in Male Rats. *Nutrients*. 2013, *143*(7), 1067. DOI: 10.3945/jn.113.176636.
[84] Thuy, T. D.; Phan, N. N.; Wang, C. -Y.; Yu, H. -G.; Wang, S. -Y.; Huang, P. -L.; Do, Y. -Y.; Lin, Y. -C. Novel Therapeutic Effects of Sesamin on Diabetes-Induced Cardiac Dysfunction. *Mol. Med. Rep.* 2017, *15*(5), 2949. DOI: 10.3892/mmr.2017.6420.
[85] Zhang, W.; Wang, Y.; Geng, Z.; Guo, S.; Cao, J.; Zhang, Z.; Pang, X.; Chen, Z.; Du, S.; Deng, Z. Antifeedant Activities of Lignans from Stem Bark of Zanthoxylum Armatum DC. Against Tribolium Castaneum. *Molecues*. 2018, *23*(3), 617. DOI: 10.3390/molecules23030617.

[86] Nantarat, N.; Mueller, M.; Lin, W. -C.; Lue, S. -C.; Viernstein, H.; Chansakaow, S.; Sirithunyalug, J.; Leelapornpisid, P. Sesaminol Diglucoside Isolated from Black Sesame Seed Cake and Its Antioxidant, Anti-Collagenase and Anti-Hyaluronidase Activities. *Food Biosci*. 2020, *36*, 100628. DOI: 10.1016/j.fbio.2020.100628.

[87] Jan, K. -C.; Ku, K. -L.; Chu, Y. -H.; Hwang, L. S.; Ho, C. -T. Tissue Distribution and Elimination of Estrogenic and Anti-Inflammatory Catechol Metabolites from Sesaminol Triglucoside in Rats. *J. Agric. Food Chem*. 2010, *58*(13), 7693. DOI: 10.1021/jf1009632.

[88] Wikul, A.; Damsud, T.; Kataoka, K.; Phuwapraisirisan, P. (+)-Pinoresinol is a Putative Hypoglycemic Agent in Defatted Sesame (Sesamum Indicum) Seeds Though Inhibiting α-Glucosidase. *Bioorg. Med. Chem. Lett*. 2012, *22*(16), 5215. DOI: 10.1016/j.bmcl.2012.06.068.

[89] Takeuchi, H.; Mooi, L. Y.; Inagaki, Y.; He, P. Hypoglycemic Effect of a Hot-Water Extract from Defatted Sesame (Sesamum Indicum L.) Seed on the Blood Glucose Level in Genetically Diabetic KK-Ay Mice. *Biosci. Biotechnol., Biochem*. 2001, *65*(10), 2318. DOI: 10.1271/bbb.65.2318.

[90] Das, R.; Dutta, A.; Bhattacharjee, C. Preparation of Sesame Peptide and Evaluation of Antibacterial Activity on Typical Pathogens. *Food Chem*. 2012, *131*(4), 1504. DOI: 10.1016/j.foodchem.2011.09.136.

[91] NAKANO, D.; OGURA, K.; MIYAKOSHI, M.; ISHII, F.; KAWANISHI, H.; KURUMAZUKA, D.; KWAK, C. -J.; IKEMURA, K.; TAKAOKA, M.; MORIGUCHI, S., et al. Antihypertensive Effect of Angiotensin I-Converting Enzyme Inhibitory Peptides from a Sesame Protein Hydrolysate in Spontaneously Hypertensive Rats. *Biosci. Biotechnol. Biochem*. 2006, *70*(5), 1118. DOI: 10.1271/bbb.70.1118.

[92] Aondona, M. M.; Ikya, J. K.; Ukeyima, M. T.; Gborigo, T. J. A.; Aluko, R. E.; Girgih, A. T. In vitro Antioxidant and Antihypertensive Properties of Sesame Seed Enzymatic Protein Hydrolysate and Ultrafiltration Peptide Fractions. *Food Biochem*. 2021, *45*(1), e13587. DOI: 10.1111/jfbc.13587.

[93] Ma, X.; Cui, X.; Li, J.; Li, C.; Wang, Z. Peptides from Sesame Cake Reduce Oxidative Stress and Amyloid-β-Induced Toxicity by Upregulation of SKN-1 in a Transgenic Caenorhabditis Elegans Model of Alzheimer's Disease. *J. Funct. Foods*. 2017, *39*, 287. DOI: 10.1016/j.jff.2017.10.032.

[94] Ma, X.; Li, J.; Cui, X.; Li, C.; Wang, Z. Dietary Supplementation with Peptides from Sesame Cake Alleviates Parkinson's Associated Pathologies in Caenorhabditis Elegans. *J. Funct. Foods*. 2020, *65*, 103737. DOI: 10.1016/j.jff.2019.103737.

[95] Ma, X.; Li, J.; Cui, X.; Li, F.; Wang, Z. Dietary Supplementation with Peptides from Sesame Cake Protect Caenorhabditis Elegans from Polyglutamine-Induced Toxicity. *J. Funct. Foods*. 2019, *54*, 199. DOI: 10.1016/j.jff.2019.01.002.

[96] Visavadiya, N. P.; Narasimhacharya, A. V. Sesame as a Hypocholesteraemic and Antioxidant Dietary Component. *Food. Chem. Toxicol*. 2008, *46*(6), 1889. DOI: 10.1016/j.fct.2008.01.012.

[97] Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J. P.; Tognolini, M.; Borges, G.; Crozier, A. Dietary (Poly) Phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects Against Chronic Diseases. *Antioxid. Redox Signal*. 2013, *18*(14), 1818. DOI: 10.1089/ars.2012.4581.

[98] Chen, M.; Meng, H.; Zhao, Y.; Chen, F.; Yu, S. Antioxidant and in vitro Anticancer Activities of Phenolics Isolated from Sugar Beet Molasses. *BMC Complementary Altern. Med*. 2015, *15*(1), 1. DOI: 10.1186/s12906-015-0847-5.

[99] Díaz-de-Cerio, E.; Verardo, V.; Gómez-Caravaca, A. M.; Fernández-Gutiérrez, A.; Segura-Carretero, A. Exploratory Characterization of Phenolic Compounds with Demonstrated Anti-Diabetic Activity in Guava Leaves at Different Oxidation States. *Int. J. Mol. Sci*. 2016, *17*(5), 699. DOI: 10.3390/ijms17050699.

[100] Tarko, T.; Duda-Chodak, A.; Soszka, A. Changes in Phenolic Compounds and Antioxidant Activity of Fruit Musts and Fruit Wines During Simulated Digestion. *Molecules*. 2020, *25*(23), 5574. DOI: 10.3390/molecules25235574.

[101] Marín, L.; Miguélez, E. M.; Villar, C. J.; Lombó, F. Bioavailability of Dietary Polyphenols and Gut Microbiota Metabolism: Antimicrobial Properties. *Biomed Res. Int*. 2015, *2015*, 1–18. DOI: 10.1155/2015/905215.

[102] D'Archivio, M.; Filesi, C.; Varì, R.; Scazzocchio, B.; Masella, R. Bioavailability of the Polyphenols: Status and Controversies. *Int. J. Mol. Sci*. 2010, *11*(4), 1321. DOI: 10.3390/ijms11041321.

[103] Serra, V.; Salvatori, G.; Pastorelli, G. Dietary Polyphenol Supplementation in Food Producing Animals: Effects on the Quality of Derived Products. *Animals (Basel)*. 2021, *11*(2), 2. DOI: 10.3390/ani11020401.

[104] Jaganath, I. B.; Crozier, A. Dietary Flavonoids and Phenolic Compounds. In *Plant Phenolics and Human Health: Biochemistry, Nutrition, and Pharmacology*, Fraga, C. G., Ed.; New York: John Wiley & Sons, 2010; pp 1.

[105] Ferreyra, M. L. F.; Rius, S.; Casati, P. Flavonoids: Biosynthesis, Biological Functions, and Biotechnological Applications. *Front. Plant Sci*. 2012, *3*, 222. DOI: 10.3389/fpls.2012.00222.

[106] Kumar, S.; Pandey, A. K. Chemistry and Biological Activities of Flavonoids: An Overview. *Sci. World J*. 2013, *2013*, 162750. DOI: 10.1155/2013/162750.

[107] Pandey, K. B.; Rizvi, S. I. Plant Polyphenols as Dietary Antioxidants in Human Health and Disease. *Oxid. Med. Cell. Longev*. 2009, *2*(5), 270. DOI: 10.4161/oxim.2.5.9498.

[108] Ozdal, T.; Sela, D. A.; Xiao, J.; Boyacioglu, D.; Chen, F.; Capanoglu, E. The Reciprocal Interactions Between Polyphenols and Gut Microbiota and Effects on Bioaccessibility. *Nutrients*. 2016, *8*(2), 78. DOI: 10.3390/nu8020078.
[109] Lafay, S.; Gil-Izquierdo, A. Bioavailability of Phenolic Acids. *Phytochem. Rev*. 2008, *7*(2), 301. DOI: 10.1007/s11101-007-9077-x.
[110] Quirós-Sauceda, A.; Palafox-Carlos, H.; Sáyago-Ayerdi, S.; Ayala-Zavala, J.; Bello-Perez, L. A.; Alvarez-Parrilla, E.; De La Rosa, L.; González-Córdova, A.; González-Aguilar, G. Dietary Fiber and Phenolic Compounds as Functional Ingredients: Interaction and Possible Effect After Ingestion. *Food Funct*. 2014, *5*(6), 1063. DOI: 10.1039/C4FO00073K.
[111] Vinholes, J.; Silva, B.; Silva, L. Hydroxycinnamic acids (HCAS): Structure, biological properties and health effects. In *Advances in Medicine and Biology*, New York: Nova Science Publishers, 2015; Vol. *88*; pp 1.
[112] Cederbaum, A. I. Alcohol Metabolism. *Clin. Liver Dis*. 2012, *16*(4), 667. DOI: 10.1016/j.cld.2012.08.002.
[113] Olthof, M. R.; Hollman, P. C.; Zock, P. L.; Katan, M. B. Consumption of High Doses of Chlorogenic Acid, Present in Coffee, or of Black Tea Increases Plasma Total Homocysteine Concentrations in Humans. *Am. J. Clin. Nutr*. 2001, *73*(3), 532. DOI: 10.1093/ajcn/73.3.532.
[114] Dall'Asta, M.; Bresciani, L.; Calani, L.; Cossu, M.; Martini, D.; Melegari, C.; Del Rio, D.; Pellegrini, N.; Brighenti, F.; Scazzina, F. In vitro Bioaccessibility of Phenolic Acids from a Commercial Aleurone-Enriched Bread Compared to a Whole Grain Bread. *Nutrients*. 2016, *8*(1), 42. DOI: 10.3390/nu8010042.
[115] Jan, K. C.; Hwang, L. S.; Ho, C. T. Tissue Distribution and Elimination of Sesaminol Triglucoside and Its Metabolites in Rat. *Mol. Nutr. Food Res. Int*. 2009, *53*(7), 815. DOI: 10.1002/mnfr.200800380.
[116] Deyama, T. The Constituents of Eucommia Ulmoides Oliv. I. Isolation of (+)-Medioresinol di-O-β-D-Glucopyranoside. *Chem. Pharm. Bull*. 1983, *31*(9), 2993. DOI: 10.1248/cpb.31.2993.
[117] Katsuzaki, H.; Kawakishi, S.; Osawa, T. Sesaminol Glucosides in Sesame Seeds. *Phytochemistry*. 1994, *35*(3), 773. DOI: 10.1016/S0031-9422(00)90603-4.
[118] Katsuzaki, H.; Kawasumi, M.; Kawakishi, S.; Osawa, T. Structure of Novel Antioxidative Lignan Glucosides Isolated from Sesame Seed. *Biosci. Biotechnol. Biochem*. 1992, *56*(12), 2087. DOI: 10.1271/bbb.56.2087.
[119] Moazzami, A.; Haese, S.; Kamal-eldin, A. Lignan Contents in Sesame Seeds and Products. *Eur. J. Lipid Sci. Technol*. 2007, *109*(10), 1022. DOI: 10.1002/ejlt.200700057.
[120] Park, S. -H.; Ryu, S. -N.; Bu, Y.; Kim, H.; Simon, J. E.; Kim, K. -S. Antioxidant Components as Potential Neuroprotective Agents in Sesame (Sesamum Indicum L.). *Food Rev. Int*. 2010, *26*(2), 103. DOI: 10.1080/87559120903564464.
[121] Peng, Z.; Xu, Y.; Meng, Q.; Raza, H.; Zhao, X.; Liu, B.; Dong, C. Preparation of Sesaminol from Sesaminol Triglucoside by β-Glucosidase and Cellulase Hydrolysis. *J. Am. Oil Chem. Soc*. 2016, *93*(6), 765. DOI: 10.1007/s11746-016-2819-4.
[122] Jan, K.; Hwang, L.; Ho, C. Biotransformation of Sesaminol Triglucoside to Mammalian Lignans by Intestinal Microbiota. *J. Agric. Food Chem*. 2009, *57*(14), 6101. DOI: 10.1021/jf901215j.
[123] Raffaelli, B.; Hoikkala, A.; Leppälä, E.; Wähälä, K. Enterolignans. *J. Chromatogr. B*. 2002, *777*(1–2), 29. DOI: 10.1016/S1570-0232(02)00092-2.
[124] Penalvo, J. L.; Heinonen, S. -M.; Aura, A. -M.; Adlercreutz, H. Dietary Sesamin is Converted to Enterolactone in Humans. *J. Nutr*. 2005, *135*(5), 1056. DOI: 10.1093/jn/135.5.1056.
[125] Clavel, T.; Henderson, G.; Alpert, C. -A.; Philippe, C.; Rigottier-Gois, L.; Doré, J.; Blaut, M. Intestinal Bacterial Communities That Produce Active Estrogen-Like Compounds Enterodiol and Enterolactone in Humans. *Appl. Environ. Microbiol*. 2005, *71*(10), 6077. DOI: 10.1128/AEM.71.10.6077-6085.2005.
[126] Wang, L. -Q.; Meselhy, M. R.; Li, Y.; Qin, G. -W.; Hattori, M. Human Intestinal Bacteria Capable of Transforming Secoisolariciresinol Diglucoside to Mammalian Lignans, Enterodiol and Enterolactone. *Chem. Pharm. Bull*. 2000, *48*(11), 1606. DOI: 10.1248/cpb.48.1606.
[127] Rodríguez-García, C.; Sánchez-Quesada, C.; Toledo, E.; Delgado-Rodríguez, M.; Gaforio, J. J. Naturally Lignan-Rich Foods: A Dietary Tool for Health Promotion? *Molecules*. 2019, *24*(5), 917. DOI: 10.3390/molecules24050917.
[128] Xie, L. -H.; Akao, T.; Hamasaki, K.; Deyama, T.; Hattori, M. Biotransformation of Pinoresinol Diglucoside to Mammalian Lignans by Human Intestinal Microflora, and Isolation of Enterococcus Faecalis Strain PDG-1 Responsible for the Transformation of (+)-Pinoresinol to (+)-Lariciresinol. *Chem. Pharm. Bull*. 2003, *51*(5), 508. DOI: 10.1248/cpb.51.508.
[129] Luo, J.; Li, M.; Wu, H.; Liu, Z.; Barrow, C.; Dunshea, F.; Suleria, H. A. R. Bioaccessibility of Phenolic Compounds from Sesame Seeds (Sesamum Indicum L.) During in vitro Gastrointestinal Digestion and Colonic Fermentation. *J. Food Process. Preserv*. 2022, *46*(7), e16669. DOI: 10.1111/jfpp.16669.
[130] Scholz, S.; Williamson, G. Interactions Affecting the Bioavailability of Dietary Polyphenols in vivo. *Int. J. Vitam. Nutr. Res*. 2007, *77*(3), 224. DOI: 10.1024/0300-9831.77.3.224.
[131] Appeldoorn, M. M.; Vincken, J. -P.; Aura, A. -M.; Hollman, P. C.; Gruppen, H. Procyanidin Dimers are Metabolized by Human Microbiota with 2-(3, 4-Dihydroxyphenyl) Acetic Acid and 5-(3, 4-Dihydroxyphenyl)-γ-Valerolactone as the Major Metabolites. *J. Agric. Food Chem*. 2009, *57*(3), 1084. DOI: 10.1021/jf803059z.

[132] Elferink, H.; Bruekers, J. P. J.; Veeneman, G. H.; Boltje, T. J. A Comprehensive Overview of Substrate Specificity of Glycoside Hydrolases and Transporters in the Small Intestine. *Cell. Mol. Life Sci.* 2020, *77*(23), 4799. DOI: 10.1007/s00018-020-03564-1.

[133] Erlund, I.; Kosonen, T.; Alfthan, G.; Mäenpää, J.; Perttunen, K.; Kenraali, J.; Parantainen, J.; Aro, A. Pharmacokinetics of Quercetin from Quercetin Aglycone and Rutin in Healthy Volunteers. *Eur. J. Clin. Pharmacol.* 2000, *56*(8), 545. DOI: 10.1007/s002280000197.

[134] Brand, W.; Shao, J.; Hoek-Van Den Hil, E. F.; Van Elk, K. N.; Spenkelink, B.; De Haan, L. H.; Rein, M. J.; Dionisi, F.; Williamson, G.; Van Bladeren, P. Stereoselective Conjugation, Transport and Bioactivity of S-And R-Hesperetin Enantiomers in vitro. *J. Agric. Food Chem.* 2010, *58*(10), 6119. DOI: 10.1021/jf1008617.

[135] Ottaviani, J. I.; Momma, T. Y.; Heiss, C.; Kwik-Uribe, C.; Schroeter, H.; Keen, C. L. The Stereochemical Configuration of Flavanols Influences the Level and Metabolism of Flavanols in Humans and Their Biological Activity in vivo. *Free Radic. Biol. Med.* 2011, *50*(2), 237. DOI: 10.1016/j.freeradbiomed.2010.11.005.

[136] Muthyala, R. S.; Ju, Y. H.; Sheng, S.; Williams, L. D.; Doerge, D. R.; Katzenellenbogen, B. S.; Helferich, W. G.; Katzenellenbogen, J. A. Equol, a Natural Estrogenic Metabolite from Soy Isoflavones: Convenient Preparation and Resolution of R-And S-Equols and Their Differing Binding and Biological Activity Through Estrogen Receptors Alpha and Beta. *Bioorg. Med. Chem.* 2004, *12*(6), 1559. DOI: 10.1016/j.bmc.2003.11.035.

[137] Kiela, P. R.; Ghishan, F. K. Physiology of Intestinal Absorption and Secretion. *Best Practice & Research. Clin. Gastroenterol.* 2016, *30*(2), 145. DOI: 10.1016/j.bpg.2016.02.007.

[138] Williamson, G.; Manach, C. Bioavailability and Bioefficacy of Polyphenols in Humans. II. Review of 93 Intervention Studies. *Am. J. Clin. Nutr.* 2005, *81*(1), 243S. DOI: 10.1093/ajcn/81.1.243S.

[139] Averina, E.; Kutyrev, I. Perspectives on the Use of Marine and Freshwater Hydrobiont Oils for Development of Drug Delivery Systems. *Biochem. Adv.* 2011, *29*(5), 548. DOI: 10.1016/j.biotechadv.2011.01.009.

[140] Frank, J.; Lee, S.; Leonard, S. W.; Atkinson, J. K.; Kamal-Eldin, A.; Traber, M. G. Sex Differences in the Inhibition of γ-Tocopherol Metabolism by a Single Dose of Dietary Sesame Oil in Healthy Subjects. *Am. J. Clin. Nutr.* 2008, *87*(6), 1723. DOI: 10.1093/ajcn/87.6.1723.

[141] Sachdeva, A. K.; Misra, S.; Kaur, I. P.; Chopra, K. Neuroprotective Potential of Sesamol and Its Loaded Solid Lipid Nanoparticles in ICV-STZ-Induced Cognitive Deficits: Behavioral and Biochemical Evidence. *Eur. J. Pharmacol.* 2015, *747*, 132. DOI: 10.1016/j.ejphar.2014.11.014.

[142] Kakkar, V.; Mishra, A. K.; Chuttani, K.; Chopra, K.; Kaur, I. P. Delivery of Sesamol-Loaded Solid Lipid Nanoparticles to the Brain for Menopause-Related Emotional and Cognitive Central Nervous System Derangements. *Rejuvenation Res.* 2011, *14*(6), 597. DOI: 10.1089/rej.2011.1193.

[143] Kakkar, V.; Kaur, I. P. Preparation, Characterization and Scale-Up of Sesamol Loaded Solid Lipid Nanoparticles. *Nanotechnol. Dev.* 2012, *2*(1), e8. DOI: 10.4081/nd.2012.e8.

[144] Geetha, T.; Kapila, M.; Prakash, O.; Deol, P. K.; Kakkar, V.; Kaur, I. P. Sesamol-Loaded Solid Lipid Nanoparticles for Treatment of Skin Cancer. *J. Drug Targeting.* 2015, *23*(2), 159. DOI: 10.3109/1061186X.2014.965717.

[145] Singh, N.; Khullar, N.; Kakkar, V.; Kaur, I. P. Sesamol Loaded Solid Lipid Nanoparticles: A Promising Intervention for Control of Carbon Tetrachloride Induced Hepatotoxicity. *BMC Complementary Altern. Med.* 2015, *15*(1), 142. DOI: 10.1186/s12906-015-0655-y.

[146] Liu, F.; Liu, H.; Liu, R.; Xiao, C.; Duan, X.; McClements, D. J.; Liu, X. Delivery of Sesamol Using Polyethylene-Glycol-Functionalized Selenium Nanoparticles in Human Liver Cells in Culture. *J. Agric. Food Chem.* 2019, *67*(10), 2991. DOI: 10.1021/acs.jafc.8b06924.

[147] Singh, N.; Khullar, N.; Kakkar, V.; Kaur, I. P. Hepatoprotective Effects of Sesamol Loaded Solid Lipid Nanoparticles in Carbon Tetrachloride Induced Sub-Chronic Hepatotoxicity in Rats. *Environ. Toxicol.* 2016, *31*(5), 520.

[148] ElMasry, S. R.; Hathout, R. M.; Abdel-Halim, M.; Mansour, S. In Vitro Transdermal Delivery of Sesamol Using Oleic Acid Chemically-Modified Gelatin Nanoparticles as a Potential Breast Cancer Medication. *J. Drug Delivery Sci. Technol.* 2018, *48*, 30. DOI: 10.1016/j.jddst.2018.08.017.

[149] Hassanzadeh, P.; Atyabi, F.; Dinarvand, R.; Dehpour, A. -R.; Azhdarzadeh, M.; Dinarvand, M. Application of Nanostructured Lipid Carriers: The Prolonged Protective Effects for Sesamol in in vitro and in vivo Models of Ischemic Stroke via Activation of PI3K Signalling Pathway. *DARU J. Pharm. Sci.* 2017, *25*(1), 1. DOI: 10.1186/s40199-017-0191-z.

[150] Yashaswini, P. S.; Kurrey, N. K.; Singh, S. A. Encapsulation of Sesamol in Phosphatidyl Choline Micelles: Enhanced Bioavailability and Anti-Inflammatory Activity. *Food Chem.* 2017, *228*, 330. DOI: 10.1016/j.foodchem.2017.02.002.

[151] Santos Basurto, M. A.; Cardador Martínez, A.; Castaño Tostado, E.; Bah, M.; Reynoso Camacho, R.; Amaya Llano, S. L. Study of the Interactions Occurring During the Encapsulation of Sesamol Within Casein Micelles Reformed from Sodium Caseinate Solutions. *J. Food Sci.* 2018, *83*(9), 2295. DOI: 10.1111/1750-3841.14293.

[152] Yashaswini, P.; Rao, A.; Singh, S. Inhibition of Lipoxygenase by Sesamol Corroborates Its Potential Anti-Inflammatory Activity. *Int. J. Biol. Macromol.* 2017, *94*(Pt B), 781. DOI: 10.1016/j.ijbiomac.2016.06.048.

[153] Puglia, C.; Lauro, M. R.; Offerta, A.; Crascì, L.; Micicchè, L.; Panico, A. M.; Bonina, F.; Puglisi, G. Nanostructured Lipid Carriers (NLC) as Vehicles for Topical Administration of Sesamol: In vitro Percutaneous Absorption Study and Evaluation of Antioxidant Activity. *Planta. med*. 2017, *83*(05), 398. DOI: 10.1055/s-0042-105293.
[154] Rossi, L.; ten Hoorn, J. W. S.; Melnikov, S. M.; Velikov, K. P. Colloidal Phytosterols: Synthesis, Characterization and Bioaccessibility. *Soft Matter*. 2010, *6*(5), 928. DOI: 10.1039/B911371A.