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Reviews

Lignans of sesame: Purification methods, biological activities and biosynthesis – A review

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ABSTRACT

Lignans are a group of compounds consisting of dimers of phenyl propane units. They are found in diverse forms distributed in a variety of plants. Sesame lignans in particular are obtained from *Sesamum indicum*, a highly prized oilseed crop cultivated widely in many countries in the east. The plant is the main source of clinically important antioxidant lignans such as sesamin, sesamolin, sesaminol and sesamol. These lignans exhibit antihypertensive, anticancerous and hypocholesterolemic activities as well especially in humans due to which they have become compounds of tremendous research interest in recent times. Sesamin is synthesized from shikimic acid through phenylpropanoid pathway and metabolised into enterolignans which play a pivotal role in protection against several hormone related diseases. In this paper we present an overview of current status of research on sesame lignans with respect to the analytical methods employed, the biological activities and biosynthesis of sesame lignans.

Contents

1. Introduction

The term lignan was coined by Haworth in 1936 to describe a group of phenylpropanoid dimers in which C6–C3 units are linked by the central carbon of their propyl side chains [1,2]. Under IUPAC nomenclature, the lignans are 8,8′-coupled dimers of coniferyl or cinnamyl alcohols. The lignans are currently known for their role in conferring health benefits such as lowering the cholesterol and blood glucose levels in humans [3] Based on the way in which oxygen is incorporated into the skeleton and the cyclization pattern, the lignans are classified into the eight subgroups, namely, furofuran, furan, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphthalene, dibenzocyclooctadiene and dibenzylbutyrolactol[1,4]. These compounds are found in diverse species in the plant kingdom including members of pteridophytes, gymnosperms and angiosperms [5,6]. In angiosperms, lignans have been isolated from members belonging to Asterales, Scropholariales, Lamiales, Solanales, Apiales, Sapindales, Aristolochiales, Piperales, Laurales, Malvales, Malpighiales and Magnoliales orders in the division

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Table 1
List of plant species that are sources of sesamin.

S. No.	Plant	Method of analysis	Solvent for extraction	Source	Quantity (mg/100 g)	Reference
1	*Anacyclus pyrethrum*	NA	Ethanol	Roots	NA	[7]
2	*Zanthoxylum. armatum*	NA	NA	Bark	NA	[8]
3	*Vitex negundo*	Silica gel column chromatography	80% Ethanol	Dried seeds	0.024	[9]
4	*Aristolochia cymbifera*	NA	NA	Leaves	NA	[10]
5	*Piper longum*	NA	Dichloromethane	Fruit	NA	[11]
6	*Knema glauca*	Sephadex column chromatography	*n*-Hexane	Dried and milled fruits	2.83	[12]
7	*Magnolia denudata*	NA	NA	Fruit	NA	[13]
8	*M. kobus*	Sephadex column chromatography	95% Ethanol	Dried barks	4.16	[14]
9	*Piper retrofractum*	Chromatographic separation	*n*-hexane	Stem hexane extract	366.66	[15]
10	*Camellia oleifera*	HPLCs	Methanol, Ethanol, Acetone, Ethyl acetic, and Acetonitrile	Seed oil	33.88	[16]
11	*Chrysanthemum cinerariaefolium*	Gas chromatography – mass spectrometery	Diethyl ether, Hot methanol and boiling water	Dried flower	10.00	[17]
12	*Eucalyptus globulus*	Preparative TLC and GC–MS	Acetone and petroleum (1:1)	Freshly capsules	0.278	[18]
13	*Machilus thunbergii*	NA	NA	Bark	NA	[19]
14	*Piper sarmentosum*	NA	NA	Fruit	NA	[20]
15	*Acanthopanax senticosus*	Silica gel column chromatography	Water and chloroform	Chloroform extract of dried stem	75.00	[21]
16	*Artemisia absinthium*	Silica gel column chromatography	Methanol	Dried roots	7.2	[22]
17	*Paulownia tomentosa*	NA	NA	Leaves	NA	[23]
18	*Ginkgo biloba*	Vacuum liquid chromatography	Acetone	Dried leaves	NA	[24]
19	*Acanthopanax sessiliflorus*	Silica gel column chromatography	Hot methanol	Dried fruits	0.25	[25]
20	*Chamaecyparis obtusa*	Silica gel column chromatography and HPLC	Hot methanol	Young shoots and leaves	11.38	[26]
21	*Semen Cuscutae*	Gas chromatography	Chloroform	Dried stem	112–200	[27]
22	*Zanthoxylum integrifoliolum*	Column chromatography and TLC	Methanol	Dried fruits	1.57	[28]
23	*Magnolia coco*	NA	NA	Leaves	NA	[29]
24	*Caryodaphnopsis baviensis*	Flash column chromatography	95% Methanol	Fruits	220	[30]
25	*Virola surinamensis*	Flash column chromatography and TLC	Hexane and chloroform	Seeds and pericarps	70.00	[31]
				Tegments and kernels of seeds	6.00	
26	*Pericarpium zanthoxyli*	TLC	*n*-Hexane	Fruits	NA	[32]
27	*V. venosa*	Flash column chromatography and TLC	Dichloromethane	Pericarp crude extract	8516.48	[33]
28	*Nectandra amazonum*	Chromatography	Ethanol	Fruit calyces	14.63	[34]
29	*Virola flexuosa*	Silica gel column chromatography	Chloroform	Seeds	737.5	[35]
	V. multinervia				5.00	
30	*Piper guineense*	TLC	Light petroleum and chloroform	Fruit	2.66	[36]

NA = Data not available.

Magnoliophyta [1]. A list of plants that serve as sources of sesamin, an important furofuran lignan are presented in Table 1. Sesame of scrophulariales is a source of several dibenzyl butyrolactone lignans such as sesamin. Though sesamin has been isolated from *Piper* sp., *Virola* sp., *Magnolia sp*. and *Camellia* sp. in respectable amounts the oilseed crop *Sesamum indicum* still continues to be the major source of sesamin. The following is an overview on the current status of research on lignans of sesame in terms of distribution, biological significance, biosynthesis and analytical methods adopted.

2. Lignans in sesame

There are sixteen types of lignans isolated from sesame (Fig. 1). Most of them are fat soluble aglycons and therefore elute into the oil on extraction. The remaining are glycosylated and have been isolated from the oil free meal. The major aglycon lignans are sesamin and sesamolin [37,38]. Sesamol, sesaminol, sesamolinol, pinoresinol, matairesinol, lariciresinol and episesamin form minor aglycons of sesame oil [39–42]. The lignan glycosides include mono- di- and triglucosides of sesaminol, sesamolinol and pinoresinol [40,43–45,36,47–49]. Sesaminol triglucoside, sesaminol diglucoside and sesaminol monoglucoside are the most abundant lignan glycosides in sesame [50]. Sesame also contain biologically active tocopherol homologues [α-tocopherol (αT), δ-tocopherol, (δT) and γ-tocopherol (γT)], tocotrienols and naphthoquinones (like chlorosesamone, hydroxysesamone and 2,3 epoxysesamone [51,52]. *Sesamum alatum,* a species with winged seeds, is said to be devoid of both sesamin and sesamolin but has a novel furofuran lignan, 2-episesalatin [53]. Three additional lignans namely saminol, episesaminone-9-O-*β*-D-sophoroside, and semamolactol have been detected in the perisperm of *Sesamum indicum* [54]. Episesaminone, a furanoketone was characterized in part via hemisynthesis from sesamolin. Recently these authors have isolated two new lignans namely, sesamolinol-4́-*O*-β-D glucoside and disaminyl ether (samin dimer) from sesame seeds [55].

3. Analytical methods used for the isolation, identification and quantification of lignan

There were several bioseparation techniques used for analysis and quantitation of lignans in sesame (Table 2). Some of the studies that have contributed significantly to an understanding on the

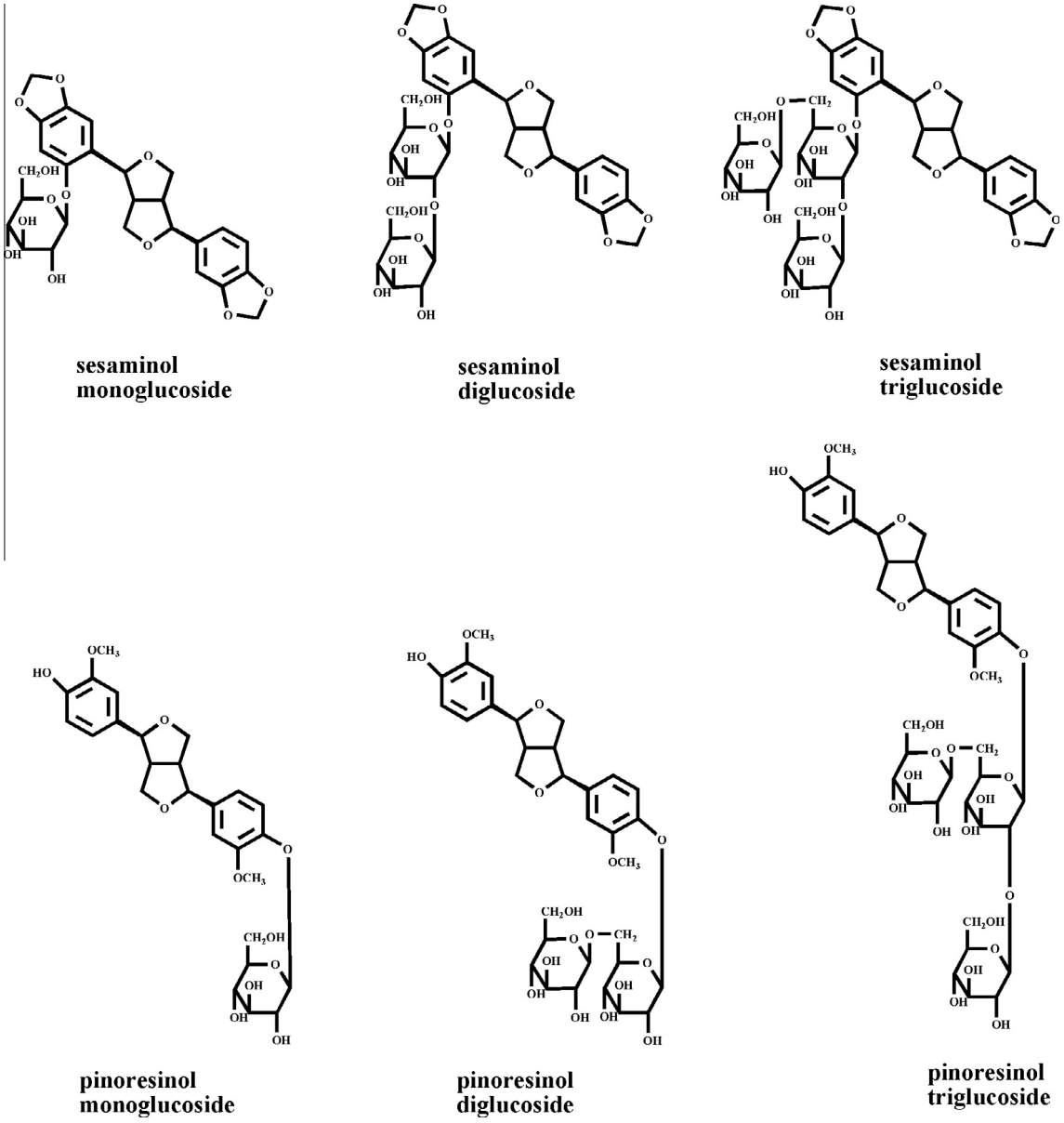

Fig. 1. Structures of different lignans reported from *Sesamum indicum*.

biology of sesame lignans is reviewed in the following paragraphs. The survey of literature since last 15 years (1998–2012) reveal that there was a revolutionary change in the type of techniques used, which ranged from the Thin Layer Chromatography (TLC), High-Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), High Performance Thin Layer Chromatography (HPTLC) to ultra performance liquid chromatography-fluorescence detection (UPLC-FLD), fractionation and quantification of sesame lignans.

Chromatography is the technique of choice employed for separation and quantification of sesame lignans from the solvent extracts. The three main types of chromatography used for the quantification purpose were TLC, HPLC and GC. According to Slanina et al. [6] there are advantages and limitations with each of the method. Following is a brief description for some of the methods used so far. TLC is the simplest, inexpensive and therefore the first method used for lignan separation. Kamal-Eldin et al. [65] and Shahidi et al. [66] reported qualitative analysis and isolation of lignans from unsaponifiable fraction of sesame oil using one dimensional (1D-) and two dimensional (2D-) TLC. Two-dimensional TLC not only provided better fractionation but gave fractions for further analysis by GC [67]. Improved resolution of 2D-TLC as compared to one-dimensional systems is a valuable tool in qualitative screening studies on the identity and relative amounts of the sesamin-type compounds in different sources [38,68]. Use of HPTLC method for the quantification of sesamin and sesamolin in sesame oil without saponification was reported by Sukumar et al. [60]. The method would find application in fingerprinting, quality assurance and quantification of lignans as markers. HPTLC plates with uniform particles of size 5–6 μm has been attributed to the excellent resolution and reproducibility. GC especially Gas Chromatography coupled with Mass Spectrometry (GC–MS) is useful in establishing the presence of lignans in the test sample. In 1969 GC was used for the first time for the lignan separation [69]. GC has been proposed as a powerful technique for qualitative analysis of lignans. For quantification GC in fact involves many preparative steps and it appears that no suitable internal standard is available. However, GC–MS has been reliably used to identify the presence of specific compounds [65]. Amarowicz et al. [70] con-

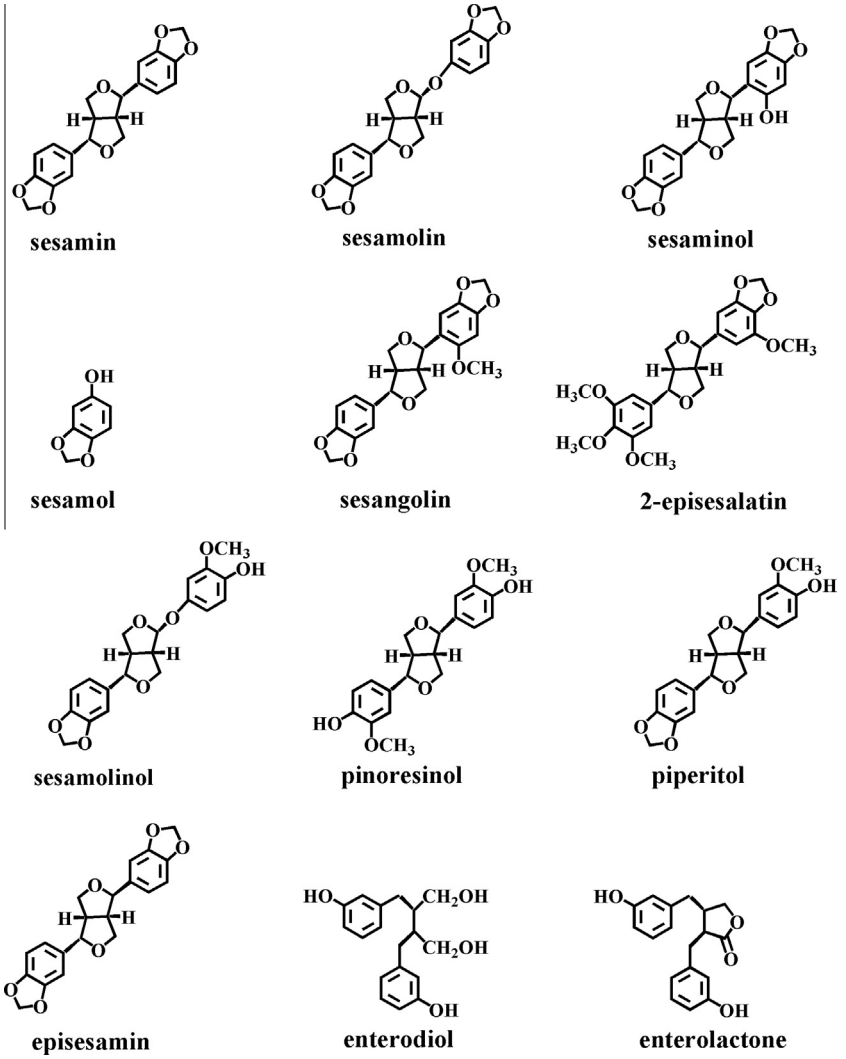

Fig. 1 (*continued*)

firmed the chemical structures and identity of purified sesamin and sesamolin by gas chromatography–mass spectrometry using a Magnum GC–MS system.

HPLC is the most frequently used analytical method for determination of lignans in sesame. The HPLC method of analyzing sesamin and sesamolin content in sesame seeds was first reported by Fukuda et al. [71]. It has been proposed as one-step technique suitable for quantitative analyses, as it could tolerate direct injection of oil as well for analysis [65]. Reversed-phase columns have been successfully used for analysis of medium polarity lignans [2]. In reversed-phase HPLC, mobile phase generally consists of a mixture of organic solvents, typically methanol or acetonitrile, and an aqueous phase such as water, acidic buffer or diluted acid [6]. Normal-phase HPLC has been successfully used for separation of sesamol, sesamin, sesamolin and sesangolin, thereby making it a good system for co-analysis of these components [65]. Subsequently, Mohamed and Awatif [72] used HPLC with reversed phase C18 column and UV detector for analysis of sesamin and sesamolin in crude extracts. On one occasion semipreparative RP-18 HPLC was employed to isolate sesamin and sesamolin of high purity and use as standards in subsequent chromatographic investigations [70]. Yasumoto et al. [73] reported a rapid and reliable method for qualitative and quantitative analysis of major lignans of Sesamum. This appeared to be the fastest of the method reported so far for quantification of sesame lignans. 80% methanol was used for extraction and the extract analyzed by RP18 HPLC with Methanol and Water (8:2) as solvent system. It was shown that the analysis could be completed within 5 min. Hemalatha et al. [44] were the most successful in getting better yield of lignans from oils and seeds by extraction with petroleum ether and quantification by HPLC on a reverse phase C18 column. Subsequently Mozzami et al. [62,63] using Hexane and Isopropanol (3:1) isolated the sesame lignans and analyzed by quantification using Alltima SI 5U silica column. Sukumar et al. [60] used methanol for isolation and quantification purpose. Hata et al. [58] isolated the sesamin from leaves using the technique of UPLC-FLD. Though the yield was low but proved that sesamin can be isolated from leaves as well.

Counter current chromatography (CCC) based on the principle of liquid–liquid partition in combination with MS is yet another method of choice used for the identification of lignans [74]. The method is highly selective and therefore lignans identified even if they could not be completely separated. The absence of column in CCC coupled with mass spectrometry (CCC–MS) eliminates the complication arising from stationary phase adsorption, deactivation and contamination often observed in HPLC [6]. A photodiode array detector (PAD) was used for determination of sesamin levels [61]. The time, cost, and labor can be further reduced by use of

Table 2
Details of analytical techniques employed for quantitation of sesame lignans.

S. No.	Instrumentation	Column specification	Solvent for extraction	Source	Lignan quantity (mg/100 g)	Reference
1	HPLC (Alliance 2695, Waters Millford)	C-18 RPC (10 μm, 4.6 × 250 mm column), with photodiode array detector, 474 scanning fluorescent detector	Methanol	Oil (sigma)	Sesamin = 190 Asarinin = 90 Sesamolin = traces	[56]
2	HPLC (Agilent 1100, Agilent technologies)	RP Hypersil BDS C18 column, (5 μm, 150 × 4 mm i.d.), with Diode-array detector	80% Ethanol	Seed	Sesamin + Sesamolin = 854	[57]
3	UPLC-FLD (ACQUITY UPLC, Waters Millford)	UPLC HSS T3 Column (100 mm × 2.1 mm, 1.8 μm), Scanning Fluorescence Detector	Ethanol	Leaf	Sesamin = 0.26	[58]
4	HPLC (Agilent 1100, Agilent technologies)	RP Hypersil BDS C18 column, (5 μm, 150 × 4 mm i.d.), with Diode-array detector	80% methanol	Seed	Sesamin = 155 Sesamolin = 62	[59]
5	HPTLC (CAMAG HPTLC system, EMerck)	Silica gel HPTLC aluminum plates 60F254 (20 cm × 20 cm, 0.2 mm thickness, 5–6 μm particle size)	Methanol	Oil	Sesamin = 720 Sesamolin = 400	[60]
6	HPLC-PAD (582 HPLC ESA, Waters Millford)	RP ODS-TM C1 8 analytical column (250 × 4.6 mm i.d.; 5 μm particle Size), with 996 PAD detector upstream	Methanol	Seed	Sesamin = 67–635	[61]
7	HPLC (Bischoff Analysentechnikund-gerate GmbH, Agilent technologies)	Alltima SI 5U silica column (4.6 × 250 mm), with fluorescence detector	Hexane plus Isopropanol (3:1)	Seed	Sesamin = 167–804 Sesamolin = 48–279 Sesaminol = 32–298 Sesamolinol = tr.-58 Episesamin = 5–35 Total lignans = 405–1178	[62]
8	HPLC (Dionex, Alltech Co.)	Econosil ODS column (5 μm, 250 × 4.6 mm), with Diode array detector (PDA)	*n*-Hexane and 80% Ethanol	Seed	Sesamolinol diglucoside = 5–232	[47]
9	HPLC (Dionex, Alltech Co.)	Econosil ODS column (5 μm, 250 × 4.6 mm), with Diode array detector (PDA)	*n*-Hexane and 80% Ethanol	Seed	Sesamolinol triglucoside = 36–1560 Sesamolinol diglucoside = 0–493	[48]
10	HPLC (Bischoff Analysentechnikund-gerate GmbH, Agilent technologies)	Alltima SI 5U silica column (4.6 × 250 mm), with fluorescence detector	Hexane plus Isopropanol (3:1)	Seed	Sesamin = 7–712 Sesamolin = 21–297	[63]
11	LC-tandem MS method (MA Alliance chromatography separation Module 2690, Waters Millford)	C18 column (150 mm × 3.0 mm i.d., 5 μm), with Detector Micromass Quatro Ultima MS	70% Methanol with 0.3 M NaOH	Seed	Pinoresinol = 29 Lariciresinol = 9 Secoisolariciresinol = 0.066 Matairesinol = 0.5 Total lignans = 39	[64]
11	HPLC (LC-10A, Shimadzu)	Shodex C18 RP column (4.6 mm i.d × 250 mm), with SPD-10A UV–vis detector	Ether	Seed	Sesamin = 1800 Sesamolin = 1000 Total lignans = 2880	[44]
12	HPLC (VISTA 5000 LC, Nomura Chemical Co.)	Stainless-steel column (20 mm i.d. × 250 mm) packed with Develosil ODS	*n*-Hexane and 80% Ethanol	Seed	Sesaminol triglucoside = 68.4 Sesaminol diglucoside = 11.6 Sesaminol monoglucoside = 8.3	[50]

Near Infrared Reflectance Spectroscopy (NIRS). The NIRS is non-destructive method for the determination of lignan and lignan glycoside contents and therefore is proposed as a method of immense use in the breeding programs for raising high quality sesame [75]. Recently Grougnet et al. [55] reported a method based on XAD-4 adsorption resin that permits the analysis of lignans in polyphenolic extracts of *Sesamum indicum* perisperm (coat) and seeds. UPLC-FLD analysis enabled the quantification of sesamin in sesame leaves for the first time [58]. HPLC–NMR technique allows complete structural characterization of compounds in complex mixtures at microgram levels. HPLC–MS/MS is yet another powerful method employed for quantification of sesame lignans, but requires highly pure, deuterated compounds [2]. Structural elucidation of the lignans is possible if a combination of 1D and 2D NMR techniques (Heteronuclear Multiple-Quantum Correlation – HMQC, Heteronuclear multiple-bond correlation spectroscopy – HMBC, and Nuclear Overhauser effect spectroscopy – NOESY)) with mass spectroscopy is used [52,54,63].

The furofuran lignans, tocopherols, minerals, vitamins, mono and polyunsaturated fatty acids present in sesame have high beneficial effect on human health. But the crop of sesame as a source of these lignans remains as a neglected and underutilised crop. There is a need to evolve programme for genetic improvement of the crop by genetic engineering and modern breeding methods, and conservation of the germplasm. Sesame has wide applications in pharmaceutical and medical science as discussed in the review. The ethno-botanical and medicinal importance of nutrionally rich oilseed needs to be explored much for better utilization.

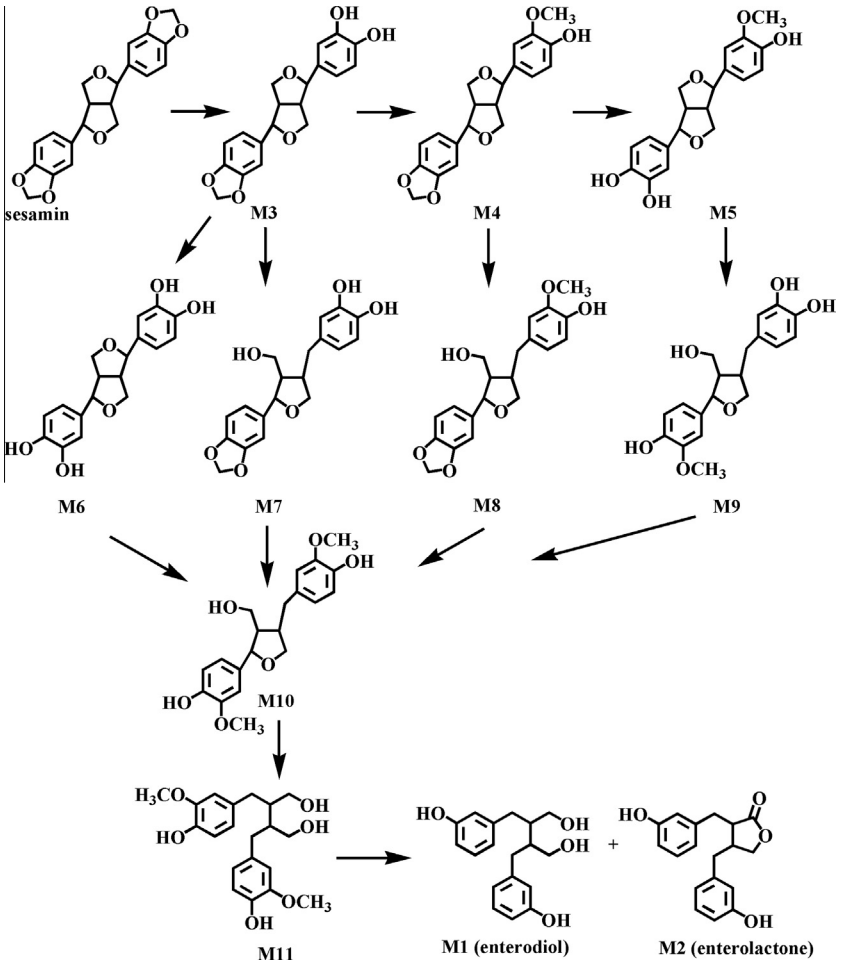

Fig. 2. Structures of Intermediates formed during the Metabolism of sesamin in the gut of human as cited in reference [42].

4. Biological activities of sesame lignans

Sesame lignans individually as well as in combination have been found to exhibit varied biological activities. The reports that appeared till recent time on these activities are reviewed in the following paragraphs.

4.1. Sesamin

This is a furofuran type lignan with a number of beneficial health effects in humans. It has been found to play significant role in lipid and glucose metabolism, hypertension, anti-inflammation and free radical scavenging. Sesamin binds to Peroxisome Proliferator- Activator Receptor Alpha (PPAR α) downregulating the expression of lipogenic enzymes [76]. This leads to increased expression of the mitochondrial enzyme carnitine palmitoyl transferase with more fatty acids to be transported into the mitochondria for oxidation. The presence of sesamin has been associated with decreased expression of sterol regulatory element binding protein-1 (SREBP-1), acetyl-CoA carboxylase and fatty acid synthase [77] and inhibition of cholesterol absorption and biosynthesis in rats and humans [78,79]. Later on this has been correlated with reduction in low density lipoprotein (LDL) and increase in high density lipoprotein (HDL) levels [77,79]. It can be said that sesamin increases the fat burning process, decreases the storage of fat and blood cholesterol level in the body, thereby preventing the obesity and atherosclerosis in humans.

Sesamin exhibited anti inflammatory activity by inhibiting delta 5-desaturase, a key enzyme in arachidonic acid biosynthesis that leads to a reduction in the formation of pro-inflammatory mediators [80,81]. Sesamin has been shown to increase the production of ketone bodies, when glucose is low in the brain tissue [82]. It is also found to significantly quench the excess generation of nitric oxide induced by lipopolysaccharide in the murine microglial cell line BV-2 and rat primary microglia cells [83]. Cheng et al. [84] demonstrated that pretreatments with sesamin and crude sesame oil significantly reduced the infarct sizes of gerbil brains by 56% and 49%, respectively in 4-Vessel Occlusion rat model. Thus sesamin exert effective neuroprotection against cerbral ischemia.

Wu et al. [85] showed inhibition of certain CYP450 enzymes and 20-hydroxyeicosatetraenoic acid (20-HETE) production that effect blood pressure by this compound. It has increased Ca^{2+} antagonistic vasorelaxing activity and enhanced hepatic detoxification, thereby protecting oxidative stress and preventing hypertension. Sesamin elevated γ-tocopherol in plasma and liver of rats and humans [86–89]. These reports suggest a beneficial effect of sesamin on prevention of Cardio Vascular Diseases. In addition to these, sesamin has been found to afford protection against ethanol- and carbon tetrachloride-induced liver damage [90], inhibit vascular superoxide production [91], promote angiogenesis [92], neuroprotection [93] and bactericide and insecticide activities as well [94].

4.2. Sesamolin

This compound is known to increase both the hepatic mitochondrial and the peroxisomal fatty acid oxidation rate [95] and act as a synergist for pyrethrum insecticides [96,97]. It has induced

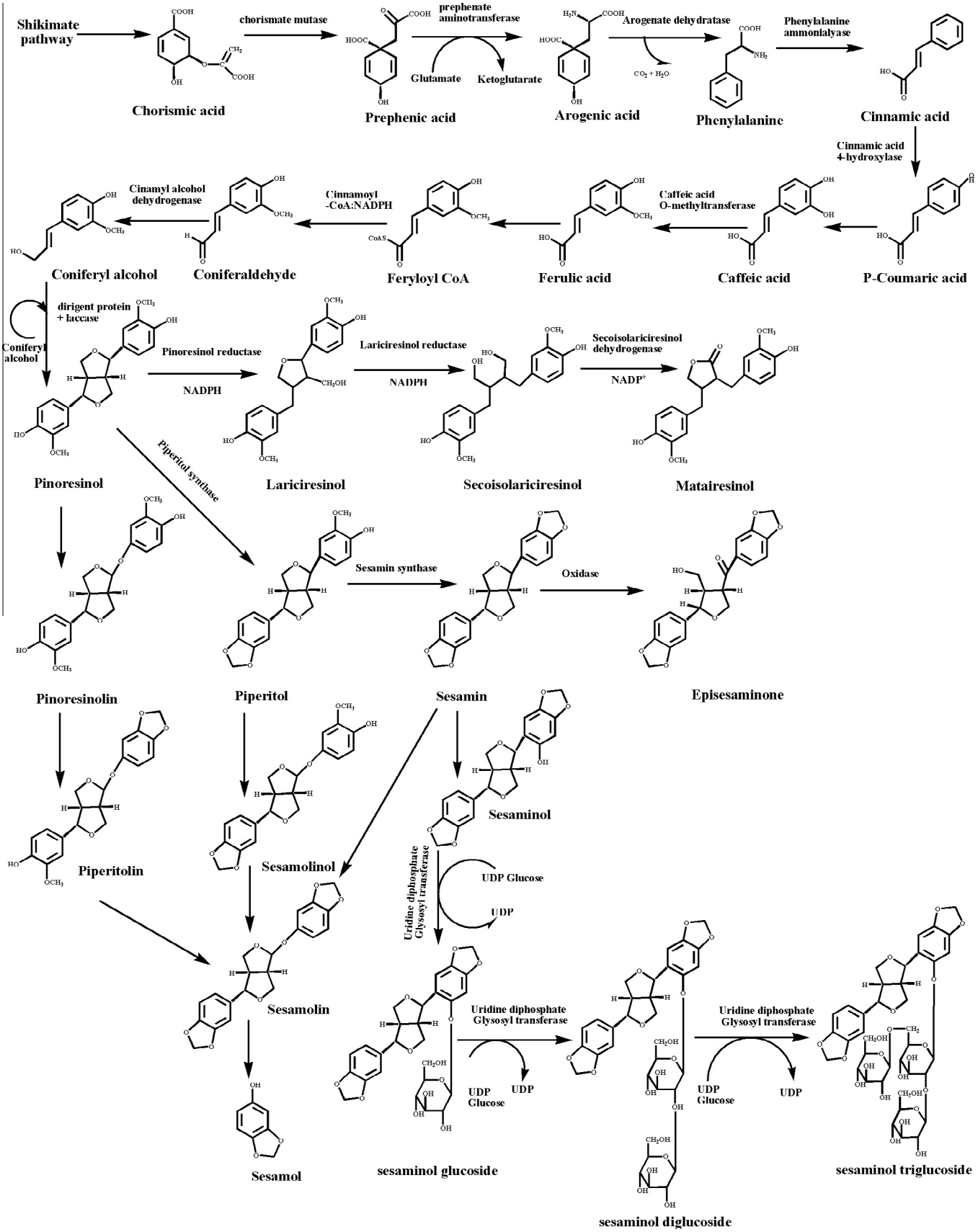

Fig. 3. Proposed lignan biosynthetic pathway reconstructed from the published reports [1,128,129,131–139].

apoptosis in human lymphoid leukemia Molt 4B cells [98], inhibited mutagenesis induced by H_2O_2 [55] and suppresses ROS generation in neurons against excitotoxicity or lipopolysaccharide (LPS)-induced neurotoxicity [49].

4.3. Sesaminol

This compound also has the property of inhibiting the membrane lipid peroxidation [99], the microsomal peroxidation induced by ADP-Fe3+/NADPH [100] and the oxidation of LDL induced by copper ions [100,101]. Sesaminol has been shown to increase the availability of tocopherols in biological systems by synergistic effects in raising liver and plasma concentrations of vitamin E. It was also found to inhibit oxidative damages in DNA [102,103]. Sesaminol glucosides present in defatted sesame flour were proved to decrease susceptibility to oxidative stress and inhibit allergen absorption in vitro [104,105].

4.4. Sesamol

Using a nanosecond pulse radiolysis technique, sesamol has been reported to show antioxidant and free radical scavenging activities [106,107]. The antioxidant activity of sesamol was found to be higher than that of sesamin and sesamolin. Due to this high antioxidant activity, sesamol is reported to protect cell membrane against lipid peroxidation, prevent LDL oxidation and microsomal peroxidation [99,101,108]. The study by Prisna et al. [109] suggested that sesame lignans and their metabolites possess weak estrogenic/antiestrogenic activity in hormone dependent manner in breast cancer cells. The estrogen agonistic effect of sesame lignan makes it to be useful for conventional hormone replacement therapy in postmenopausal women.

4.5. Pinoresinol and other minor lignans

Pinoresinol which is found in minor amount in sesame has also been shown to inhibit membrane lipid peroxidation and the LDL oxidation [99–101]. Apart from the well known lignans described above, three lesser known lignans that show the antifungal activity were also isolated from sesame. They are chlorosesamone, hydroxysesamone and 2,3-epoxysesamone which have inhibitory effects on the spore germination of the pathogenic fungus*Cladosporium fulvum* [51,52,110]. The episesamin was also reported to possess anticancer activity against human lymphoid leukemia cells in vitro [111].

5. Lignans in Human diet

The lignans consumed by human are in fact digested by the microflora present in the intestine. Series of steps involved in the metabolism of sesamin is presented in Fig. 3. Sesamin is converted to the phytoestrogens and enterolactones. The phytoestrogens are known to play protective role against breast cancer [42,112]. The assays for enterolignans, showed the presence of these lignans in body fluids – urine, plasma, saliva, semen, and prostatic fluid of humans and animals [6]. The mammalian lignan appearance rate in plasma shows that sesamin is a major precursor of enterolactone in vivo. Enterolignans possess a range of biological activities such as antioxidant, weakly estrogenic and anti-estrogenic properties [113]. A correlation was observed between the presence of the mammalian lignans, enterolactone (EL) and enterodiol (ED) and the reduced incidences of breast, prostate and colon cancers [114,115]. However some recent studies indicated neutrality between a high serum concentration of enterolactone and the cancer risks [116,117]. A population based study done recently showed association of a high serum enterolactone level with reduced coronary heart disease. This study also showed that the action of enterolignans appears to be concentration dependent [118].

The sesaminol glucosides are hydrolyzed to sesaminol, which is a strong antioxidative lipid soluble lignan, by an intestinal β-glucosidase [119]. Liu et al. [42] showed for the first time that in rats sesamin from sesame seed, is converted to the mammalian lignans ED and EL with a higher level of ED in the urine of rats fed with sesamin and sesame seed followed by EL [120–122]. A series of steps involved in metabolism of sesamin in mammals is presented in Fig. 2. Sesamin appears to be demethylenated into dimethylpiperitol (M3) and then further demethylenated to 2,6-bis(3,4-dihydroxyphenyl)-3,7dioxabicyclo[3,3,0]octane (M6) or methylated in its catechol moiety to piperitol (M4), possibly by liver catechol-O-methyl transferase. Piperitol is further demethylenated to 39-O demethylepipinoresinol (M5). The formation of M3–M6 may occur predominantly in the liver [90], whereas intestinal microbiota appear to play a part in their production [112]. The lignan derivatives appears to undergo reductive cleavage of their furofuran rings to 2-(3,4-dihydroxytolyl)-4-(3,4-methylenedioxyphenyl)-3hydroxyl methylene-furan(M7), 2-(4-hydroxy-3-methoxytolyl)-4-(3,4-methylenedioxyphenyl)-3hydroxylmethylenefuran (M8) and 39-demethyl-lariciresinol (M9) respectively [122]. M6–M9 intermediates are further metabolised to lariciresinol (M10) and secoisolariciresinol (M11) respectively. Finally secoisolariciresinol is metabolised to Enterodiol (M1) and Enterolactone (M2) [123–125]. These studies showed that rats administered with dietary sesame seed excreted large amounts of urinary ED and EL compared with the control and no sesamin or other sesame lignans could be detected in the urine of the treated rats. These results demonstrate that sesame is one of the richest dietary sources of mammalian lignan precursors [42].

6. Biosynthesis of lignans in sesame

A biosynthetic pathway is generally deduced from radio tracer studies and by enzyme assays [126]. Similar studies on lignan biosynthesis revealed that these compounds are synthesized from phenylalanine through several phenylpropanoid modifications [127]. Sesamolin a precursor of sesamol was already known but the formation of the sesamolin precursor is reported only recently [128]. Two achiral molecules of E-coniferyl alcohol are formed via the cinnamate/monolignol pathway which undergoes stereoselective coupling to form pinoresinol in *Sesamum indicum* seeds [129,130]. Stepwise methylene dioxy bridge formation of pinoresinol is catalyzed by two consecutively acting cytochrome P450 (SiP450) enzymes. One of them is piperitol synthase (PS) which catalyzes the conversion of pinoresinol to piperitol. Introduction of methylene dioxy bridge requires sesamin synthase (SS) to afford sesamin [129,131]. Sesamin is further metabolised to episesaminone by a single oxidation [131]. Later Ono et al. [128] isolated a cDNA encoding a cytochrome P-450, CYP81Q1 from microsomal fraction of *S. indicum* and showed its functional role in catalysis that lead to formation of methylenedioxy bridge with pinoresinol giving rise to sesamin. This study also showed that CYP81Q1 is a gene that encodes for both piperitol/sesamin synthase (PSS). Based on the literature survey, we may deduce a more comprehensive pathway of sesamin biosynthesis to look like the one presented in Fig. 3. Analysis of F2 populations from reciprocal crosses between high and low sesamin containing varieties showed a normal distribution curve for sesamin content and the correlation coefficients between F2 and F3 generations were positive. This study indicated that the genes controlling accumulation of sesamin is polygenic in nature [140]. In addition Hata et al. [58] showed that sesamin content in different parts of the sesame plants is correlated with different level of CYP81Q1 expression. By this, it is speculated that the level of CYP81Q1 gene expression should be

controlled by several modifier genes that highly contributes to genotypic and tissue specific variation in sesamin content. Leaf sesamin synthesis seems to have no connection with seed sesamin accumulation and seed sesamin might be synthesized de novo in the seeds.

7. Future prospects and conclusion

The application of sesamin in auguring human health is one of the main themes of current research in medical science. Focus is required on validating the biological activities of furofuran lignans other than sesamin. Another point of concern at this juncture is to ensure the availability of sesamin in reasonable quantity for medical application, as Sesame is the only major source of these lignans. Therefore, it may be concluded that there is potential of a tremendous research on qualitative and quantitative improvement of the sesame crop for sesamin production. High throughput analytical methods based on cell culture techniques would be a way out in advancing our knowledge on biosynthesis of sesamin both for productivity and human health.

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References

[1] T. Umezawa, Phytochem. Rev. 2 (2003) 371–390.
[2] S.M. Willfor, A.I. Smeds, B.R. Holmbom, J. Chromatogr. A 1112 (2006) 64–77.
[3] A.M. Hutchins, B.D. Brown, S.C. Cunnane, S.G. Domitrovich, E.R. Adams, C.E. Bobowiec, Nutr. Res. (2013). <http://dx.doi.org/10.1016/j.nutres.2013.02.012>.
[4] D.A. Whiting, Nat. Prod. Rep. 2 (1985) 191–211.
[5] E. Fuss, Overview Phytochem. Rev. 2 (2003) 307–320.
[6] J. Slanina, Z. Glatz, J. Chromatogr. B 812 (2004) 215–229.
[7] O.P. Gautam, S. Verma, S.K. Jain, Pharmacology 1 (2011) 121–125.
[8] T.P. Singh, O.M. Singh, Indian J. Nat. Prod. Res. 2 (2011) 275–285.
[9] C.J. Zheng, X.P. Lan, R.B. Cheng, B.K. Huang, T. Han, Q.Y. Zhang, H. Zhang, K. Rahman, L.P. Qin, Phytochem. Lett. 4 (2011) 298–300.
[10] P. Sartorelli, C.S. Carvalho, J.Q. Reimao, H. Lorenzi, A.G. Tempone, Planta Med. 76 (2010) 1454–1456.
[11] M. Zaveri, A. Khandhar, S. Patel, A. Patel, Int. J. Pharma. Sci. Rev. Res. 5 (2010) 67–76.
[12] N. Rangkaew, R. Suttisri, M. Moriyasu, K. Kawanishi, Arch. Pharm. Res. 32 (2009) 685–692.
[13] S.W. Yang, S.R. Park, H.J. Lee, J.H. Yang, B.S. Chae, H.J. Kim, D.K. Kim, Korean J. Pharmacogn. 40 (2009) 315–318.
[14] H.J. Lee, S.M. Seo, O.K. Lee, H.J. Jo, H.Y. Kang, D.H. Choi, K.H. Paik, M. Khan, Helv. Chim. Acta 91 (2008).
[15] H.S. Bodiwala, G. Singh, R. Singh, C.S. Dey, S.S. Sharma, K.K. Bhutani, I.P. Singh, J. Nat. Med. 61 (2007) 418–421.
[16] C.P. Lee, G.C. Yen, J. Agric. Food Chem. 54 (2006) 779–784.
[17] A. Kumar, S.P. Singh, R.S. Bhakuni, Curr. Sci. 89 (2005) 1489–1501.
[18] S.I. Pereira, C.S. Freire, N.C. Pascoal, A.J. Silvestre, A.M. Silva, Phytochem. Anal. 16 (2005) 364–369.
[19] C.J. Ma, S.H. Sung, Y.C. Kim, Planta Med. 70 (2004) 79–80.
[20] T. Rukachaisirikul, P. Siriwattanakit, K. Sukcharoenphol, C. Wongvein, P. Ruttanaweang, P. Wongwattanavuch, A. Suksamrarn, J. Ethnopharmacol. 93 (2004) 173–176.
[21] J. Ryu, D. Son, J. Kang, H.S. Kim, B.K. Kim, S. Lee, Arch. Pharm. Res. 27 (2004) 912–914.
[22] A. Yamari, D. Boriky, M.L. Bouamrani, M. Blaghen, M. Talbi, J. Chin. Chem. Soc. 51 (2004) 637–638.
[23] S. Ayan, I. Sadlam, A. Sivaciodlu, *Paulownia* Sieb. & Zucc: A New Exotic Genus for Multi-Purpose Uses In Kastamonu – Turkey, Decision Support for Multiple Purpose Forestry, Vienna – Austria, 2003, pp. 1–9.
[24] E. Bedir, I.I. Tatli, R.A. Khan, J. Zhao, S. Takamatsu, L.A. Walker, P. Goldman, I.A. Khan, J. Agric. Food Chem. 50 (2002) 3150–3155.
[25] S. Lee, B.K. Kim, S.H. Cho, K.H. Shin, Arch. Pharm. Res. 25 (2002) 280–284.
[26] N. Takaku, D.H. Choi, K.M. Mikame, T. Okunishi, S. Suzuki, H. Ohashi, T. Umezawa, M. Shimada, J. Wood Sci. 47 (2001) 476–482.
[27] L.I. Yan, Y.E. Min, H.W. Liu, X.H. Ji, Y.N. Yan, Chin. Chem. Lett. 11 (2000) 1073–1076.
[28] I.S. Chen, T.L. Chen, Y.L. Chang, C.M. Teng, W.Y. Lin, J. Nat. Prod. 62 (1999) 833–837.
[29] H.J. Yu, C.C. Chen, B.J. Shieh, J. Nat. Prod. 61 (1998) 1017–1019.
[30] N.H. Anh, H. Ripperger, A. Porzel, T.V. Sung, G. Adam, Phytochemistry 46 (1997) 557–569.
[31] E.E. A Blumenthal, M.S. Silva, M. Yoshilia, Phytochemistry 46 (1997) 745–749.
[32] P.X. Chin, Chromatograp. Fingerprint Anal. Herb. Medicines (1997) 191–202.
[33] M.J. Kato, M. Yoshida, O.R. Gottlieb, Phytochemistry 31 (1992) 283–287.
[34] J.M. Barbosa-Filho, M. Yoshida, O.R. Gottlieb, Phytochemistry 28 (1989) 1991.
[35] S. H Cavalcante, D. Fernandes, H.F.P. Fo, M. Yoshida, O. R Gottlieb, Phytochemistry 24 (1985) 1865–1866.
[36] J.I. Okogun, D.E.U. Ekong, JCS Perkin I (1974) 2195–2198.
[37] P. Budowski, K.S. Markley, Chem. Reo. 48 (1951) 125–151.
[38] D. Bedigian, D.S. Seigler, J.R. Harlan, Biochem. Syst. Ecol. 13 (1986) 133–139.
[39] T. Osawa, M. Nagata, M. Namiki, Y. Fukuda, Agric. Biol. Chem. 49 (1985) 3335–3351.
[40] H. Katsuzaki, M. Kawasumi, S. Kawakishi, T. Osawa, Biosci. Biotechnol. Biochem. 56 (1992) 2087–2088.
[41] S.R. Chavali, T. Utsunomi, R.A. Forse, Crit. Care Med. 29 (2001) 140–143.
[42] Z. Liu, N.M. Saarinen, U. Lilian, U. Thompson, J. Nutr. 136 (2006) 906–912.
[43] H. Katsuzaki, S. Kawakishi, T. Osawa, Phytochemistry 35 (1994) 773–776.
[44] S. Hemalatha, J. Am. Oil Chem. Soc. 81 (2004) 467–470.
[45] K.C. Jeng, R.C. Hou, Curr. Enzyme Inhib. 1 (2005) 11–20.
[47] A.A. Moazzami, R.E. Andersson, A. Kamal-Eldin, J. Agric. Food Chem. 54 (2006) 633–638.
[48] A.A. Moazzami, R.E. Andersson, A. Kamal-Eldin, Biosci. Biotechnol. Biochem. 70 (2006) 1478–1481.
[49] S.H. Park, S.N. Ryu, Y. Bu, H. Kim, E. James, J.E. Simon, K.S. Kim, Food Rev. Int. 26 (2010) 103–121.
[50] S.N. Ryu, C.T. Ho, T. Osawa, J. Food Lipids 5 (1998) 17–28.
[51] A.F.M. F Hasan, S. Begum, T. Furumoto, H. Fukui, Biosci. Biotechnol. Biochem. 64 (2000) 873–874.
[52] A.F.M. F Hasan, T. Furumoto, S. Begum, H. Fukui, Phytochemistry 58 (2001) 1225–1228.
[53] A. Kamal-Eldin, G. Yousif, Phytochemistry 31 (1992) 2911–2912.
[54] R. Grougnet, P. Magiatis, S. Mitaku, A.T.F. Tillequin, A.L. Skaltsounis, J. Agric. Food Chem. 54 (2006) 7570–7574.
[55] R. Grougnet, P. Magiatis, H. Laborie, D. Lazarou, A. Papadopoulos, A.L. Skaltsounis, J. Agric. Food Chem. 60 (2012) 108–111.
[56] A.S. Harvey, C.R. Deborah, J. Am. Oil Chem. Soc. 89 (2012) 1943–1950.
[57] L. Wang, Y. Zhang, P. Li, X. Wang, W. Zhang, W. Wei, X. Zhang, J. Am. Oil Chem. Soc. 89 (2012) 1011–1020.
[58] N. Hata, Y. Hayashi, A. Okazawa, E. Ono, H. Satake, A. Kobayashi, Plant Sci. 178 (2010) 510–516.
[59] N. Rangkadilok, N. Pholphana, C. Mahidol, W. Wongyai, K. Saengsooksree, S. Nookabkaew, J. Satayavivad, Food Chem. 122 (2010) 724–730.
[60] D. Sukumar, R. Arimboor, C. Arumughan, J. Pharm. Biomed. Anal. 47 (2008) 795–801.
[61] K.S. Williamson, J.B. Morris, N. Quentin, Q.N. Pye, D.K. Chandrashekhar, K. Hensley, Phytochem. Anal. 19 (2008) 311–322.
[62] A.A. Moazzami, S.L. Haese, A. Kamal-Eldin, Eur. J. Lipid Sci. Technol. 109 (2007) 1022–1027.
[63] A.A. Moazzami, Sesame seed lignans: Diversity, human metabolism and bioactivities. Doctoral Thesis, Swedish University of Agricultural Sciences Uppsala, 2006c, pp. 7147–7148 (ISBN: 91-576).
[64] I.E.J. Milder, I.C.W. Arts, B. Van de Putte, D.P. Venema, P.C.H. Hollman, Br. J. Nutr. 93 (2005) 393–402.
[65] A. Kamal-Eldin, L.A. Appelqvist, G. Yousif, J. Am. Oil Chem. Soc. 71 (1994) 141–147.
[66] F. Shahidi, R. Amarowicz, H.A. Abou-Gharbia, A.Y. Shehata, J. Am. Oil Chem. Soc. 74 (1997) 147–148.
[67] A. Kamal-Eldin, G. Yousif, L.A. Appelqvist, J. Am. Oil Chem. Soc. 68 (1991) 844–847.
[68] E.M. Gaydou, J.P. Bianchini, J.V. Ratovoheryn, J. Agric. Food Chem. 31 (1983) 833–836.
[69] D.C. Ayres, R.B. Chater, Tetrahedron 25 (1969) 4093–4098.
[70] R. Amarowicz, F. Shahidi, R.B. Pegg, J. Food Lipids 8 (2001) 85–94.
[71] Y. Fukuda, T. Osawa, R. Kawagishi, M. Namiki, Nippon Shokuhin Kogyo Gakkaishi 35 (1998) 483–486.
[72] H.M.A. Mohamed, I.I. Awatif, Food Chem. 62 (1998) 269–276.
[73] S.S. Yasumoto, M. Komeichi, Y. Okuyama, A. Horigane, J. Breed. Genet. 35 (2003) 27–34.
[74] Y.W. Lee, R.D. Voyksner, T.W. Pack, C.E. Cook, Q. C Fang, Y. Ito, Anal. Chem. 62 (1990) 244.
[75] K.S. Kim, S.H. Park, M.G. Choung, J. Agric. Food Chem. 54 (2006) 4544–4550.
[76] J.L. Penalvo, A. Hopia, H. Adlercreutz, Eur. J. Nutr. 45 (2006) 439–444.
[77] T. Ide, M. Kushiro, Y. Takahashi, K. Shinohara, N. Fukuda, S. Yasumoto, JARQ 37 (2003) 151–158.
[78] N. Hirose, T. Inoue, M. Sugano, K. Akimoto, H. Shimizu, H. Yamada, J. Lipid Res. 32 (1991) 629–638.
[79] F. Hirata, K. Fujita, Y. Ishikura, K. Hosoda, T. Ishikawa, H. Nakamura, Atherosclerosis 122 (1996) 135–136.
[80] S. Shimizu, K. Amimoto, H. Kawashim, M. Sugano, H. Yamada, Lipids 26 (1991) 512–516.
[81] S. Chavali, W. Zhong, R. Forse, Fatty Acids 58 (1998) 185–191.
[82] K.R. Anilakumar, K. Ajay Pal, K. Farhath, S.B. Farhath, Agri. Conspect. Sci. 75 (2010) 159–168.
[83] R.C.W. Hou, H.L. Chen, J.T.C. Tzen, et al., NeuroReport 14 (2003) 1815–1819.

[84] F.C. Cheng, T.R. Jinn, R.C.W. Hou, J.T.C. Tzen, Int. J. Biomed. Sci. 2 (2006) 284–288.
[85] J.H. Wu, J.M. Hodgson, M.W. Clarke, A.P. Indrawan, A.E. Barden, I.B. Puddey, K.D. Croft, Hypertension 54 (2009) 1151–1158.
[86] A. Kamal-Eldin, D. Pettersson, L. Appelqvist, Lipids 30 (1995) 499–505.
[87] Y. Matsumura, S. Kita, S. Morimoto, et al., Biol. Pharm. Bull. 18 (1995) 1016–1019.
[88] M. Lemcke-Norojarvi, A. Kamal-Eldin, L.A. Appelqvist, L.H. Dimberg, M. Ohrvall, B. Vessby, J. Nutr. 131 (2001) 1195–1201.
[89] D. Nakano, C.J. Kwak, K. Fujii, K. Ikemura, K. Satake, M. Ohkita, M. Takaoka, Y. Ono, M. Nakai, N. Tomimori, Y. Kiso, Y. Matsumura, J. Pharmacol. Exp. Ther. 318 (2006) 328–335.
[90] M. Nakai, M. Harada, K. Nakahara, K. Akimoto, H. Shibata, W. Miki, Y. Kiso, J. Agric. Food Chem. 51 (2003) 1666–1670.
[91] D. Nakano, C. Itoh, F. Ishii, H. Kawanishi, M. Takaoka, Y. Kiso, N. Tsuruoka, T. Tanaka, Y. Matsumura, Biol. Pharm. Bull. 26 (2003) 1701–1705.
[92] B.H. Chung, J.J. Lee, J.D. Kim, D. Jeoung, H. Lee, J. Choe, K.S. Ha, Y.G. Kwon, Y.M. Kim, Biochem. Biophys. Res. Commun. 391 (2010) 254–260.
[93] M.M. Khan, T. Ishrat, A. Ahmad, M.N. Hoda, M.B. Khan, G. Khuwaja, P. Srivastava, S.S. Raza, F. Islam, S. Ahmad, Chem. Biol. Interact. 183 (2010) 255–263.
[94] Home Cooking, Sesame Seeds, 1998, <http://homecooking.about.com/library/weekly/aa060898.htm>.
[95] J.B. Morris, Food, Industrial, Nutraceutical, and Pharmaceutical Uses of Sesame Genetic Resources Trends in New Crops And New Uses. 2002.
[96] J.E. Simon, A.F. Chadwick, L.E. Craker, Herbs Index. Bibliogr. (1984) 1971–1980.
[97] S.M. Beckstrom-Sternberg, J.A. Duke, K.K. Wain, The Ethnobotany Database, 1994. <http://arsgenome.cornell.edu/cgibin/WebAce/webace?db=ethnobotdb>.
[98] Y. Miyahara, H. Hibasami, H. Katsuzaki, K. Imai, T. Komiya, Int. J. Mol. Med. (2001) 369–371.
[99] P. Nishant, A.V.R.L. Visavadiya, Narasimhacharya, Food Chem. Toxicol. 46 (2008) 1889–1895.
[100] M.H. Kang, T. Osawa, Lipids 33 (1998) 1031–1036.
[101] M.H. Kang, M. Naito, K. Sakai, K. Uchida, T. Osawa, Life Sci. 66 (1999) 161–171.
[102] T. Osawa, Mech. Ageing Develop. 111 (1999) 133–139.
[103] K. Yamashita, Y. Nohara, K. Katayama, M. Namiki, J. Nutr. 122 (1992) 2440–2446.
[104] M.H. Kang, Y. Kawai, Y. Naito, T. Osawa, J. Nutr. 129 (1999) 1885–1890.
[105] S. Kobayashi, J. Watanabe, J. Kawabata, E. Fukushi, H. Shinmoto, Biosci. Biotechnol. Biochem. 68 (2004) 300–305.
[106] M.K. Unnikrishnan, M.S. Kumar, K. Satyamoorthy, R. Joshi, J. Agric. Food Chem. 53 (2005) (2005) 2696–2703.
[107] X. Juan, S. Chen, H. Qiuhui, Food Chem. 91 (2005) 79–83.
[108] J. Lee, E. Choe, J. Food Sci. 71 (2006) 430–436.
[109] P. Prisna, T. Apinya, R. Nuchanart, W. Piyajit, M. Chulabhom, S. Jutamaad, J. Agri. Food Chem. 59 (2011) 212–221.
[110] H. Fukui, A.F.M.F. Hasan, M. Kyo, Phytochemistry 51 (1999) 511–515.
[111] Y. Miyahara, T. Komiya, H. Katsuzaki, K. Imai, M. Nakagawa, Y. Ishi, H. Hibasami, Int. J. Mol. Med. 1 (2000) 43–46.
[112] J.L. Penalvo, S.M. Heinonen, A.M. Aura, H. Adlercreutz, J. Nutr. 135 (2005) 1056–1062.
[113] H. Adlercreutz, Human health and phytoestrogens, in: K.S. Korach (Ed.), Reproductive and Developmental Toxicology, Marcel Dekker, New York, 1998, pp. 298–371.
[114] D. Ingram, K. Sanders, M. Kolybaba, D. Lopez, Lancet 350 (1997) 990–994.
[115] P. Pietinen, K. Stumpf, S. Mannisto, V. Kataja, M. Uusitupa, H. Adlercreutz, Cancer Epidemiol. Biomark. Prev. 10 (2001) 339–344.
[116] A. Kilkkinen, J. Virtamo, M.J. Virtanen, H. Adlercreutz, D. Albanes, P. Pietinen, Biomark. Prev. 12 (2003) 1209–1212.
[117] A. Kilkkinen, J. Virtamo, E. Vartianen, R. Sankila, M.J. Virtanen, H. Adlercreutz, P. Pietinen, Int. J. Cancer 108 (2004) 277–280.
[118] M. Vanharanta, S. Voutilainen, T.H. Rissanen, H. Adlercreutz, J.T. Salonen, Arch. Intern. Med. 163 (2003) 1099–1104.
[119] G. Tamura, C. Gold, A. Ferro-Luzzi, B.N. Ames, Fecalase: a model for activation of dietary glycosides to mutagens by intestinal flora, Proc. Natl. Acad. Sci. USA 77 (1980) 4961–4965.
[120] O.A. Van, J.F.G.A. Jansen, B.L. Feringa, J. Org. Chem. 59 (1994) 5999–6007.
[121] E. Jacobs, S.E. Kulling, M. Metzler, J. Steroid Biochem. Mol. Biol. 68 (1999) 211–218.
[122] H.B. Niemeyer, D. Honig, A. Lange-Bohmer, E. Jacobs, S.E. Kulling, M. Metzler, J. Agric. Food Chem. 48 (2000) 2910–2919.
[123] L.H. Xie, T. Akao, K. Hamasaki, T. Deyama, M. Hattori, Chem. Pharm. Bull. (Tokyo) 51 (2003) 508–551.
[124] H.B. Niemeyer, D.M. Honig, S.E. Kulling, M. Metzler, J. Agric. Food Chem. 51 (2003) 6317–6325.
[125] T. Sicilia, H.B. Niemeyer, D.M. Honig, M. Metzler, J. Agric. Food Chem. 51 (2003) 1181–1188.
[126] L.B. Davin, N.G. Lewis, Phytochem. Rev. 2 (2003) 257–288.
[127] S. Suzuki, T. Umezawa, J. Wood Sci. 53 (2007) 273–284.
[128] E. Ono, M. Nakai, Y. Fukui, N. Tomimori, M. Fukuchi-Mizutani, M. Saito, H. Satake, T. Tanaka, M. Katsuta, T. Umezawa, Y. Tanaka, PNAS 103 (2006) (2006) 10116–10121.
[129] M.J. Kato, A. Chu, L.B. Davin, N.G. Lewis, Phytochemistry 47 (1998) 583–591.
[130] T. Umezawa, Kagaku to Seibutsu 43 (2005) 461–467.
[131] Y. Jiao, L.B. Davin, N.G. Lewis, Phytochemistry 49 (1998) 387–394.
[132] P.A. Marchand, M.J. Kato, N.G. Lewis, J. Nat. Prod. 60 (1997) 1189–1192.
[133] P. Budowski, J. Am. Oil. Chem. Soc. 27 (1950) 264–267.
[134] K.M. Herman, Plant Cell 7 (1995) 907–919.
[135] N.G. Lewis, L.B. Davin, S. Sarkanen, Distinctions Reconciliations (1998) 1–27.
[136] B. Milles, Biosynthesis of Aromatic Amino Acids & Porphyrins, 2003.
[137] J.L. Ferrer, M.B. Austi, J.C. Stewart, J.P. Noel, Plant Physiol. Biochem. 46 (2008) 356–370.
[138] T. Nakatsubo, M. Mizutani, S. Suzuki, T. Hattori, T. Umezawa, J. Biol. Chem. 283 (2008) 15550–15557.
[139] A. Noguchi, Y. Fukui, A. Iuchi-Okada, S. Kakutani, H. Satake, T. Iwashita, M. Nakao, T. Umezawa, E. Ono, Plant J. 54 (2008) 415–427.
[140] S.S. Yasumoto, Bull., Natl. Inst. Crop Sci. 9 (2008) 27–61.