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A comprehensive review on the anti-cancer properties of sesame lignans: chemical composition, molecular mechanisms and prospects

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This review presents a comprehensive report on recent advances in the chemical composition, structures, and diversity of sesame lignans, as well as their anti-cancer properties and underlying molecular mechanisms. An in-depth examination of preclinical and clinical evidence pertaining to the role of sesame lignans in chemotherapy and chemoprevention, focusing on reports of the effects on various indicators of cancer, including cell proliferation, cytotoxicity, apoptosis, invasion, migration, metastasis, signaling pathways, *etc.* was performed. Of over 40 sesame lignans identified, three, namely sesamin, sesamol, and sesamolin stood out for their significant anticancer properties against the most common cancer types, including lung, breast, colorectal, prostate, cervical, and liver cancer. The findings suggest that these sesame lignans could be applied in the development of chemotherapeutic agents, as adjuvants, or as part of combination therapies with traditional chemotherapeutic agents. In the latter case, sesame lignans could augment, potentiate the chemotherapeutic efficacy, and/or mitigate the adverse side-effects of the conventional agents. Furthermore, challenges, prospects, and recommendations towards the clinical translation of sesame lignans as bedside cancer therapies have been highlighted. For example, since most of the available evidence thus far is preclinical in nature, there is a need for further robust clinical investigations to ascertain the anti-cancer potency and safety in humans. This work is replete with insights that can serve as a valuable reference for understanding the role of sesame lignans and their potential for development of novel effective anti-cancer chemotherapeutics.

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1. Introduction

Cancer remains one of the most pressing global health challenges of recent times, being the second leading cause of deaths worldwide (9.89 million), and even surpassing COVID-19 (7.89 million) in 2021.[1] In fact, one out of every five persons will be affected by cancer in the course of their lifetime, and it is responsible for the death of one in every 10 people. It is among the three-leading causes of death among those aged 30–69 years in 177 of 183 countries,[2] a major impediment to increasing life expectancy, and harbinger of enormous suffering, pain and socio-economic costs to millions of individuals, families and communities.[3] Cancer remains one of the most common diseases worldwide, with an estimated 20 million new cases recorded in 2022.[4,5] Progress in cancer prevention, diagnosis, treatment, and care has been nothing short of remarkable in the previous decades; nonetheless, cancer-related morbidity and mortality is still on the increase with incidence projected at 35 million new cases in 2050.[4] Thus, this group of diseases (over 200 cancer types), represents a major public health and socio-economic problem. Fortunately, many options exist for treating cancer, the most common being surgery, radiation, and chemotherapy. Chemotherapy can be used to treat a wide range of cancers (primary and metastatic) and is deployed in several modalities, for example, as adjuvant, curative, neoadjuvant or palliative therapy. Despite the effectiveness of chemotherapeutic intervention, there has been several reports of adverse side effects, recess, as well as cases of multidrug cancer resistance.[6] This has necessitated the search for novel anti-cancer agents with improved efficacy and safety profiles.[7]

Natural products have been integral in health advancement dating back to times immemorial. Nowadays, natural products still play an important role in the improvement of health as components of many traditional medicines and sources of active pharmaceutical ingredients or leads in the development of modern pharmacotherapies. In fact, more than six out of

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every ten pharmaceutical drugs approved for use in the previous decade can be traced back to a natural compound.[8] This fact has continued to inspire phytochemical research in the quest for identification and development of novel treatment options for diseases such as cancers. Classes of phytochemical compounds that have continued to garner substantial attention include phenolics,[9,10] alkaloids,[11] flavonoids,[10] anthraquinones,[12] and lignans.[13]

Lignans are some of the secondary metabolites that have recently captured the fascination of researchers for their anti-cancer properties.[14] These compounds are essentially polyphenol-derivatives composed of phenylpropanoid moieties. Lignans are primarily found in vascular plants, having been identified in various aerial parts such as stems, leaves, woody tissues, as well as rhizomes, roots and exudates of plants.[15] Lignans have been found in food and medicinal plants, occurring in species belonging to more than 70 different families. In genera such as *Justicia*, *Ocotea*, *Schisandra*, *Machilus*, and *Nectandra*, lignans are the major plant bioactive compounds.[16,17] Meanwhile, in other genera such as *Vachellia*, they are in the minority.[18] It has been widely recognized that sesame and flaxseed are the major dietary sources of lignan compounds.[19] Nonetheless, these compounds can also be present in considerable amounts in other food sources, such as vegetables, whole grains, legumes, and some beverages.[15]

Sesame seeds are the oldest oilseeds in the world, having been cultivated for over four millennia. Edible oil from sesame seeds is known for its high-quality, oxidative stability, aromatic, nutritional, and nutraceutical properties due to abundant amounts of unsaturated fatty acids and bioactive compounds – primarily lignans, but also phenolics, flavonoids, vitamin E, *etc.*[20–22] Sesame lignans, such as sesamin, sesamolin, sesaminol, sesamol, and their metabolic end-products generated by gut microbiota and liver enzyme transformation – enterodiol and enterolactone (Fig. 1)[23] have been recognized for their manifold beneficial health properties. Sesame lignans and their derivatives have been found to exhibit a wide range of biological attributes, including antioxidative,[24] anti-inflammatory, immunomodulatory,[25] anti-hypertensive,[26] neuroprotective,[27] anti-hyperlipidemic,[28] and estrogenic properties.[29] This implies that sesame lignans could have health-promoting and disease countering roles in metabolic conditions such as diabetes mellitus as well as in the management of chronic conditions such as cardiovascular diseases and cancers.[30] Sesame lignans have been generally considered as safe given their abundance in sesame products, which have been consumed for a very long time without adverse effects. Their high content and biological activity have sparked intense interest in their applications as functional food ingredients and therapeutic candidates for various diseases.

Although there is a growing number of investigations on the anti-cancer effects of sesame lignans,[30] and a few review reports on the individual lignans, a robust, in-depth and up-to-date evaluation and discussion in light of their potential for prevention, treatment and management of cancer is currently lacking. This review presents a detailed exposition on the recent advances on sesame lignans, focusing on their chemical composition, anticancer properties in the most common cancer subtypes, as well as the mechanistic underpinnings responsible for chemo-therapeutic/preventive properties, challenges, prospects, recommendations, and potential for clinical application as anti-cancer drug candidates.

2. Review methodology

The review approach involved gathering information from all major public online sources of literature. Online literature archives perused for relevant publications included ScienceDirect, PubMed/MedLine, Google Scholar, *etc.* Keywords and phrases used in the search along with sesame lignans, *Sesamum indicum* L., sesamin, sesamol, or sesamolin, included chemical composition, anti-cancer, cytotoxic, apoptosis, cell proliferation, anti-neoplastic, cell migration, metastasis, tumor, signaling pathways, chemoprevention, chemotherapy, bioactive properties, amongst others. All documents analyzed as part of the review were in English language, full length, and accessible. Published articles that were not relevant, not in English language, incomplete text, and inaccessible were excluded.

3. Chemical composition of sesame lignans

3.1 Lignans in plants: structure and synthesis

In general, all lignans are produced *via* the shikimate pathway. They are formed through coupling of phenylpropanoid (C6–C3) units by oxidative dimerization. Natural lignans are essentially derived from cinnamoyl monomeric units, including arylpropenes (allyl benzenes and propenyl benzenes) and monolignols (*p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol). In other words, these metabolic products of tyrosine or phenylalanine form the building blocks of all natural lignans.[16]

Lignans exhibit a wide range of structural diversity. The most predominant structural forms are dimers, although trimeric and tetrameric structures have also been recorded.[15] The range of structures in lignans is made possible by the different coupling possibilities of the cinnamoyl monomeric derivatives, the manner and extent of oxygenation within the carbon skeleton, as well as the degree of unsaturation. The coupling reactions leading to the formation of lignans occur with phenoxyradicals. These radicals are formed from the cinnamoyl monomers *via* a series of reactions in which the phenolic hydroxy group is deprotonated to form their corresponding phenolate, which then lose an electron to generate the radical species. The oxygen atom on the phenoxyradical, as well as all carbon atoms *para* and *ortho* to it have spin density. Of note is the fact that the spin density can also be extended to the side chains at 8′-(or β′-) positions. This implies that coupling can also occur at this position.[15] The generated radicals can accumulate in adequate amounts to allow cross or homo coupling reactions. This accumulation is made possible because the radicals are persistent, being resonance stabilized through mesomeric effects.[31] Coupling of these mesomeric forms occurs with stereo- and regioselective precision in plants (and

mediated by a dirigent protein and specific enzymes), involving *O*,*C* and *C*,*C*-linkages, leading to a wide range of structurally diverse lignans, such as 8,5′-, 5,5′-, 8,*O*-4′-, and 8,8′-dimers.[32]

For the most part, lignans are classified according to their structural characteristics, which are products of the linkage positions of the monomeric subunits. On this basis, there are four broad categories of lignans. The first group is composed of compounds known as the classical lignans. These are formed when two radicals are phenol-oxidatively dimerized or coupled at the 8,8′- (or β, β′-) positions in the propyl side chain.[33] The second group consists of compounds referred to as the neolignans. These originates from various other coupling possibilities. Examples of these include oxyneolignans, which are formed when the dimerization involves the phenolic oxygen to create an ether bond. The third group of lignans are referred to as norlignans. This group of compounds are similar to the classical lignans (C18 dimer) but short of one or two carbon atoms. The fourth group of lignans are the hybrid lignans. These are compounds in which the lignan scaffold has been incorporated into the core structure of another phytochemical. Examples include terpenolignans, coumarilignans, flavolignans, and xantholignans.[15] It is worth mentioning that previously and less successfully, lignans were categorized on the basis of their biosynthetic origin. This categorization regards all derivatives arising from cinnamoyl alcohols as lignans, while those originating from allyl phenol and propenyl phenol as neolignans.[34]

The classical lignans have been further subcategorized into ten different groups depending on how oxygen atom(s) is/are incorporated into the carbon skeleton as well as the

Fig. 1 Sesame seeds as well as lignan aglycones and lignan glycosides commonly found in sesame seeds and oil. Sesamin and sesamolin are found in high abundance in raw sesame seeds. Sesamolinol and sesamol are present in trace amounts in dried seeds and virgin oil, but in considerable amounts in refined oil. The glycosides of pinoresinol and sesaminol are present in low amounts in seeds.

cyclization pattern of the carbon skeleton (Fig. 2). The dibenzylbutanes lignans are made of two phenylpropanoid (C6–C3) units oxidatively coupled only *via* β,β′-positions. Meanwhile for aryltetralines, arylnaphthalenes, and dibenzocyclooctadienes, there is an additional C–C linkage in the carbon skeleton. Among the furans (3,4-dibenzyltetrahydrofuran, 2-aryl-4-benzyltetrahydrofuran, 2,5-diaryltetrahydrofuran), furofurans (2,6-diarylfurofurans), dibenzylbutyrolactols and dibenzylbutyrolactone subtypes, an oxygen bridge is present as an additional structural feature.[33]

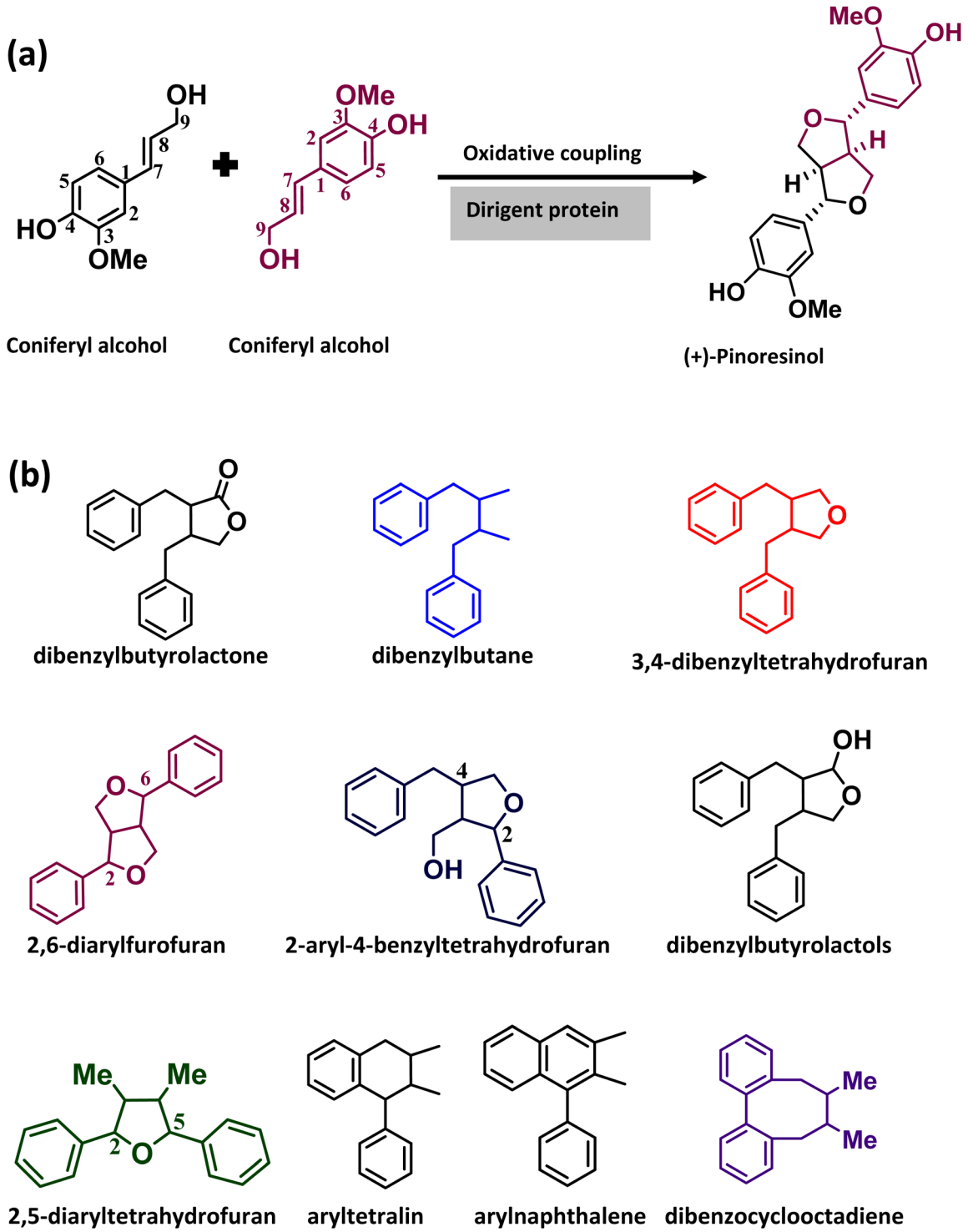

Fig. 2 (a) Oxidative dimerization of two monolignol monomers (coniferyl alcohol) leading to the formation of a minor sesame lignan, pinoresinol. (b) Chemical structures depicting scaffolds of the ten subtypes of classical lignans. It can be seen that the major sesame lignans consist of furofuran core structures. Reprinted from ref. 15 Copyright © 2025, Elsevier.

3.2 Sesame lignans: structure and synthesis

Sesamin and sesamolin represents the two most prominent and major sesame lignans in terms of abundance in sesame seeds as well as the depth of research performed on their biological properties. Structurally, these lignans are classified under the subcategory of furolignans. Their biosynthesis in plants consist of coupling of the two coniferyl alcohols. This is then proceeded by the formation of benzodioxols, oxidation as well as glycosylation (Fig. 3). As mentioned earlier, sesamin and sesamolin have a high content in seeds, and the amounts could be upwards of 1.4%. Of course, there are other lignans present in the raw seed, but their content is lesser. These include sesaminol, sesamol, and episesamin.[35,36] These lignans are produced as a result of chemical transformation and/or degradation of the major furofuran lignans during processing of the sesame seed (drying, roasting, *etc.*) or refining of the oil. The total concentration of lignan is an important component of sesame seed quality since it influences both the functional and nutritional value of the oil obtained from it. Hence, lignan content is one of the quality traits targeted during breeding improvement of sesame seeds.

During synthesis of sesame lignans, the oxopropane side chains of the two coniferyl alcohol monomers fuse to form the furofuran core (3,7-dioxabicyclo[3.3.0]octane), hence the obtained secondary metabolites are referred to as furofuran lignans (Fig. 2a). This is accomplished by a multi-step process catalyzed by many enzymes, with some of the enzymes catalyzing more than one step (Fig. 3). Unlike the major lignans which exist mainly as benzodioxol substituted furofurans, the minor lignans, including matairesinol, secoisolariciresinol, lariciresinol, *etc.* full under three subcategories *viz.* tetrahydrofurans, furofurans and butyrolactones.

Other notable lignans which have been found in sesame in little amounts include pinoresinol, sesaminol, sesamolinol, episesaminone, and (−)-sesamolactol. In raw unroasted sesame seeds, lignans such as sesaminol, sesaminol epimers, sesamol and episesamin have been reported, but only found in trace amounts (Table 1). These lignans are produced primarily as degradation or transformation products during roasting of sesame seeds or processing of sesame oil.

It is worth mentioning that the sesame lignans described thus far are aglycons. However, in sesame seeds, pinoresinol

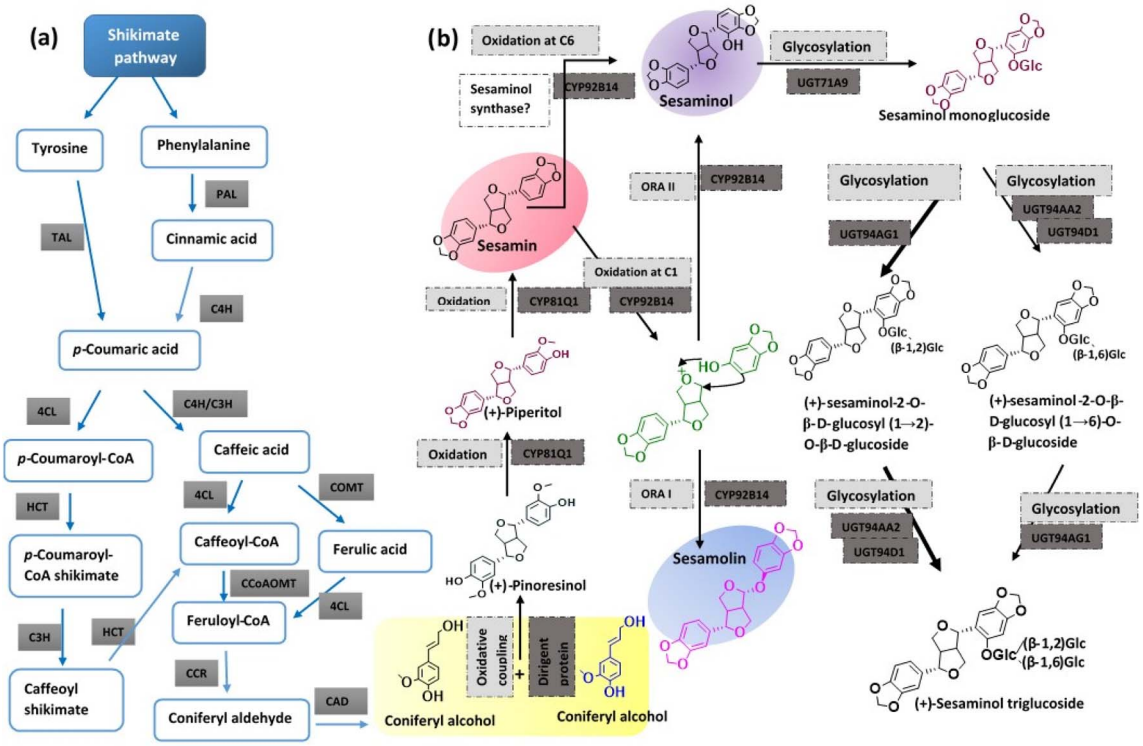

Fig. 3 Representation of the biosynthetic pathway of the major lignans in sesame. (a) Cascade of reactions from shikimate pathway to monolignol monomers (coniferyl alcohol) (blue arrows). Main enzymes catalyzing these reactions include: TAL, tyrosine ammonia-lyase; PAL, phenylalanine ammonialyase; C4H, cinnamate 4-hydroxylase; 4CL, 4 coumaroyl-coenzyme A ligase; C3H, *p*-coumarate 3-hydroxylase; HCT, hydroxycinnamoyl-CoA shikimate/quinate hydroxycinnoyltransferase; COMT, caffeic acid *O*-methyltransferase; CCoAOMT, caffeoyl-CoA *O*-methyltransferase; CCR, cinnamoyl-CoA reductase; CAD, cinnamyl alcohol dehydrogenase; (b) series of reactions from oxidative dimerization of coniferyl alcohol monomers to the subsequent formation of various sesame lignans (black arrows). Key reactions include oxidative coupling involving diregent enzyme, sesaminol formation from pinoresinol by two cytochrome P450s, many glucosylation reactions of sesaminol catalyzed by UGTs. Oxidative rearrangement (ORA) of α-oxy-substituted aryl groups, where ORA-I depicts C–O bond formation to produce sesamolin and ORA-II denotes C–C bond formation to produce (+)-sesaminol, respectively. The key enzymes include dirigent protein; CYP81Q1, piperitol/sesamin synthase and CYP92B14, sesaminol and sesamolin synthase. Thick black arrows indicate the putative major pathway. Schematic is an adaptation based on reports by ref. 41 Copyright © 2020, Wiley and ref. 42 Copyright © 2023, Elsevier.

Table 1 Lignans identified in sesame, their content and chemical features

S/no.	Sesame lignan	Plant part/sample	Amount	Identification	Molecular formula	Monoisotopic/theoretical mass	UV	Reference
1	Sesamin	Seed	0.37–8.72 mg g^{-1}	LC-MS/MS, HPLC	$C_{20}H_{18}O_6$	354.1103383	290 nm	56
2	Episesamin	Seed, refined oil	0.12–2.06 mg g^{-1}	HPLC, IR, HRMS, UV, NMR	$C_{20}H_{18}O_6$	354.1103383	—	36 and 57
3	Sesamolin	Seed	0.60–7.04 mg g^{-1}	LC-MS/MS, HPLC	$C_{20}H_{18}O_7$	370.10525292	290 nm	4 and 46
4	Sesamol	Seed	0.01–3.27 mg g^{-1}	LC-MS/MS, HPLC	$C_7H_6O_3$	138.031694053	290 nm	56 and 58
5	(+)-Episesaminone	Seed	0.001 mg g^{-1}	UV, 1H-NMR, 13C-NMR, HRMS, IR	$C_{20}H_{18}O_7$	370.10525291	313 nm	57
6	Sesaminone diglucoside	Defatted seed meal	—	NMR, HRESIMS	—	—	—	59
7	(+)-Piperitol	Seed	0.002–0.013 mg g^{-1}	UV, 1H-NMR, 13C-NMR, HRMS, IR	$C_{10}H_{18}O$	154.135765198	—	57 and 60
8	Piperitol diglucoside	Defatted seed meal		NMR, HRESIMS	$C_{32}H_{40}O_{16}$	$[M + Na]^+$ 703.2209	283 nm	59
9	Piperitol triglucoside	Defatted seed meal		NMR, HRESIMS	$C_{38}H_{50}O_{21}$	$[M + Na]^+$ 865.2737	284 nm	59
10	Pinoresinol	*In vitro* digested oilseed meal	0.29–0.38 mg g^{-1}	HPLC, LC-MS	$C_{20}H_{22}O_6$	358.141638428	—	60–62
11	(−)-Pinoresinol 4-*O*-glucoside	Seed	—	HPLC, NMR	—	—	—	37
12	(+)-Pinoresinol di-*O*-β-D-glucopyranoside	Seed	1.4–2.1 mg/100 g	HPLC, NMR	—	—	—	37 and 63
13	(+)-Pinoresinol 4-*O*-[-D-glucopyranosyl-(1→2)-[-D-glucopyranosyl-(1→6)]-β-D-glucopyranoside]	Seed	5.22 mg/100 g	HPLC, LC-MS	—	—	—	63
14	Sesaminol	Whole seed	278 ± 2.5 μmol/100	LC-MS	$C_{20}H_{18}O_7$	370.10525292	—	64
15	Episesaminol/sesaminol	Oil	3.3 mg/100 mL	NMR, HPLC, HRMS	$C_{20}H_{18}O_7$	370.10525292	—	65
16	(+)-Sesaminol 2-*O*-β-D-glucoside	Seed	5.4–19.5 mg/100 g	HPLC, GC-MS, NMR	—	—	—	63 and 66
17	Sesaminol diglucoside	Defatted flour	Trace-0.42 mg g^{-1}	HPLC, LC-MS	$C_{26}H_{28}O_{12}$	532.15807632	—	67
18	(+)-Sesaminol 2-*O*-β-D-glucosyl (1→2)-*O*-[β-D-glucosyl (1→6)]-β-D-glucoside	Seed/defatted flour	0.36–15.60 mg g^{-1}	HPLC, GC-MS, NMR	—	—	—	63 and 67
19	Sesaminol acetyl-hexoside	Defatted seed meal	1.67 ug g^{-1}	HPLC-DAD-QTOF-MS/MS	$C_{28}H_{30}O_{13}$	$[M - H]^-$ 573.1596	—	68
20	Sesamolinol	Raw seeds	0.32–3.01 mg g^{-1}	HPLC	—	—	—	36
21	(+)-Sesamolinol 4′-*O*-β-D-glucoside	Dried seed	4.0 mg/100 g	MPLC, NMR, TLC, mass spectra	—	—	—	69
22	Sesamolinol 4′-*O*-β-D-glucosyl (1→6)-*O*-β-D-glucoside	Seed	<5–232 mg/100 g	NMR, HPLC	—	—	290 nm	40
23	Sesamolinol acetyl-hexoside	Defatted seed meal	5.63 ug g^{-1}	HPLC-DAD-QTOF-MS/MS	$C_{28}H_{32}O_{13}$	$[M - H]^-$ 575.1775	—	68
24	Matairesinol	Whole seed	0.3 ± 0.0 μmol/100 g	LC-MS	—	—	—	64
25	7′-Hydroxymatairesinol	Defatted seed meal		NMR, HRESIMS	$C_{20}H_{22}O_7$	374.136553058	280 nm	59
26	Matairesinol dihexoside	Defatted seed meal	170.47 ug g^{-1}	HPLC-DAD-QTOF-MS/MS	$C_{32}H_{42}O_{16}$	$[M - H]^-$ 681.2391	—	68
27	Nortracheloside I	Defatted seed meal	2.33 ug g^{-1}	HPLC-DAD-QTOF-MS/MS	$C_{26}H_{32}O_{12}$	$[M - H]^-$ 535.1766	—	68
28	Matairesinol/pinoresinol (acetyl)-dihexoside	Defatted seed meal	15.5 ug g^{-1}	HPLC-DAD-QTOF-MS/MS	$C_{34}H_{44}O_{17}$	$[M - H]^-$ 723.2519	—	68
29	Nortrachelogenin	Defatted seed meal	14.93 ug g^{-1}	HPLC-DAD-QTOF-MS/MS	$C_{20}H_{22}O_7$	$[M - H]^-$ 373.1281	—	68

Table 1 (*Contd.*)

S/no.	Sesame lignan	Plant part/sample	Amount	Identification	Molecular formula	Monoisotopic/theoretical mass	UV	Reference
30	Samin	Oil	4.7 mg/100 mL	NMR, HPLC, HRMS	$C_{13}H_{14}O_5$	249.0768	—	65 and 70
31	Methoxy samin	Defatted seed meal	—	NMR, HRESIMS	$C_{14}H_{16}O_5$	$[M + Na]^+$ 287.0895	286 nm	59
32	Sesangolin	Seeds	—	NMR	$C_{21}H_{20}O_7$	384.12090297	—	71
33	Disaminyl ether	Dried seed	3.27 mg/100 g	MPLC, NMR, TLC, mass spectra	—	—	—	69
34	Lariciresinol	Whole seed	0.8 ± 0.0 μmol/100 g	LC-MS	$C_{20}H_{24}O_6$	360.15728848 Da	—	64
35	Lariciresinol dihexoside	Defatted seed meal	2.33 ug g^{-1}	HPLC-DAD-QTOF-MS/MS	$C_{32}H_{44}O_{16}$	$[M - H]^-$ 683.2579	—	68
36	Secoisolariciresinol	Whole seed	0.2 ± 0.0 μmol/100 g	LC-MS	$C_{20}H_{26}O_6$	362.17293854 Da	—	64
37	Secoisolariciresinol diglucoside							72
38	Medioresinol	Defatted seed meal	—	NMR, HRESIMS	$C_{21}H_{24}O_7$	388.15220310	—	59
39	Simplexoside	Defatted seed meal	—	NMR, HRESIMS	$C_{26}H_{30}O_{11}$	518.178812	—	59
40	Shanzhiside methyl ester	Defatted seed meal	—	NMR, HRESIMS	$C_{17}H_{26}O_{11}$	406.14751164	—	59
41	Sesaminol tetrahexoside I	Oil	—	LC-MS/MS	$C4_4H_{58}O_{27}$	$[M - H]^-$ 1018.3165	280 nm	73
42	Hydroxysesamolin trihexoside	Oil	—	LC-MS/MS	$C_{38}H_{48}O_{23}$	$[M - H]^-$ 872.2586	277 nm	73

and sesaminol mainly exist as glycosides. The major glycosylated forms of lignans in sesame seed include pinoresinol mono-, di- and tri-glucosides,[37,38] sesaminol triglucoside[39] and sesamolinol diglucoside.[40] The oil extracted from sesame typically contains aglycon lignans and some monoglycosides. The oilseed meal that is generated post oil extraction is rich in diglycosylated and triglycosylated forms of the lignans.

3.3 Chemical and physiological transformation of sesame lignans

A very important step in the processing of sesame seeds is roasting. This is required not only for moisture reduction and shelf life extension, but most importantly for improving the sensory properties of the oil that is subsequently extracted from the seeds. The oil that is obtained is often further processed or refined by bleaching with acid clay as well as alkaline saponification. The bleaching process with acid clay and heating is required for decolorization of the crude sesame oil. This process allows sesamolin to be converted to sesamol. With further heating, the sesamol can be dimerized into sesamol dimers. It has been reported that both sesamol and its dimer are potent antioxidant compounds.[43] Bleaching also converts sesamolin into sesaminol and epimers of sesaminol. In the same vein, sesamin is known to be transformed into episesamin by bleaching. Given the effect of heating on the chemical transformation of sesamin lignans, researchers have also investigated the impact of thermal treatment on the antioxidant properties.[44]

In addition to the chemical transformations that occur to sesame lignan aglycons during heating, another important chemical reaction is that of alkaline hydrolysis of the lignan glycosides. Deglycosylation allows for the estimation of the total content of lignan aglycons in the seed or oil during analysis. Alkaline hydrolysis is facilitated by sonication in a solution of sodium methoxide in methanol for 3 h at 40 °C,[45] by treating the sample with an aqueous solution of 9 M NaOH at room temperature for 12 h (ref. 46) or refluxing with ethanolic solution of 1 M KOH[35] deglycosylated the lignans glycosides into their corresponding aglycons. The biological equivalent of this process occurs in mammalian gut where deglycosylation of sesame lignan glycosides by microbiota constitutes the first step in their metabolism.[47–49]

Deglycosylation is the first step in the metabolism of lignan glucosides by mammalian gut microbiota. This process can also be replicated *in vitro* using β-glucosidases. For example, deglycosylation of pinoresinol diglucoside by β-glucosidase led to the production of pinoresinol.[50] In the gut, bacteria metabolize lignans as well as their glucosides into products referred to as enterolignans.[51] As previously mentioned, enterodiol and enterolactone are the two primary enterolignans produced in mammals *via* the metabolic action of gut microbiota. The multistep process for the conversion of lignan into enterolignan involves deglucosylation (for the lignan glucosides), demethylation, dehydrogenation, and dihydroxylation. One or two extra reduction processes may be involved, depending the on type of lignan.[52,53] Broadly speaking, the different steps highlighted are

catalyzed by different bacteria species in the gut. For instance, the strict anaerobic bacteria, *Lactonifactor longoviformis* was noted for mediating the dehydrogenation of enterodiol into enterolactone.[54] This transformation can also be catalyzed by gut *Ruminococcus* spp.[55] In the liver, catabolism of lignans involves their transformation into catechol (vicinal dihydroxyphenol) derivatives. This entails opening and demethylating the methylenedioxy moieties.[74,75] Following its glucuronidation and methylation, the sesame monocatechol derivative is excreted in urine and bile.[76]

4. Biological properties of sesame lignans

Redox balance is essential for normal physiological functions and maintenance of good health. Perturbations in redox homeostasis, especially one that is in favor of the production and accumulation of reactive oxygen and nitrogen species as opposed to the capacity of the cellular antioxidant system to modulate it is likely to result in a situation of excessive reactive species. This does not auger well for normal cellular functions given that the excessive ROS causes manifold damages to macromolecules, such as lipid peroxidation, protein oxidation and damages to DNA and RNA, leading to disruption in cellular functions, structures as well as the development of pathological conditions.[77,78] Plant polyphenols and flavonoids as well as fruits and vegetables rich in these bioactive metabolites have been associated with the ability to protect health and reduce the risk of chronic ailments such as cardiovascular disease, certain types of cancers, stroke, coronary heart disease, and some neurodegenerative diseases. These compounds protect against harmful reactive species and free radicals *via* single electron transfer (SET) and/or hydrogen atom transfer (HAT). As a result, the free radical becomes stable and its radical activity is neutralized. Antioxidant compounds can also chelate metal ions required for catalyzing radical generating reactions such as Fenton, inhibit the activity of enzymes involve in the production of ROS or scavenge free radicals. Because of the multi-targeted effect of antioxidant molecules, it is often the case that bioactive compounds suspected of having antioxidant property are evaluated using an array of antioxidant assays including DPPH, FRAP, TEAC, and ORAC amongst others. ORAC is based on HAT (measures the transfer of hydrogen from the antioxidant to the radical species) while the other assays are based on SET (measures transfer of electron).[79]

Sesame lignans have been widely investigated for their antioxidant activity and antioxidative properties. Sesamin, sesamolin, and sesamol have been noted for their antioxidant capacity and ability to scavenge free radicals as evinced in DPPH, FRAP, β-carotene bleaching, and linoleic acid emulsion assays. The *in vitro* antioxidant effect of sesamol was ostensibly more potent compared to that of sesamin and sesamolin, with inhibitory effect against DPPH (IC_{50} = 5.44 μg mL^{-1}) that is comparable to that of the positive control, BHT (DPPH IC_{50} = 5.81 μg mL^{-1}). The DPPH radical scavenging activity of sesamin and sesamol were relatively low with values of 30% and 32% at a concentration of 250 μg mL^{-1}.[80] The three sesame lignans were also found to inhibit lipid peroxidation, bleach β-carotene as well as exhibit considerable reducing antioxidant activity with FRAP values of 1.83 μM TE (Trolox equivalent), 0.06 TE, and 0.12 TE for sesamol, sesamin, and sesamolin, respectively, compared to 0.6 TE for the antioxidant control, BHT. The potency of sesamol as an antioxidant compound was also reflected in its ability to scavenge peroxyl radicals in ORAC assay. It was shown that sesamol exhibited an ORAC value of 4.4 μmol TE per mL compared to 0.8, 1.52 and 2.26 μmol TE per mL for sesamin, sesamolin, and BHT, respectively.[80] This strong antioxidant and radical scavenging property of sesamol towards hydroperoxides was credited not just to its solubility in both aqueous and oil milieu or high thermal stability, but more importantly to its benzodioxol-containing structure. This structural moiety is known to scavenge hydroxyl radical with the concomitant formation of 1,2-dihydroxybenzene. Interestingly, although the *in vitro* antioxidant capacity of sesamin was less potent relative to sesamol, it was found that the compound has an impressive ability to potentiate and enhance the antioxidant effect of γ-tocopherol against DPPH. For example, γ-tocopherol alone exhibited an IC_{50} value of 4.5 μg mL^{-1} against DPPH radicals. Whereas, in combination with 10 μg sesamin and 2 μg of sesamol, the IC_{50} value of γ-tocopherol against DPPH was substantially improved to 2.74 and 1.6 μg mL^{-1}, with sesamol synergistic activity resulting in a threefold improvement.[80]

The phenolic hydroxy group in sesamol and sesamolinol is absent in the structure of sesamolin. As afore-mentioned, this functional group is a superb donor of electrons to free radicals. The putative antioxidant mechanism of sesamolin is based on HAT involving the hydrogen atom at C-8 position of the allylic moiety. This has been substantiated using density functional theory (DFT) as well as C–H bond dissociation enthalpy values. On this basis, sesamolin was hypothesized to be a less potent antioxidant compared to sesamin, seeing that the latter has two allylic hydrogens. Sesamolin was also found to be less potent than sesamol, which possesses a phenolic group capable of providing electrons to free radicals.[81]

In rat liver microsomes subjected to lipid peroxidation by ADP–Fe^{2+}/NADPH, sesaminol was incapable of attenuating lipid peroxidation. Although sesamolin is well-known for its weak antioxidant property *in vitro*, the *in vivo* effect of the lignan is quite interesting. For example, dietary supplementation with an extract containing 1% sesamolin attenuated peroxidation in rat kidney and liver. The authors attributed the antioxidative effect of sesamolin to its metabolic conversion into sesamol and sesamolinol, which are more potent antioxidant metabolites.[82] This effect was only noticeable in microsomal system, for instance in rat liver microsomes and cumene hydroperoxide (CumOOH)/Fe^{2+}–NADPH, but not in a non-enzymatic system containing rat liver mitochondria and Fe^{2+}–ascorbate.[22]

The antioxidative effect of sesame lignans has also been noted in human clinical studies. In a randomized controlled trial involving osteoarthritis patients, 25 were orally administered a daily dose (40 g) of sesame seed for two months (sesame group) while the control group of 25 patients received a placebo powder (40 g) instead. The level of serum malondialdehyde

(MDA) in the sesame group was significantly reduced ($p = 0.046$) after two months whereas no such effect was noted in the control group ($p = 0.709$).[83] MDA is a byproduct of lipid peroxidation and thus widely used as a marker for oxidative stress. Although the exact mechanism behind the observed reduction in the level of serum MDA was not probed, the authors believed it could be associated with the presence of lignans in the sesame seeds.[83]

In a separate double-blind, self-controlled and crossover clinical study, Fu *et al.*[84] explored the beneficial effects of sesamin (94.0 mg per day) supplementation on patients susceptible to obstructive sleep apnea syndrome (OSAS) or with low arousal threshold for OSAS. Patients were administered sesamin supplement for eight weeks followed by evaluation of its effect on sleep quality and antioxidant status.[84] Intake of sesamin was found to be beneficial for sleep quality and reduced daytime sleepiness syndrome. Also, there was a significant improvement in the antioxidant status of the patients post sesamin supplementation as evinced in increase in the activities of glutathione peroxidase and glutathione reductase, the content of glutathione, as well as a reduction in the level of plasma malondialdehyde.[84]

Pertaining to inflammation, it is worth mentioning that experimental evidence had shown very promising results of the potential health benefits of sesame lignans for preventing and managing inflammation and inflammatory disorders, such as colitis, inflammatory bowel disease, osteoarthritis, and skin inflammation.[25,85–87] This is mediated *via* diverse mechanisms including the modulation of inflammatory responses, oxidative stress, mediating gut barrier integrity and reshaping gut microbiome, *etc.*[85–87] Sesame lignans have also been reported for their immunomodulatory[25] and cardio-protective properties.[88,89] Also, ample research evidence have been provided for the health-promoting properties of sesame lignans in relationship to neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.[90,91] Furthermore, sesame lignans have shown impressive capacity in the amelioration of diabetes[92] and modulation of metabolic syndrome.[93] The afore-mentioned diseases are by no means exhaustive with respect to the beneficial health properties of sesame lignans. One group of disease where mounting evidence indicates an important role of sesame lignans is cancer. The following section delved deeper into the impact of sesame lignans on various major cancer types and the detailed molecular mechanisms of action.

5. Anti-cancer properties of sesame lignans

Increasingly, mounting evidence from *in vitro* and *in vivo* investigations have shown that sesame lignans possess strong potential for countering tumorigenesis by targeting key signaling pathways and regulating different cellular and extracellular mechanisms involved in cancer development. Since cancer affects different organs, the anti-cancer effect of sesame lignans has also been investigated in cell lines and tissues derived from different organs in order to understand their potential utility in treating cancers affecting or emanating from those tissues.

5.1 Effect of sesame lignans on lung cancer

According to recent Fact Sheets of the IARC's Global Cancer Observatory of the WHO, lung cancer was ranked as number one among all cancers in terms of incidence and mortality. In the year 2022, 2.48 million new cases of lung cancer were recorded and in the same year the disease was responsible for the death of 1.82 million people, accounting for 18.7% of all cancer-related deaths worldwide.[5] The two most common types of lung cancer consist of small cell carcinoma (SCLC) and non-small cell carcinoma (NSCLC). Although the latter is more common, accounting for 85% of all lung cancer cases, it nonetheless grows slowly. The former, *i.e.* SCLC is the less prevalent form of lung cancer and grows rapidly. Nonetheless, the high mortality caused by NSCLC due to its ability to metastasize and its resistance to many chemotherapeutic interventions make it a more dreadful and severe disease to contend with.[94,95] Although there is an array of interventions currently available for the treatment of lung cancer, such as radiotherapy (radiation), surgery, immunotherapy and chemotherapy, chemotherapy remains the first-line of action for the vast majority of lung cancer patients. It is against this backdrop that the search for and development of novel chemotherapeutic agents with greater efficacy and safety profile continues to be an imperative.

Sesamin lignans have attracted growing attention as a potential source for the identification and development of novel anti-cancer agents (Table 2). Researchers have explored the effects of the major sesame lignans in the modulation of lung cancer using *in vitro* and *in vivo* models, with some interesting findings.[96,97] Cancer is typified by unrestrained cell proliferation. This is partly because the cellular guardrails in the form of proteins which modulate cell cycle are themselves deregulated. One of such crucial proteins is cyclin D (determines transition of G1/S phase), which is involved in the malignant progression of NSCLC.[98] The gene coding for cyclin D, CCND1 is upregulated and its coded protein, cyclin D1 is overexpressed in NSCLC. This leads to imbalance in the activity of CDK, resulting in rapid and unregulated cell growth.[99] Thus, it has been proposed that inhibition of cyclin D1 could be a useful approach in attenuating NSCLC growth. Sesamin (5–30 μM) was found to significantly suppress the proliferation of human NSCLC (A549 and H1792) cells in a concentration-dependent manner. Sesamin also induced apoptosis in the cancer cell lines within 24 h. In contrast, sesamin (10–30 μM) had little cytotoxic effect on the normal bronchial epithelial BEAS-2B cells, suggesting that its anticancer activity was selective. Furthermore, it was revealed that the lignan induced cell cycle arrest at G1 phase and suppressed the expression of cyclin D1 and CDK2. Besides, sesamin mitigated the activity of Akt while upregulating the expression of p53. These series of facts strongly suggested that the cell-cycle arrest, antiproliferative and pro-apoptotic effect of sesamin in NSCLC cells was modulated *via* the Akt/p53 pathway. The modulatory effect of sesamin

Table 2 Anticancer properties of sesame lignans on different cancer types and molecular mechanisms of action[a]

Lignan	Cancer type	Model	Pharmacological intervention	Outcome and mechanism of action	Reference
Sesamin	Lung cancer	*In vitro* (NSCLC cancer cell lines A549 and H1792) and *in vivo* (xenograft mice models bearing tumors from A549 cells)	Cancer cell lines were treated with sesamin (10–30 μM) for 24 h and 48 h. Xenograft mice models bearing A549-derived tumors were treated with 100 mg kg^{-1} and 150 mg kg^{-1}	NSCLC cell proliferation↓, apoptosis↓, G1-phase cell cycle arrest↑, cyclin D1 and CDK2 expression↓, Akt protein kinase activity↓, pAkt and pMDM2 expression↓, p53 tumor suppressor protein expression↑ (modulated Akt/p53 signaling pathway). Tumor growth in xenograft models↓ Non-cancer cell (BEAS-2B) viability and non-cancer tissues in xenograft model were unaffected	96
Sesamol	Lung cancer	*In vitro* in human lung adenocarcinoma cell line (SK-LU-1) and normal African green monkey kidney cell line (Vero)	Cells were treated with sesamol (0–10 mM) for 48 h	Sesamol inhibited cancer cell proliferation (IC_{50} = 2.7 mM) and non-cancer cells at a lesser extent (IC_{50} = 7.6 mM). Anticancer effect involved activation of both extrinsic and intrinsic apoptotic pathways (caspases 8, 9, 3/7↓), MMP↓, Bid expression↓	107
Sesamin	Lung cancer	*In vitro* human NSCLC cancer cell lines (A549, NCI-H446 and H1299)	Cell lines were treated with sesamin (10–150 μM) for 24–72 h	NSCLC cell viability↓, G1-phase cell cycle arrest↑, apoptosis induction↑, inhibition of Akt-PI3K signaling pathway↑ (pAKT and PI3K levels↓), accompanied by COX-2 activity↓, IL1β, IL6, TNFα expression↓, pro-apoptotic Bax expression↑, anti-apoptotic Bcl-2 expression↓	97
Sesamin	Lung cancer	NSCLC cell lines (MRC-5, HEL299, H1299, and A549)	Cell lines were treated with sesamin (20–60 μM) for 12–48 h	Dose-and time dependent inhibition of cell proliferation↑, induction of apoptosis↑, and G1/S-phase cell cycle arrest triggered by inhibition of mitochondrial Lon protease activity and excess intracellular ROS generation leading to DNA double strand break which then activate DNA damage response (checkpoint activation and apoptosis)	102
Sesamol	Lung cancer	*In vitro*, human NSCLC cell line (A549) and normal macrophages (RAW 264.7)	Cell lines were treated with sesamol (0–1000 μM) for 24 h	Sesamol was not toxic on normal cells (IC_{50} value >1000 μM) while exerting notable antiproliferative effect on cancer cells (IC_{50} value of 501 μM). Anticancer effect was *via* the induction of intrinsic apoptotic pathway (Bcl-2 mRNA expression↓, expression of caspase-3 and caspase-9 mRNA levels ↑) triggered by excessive ROS accumulation and disruption in MMP.	108
Sesamin	Lung cancer	*In vitro*, NSCLC cell line (H1299)	Cells were treated with sesamin (25–100 μM) for 2, 4 and 6 days	Concentration- and time-dependent inhibition of cell proliferation, IC_{50} value of 40.1 μM, activate apoptosis, *via* suppression of the NF-κB signaling pathway and expression of NF-κB regulated gene products, *viz.* cell survival (survivin & Bcl-2), cell proliferation (cyclin D1), inflammation (COX-2), invasion (MMP-9 & ICAM-1), and angiogenesis (VEGF)	104

Table 2 (*Contd.*)

Lignan	Cancer type	Model	Pharmacological intervention	Outcome and mechanism of action	Reference
Sesamin	Breast cancer (BC)	*In vitro* in neoplastic mouse (+SA) and human (MCF-7 and MDA-MB-231) breast cancer cell line as well as normal mammary epithelial cell lines (CL-S1 and MCF-10A)	Cells were treated with sesamin (5–150 μM) with or without γ-tocotrienol (1–30 μM) for 96 h	Significant concentration dependent inhibition of cancer cell proliferation by sesamin with IC_{50} values of 91.1 μM, 98.0 μM, and 43.9 μM against mouse +SA, human MCF-7 and human MDA-MB-231 cell lines, respectively. G1 cell cycle arrest↑ and cyclin D1↓. Sesamin & γ-tocotrienol demonstrated synergistic anticancer effects. Not toxic to normal cells. Anticancer mechanism involved suppression of EGF-dependent mitogenic signaling pathway. EGF-induced ErbB3 & ERbB4 receptors (activation) ↓, intracellular total and/or phosphorylated levels of c-Raf, MEK1/2, ERK1/2, PI3K, PDK1, Akt, p-NF-κB, Jak1, Jak2, and STAT2↓	110 and 153
Sesamol	Breast cancer	BC mice model bearing Ehrich solid tumor	BC tumor bearing mice were administered saline, sesamol (70 mg per kg per day)/sesamol nanosuspension (10 mg per kg per day) with or without Epirubicin (2.5 mg per kg per week) for total of 21 days	Treatment with sesamol, especially sesamol nanosuspension with or without Epirubicin resulted in: tumor growth↓, cell proliferation↓, apoptosis↑ autophagy↑, angiogenesis↑, and anti-Epirubicin toxicity	101
Sesamin	Breast cancer	*In vitro*, human breast cancer cell line (MCF-7)	Cancer cells were treated with sesamin (1, 10 and 50 μM) for 24 h	Cell viability↓, LDH release & apoptosis↓, cell cycle arrest at sub-G1 phase↑, Bax & caspase-3 expression (apoptosis)↑, p53 and checkpoint kinase 2 expression (cell cycle control) ↑	154
Sesamol	Breast cancer	*In vitro* in TNBC cell lines (MDA-MB-231 and Hs-578T) and *in vivo* in xenograft tumor model of nude mice	Cancer cells were treated with sesamol (20–80 μM) for 24 h. Mice bearing TNBC tumors were orally administered without or with sesamol (75–300 mg kg^{-1}) for 28 days	Sesamol treatment markedly reduced cancer cell proliferation (IC_{50} of 75.4 and 33.9 against MDA-MB-231 and Hs-578T, respectively). Sesamol also suppressed cell migration, invasion and tumor growth in xenograft model	122
Sesamin	Breast cancer	*In vivo* in athymic mice bearing human breast cancer (MCF-7) tumor and with high serum estrogen	Mice were fed a basal diet for 8 weeks (control) or basal diet + sesamin (1 g kg^{-1})	Relative to control, sesamin treatment reduced the size of palpable tumor by 23%, reduced tumor cell proliferation and increased apoptosis. Expression of HER2, EGFR, and downstream pMAPK↓	113
Sesamin	Breast cancer	*In vitro* in human triple negative breast cancer cell line (MDA-MB-231)	Cancer cells were treated with sesamin (50–200 μM) for 72 h	Sesamin treatment significantly inhibit cell proliferation, IC_{50} value of 180.32 μM. Also induced downregulation of PD-L1 expression (mRNA and protein) level *via* inhibition of AKT, NF-κB and JAK/Stat signaling pathways. Attenuated cell migration by preventing the activation of MMP-9 and MMP-2	14

Table 2 (*Contd.*)

Lignan	Cancer type	Model	Pharmacological intervention	Outcome and mechanism of action	Reference
Enterolactone	Breast cancer	*In vitro* in human triple negative breast cancer cell line (MDA-MB-231)	Cancer cells were treated with enterolactone (25, 50, and 75 μM) for 48 h	Treatment with enterolactone exhibited significant inhibition of cell proliferation (IC_{50} value of 73 μM), migration, and metastasis *via* countering uPA-induce plasmin activation and induction of ECM remodeling by MMPs. Impaired metastasis *via* inhibition of TGF-β-mediated EMT (epithelial–mesenchymal transition) by abrogating ERK/NF-κB/snail signaling pathway	115 and 116
Sesamin	Breast cancer	*In vitro*, Matrigel assay and three-dimensional (3D) collagen gel assay of human breast cancer cell lines (MCF-7 and MDA-MB-231) for proangiogenic activity	Cell were pretreated with sesamin prior to subjection to Matrigel and 3D-collagen gel assay	Sesamin inhibited angiogenesis. Cocultivation of cancer cells and macrophages enhanced angiogenesis (VEGF & MMP-9 activation↑). Treatment with sesamin abrogated macrophage enhanced angiogenesis (VEGF & MMP-9↓ along with HIF-1α & NF-κB↓). Also inhibited Akt and $p38^{MAPk}$ activities	119
Sesamin	Colorectal cancer	*In vitro* tube formation assay CRC cell lines (HCT116 and SW480) and *in vivo* in nude mice with Matrigel plugs of HCT116 and SW480 cells	Cancer cells were exposed to sesamin and nude mice with Matrigel plugs of CRC cells were orally administered with sesamin	Sesamin treatment significantly inhibited CRC angiogenesis *in vitro* in a dose-dependent manner. *In vivo*, neovessel formation of Matrigel plugs of CRC cells was suppressed. Mediated *via* inhibition of VEGFA expression through regulation of NF-κB/HIF-1α signaling pathway-	124
Sesamin	Colorectal cancer	*In vitro*, human CRC cell line (HCT116)	Cancer cells were treated with sesamin (25–100 μM) for 2, 4, and 6 days	Concentration- and time-dependent inhibition of cell proliferation, IC_{50} value of 57.2 μM, activate apoptosis, *via* suppression of the NF-κB signaling pathway and expression of NF-κB regulated gene products, *viz.* cell survival (survivin & Bcl-2), cell proliferation (cyclin D1), inflammation (COX-2), invasion (MMP-9 & ICAM-1), and angiogenesis (VEGF)	104
Sesamolin	Colorectal cancer	*In vitro*, human CRC cell line (HCT116) and non-cancerous (Vero) cells	Cells were treated with sesamolin and nano-encapsulated sesamolin for 48 h	Sesamolin treatment did not affect the viability of non-cancer cells, but markedly inhibited the viability of cancer cells, $IC_{50} = 725$ μg mL^{-1}. Cell death was *via* ROS-mediated necrosis as opposed to apoptosis (no effect on caspase-3/7 activity	129
Sesamolin	Colorectal cancer	*In vitro*, human CRC cell line (HCT116)	Cancer cells were treated with sesamolin (5–40 μM) for 48 h	Sesamolin treatment induced concentration dependent inhibition of cell proliferation, induced apoptosis, and suppressed migration *via* JAK2/STAT3 signaling pathway	130
Sesamol	Colorectal cancer	*In vitro*, human CRC cell line (HCT116)	Cancer cells were treated with sesamol (0.5–5.0 mM) for 48 h	Sesamol treatment exerted substantial reduction in cell viability with IC_{50} value of 2.59 mM. Sesamol induced S-phase cell cycle arrest, and induced apoptosis *via* accentuation of intracellular ROS.	134
Sesamin	Prostate cancer	*In vitro* in human prostate cancer cell lines (DU145 and PC-3) and *in vivo* using a subcutaneous PCa tumor mice model	Cancer cells were treated with different concentrations of sesamin and mice model of subcutaneous PCa was intraperitoneally injected with sesamin	Sesamin inhibited cell survival, proliferation, migration, invasion, and anoikis resistance *in vitro*. Also inhibited tumor growth *in vivo*. Mechanism involved downregulation of ADAM9 *via* the JNK and c-Jun signaling pathways	141

Table 2 (*Contd.*)

Lignan	Cancer type	Model	Pharmacological intervention	Outcome and mechanism of action	Reference
Sesamin	Prostate cancer	*In vitro* in human prostate cancer cell line (DU145)	Cancer cells were treated with sesamin (25–100 μM) for 2–6 days	Sesamin induced antiproliferative effect with IC_{50} value of 60.2 μM *via* inhibition of NF-κB signaling and suppression of the expression of NF-κB gene products, survivin, Bcl-2, and cyclin D1	104
Sesamin	Prostate cancer	*In vitro* in human prostate cancer cell line (PC-3) and *in vivo* in BALB/c nude mice carrying a PC-3 tumor xenograft	Cancer cells were pretreated with sesamin (10–100 μg mL^{-1}). *In vivo*, mice bearing prostate cancer tumor were orally administered 10 mg per kg sesamin	Treatment with sesamin inhibited LPS-induced cell proliferation (Bcl-2, survivin, cyclin D1 and COX-2 levels↓) and cell invasion (MMP-9, ICAM-1) and VEGF, TNF-α, and IL6 levels↓) *via* suppression of p53/NF-κB signaling. Sesamin suppressed PCa tumor growth in mice	142
Sesamol and it derivative 3′,4′-(methylenedioxy) acetophenone (3′MA)	Prostate cancer	*In vitro* in prostate cancer cell line (LNCaP) and *in vivo* in MNU/TU-induced prostate tumor mice model	Cancer cells were treated with sesamin or 3′MA. Mice with PCa tumor were orally administered sesamol or 3′MA (0, 50 or 100 mg per kg per day)	Sesamol and 3′MA exerted marked antiproliferative effect on prostate cancer cells, IC_{50} values of 3.94 mM and 4.43 mM, respectively. Effect was due to downregulation of androgen receptor (AR) signaling pathway and AR target genes in PCa, including PSA), FKBP5, and TMPRSS2. In mice, sesamol/3′MA decreased prostate tumor by 25 and 33%/31, 57%, respectively	145
Sesamin	Prostate cancer	*In vitro*, prostate cancer cell lines (LNCaP and DU145)	Cancer cells were treated with sesamin (0–200 μM) for 48 h	Sesamin treatment dose-dependently inhibited cancer cell proliferation with IC50 values of 45.36 μM and 52.98 μM against DU145 and LNCaP cells, respectively. Anticancer effect was due to inhibition of transient receptor potential melastatin 8 (TRPM8)	155
Sesamol	Cervical cancer	*In vitro* using human cervical cancer cell line, HeLa	Cancer cells were pretreated with sesamol (0–10 μM) followed by paclitaxel	Sesamol chemosensitized HeLa cells and potentiated the antiproliferative effect of paclitaxel, with reduction in IC_{50} value from 7.5 nM to 0.55–0.05 nM. Effect of sesamol was attributed to increased intracellular ROS levels, DNA damage and apoptosis *via* MMP alterations	156
Sesamin	Cervical cancer	*In vitro* in human cervical cancer cell line, HeLa and SiHa as well as normal cell line dermal fibroblast, Hs60	Cells were treated with sesamin (15–300 μM) for 24 h and 48 h	Sesamin did not affect the proliferation of the normal cells, but dose-dependently inhibit the proliferation of the cancer cell lines *via* G0/G1-phase cell cycle arrest and induction of apoptosis *via* p53-mediated cascade (p53↑, p53 phosphorylation↑, PUMA, Bax, & PTEN↑ as well as AKT phosphorylation↓	157
Sesamin	Cervical cancer	*In vitro* in human cervical cancer cell line, HeLa	Cancer cells were treated with sesamin (0–125 μM) for 24 h and 48 h	Sesamin treatment inhibited cancer cell proliferation and migration *via* ER-mediated apoptosis through IRE1α/JNK pathway, evidenced by Bax, caspase-12, GRP78, GADD153, p-IRE1α, p-JNK, LC3I/II and beclin expression ↑ while Bcl-2↓	158

Table 2 (*Contd.*)

Lignan	Cancer type	Model	Pharmacological intervention	Outcome and mechanism of action	Reference
Sesamol	Hepatocellular carcinoma (HCC)	HCC cell line (HepG2) and normal hepatocytes (BRL-3A). HCC tumor xenograft in nude mice model	Cells were treated with sesamol (0.01–1.0 mM) for 24 h. I.p. injection of sesamol (100 mg kg^{-1} or 200 mg per kg per day) into HepG2 tumor cell xenograft bearing nude mice	*In vitro*, sesamol treatment suppressed colony formation, induced S-phase cell cycle arrest, and induced both intrinsic and extrinsic apoptotic pathway dose-dependently. Sesamol also induced mitochondrial dysfunction by triggering a loss of MMP. Impaired mitochondria and accumulated excess ROS H_2O_2, resulting in redox-sensitive signaling perturbation, including Akt and MAPKs pathways. *In vivo*, sesamol triggered marked reduction in tumor growth	159
Sesamin	Hepatocellular carcinoma	Human HCC cell line (HepG2) and human normal liver cell line (L02)	Cancer cells were treated with sesamin (25–125 μM) for 24 and 48 h	Treatment with sesamin induced a concentration-dependent inhibition of cancer cell viability, with IC_{50} value of 98 μM *via* enhancement of G2/M-phase cell cycle arrest & apoptosis through inhibition of STAT3 signaling pathway. Sesamin was less cytotoxic to normal cells *vs.* cancer cells	160
Sesamin	Esophageal squamous cell carcinoma (ESCC)	*In vitro* in ESCC cell lines (ECA109, EC9706, KYSE150, and TE2). *In vivo* using ECA109 tumor xenograft in nude mice ESCC model	Cancer cells were treated with sesamin (10–40 μM) for 12 h to assess viability. Mice with ESCC tumor were orally treated with sesamin (100 mg kg^{-1} or 150 mg per kg thrice per week) for 21 days	Treatment with sesamin strongly reduced ESCC cell viability in a concentration dependent manner. Sesamin treatment also significantly reduced tumor growth in mice compared to control. Mechanism involved downregulation of TRIM44 through inhibition of NF-κB signaling pathway	161
Sesamin	Nasopharyngeal carcinoma (NPC)	*In vitro* NPC cell lines (C666-1 and HK-1) and normal cell line NP69	Cells were treated with sesamin (10–200 μmol L^{-1}) for 24 h	Sesamin exerted marked inhibition of NPC cells' viability, proliferation, cell cycle progression (G0/G1-phase arrest), migration and induced apoptosis. Increased ROS accumulation, decrease MMP, and induced autophagy. Effect of sesamin on normal cells was lesser relative to NPC cells. Sesamin also suppressed growth of xenografted tumor in mice *via* apoptosis↑, autophagy↑, & ROS↑	162
Sesamin	Head and neck cancer (HNSCC)	*In vitro* in human oral cancer cell lines (HSC-3, FaDu, Ca9-22)	Cancer cells were treated with sesamin (10–40 μM) for 24 h	Treatment with sesamin significantly and dose-dependently inhibited oral cancer cells migration and invasion, but not viability. Anti-metastatic effect was credited to suppression of MMP-2 expression	163

[a] ↑ indicates increase while ↓ denotes decrease.

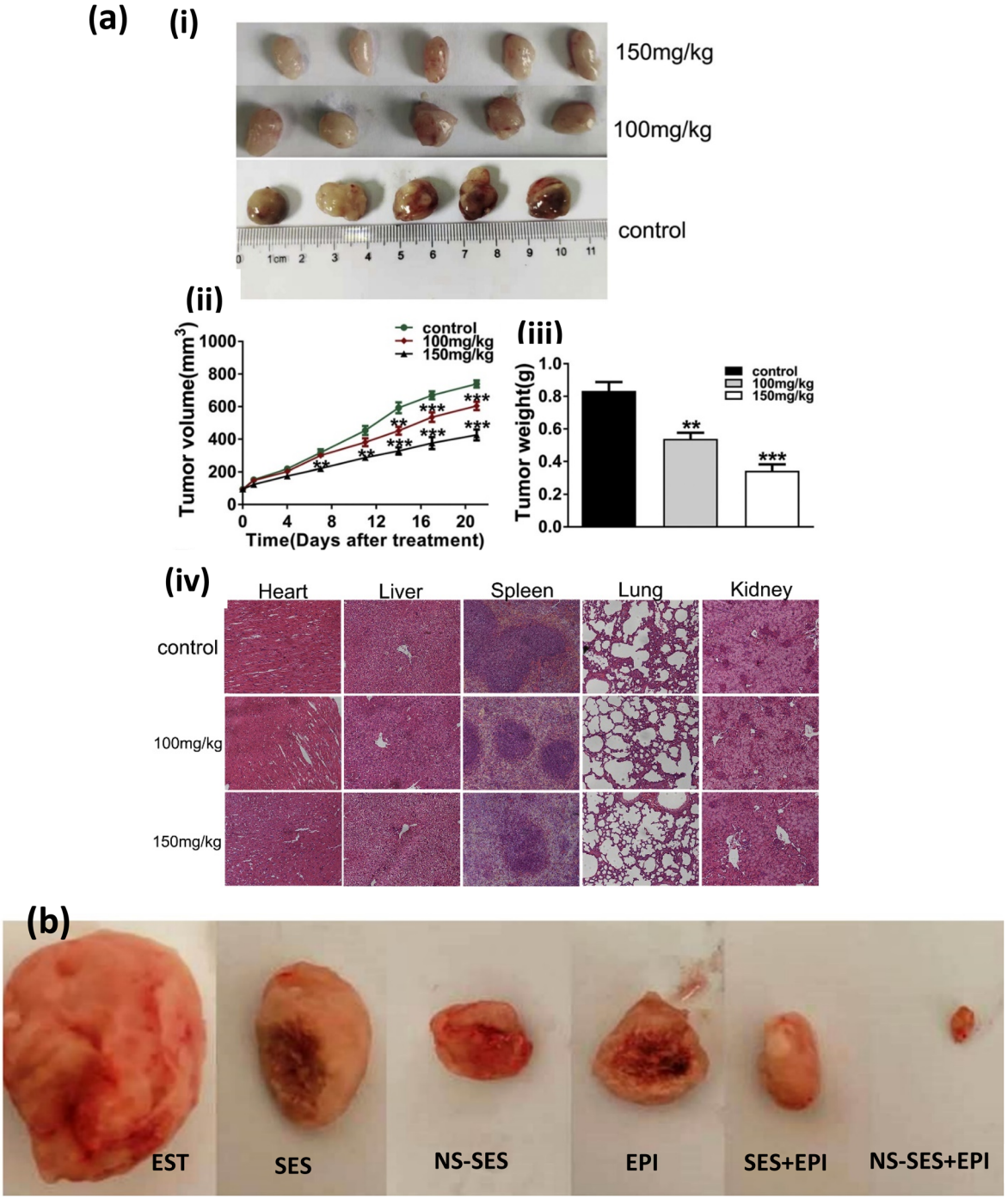

Fig. 4 (a) Suppression of NSCLC tumor growth by sesamin in xenograft models. (i) Suppression of tumor growth in sesame treated groups *vs.* control group. (ii) Significant decrease in tumor volume of sesame group *vs.* control group (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). (iii) Significant reduction in tumor weight of sesame group *vs.* control group (**$p < 0.01$, ***$p < 0.001$). (iv) Histopathologic analyses of major organs from sesamin treated and control groups. Reproduced from ref. 96 Copyright © 2020, Elsevier. (b) Suppression of breast cancer tumor growth by sesamol in Ehrlich solid carcinoma bearing mice. Tumor weight in all experimental groups: EST (Ehrlich solid tumor), SES (sesamol), SES-NS (nanosuspension of sesamol), EPI (Epirubicin), SES + EPI (sesamol + Epirubicin), and SES-NS + EPI (nanosuspension of sesamol + Epirubicin), reproduced from ref. 101 with permission from MDPI,[101] copyright © 2024.

on Akt activity and p53 expression was also confirmed *in vivo* in xenograft models of 5–6-week-old tumor-bearing (80–100 mm^3) female nude mice.[96] In the xenograft murine model, sesamin (at 100 mg kg^{-1} and 150 mg kg^{-1}) supplementation for 21 days substantially suppressed tumor growth compared to control group. In the treatment group, it was revealed from histological analysis that sesamin supplementation did not cause any significant impairment or alteration in the major organs (heart,

liver, spleen, kidney and lung), indicating its ability to selectively exert cytotoxic action against the cancer cells while sparing normal cells and tissues from noticeable adverse side-effects (Fig. 4a).[96] The anticancer effects of sesamin has been supported by research from other authors. Cyclooxygenase 2 (COX-2) is an enzyme that can be induced by many stimuli including cytokines and oncogenes. COX-2 has been implicated in lung carcinogenesis and the progression of carcinomas. Particularly, COX-2 is overexpressed in NSCLC and is apparently linked to the progression and metastasis of tumors.[100] In fact, Fang *et al.* observed that the expression of COX-2 was upregulated in lung cancer cell lines (A549, NCI-H446 and H1299) compared to human normal lung epithelial cell line (BEAS-2B).[97] The authors found that exposure of NSCLC cells to sesamin attenuated the amount of COX-2, cell proliferation and enhanced apoptosis markedly. Meanwhile, it was also noticed that suppression of COX-2 activity enhanced the potency of sesamin in its mediation of apoptosis, cell cycle arrest at G1-phase, as well as downstream gene products associated apoptosis, *viz.* Bcl-2 and Bax as well as cell cycle, cyclin E1.[97] When sesamin was co-administered with COX-2 inhibitor, CAY10404, both compounds were found to elicit a synergistic effect, resulting in the down-regulation of COX-2 expression along with its downstream molecules, such as IL-6, IL-1β, and TNF-α. In addition, the amounts of p-Akt (phosphorylated protein kinase B), PI3K (phosphoinositide-3 kinase) in the lung cancer cells were substantially reduced. Reduction in the levels of PI3K triggered apoptosis and cell cycle arrest at G1-phase in A549 cells. These findings had two implications. Firstly, it suggested that sesamin down-regulated the expression of COX-2, which in turn abrogated Akt/PI-3k signaling pathway, which then resulted in G1-phase cell cycle arrest and apoptosis. Secondly, the findings indicated that suppression of COX-2 enhanced the susceptibility of NSCLC cells to the anticancer activity of sesamin *via* the Akt/PI3K pathway. Together, these results suggested the potential role of sesamin cancer chemotherapy as adjuvant or potential drug candidate.[97] Another route *via* which sesamin is able to exert anticancer effect on lung cancer is through its modulation of the mitochondrial protease, Lon. Lon is reportedly upregulated in NSCLC and its action is vital in tumorigenesis. In corollary, downregulation of Lon induces caspase-3-based apoptosis.[102] According to Wang *et al.*, sesamin caused reduction in cell viability and promoted apoptosis in lung cancer cell lines (MRC-5, HEL299, H1299, A549, and 2937). The apoptotic effect of sesamin on the NSCLC cells was partly attributed to the suppression of Lon protease activity. Besides, sesamin also induced damages to DNA double strands which in turn activated a series of non-p53 dependent DNA damage responses, such as activation of G1/S checkpoint and apoptosis. These were accompanied by cleavage of caspase-3 and accumulation of sub-G1 as well as enhanced phosphorylation of checkpoint proteins including Nbs1 or nibrin (Nijmegen breakage syndrome 1), Chk2 (checkpoint kinase 2), and histone 2 A variant X (H2AX).[102] In another instance, it was revealed that the anticancer effect of sesamin on lung cells was mainly related to its effect on the nuclear factor kappa B (NF-κB) pathway. The pleiotropic transcription factor, (NF-κB), is known to have crucial roles not only in inflammation, but also in oncogenesis, tumor cell survival, proliferation and malignancy.[103] The involvement of NF-κB in the progression and spread of lung tumorigenesis has encouraged research toward development of NF-κB antagonists as chemotherapeutics for lung cancer. Sesamin was found to inhibit the viability of NSCLC cell line (H1299) and promoted tumor necrotic factor-α-mediated apoptosis.[104] This was accompanied by attenuation of proteins linked to inflammation (COX-2), cell survival or anti-apoptosis (survivin and Bcl-2), proliferation (cyclin D1), invasion (matrix metalloproteinase-9, intercellular adhesion molecule 1), as well as angiogenesis (vascular endothelial growth factor). Importantly, both constitutive and inducible NF-κB were suppressed and downregulated by sesamin. Sesamin also rescued IκBα (the inhibitor of NF-κB) from degradation by inhibiting the phosphorylation of IκBα and suppressing the activation of IκBα protein kinase (IKK). As a result, p65 phosphorylation and nuclear translocation, as well as NF-κB-mediated transcriptional activity were all suppressed. The findings indicated that sesamin mediated its anticancer activity on H1299 (human lung adenocarcinoma) cells *via* suppression of the NF-κB signaling pathway and its attendant attenuation of gene products related to cell survival, invasion, and angiogenesis.[104] The role of an active NF-κB pathway in obviating apoptosis and promoting chemoresistance is well-known.[105] By targeting the NF-κB pathway, sesamin alone or in combination with other active ingredients could be useful in impairing lung adenocarcinoma development, treating lung cancer, and overcoming the resistance to chemotherapeutic intervention.[106]

Besides sesamin, sesamol was also shown to exert anti-lung cancer activity. In an *in vitro* study, human lung adenocarcinoma cell line (SK-LU-1) as well as normal African green monkey kidney cell line (Vero) were treated without (untreated) or with sesamol (0.05–10 mM) for 48 h to ascertain the anticancer effect of the lignan.[107] Data revealed a substantial dose-dependent inhibition of cancer cell proliferation by the lignan, with an IC_{50} value of 2.7 mM. Meanwhile, the impact of sesamol on normal Vero cells was less potent, with an IC_{50} value of 7.6 mM, indicating that the cytotoxic effect of the compound against cancer cells was selective (selectivity index = 3). With notable increase in the activity of caspases-8, 9, 3/7 as well as loss in mitochondrial membrane potential (MMP) and decreased Bid expression, the anti-lung cancer effect of sesamol was attributed to induction of both the extrinsic and intrinsic apoptotic pathways in SK-LU-1.[107] Further evidence on the anti-lung cancer effect of sesamol was made available through the research of Hu *et al.*[108] The authors noted that incubation of NSCLC cell line (A549) or normal macrophage cell line (RAW 264.7) with sesamol (1–1000 μM) for 24 h resulted in a dose-dependent and selective cytotoxic effect against the cancer cells (IC_{50} of 501 μM) vis-à-vis the normal cells with IC_{50} value >1000 μM. Sesamol was found to stimulate apoptosis in A549 cells *via* the intrinsic pathway evinced by downregulation of Bcl-2 mRNA expression and enhanced expression of caspase-3 and caspase-9 mRNA levels, and mediated by excess ROS generation and disruption in mitochondrial membrane potential.[108]

5.2 Impact of sesame lignans on breast cancer

Breast cancer is a disease characterized by uncontrolled growth of abnormal cells in the breast leading to the formation of tumors. Without proper intervention, these tumors can metastasize to other parts of the body, causing great damage and even death.[5] Breast cancer was ranked as number two of all new cancer cases in 2022, second only to lung cancer, and accounted for a total of 2.30 million cases. Breast cancer was responsible for the death of 0.67 million people globally in 2022 and was reported as the fourth leading cause of all cancer-related deaths. In 157 of 185 countries surveyed, breast cancer was the most common type of cancer in women.[5] Treatment often depends on the type and stage of the breast cancer and would typically involve a combination of surgery, radiotherapy and medications, such as chemotherapy, hormonal or targeted biological therapies. Given the unwanted side-effects of these therapies on patients and the huge burden caused by breast cancer on the individual patients, their families, and the national healthcare system, there is a compelling interest and incentive to uncover more efficacious and safer therapeutic options against this disease.

Sesame seeds and sesame lignans have been reported to exhibit significant reduction of 7,12-dimethylbenz(*a*) anthracene-induced breast tumor in rats[109] and suppressed proliferation of human luminal (MCF-7) and triple negative breast cancer (MDA-MB231) cell lines.[110] Sesamin caused G1-phase cell cycle arrest in MCF-7 cells by promoting the dephosphorylation of RB (retinoblastoma tumor suppressor protein), a regulator of cell cycle progression. In addition, the lignan induced the degradation of cyclin D1, which is typically over-expressed in and crucial in human tumor cell development.[111] Further insights were provided in another study by Akl *et al.*[110] using sesamin and γ-tocotrienol. γ-tocotrienol is a natural form of vitamin. Sesamin in combination with γ-tocotrienol was found to significantly and synergistically inhibit the proliferation, but not induce apoptosis of human (MCF-7 and MDA-MB-231) and neoplastic murine (+SA) breast cancer cells.[110] Interestingly, at similar concentrations, both compounds did not exert significant adverse effects on the growth and viability of normal human (MCF-10A) and mouse (CL-S1) breast cancer cells, suggesting that the compounds were selective in their activity. When the cancer cells were exposed to sub-effective (low) concentration of both compounds at the same time, they mediated cell cycle arrest at G1-phase as well as decrease in levels of phosphor-RB, E2F1, CDK2, CDK4, CDK6 and cyclin D1 on one hand and enhancement in the levels of p27 and p16 on the other hand. The lack of apoptotic effect and cytotoxicity suggested that the combined treatment was cytostatic rather that cytotoxic, with effects emanating from G1-phase cell cycle arrest.[110] Meanwhile, according to reports by Siao *et al.*[112] sesamin (1–50 μM) significantly inhibited proliferation and enhanced apoptosis in human breast cancer MCF-7 cells in a concentration-dependent manner. The dietary lignan increased cell cycle arrest at the sub-G1 phase. The expression of cell cycle checkpoint proteins (p52 and checkpoint kinase 2) and markers of apoptosis (caspase-3 and Bax) were all increased in the cells post sesamin treatment, indicating that the lignan is capable of exerting anticancer effects by inhibiting tumor cell growth and modulating apoptotic signaling pathways.[112] The anti-tumor effect of sesamin in breast cancer was also noticed *in vivo* in animal studies. It was observed that sesamin significantly reduced cell proliferation, increased apoptosis, and the growth of human breast tumors (MCF-7) at high levels of circulating estrogen in athymic mice. Administration of sesamin (1 g kg^{-1}) for eight weeks shrunk palpable tumor size by 23% compared to the control.[113] Sesamin also reduced the expression of human epidermal growth factor receptor 2 (HER2), and endothelial growth factor receptor (EGFR), and the downstream signal transduction protein, pMAPK (phosphorylated mitogen-activated protein kinase). The MAPK cascades are crucial signaling pathways for the proliferation, survival, apoptosis, angiogenesis and metastasis of cancer cells.[114] In this signaling pathway, interaction between ligands, such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF) with their respective tyrosine kinase receptors, *viz.* IGF-1R and EGFR, the dimerization of human epidermal growth factor-2 with other receptors, induces the phosphorylation and subsequent activation of signal transduction proteins Akt (to pAkt) and MAPK (pMAPK). As a result of the ensuing cascades, transcription factors and cofactors responsible for the regulation of cell growth and apoptosis become activated. Analogously, interaction between vascular endothelial growth factor and its receptor, promotes angiogenesis – vital for the supply of nourishment for tumor growth. Apparently, suppression of the aforementioned growth factors can reduce the growth and proliferation of tumors. In the (MCF-7) tumor bearing athymic mice with high levels of circulating estrogen, only HER-2, EGFR, and pMAPK expression were suppressed. VEGFR-1 expression was not affected, suggesting that the angiogenesis was not impacted as a target in this instance.[113] Thus, it was suggested that sesamin restricted the growth of breast tumor *via* its down-regulatory effect on the growth factor cell signaling pathway, specifically the phosphorylation and activation of MAPK. This was in contrast to the minor lignan, secoisolariciresinol diglucoside, which failed to downregulate pMAPK expression. Furthermore, the antitumor effect of sesamin was attributed to the unmetabolized lignan, rather than its metabolic products, estradiol and enterolactone.[113] Further evidence of the anti-tumor effect of sesamin on breast cancer was offered in a recent study by Kongtawelert *et al.*[14] MDA-MB-231 is a triple negative breast cancer (TNBC) cell line, which is representative of cancer subtypes with some of the worst prognosis. Its tumorigenesis is partly due to the over-expression of programmed death ligand-1(PD-L1), which is highly expressed (mRNA and protein levels) in TNBC (*e.g.*, MDA-MB-231), but not in its luminal counterpart (*e.g.*, MCF-7). PD-L1 is capable of breaching the immune barriers against tumorigenesis, thereby promoting tumor cell survival and proliferation. It was noticed that sesamin inhibited the proliferation of both luminal MCF-7 and TNBC MDA-MB-231 cells *in vitro*.[14] In MDA-MB-231 cells, sesamin was found to downregulate the expression of both PD-L1 mRNA and protein. This action was due to the suppression of AKT, NF-κB and JAK/Stat signaling in the cancer cells. Interestingly,

sesamin also impeded MDA-MB231 cell migration by attenuating MMP-9 and MMP-2 activation.[14] This indicated that anti-cancer property of sesamin on MDA-MB231 cells involved modulation of the proliferative and metastatic activities of the cell line. It is germane to mention that studies have demonstrated that beyond sesamin, the metabolic product of the lignan – enterolactone, also has a crucial role in the modulation of TNBC.[115] A key feature of TNBC invasiveness is its high level of metastasis. Targeting metastasis and pathways associated with it is useful for development of breast cancer therapies in highly malignant form of the disease. Enterolactone had been shown to inhibit proliferation of MDA-MB-231 cells (IC_{50} value of 73 μM for 48 h), promoted apoptosis, and inhibited migration and metastasis by impeding urokinase-type plasminogen activator (uPA)-mediated plasmin activation and matrix metalloproteinases-induced ECM remodeling.[116] Meanwhile, in breast cancer, induction of epithelial–mesenchymal transition (EMT) through the ERK/NF-κB/snail signaling pathway is known to promote breast cancer metastasis (invasion and migration). The transforming growth factor-β (TGF-β) plays a crucial role in cancer cell metastasis *via* its induction of EMT. It was revealed that treatment of MDA-MB-231 cells with enterolactone inhibited TGF-β-mediated EMT by abrogating ERK/NF-κB/snail signaling pathway.[115] Thus, with further research, enterolactone could present an interesting opportunity for the development of anti-metastasis therapy for treating breast cancer.

Other minor lignans have also indicated anti-breast cancer activity. In breast cancer (MDA-MB-231 and MCF-7) cells, pinoresinol treatment exerted anti-proliferative and pro-oxidant effects independent of estrogen receptor status. In normal MCF10A human mammary epithelial cells, the lignan exhibited antioxidant effect and protective effect against oxidative stress-associated DNA damage.[117] This selective anti-tumor effect of pinoresinol as well as lariciresinol against breast cancer was confirmed in a recent *in vitro* study,[118] suggestive of its chemo-preventive property.

In another study using vascular endothelial cell capillary tube and network formation *in vitro* assay, it was revealed that sesamin displayed potent anti-angiogenic effect against breast cancer cells, MCF-7 and MDA-MB-231.[119] Co-cultivation of the cancer cell lines with macrophage markedly enhanced angiogenesis of the cells *via* the induction of vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9). When sesamin was introduced into the system, the level of angiogenesis was potently suppressed by inhibiting the induction of VEGF and MMP-9. This effect was accomplished by substantially suppressing the activities of Akt and p38 (MAPK). Meanwhile, the expression of cytokines (IL-6, IL-8 and TNF-α) which are upregulated and involved in the induction of VEGF and MMP-9 by the macrophage, was also found to be suppressed by sesamin treatment.[119] Recently, sesamin (1.5–10 μM) was shown to inhibit VEGFA-induced pathological angiogenesis in the chick chorioallantoic membrane (CAM) model.[120] This was attributed to the ability of sesamin to impede the proliferation and migration of endothelial cells by abrogating FAK and Src signaling.[120] The result highlighted the potential role of sesamin in treatment of pathologies associated with hyper-angiogenesis such as breast cancer.

Further exploration of the anti-cancer properties of sesame lignans had identified sesamol for its potent effect against breast cancer tumor *in vivo*.[101] The impact of sesamol was ascertained by administering sesamol (oral 70 mg per kg per day)/sesamol nanosuspension (oral 10 mg per kg per day) with or without Epirubicin (injected at 2.5 mg per kg per week) in a breast cancer model of mice bearing Erlich solid tumor (EST). For comparison, one group of mice (EST) were injected with normal saline for 21 days. After 21 days of treatment, it was found that sesamol strongly reduced the growth of solid tumor (2.58 g) in the mice and the nano-suspension of sesamol was more potent (1.24 g) at lower concentration when compared to EST group (3.788 g). Importantly, combination of sesamol and Epirubicin (1.238 g) as well as sesamol nano-suspension with Epirubicin (1.211 g) markedly potentiated the anti-cancer effect of the chemotherapeutic agent as evinced in the significant ($p < 0.001$) and drastic reduction in tumor size (Fig. 4b).[101] Underpinning the anticancer effect of sesamol alone or combined with Epirubicin was the reduction in cell proliferation (decreased Akt levels), promotion of apoptosis (elevated caspase-3 and Bax levels), autophagy (increase in beclin1 and Lc3-II levels), and suppression of angiogenesis (decreased VEGFR2 levels). Furthermore, by combining Epirubicin with sesamol and especially sesamol nano-formulation, the anti-cancer effect of the drug was not only enhanced, but its toxicity was also mitigated.[101]

The anti-breast cancer effect of sesamol has been supported by evidence from *in vitro* and *in vivo* studies involving triple negative breast cancer (TNBC) models. TNBC is highly invasive and aggressive, with poor clinical prognosis and response to targeted therapies; thus, making chemotherapeutic agents a key option. Nonetheless, the use of standard agents, including taxane, anthracycline and fluorouracil are limited by unwanted side-effects such as leucopenia and nausea.[121] Interestingly, it was shown that sesamol induced a dose-dependent anti-proliferative effect on TNBC cell lines MDA-MB-231 and Hs-578T with IC_{50} values of 75.4 μM and 33.9 μM, respectively.[122] Sesamol also inhibited the migration and invasion of the breast cancer cell lines. Moreover, in xenograft tumor model in nude mice, sesamol strongly reduced tumor growth compared to the untreated control. Notably, there was no obvious adverse effect on the mice due to sesamol treatment unlike some conventional TNBC drugs, such as anthracycline, platinum and fluoro-uracil.[121,123] The anticancer effect of the sesame lignan was attributed to its upregulation of WIF1, which inactivates the Wnt/β-catenin signaling pathway. Detailed exploration of the molecular mechanism revealed that incubation of TNBC cells with sesamol triggered a concentration-dependent increase in WIF1 expression through de-methylation of its promoter. This inhibited the binding of Wnt protein family to the cell membrane-bound receptors, FZD and LRP5/6. The impaired binding abrogated the expression of β-catenin through enhanced degradation, leading to a decrease in the extent of nuclear translocation and subsequent cascades resulting in the inhibition of TNBC proliferation and metastasis.[122]

5.3 Effect of sesame lignans on colorectal cancer

Colorectal cancer is cancer that occurs in the large intestine (colon) or rectum. It was responsible for more than 0.93 million deaths worldwide in 2020, making it the second leading cause of cancer-related mortality. Colorectal cancer is also known for its high incidence, with a recorded 1.9 million new cases in 2020; thus, making it the third most common type of cancer globally.[5] Treatment options depends on the type and progression as well as the individual's medical history. Typically, surgical intervention is used for early stage colorectal cancer whereas systemic chemotherapy is used for advanced stage of the disease. The unwanted side-effects often encountered in chemotherapy has been a strong motivation for research focusing on the identification and development of novel drug candidates with improved efficacy and safety profiles. Lignans from several sources have shown high promise in this regard.[104]

Recent study by Huang *et al.*[124] demonstrated that sesamin possesses anticancer effect against colorectal cancer. An essential component of colorectal cancer malignancy is its ability to metastasize into other parts of the body. For this to happen, the tumor cell is required to be angiogenic. Hypoxia, which is a key feature within the tumor mass is responsible for stimulating angiogenesis and, by extension, tumor metastasis. It has thus been proposed that abrogating tumor angiogenesis and metastasis is a valuable strategy for curtailing the growth and development of cancer.[124] To evaluate the viability of sesamin as a potential inhibitor of CRC metastasis, Huang and co-researchers employed an *in vitro* tube formation assay with CRC cell lines (HCT116 and SW480) and *in vivo* Matrigel® plug assay with CRC cells made in nude mice.[124] It was observed in the *in vitro* assay that sesamin markedly impeded hypoxia-induced CRC angiogenesis in a concentration-dependent pattern. In nude mice, oral intake of sesamin drastically reduced the formation of neovessel in Matrigel plugs with CRC cells. Furthermore, it was observed that sesamin suppressed the expression of VEGFA, required for induction of hypoxia-stimulated CRC angiogenesis. This was accompanied by the inhibition of IκBα phosphorylation, which by extension prevented the NF-κB p56 to stimulate HIF-1α.[124] Taken together, the results indicated that sesamin attenuated hypoxia-induced angiogenesis *via* its modulation of NF-κB/HIF-1α/VEGFA signaling pathway.[124] This implies that the sesame lignan could be potential candidate for the prevention or treatment of CRC metastasis.

An earlier study by Harikumar *et al.*[104] had shown that sesamin inhibited the proliferation of many cancer cells, including multiple myeloma and leukemia, as well as solid tumors, such as the colorectal cell line, HCT116 (human colon epithelial cancer). Sesamin induced a significant reduction in viability of HCT116 cells with IC_{50} value of 57.2 μM and promoted apoptosis. The anti-proliferative effect of sesamin against HCT116 cells was ascribed to the suppressive activity of the lignan on the expression of gene products associated with cell survival (Bcl-2 and survivin) and cell proliferation (cyclin D and COX-2). These gene products are downstream and regulated by the transcription factor NF-κB. It should be briefly mentioned that induction of NF-κB activity by tumor necrotic factor in HCT116 cells was suppressed by sesamin *via* inhibition of IκBα kinase (IKK) activation (which restricts the phosphorylation and degradation of IKK) and nuclear translocation of NF-κB p65 subunit. These observations suggested that the anticancer effect of sesamin against HCT116 was likely modulated *via* its regulatory effect on NF-κB signaling pathway.[104]

The role of inducible and constitutive NF-κB in the promotion of tumor survival, proliferation, angiogenesis, growth and drug resistance in CRC has been well-documented.[125,126] Sesamin inhibited the activation of NF-κB by tumor necrotic factor (TNF) as well as tumor promoters (phorbol myristate acetate and okadaic acid), carcinogens (cigarette smoke condensate), reactive oxygen species (hydrogen peroxide), inflammatory agent (lipopolysaccharide).[104] The afore-mentioned potential carcinogenic stimuli are markedly different in the mechanism through which they induce NF-κB activation.[127,128] The result therefore indicated that sesame is capable of abrogating the effect of these stimuli at a common checkpoint—NF-κB. Importantly, it was also shown that the inhibitory effect of sesamin was also effective against constitutive NF-κB activation.[104] This implies that the ability of the transcription factor which already resides in the nucleus to continuously activate target genes is abrogated by the lignan. Considering the crucial role of constitutively active NF-κB in cancer drug resistance and treatment failure, these findings indicated that sesamin is a worthy drug candidate for targeting CRC. In addition to sesamin, sesamolin was also found to exhibit anti-proliferative activity against CRC. The lignan, when loaded into nanocellulose-base emulsion was found to decrease the viability of HCT116 cell line in a concentration-dependent manner. Sesamolin displayed an IC_{50} value of 724.94 μg mL^{-1} against the viability of colon cancer cells.[129] Meanwhile, the compound did not affect the viability of non-cancerous Vero cells. In addition, it was revealed that the mode of sesamolin-induced reduction in cell viability was *via* reactive oxygen species induced necrosis. Since there was no significant change in caspase-3/7 activity, the presence of apoptosis as a major contributor of cell death was excluded.[129]

According to Wu *et al.*[130] sesamolin (5–40 μM) exerted anti-proliferative and apoptotic effect on HCT116 cells in a concentration-dependent manner after 48 h. The authors further observed that sesamolin (5 μM and 20 μM) caused a significant inhibition of HCT116 cells migration after 24 h relative to the untreated control cells.[130] In order to unravel the mechanism behind the anticancer activity of sesamolin, its impact on the signal transduction and activator of transcription-3 (STAT3) signaling pathway was investigated. Signal transduction and activator of transcription-3 (STAT3) is a transcription factor that is involved in many cellular processes, notably in immune response and development of cancer. Janus protein tyrosine kinase (JAK)/(STAT) signaling is considered as a major signaling pathway of cancer-related inflammation.[131] *In vivo*, this pathway can be activated by cytokines and growth factors, and the overexpression of STAT-3 has been implicated as a central modulator of tumorigenesis metastasis.[132] In cancers such as CRC, the JAK-2/STAT-3 pathway is known to modulate cell

proliferation, differentiation, apoptosis, and tumor development.[133] As an illustration, JAK-2, which is resident in the cytoplasm becomes activated upon the binding of IL-6 to its receptor (IL-6Rα). Activation of JAK in turn induces the phosphorylation of STAT-3 (into p-STAT-3), which then dimerizes and is translocated into the nucleus where it regulates gene expression for cell invasion and migration.[130] Thus, blocking the JAK-2/STAT-3 pathway is useful for impeding the growth and spread of cancer, and restoring immunity against tumor.

Exposure of HCT116 cells to sesamolin downregulated IL-6-induced expression of p-STAT-3. This was accompanied by the downregulation of the expression of MMP-1, MMP-2 and MMP-9 mRNAs.[130] These matrix metalloproteinases are crucial for the degradation of extracellular matrices during tumor cell invasion and migration. Their expression is upregulated in cancer cells and positively correlated with metastasis. The suppression of p-STAT-3 expression as well as inhibition of the MMPs mRNAs expression in the HCT116 by sesamolin suggested that the restrain on cancer cell invasion and migration exerted by the lignan was due to its inhibition of the JAK-2/STAT-3 signaling pathway.[130] In another study involving the same human colorectal cancer cell line HCT116, it was reported that sesamol inhibited the proliferation of HCT116 cells, with an IC_{50} value of 2.59 mM.[134] This effect of sesamol was due to S-phase cell cycle arrest and induction of apoptosis *via* production of intracellular reactive oxygen species (superoxide anion radical), mitochondrial dysfunction as well as DNA fragmentation.[134] The final metabolites of these dietary lignans, enterolactone and enterodiol have also been found to demonstrate anticancer properties.[135] According to Shin *et al.*[136] enterodiol exhibited inhibited the growth of mouse CT26 and human HT-29 colorectal cancer cell lines. Enterodiol treatment inhibited cancer cell proliferation, migration, invasion and induced apoptosis. In contrast, enterodiol was none toxic to the normal RAW264.7 macrophages. The anticancer effect of enterodiol was exerted by regulating MAPK signaling pathway involved in cell apoptosis and proliferation.[136] Based on epidemiological evidence, it has been suggested that high dietary intake of enterolactone might be associated with lower risk of colon cancer, particular in women.[137] However, a nested case-control study disputed this notion.[138] Together, these results suggest presents a strong rationale for further investigation into the anticancer properties of sesame lignans and metabolites in the control or prevention of colorectal cancer.

5.4 Impact of sesame lignans on prostate cancer

This is cancer that arises due to uncontrolled growth of cells in the tissues of the prostate, the semen-producing gland in the male reproductive system. Prostate cancer has a high global incidence of 1.5 million new cases and 397 000 deaths worldwide in the year 2022. In men, it was the second most frequently diagnosed cancer (14.2%) in 118 countries (two-thirds of the world, 185 countries), and accounted for third most common cause of death (7.3%) in 52 countries, including countries in Europe (*e.g.*, Sweden), sub-Saharan Africa and the Caribbean, Central and South America (*e.g.*, Venezuela, Ecuador, and Chile).[4] Prostate cancer in general has a positive prognosis with around 99% survival of patients in five years. A number of therapeutic interventions are available to patients, depending on the individual's particular situation, such as stage of the disease, age of patient, and whether the cancer is recurring. Surgery, radiation therapy, hormone therapy, and chemotherapy are often among the standard treatment options.[139] Terpene alkaloids, such as docetaxel and cabazitaxel are among the most commonly used drug-based agents for treatment of prostate cancer, metastatic prostate cancer and castration-resistant prostate cancer.[140] The use of these drugs is not without some major concerns. These arises due to the adverse side-effects frequently encountered with use of these anti-cancer agents, including extreme tiredness, loss of hair and hearing, pain in bone muscle and joint, *etc.* Thus, there has been a constant drive in search of chemotherapeutics that are not only effective but with less adverse effects.

Research findings from at least two major sesame lignans, *viz.* sesamin and sesamol have been quite promising in their pharmacological properties toward prostate cancer.[104,141,142] *In vitro*, sesamin was found to inhibit the proliferation and survival of classical prostate cancer cell lines, DU145 and PC-3. The sesame lignan suppressed cancer cell migration, invasion and resistance to anoikis by down-regulating a disintegrin and metalloproteinase 9 (ADAM9) expression *via* JNK and c-Jun signaling pathways.[141] ADAM9 plays a critical role stimulating the progression and advancement of solid tumors including prostate cancer, in which it is typically up-regulated in terms of mRNA and protein levels compared to normal tissues.[143,144] Crucial tumor progression functions like cell proliferation, migration and invasion are re-established with ADAM9 upregulation. Moreover patients with high levels of ADAM9 expression reportedly had shorter biochemical recurrence (BCR)-free time.[144] According to Chen *et al.*[141] sesamin did not only downregulated ADAM9 protein expression in the prostate cancer cell lines, but also inhibited its proteolytic cleavage of membrane-bound PD-L1 (mPD-L1) into its soluble counterpart (sPD-L1).[141] sPD-L1 is expressed by cancer cells to obviate immune checkpoint control. By blocking the production of sPD-L1, the sesame lignan ensures that the cancer would not be able to escape their destruction by the immune system. The anti-prostate cancer effect of sesamin was also observed *in vivo*. It was revealed that intraperitoneal injection of sesamin into mice with prostate cancer tumor resulted in a substantial suppression of prostate cancer cell-derived tumor growth. This was accompanied by markedly decrease in the expression of ADAM9 and Ki67 proteins as well as increase in mPD-L1 levels. Besides, co-administration of sesamin alongside docetaxel and cabazitaxel potentiated chemosensitivity in the prostate cancer cells.[141] Previously, it was reported that sesamin suppressed the proliferation of prostate cancer cell line DU145 in a dose- and time-dependent manner, with an IC_{50} value of 60.2 μM. The anti-proliferative effect of the lignan was related to its inhibition of NF-κB signaling and NF-κB gene products linked to cell survival (survivin and Bcl-2) and cell proliferation (cyclin D1).[104,111] In an analogous study, sesamin pretreatment (10, 50, 100 μg mL^{-1}) was found to inhibit lipopolysaccharide (LPS)-

induced proliferation of human prostate cancer cell line, PC-3.[142] LPS-induced elevation of proteins linked to cell survival (Bcl-2 and survivin) and proliferation (cyclin D1 and COX-2) in PC-3 cells was attenuated by sesamin pretreatment. In addition, sesamin abrogated LPS-induced expression of MMP-9, intercellular adhesion molecule 1 (ICAM-1) and VEGF proteins as well as TNF-α and IL6 in PC-3 cells, highlighting its anti-invasive effect. Importantly, the induction of p38 protein phosphorylation and NF-κB activity promoted by LPS in PC-3 cells was also suppressed following sesamin pretreatment. Here also, it was deduced that the inhibitory effect of sesamin against inflammation (LPS) activated proliferation and invasion in prostate cancer was achieved *via* the modulation of p38-MAPK and NF-κB signaling pathways.[142] This fact pattern was further supported by *in vivo* studies in BALB/c nude mice carrying a PC-3 tumor xenograft. Mice were administered either phosphate-buffered saline (control) only or LPS (2 mg kg^{-1}) only. Treatment groups received sesamin (10 mg kg^{-1}) or SB203580 (10 mg kg^{-1}) prior to LPS injection. The mice were treated once every three days for a total of three weeks after which they were sacrificed and tumor volume was measured using caliper. It was found that the mice which received sesamin had a substantial reduction in LPS-induced tumor growth compared to the control.[142] Meanwhile, in another report, it was revealed that sesamol and its derivative 3′,4′-(methylenedioxy)acetophenone (3′MA) were found to display considerable anti-prostate cancer properties by regulating the androgen receptor (AR) signaling pathway.[145] Androgen signaling is crucial for the development and progression of prostate cancer, being essential in cell proliferation, apoptosis, invasion, and differentiation. *In silico* studies by molecular docking showed that sesamol and 3′MA displayed meaningful interaction with androgen receptor. *In vitro*, both compounds inhibited cell proliferation in AR expressing prostate cancer cells such as LNCaP, PC-3 and DU145, with IC_{50} value of 3.94 mM (sesamol) and 4.43 (3′MA) against LNCaP cell viability. Both compounds induced a distinct downregulation of AR as well as androgen-regulated genes relevant to prostate cancer including prostate specific antigen (PSA), FK506 binding protein 5 (FKBP5), and transmembrane protease serine 2 (TMPRSS2).[145] In rats, prostate tumor was induced *via* co-administration of *N*-methyl-*N*-nitrosourea (MNU) and testosterone undecane (TU). Interestingly, when rats were concomitantly treated with sesamin (50 and 100 mg per kg per day), the lignan caused a 25.14% and 32.93% decrease in prostate tumor weight in the rats compared to control. Similarly, there was a 31.43% and 57.44% decrease in prostate weight upon oral treatment with 3′MA relative to the control. In fact, the extent of prostate decrease by 3′MA was comparable to that of the standard drug, finasteride at 25 mg per kg per day (*i.e.* 60.65% reduction in prostate). The impact of the lignan and its derivative on prostate weight was accompanied by a marked reduction in level of serum PSA, which connoted their influence on the androgen signaling pathway. Also, both compounds were found to improve the antioxidant status of the rats as evinced in increase in the levels of catalase and glutathione as well as decrease in the level of nitrite and malondialdehyde (MDA). It was thus inferred from these outcomes that sesamol and 3′MA could play a vital therapeutic or preventive role in prostate cancer by regulating the androgen signaling pathway.[145]

Doxorubicin is a broad-spectrum antineoplastic agent that has been widely used for the treatment of several cancers including cancers of the lung, ovaries, breast, and prostate. However, the use of doxorubicin can lead to severe side-effects, such as muscle damage, nephrotoxicity, osteoporosis, osteoarthritis, and irreversible heart failure.[146] Mitigating these adverse effects can dramatically improve the therapeutic benefits of doxorubicin in prostate cancer. Doxorubicin mediated cardiotoxicity and myocardial damage has been linked to oxidative stress. By virtue of its well-known antioxidant property, sesamol had been proposed as a potential candidate for amelioration of doxorubicin-induced cardiac toxicity during antineoplastic intervention. Previously, sesamol (50 μM) was shown to offer maximum protection against doxorubicin-induced oxidative, cytotoxic, and genotoxic damage in cardiac myoblasts (H9c2 cells).[147] Studies by Shah, *et al.*[148] revealed that doxorubicin at 4 mg kg^{-1} demonstrated optimal anti-prostate cancer effect in a prostate cancer rat model. But at this high drug concentration, doxorubicin also induced myocardial damage. Data obtained from serum creatine kinase-muscle/brain (CK-MB) assessment, hematological analysis, histopathological evaluation, estimation of heart weigh : tibia length ratio, and antioxidant activity revealed that treatment of the prostate cancer rats with sesamol (100 mg per kg per day) or 3′MA (100 mg per kg per day) prevented the cardiac toxicity induced by doxorubicin. The mechanism underlying the protective effect of sesamol and 3′MA against doxorubicin-mediated cardiotoxicity is likely facilitated *via* their ability to potentiate cellular antioxidant capacity and suppress oxidative stress.[148] Furthermore, in a recent study, *in silico* analysis using molecular docking uncovered that sesamin and sesamolin demonstrated compelling binding interactions with the key proteins involved in prostate cancer, *viz.* ITGB3, FYN, PDGFRB, PDGFRA, and PIK3R1, as evinced in the higher LibDock scores relative to the anti-cancer drug, 5-fluorouracil.[149] These findings together indicated that sesame lignans or their derivatives, such as 3′MA could be viable active ingredients for prevention or adjunctive agents to augment standard chemotherapeutic drugs for enhancing treatment efficacy in prostate cancer.

5.5 Impact of sesame lignan on cervical cancer

For many women around the world, cervical cancer is a life-threating malignancy. With 0.66 million new cases and 0.35 million cases of cancer-related deaths worldwide in 2022, cervical cancer represents the fourth most common type of cancer in women in terms of incidence and mortality.[4] Cervical cancer is the most commonly diagnosed cancer type in 25 countries and a leading cause of mortality in 37 countries, especially among countries in sub-Saharan Africa, South America and East Asia.[4] Although human papillomavirus infection is necessary, it is not a sufficient cause of cervical cancer. Rather, the disease is caused by persistent chronic HPV infection.[150] Globally, 71% of cervical cancers was caused by

a combination of HPV type 16 and HPV type 18. Other important risk factors include early age of sexual activity, some sexually transmitted infections (*e.g.*, HIV and *Chlamydia trachomatis*), prolonged use of oral hormonal contraceptives, higher number of childbirths and smoking.[151] Symptoms include pain during intercourse, pelvic discomfort, unusual discharge, and vaginal bleeding. Importantly, cervical cancer is not only a common cause of death in many countries, it is worth mentioning that the highest global burden is in countries with the lowest Human Development Index (HDI).[152] Thus, there is need for a multipronged approach for the prevention and treatment of cervical cancer.

Findings from various studies have shown that sesame lignans have promising pharmacotherapeutic properties towards cervical cancer cell lines.[156,157] In ascertaining the capacity of sesamol as adjunctive agent in cervical cancer chemotherapy, cervical cancer (HeLa) cell line was pretreated with sesamol at various concentrations (0, 1, 5, and 10 μM) followed by paclitaxel, a standard chemotherapeutic agent. It was found that antiproliferative effect of paclitaxel improved with increasing sesamol concentration in a dose-dependent manner as evince by the reduction in paclitaxel IC_{50} value against HeLa cells (7.5 nM, 0.55 nM, 0.1 nM, 0.025 nM).[156] In addition, calculation of combination index (CI) plot of sesamol + paclitaxel using CompuSyn software revealed a synergy between the two compounds, *i.e.* CI value <1. Mechanistically, it was observed that paclitaxel-induced ROS generation, DNA damage, and ultimately apoptosis in HeLa cells were all improved by pretreatment of the cells with sesamol.[156] In other words, sesamol displayed a chemosensitizing role when used alongside paclitaxel to improve the anti-cancer property of the drug on human cervical cancer cells, which implies that the lignan could augment the neoplastic agent in cervical cancer chemotherapy. Meanwhile, authors had also investigated the anti-cervical cancer effect of sesamin by examining its role on the tumor suppressor protein p53.[157] p53 is reportedly inactivated or degraded in HPV-infected cervical tissues, and thus, it was proposed that restoration of p53 activity might be a viable strategy for the treatment of cervical cancer *via* induction of cell cycle arrest, promotion of apoptosis and, inhibition of tumor growth.[164] Against this backdrop, it was reported that sesamin (75 and 150 μM) markedly inhibited the proliferation of human cervical cancer cell lines (HeLa and SiHa) in a concentration-dependent pattern, whereas in normal Hs68 dermal cells the lignan did not exert any noticeable effect. Additionally, sesamin induced cell cycle arrest at the sub-G1 phase and enhanced apoptosis in the cervical cancer cells.[157] Pertaining to the involvement of p53 in the apoptotic cascade, it was revealed that sesamin activated the phosphorylation of p53 at the serine-48 and serine-15 residues. This was accompanied by the upregulation of pro-apoptotic Bax, PUMA (p53 upregulated modulator of apoptosis), and PTEN levels as well as the inhibition of pro-cell survival/growth AKT phosphorylation at serine-473. Interestingly, when p53 was inhibited by pifithrin-α in SiHa cells exposed to sesamin, the levels of Bax, PUMA and PTEN were significantly reduced, while AKT phosphorylation was restored. Moreover, pifithrin-α suppressed apoptosis and restored the viability of HeLa and SiHa cells exposed to sesamin.[157] Taken together, these fact pattern indicated that sesamin possessed antiproliferative property toward cervical cancer cell lines which is probably mediated *via* the induction of p53/PTEN induced apoptosis. By virtue of its selective antiproliferative effect on cervical cancer cells, sesamin has the potential to function as an effective adjuvant agent in cervical cancer chemotherapeutic intervention.

Further evidence on the underlying mechanisms facilitating the anti-cervical cancer property of sesamin was offered in an earlier study by Dou *et al.*[158] It was shown that sesamin inhibited HeLa proliferation and migration. The lignan induced apoptosis in HeLa cells. Compared to the control group, the sesamin treated group of cells showed an increase in Bax, caspase-12, GRP78, GADD153, pIRE1α, p-JNK, LC3I/II and beclin-1 expression levels whereas Bcl-2 expression was suppressed.[158] Additional studies in which the cancer cells were exposed to 3-MA (an inhibitor of autophagy) unveiled two important insights, *viz.* sesamin activated autophagy of HeLa and that when autophagy was inhibited, proliferation of sesamin-treated HeLa cells improved. Based on these outcomes it was inferred that anti-cervical cancer action of sesamin was mediated *via* endoplasmic reticulum stress-induced apoptosis through IRE1α/JNK signaling pathway and that the lignan also triggered autophagic death, underscoring its anticancer properties.[158] Broadly speaking, these results point towards the ability of sesame lignans acting alone or in concert with conventional cancer drugs to improve chemotherapeutic efficacy against cervical cancer.

5.6 Effect of sesame on liver cancer

Liver cancer is a serious global healthcare challenge as the third leading cause of all cancer deaths (0.76 million, 7.8%) in 2022. In men, liver cancer was recorded as the leading cause of death in 24 countries. Worldwide, there was more than 0.86 million newly diagnosed cases of liver cancer in 2022.[4] It is anticipated that with increasing global population, along with rising rate of alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease, the incidence of liver cancer will increase in the years ahead.[4,5] Majority of liver cancer cases were in the form of hepatocellular carcinoma (HCC) (75%), a highly aggressive malignancy, while a minor portion were in the form of cholangiocarcinoma.[165] With overall 5-year survival rates of liver cancer patients estimated to be 17% according to the National Cancer Institute, a multidisciplinary and multi-faceted approach has been proposed for treating HCC.[165] In the past few years, it is becoming apparent that sesame lignans possess beneficial properties with respect to combating HCC.

Sesamol was shown to suppress the proliferation of human hepatocellular carcinoma (HepG2) cell line, *in vitro* and *in vivo*.[159] Treatment of the liver cancer cells with sesamol inhibited colony formation and induced cell cycle arrest at the S-phase. Sesamol treatment also activated both intrinsic and extrinsic apoptotic pathways of cell death in a concentration-dependent manner. In addition, intraperitoneal injection of sesamol (100 mg kg^{-1} or 200 mg per kg per day) into xenograft

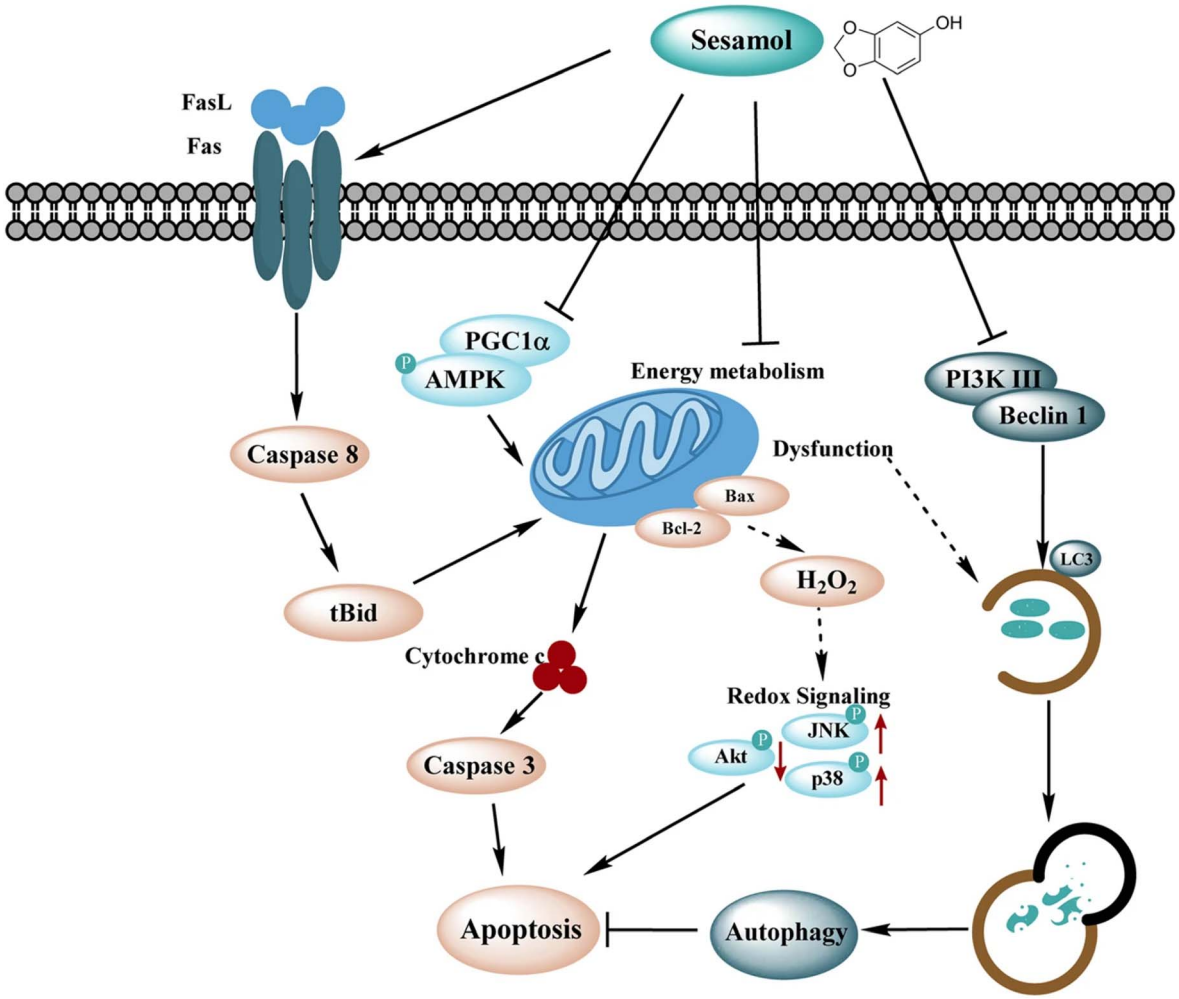

Fig. 5 An illustration of the molecular mechanism underlying sesamol-mediated apoptosis in human liver hepatocellular carcinoma (HepG2) cells, reproduced from ref. 159 with permission from Springer Nature,[159] copyright © 2017.

nude mice model bearing HepG2 tumor caused a marked reduction in tumor growth relative to control mice treated with saline. Attempts to understand the mechanisms underlying the anti-hepatoma action of sesamol revealed that the lignan inhibited mitophagy and autophagy in HepG2 cells by attenuating the PI3K Class III/Belin-1 pathway. In fact, when rapamycin (an autophagy activator) was introduced into the system, the apoptotic effect and mitochondrial-respiratory perturbations induced by sesamol were relieved, highlighting the role of impairing mitochondrial function and suppressing autophagy in the anti-liver cancer effect of sesamol. The putative pathway illustrating the mechanism of sesamol inhibition of HepG2 cells is presented in Fig. 5.[159] An earlier investigation by the same group of authors suggested that sesamol activity also involved nuclear uptake and binding of the lignan to DNA which occurred primarily by groove binding rather than intercalation, subsequently leading to DNA damage and apoptosis of the HepG2 cells.[166] The results indicated the strong chemotherapeutic opportunity inherent in sesamol for liver cancer treatment.

It has also been reported that sesamin-rich sesame extract potentiated the chemopreventive property of hesperidin against diethylnitrosamine (DEN)-induced hepatocarcinogenesis in rats.[167] DEN is a potent hepatocarcinogen present in many sources, such as some processed foods, cigarette smoke, and even some water supplies. Treatment of Wister rats with DEN induced hepatocarcinogenesis as indicated by formation of hepatic GST-P (glutathione *S*-transferase placental form)-positive foci in the livers of the rats.[167] However, when rats were fed for 10 weeks with mixed extract of sesame and orange peel (MSO) containing various amounts of sesame extract (SE) and hesperidin after DEM treatment, it was noted that the size and number of GST-P-positive foci induced by DEN were substantially decreased in the MSO and hesperidin fed rats, but not in the SE fed rats. Remarkably, it was observed that administration of high-dose of MSO produced greater protective effect against the development of preneoplastic lesions in livers vis-à-vis high-dose of hesperidin. MSO and ME contained sesamin as one of the main active ingredients, estimated (by HPLC) to be 23.37 and 20.91 mg of sesamin per g of extract, respectively. It is suspected that the antiproliferative and

proapoptotic effects as well as modulation of hepatic lipogenesis are involved in the ability of sesame extract to accentuate the chemopreventive property of hesperidin against early-stage hepatocarcinogenesis in rats.[167] Actually, in an earlier study, Deng *et al.*[160] showed that sesamin impeded cell proliferation, induced cell cycle arrest at G2/M phase, and activated apoptosis in hepatocellular carcinoma cell line, HepG2. Upon further probing, it was revealed that sesamin modulated its effect *via* suppression of STAT3 (signal transducer and activator of transcription 3) signaling pathway which regulated downstream genes such as p21, p53 as well as cyclin proteins and Bcl-2 group of proteins.[160] Meanwhile, (+)-episesamin was reported to exhibit anti-neoplastic effects in human hepatocellular carcinoma (HCC) cell lines *via* suppression of NF-κB and inhibition of MMP-9. The lignan inhibited the proliferation of HCC cell lines with an IC_{50} value of about 10 μM. When applied to HCC cells in Matrigel invasion assay, (+)-episesamin (10 μM) effectively abrogated the invasion of HCC cell lines *via* a reconstituted basement membrane.[168] In all, preclinical research evidence indicated that sesame lignans possess pharmacological properties that could be beneficial not only in the treatment but also in the prevention of hepatocellular carcinoma.

5.7 Impact of sesame lignans on other cancer types

In addition to the afore-mentioned cancers, sesame lignans have been demonstrated to exert substantive anti-tumor effects in other cancers. This section of the review presents insights on the pharmacological effect of sesame lignans on other cancer types.

Esophageal cancer (EC) remains a serious global health concern, having an incidence of 0.6 million cases (>3% of all cancers) and 0.45 million cases of cancer-related deaths worldwide in 2022.[4] Esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC) are the two most common type of EC, with the latter being more prevalent. Importantly, ESCC is highly aggressive and has a poor prognosis (five-year survival rate <30%). Moreover, the treatment options for ESCC are limited.[169] Thus, there is a strong desire to expand the range of safe and effective therapies for ESCC.

Research has shown that sesamin possesses properties that can be beneficial for the treatment of ESCC. Studies have indicated that expression of the protein, tripartite motif containing 44 (TRIM44), contributes to the prognosis of many tumors including cervical and esophageal cancers. According to Wen *et al.*[161] TRIM44 was substantially upregulated in ESCC cell lines ESCC cell lines (ECA109, EC9706, KYSE150, and TE2) and tissues from animal models of ESCC compared to normal control. Interestingly, treatment with sesamin or suppression of TRIM44 significantly suppressed ESCC cell viability in a concentration-dependent manner.[161] In addition, expression of the target protein of TRIM44, toll-like receptor 4 (TLR4), was substantially suppressed. Likewise, the expression and activity of NF-κB, which is downstream of TLR4 were also inhibited in ESCC following treatment with sesamin. Oral administration of sesamin was shown to reduce ESCC tumor growth in nude mice. This indicated that sesamin has therapeutic potential towards ESCC, and its anti-ESCC effect is likely due to inhibition of the NF-κB signaling pathway.[161] Sesamin was also recently reported to demonstrate substantial inhibitory properties against the proliferation of nasopharyngeal carcinoma (NPC) cell lines (C666-1 and HK-1). The lignan reduced NPC xenografted tumor volume and weight *via* induction of apoptosis as well as enhancement of autophagy, and production of intracellular reactive oxygen species.[162] Similarly, sesamin was found to display anti-metastatic effect (attenuation of migration and invasion) on oral cancer cell lines (HSC-3, FaDu, and Ca9-22) by regulating the expression of MMP-9.[163]

Research has also shown that sesamin could have positive implications in the treatment of lymphomas, which are malignancies of the immune system. In particular, sesamin was reported to suppress murine T-cell lymphoma in both *in vitro* and *in vivo* experiments. The sesame lignan markedly suppressed the proliferation of the murine T-lymphoblast cell line (EL4) as well as the weight and volume of EL4 tumor in mice. This was accomplished *via* promotion of apoptosis as evinced by elevated expression of pro-apoptotic Bax and cleaved caspase-3 protein levels alongside suppression of pro-survival Bcl-2 and cyclin D1 protein levels. Further evidence implicated pyroptosis *via* autophagy as part of the death pathways mediating the anti-lymphoma effect of sesamin.[170] Data also exist pointing to the fact that by suppressing NF-κB signaling pathway and gene products thereof, sesamin was capable of exerting a broad-spectrum antineoplastic effect on a wide variety of tumor cells including multiple myeloma and leukemia as well as cancers of the pancreas, prostate, lung, colon, and breast.[104] Based on the IC_{50} values of sesamin against cancer cell proliferation, tumor sensitivity of the various cell lines was in the order of human lung adenocarcinoma, H1299 (IC_{50}, 40.1 μM) > human chronic myeloid leukemia, KBM-5 (IC_{50}, 42.7 μM) > human leukemia, K562 (IC_{50}, 48.3 μM) > human breast cancer, MDA-MB-231 cells (IC_{50}, 51.1 μM) > multiple myeloma cells, U266 (IC_{50}, 51.7 μM) > human epithelial colon cancer, HCT116 (IC_{50}, 57.2 μM) > human pancreatic cancer, MiaPaCa-2 (IC_{50}, 58.3 μM) > human prostate cancer, DU145 (IC_{50}, 60.2 μM).[104] In a different study involving a panel of 55 cancer cell lines from the National Cancer Institute, it was reported that (−)-sesamin exerted substantial anti-proliferative activity with $\log_{10} IC_{50}$ values that ranged from −8.0 M (CAKI cell line) to 4.0 M (several other cell lines).[171] When the different cancer cell lines were assessed based on their IC_{50} values, it was deduced that leukemia and melanoma cells were the most sensitive, while brain tumor and ovarian cancer cell lines were the most resistant to (−)-sesamin, that is in terms of sensitivity leukemia > melanoma > colon cancer > breast cancer > prostate cancer > lung cancer > lung cancer > ovarian cancer > brain cancer. In light of tumor cell drug resistance, the role of (−)-sesamin was also examined vis-à-vis multidrug transporter, P-glycoprotein (*MDR1*/*ABCB1*) *in vitro*. The results demonstrated that P-glycoprotein did not confer resistance to these cancer cells against (−)-sesamin as there was no correlation between the expression and function of the P-glycoprotein with the IC_{50} value for (−)-sesamin in the panel of tumor cells.[171] Meanwhile, in another investigation it was shown that sesamin could improve the accumulation or

uptake of broad-spectrum chemotherapeutic agent, doxorubicin in cancer cells by suppressing the efflux function of P-glycoprotein.[172] Together, these findings lay strong credence to the notion of beneficial chemotherapeutic roles of sesame lignans that could involve obviating multidrug resistance or suppression of the drug efflux function of P-glycoprotein in cancer. In this context, therapeutic efficacy of standard drugs such as doxorubicin could be enhanced in combination with sesame lignans, such as sesamin.[171]

There has also been reports on sesamol possessing selective anticancer properties against skin cancers. Data from *in vitro* studies indicated that sesamol induced significant inhibition of human melanoma cell lines, SK-MEL-2 proliferation by activating late-stage apoptotic and necrotic cell death.[173] Sesamol displayed an IC_{50} value of 1.89 mM against SK-MEL-2 cells viability while having very minimal effect on the viability of normal Vero cells. The effect of sesamol was also ascertained on melanoma spheroid cells, given that they are a better representative of cancer cell physiological structure. Upon treatment of spheroid with sesamol, there was significant reduction in spheroid size compared to untreated control, and the reduction was concentration-dependent.[173] The anti-skin cancer effect of sesamol was further supported by evidence from a previous study where the authors also noted that the sesame lignan induced selective antiproliferative effect against SK-MEL-2 cells by inducing apoptosis aided by L-type amino acid transporter 1 (LAT1)-mediated cell uptake of the lignan.[174] Similar findings were also recorded in *in vivo* studies.[175] 7,12-Dimethylbenz[*a*]anthracene (DMBA) is a potent carcinogen known to induce skin tumors in laboratory animals. In a DMBA-induced mice model of skin cancer, it was observed that administration of sesamol (free and encapsulated) impeded the development and promotion of skin tumors as evidenced in the decreased tumor burden relative to control. This was accompanied by increase in oxidation resistance (higher level of antioxidants and decreased lipid peroxidation) as well as induction of apoptosis in tumor cells (increased expression of Bax and downregulation of Bcl-2 expression levels) upon sesamol administration. These observations indicated that sesamol could be valuable in the development of skin cancer chemotherapeutic agents.[175]

6. Prospects and challenges

There is great potential for the application of sesame lignans in different aspects of cancer prevention and/or treatment. This is especially the case with the major sesame lignans, *viz.* sesamin, sesamol, and sesamolin, for which there is currently an abundance of preclinical evidence. Sesame lignans could be applied in the development of chemotherapeutic agents, as adjuvants, or as part of combination therapy with traditional chemotherapeutic agents. In the latter case, sesame lignans could augment, potentiate the chemotherapeutic efficacy and could also mitigate the adverse side-effects of the conventional agents. Another area where sesame lignan could be potentially useful is in the development of functional food products, nutraceutical agents or dietary supplements targeted towards cancer prevention or as part of a dietary intervention strategy to augment chemotherapy. There is also an avenue for the formulation and application of anti-cancer cosmeceuticals based on sesame lignans for topical application towards the amelioration of skin cancer and skin injury.[85,176]

It is germane to underscore that while there has been much progress towards unraveling the anticancer properties of sesame lignans, there are still some limitations in taking full delivery of its potential health benefits in clinical settings. A glaring shortcoming in this regard is the paucity and absence of evidence from human clinical trials. It is therefore important for future research to focus on investigating the validity of the anticancer properties of sesame lignans in robust double-blinded and placebo-controlled human clinical studies. Furthermore, besides the major sesame lignans, there has been less emphasis on the minor lignans and even the metabolites produced following oral intake or injection. These metabolites may actually be the bioactive agents responsible for some of the biological and pharmacological properties of the lignans. Thus, there is need for detailed studies on the bioavailability, pharmacodynamic and pharmacokinetic properties as well as optimized dosage forms of the lignans and metabolites in *in vivo* models.

In additional, there is an opportunity for studies aimed at improving the therapeutic efficacy of sesame lignan. One area where there had been very promising results in terms of improved efficacy and reduced toxicity is in the application of nanocarriers for delivery of sesame lignans.[101,129,176] Future studies centered on improving the delivery and anticancer effectiveness of sesame lignan by exploring their formulation in novel drug delivery systems and treatment modalities will be useful in delivering optimal benefits to patients in clinical practice.

7. Conclusions

The preponderance of *in vitro* and *in vivo* evidence makes a strong case in favor of the anticancer properties of sesame lignans. Different sesame lignans have been shown to exert anticancer properties against a wide variety of tumors by targeting different molecular pathways. Some of the lignans have been found to have chemopreventive attributes while others have shown chemotherapeutic or sensitizing effects for improved conventional drug-based chemotherapy. In fact, sesame lignans have been found to improve the chemotherapeutic efficacy and safety profile of a number of conventional chemotherapeutic agents, opening avenues for their use as part of combination therapies against various cancers with challenging treatment profiles. The paucity of human clinical data as it pertains to anticancer effect of sesame lignans presents a fantastic opportunity for future clinical studies. In all, sesame lignans hold great prospect as potential anticancer chemotherapeutic agents as well as structural chemical scaffolds for the development of future chemotherapeutic candidates.

Author contributions

Min He: conceptualization, methodology, investigation, resources, visualization, validation, writing – original draft,

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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