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REVIEW

Antioxidant lignans sesamin and sesamolin in sesame (*Sesamum indicum* L.): A comprehensive review and future prospects



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Abstract

Sesame (*Sesamum indicum* L.) is a significantly lucrative cash crop for millions of small-holder farmers. Its seeds are an important source of a highly appreciated vegetable oil globally and two clinically essential antioxidant lignans, sesamin and sesamolin. Accordingly, many countries import millions of tons of sesame seed every year. The demand for lignan-rich sesame seeds has been increasing in recent years due to the continuous discovery of several pharmacological attributes of sesamin and sesamolin. To meet this demand, the sesame breeder's primary objective is to release sesame cultivars that are enriched in oil and lignans. Thus, it is necessary to summarize the information related to the sesamin and sesamolin contents in sesame in order to promote the joint efforts of specialized research teams on this important oilseed crop. In this article, we present the current knowledge on the sesamin and sesamolin contents in *S. indicum* L. with respect to the updated biosynthesis pathway, associated markers, governing loci, available variability in sesame germplasm, the *in planta* potential roles of these compounds in sesame, and the newly discovered pharmacological attributes. In addition, we propose and discuss some required studies that might facilitate genomics-assisted breeding of high lignan content sesame varieties.

Keywords: *Sesamum indicum*, lignan biosynthesis, antioxidants, molecular breeding, sesamin and sesamolin

1. Introduction

Sesame (*Sesamum indicum* L.) is regarded as the “queen of oilseed crops” owing to its nutritional and health benefits both for humans and animals. Its seed contains 27.89 to 62.7% oil, 16.72 to 27.79% protein, 13.5% carbohydrates, minerals, and various antioxidants (Uzun *et al.* 2008; Li C *et al.* 2014; Pathak *et al.* 2014; Dar *et al.* 2015). The main antioxidant components in sesame seeds in terms of value

Received 19 July, 2021 Accepted 13 September, 2021
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doi: 10.1016/j.jia.2022.08.097

and level are the lignans, followed by flavonoids, phenolics, tocopherol, and melatonin (Table 1) (Shahidi *et al.* 2006; Williamson *et al.* 2008; Wang *et al.* 2012, 2018; Zhou *et al.* 2016; Niu *et al.* 2018). Sesame lignans are clinically important nutraceuticals that exhibit several pharmacological properties (Majdalawieh *et al.* 2017, 2020; Majdalawieh and Mansour 2019). Lignans are plant secondary metabolites that are chemically classified as phenyl propane dimers (Fig. 1) (Dar and Arumugam 2013). Two classes of lignans, the oil-soluble and glycosylated water-soluble lignans which include a total of 17 compounds, have been isolated from sesame seeds (Fukuda 1985; Dar and Arumugam 2013). Among sesame lignans, sesamin and sesamol are the primary compounds that have gained the attention of pharmacologists and clinicians due to their health-promoting properties against lifestyle-related diseases (Dar and Arumugam 2013; Majdalawieh *et al.* 2017, 2020; Abe-Kanoh

et al. 2019). Sesamol and sesamin have been detected in more than 40 plant species (Table 2). However, due to the low amounts of sesamin in other plants (Table 3) and the unclear issue of identical conformations, sesame seeds remain the principal source of these two clinically priceless antioxidant lignans.

With regard to their tremendous health benefits, interest in sesame products is increasing continuously, especially the demand for lignan-rich seeds (Dar *et al.* 2015; Kim A Y *et al.* 2020). In Korea, the daily intake of total lignans from sesame seeds and oil in males and females is approximately 18.39 and 13.26 mg/person/day, respectively (Kim A Y *et al.* 2020). Owing to their potent antioxidant ability and solubility features, sesamin and sesamol are responsible for sesame seed and oil resistance to oxidation and rancidity. Accordingly, sesame seed flour and oil are used to improve the oxidation stability and the quality of various products, including chia oil, sunflower oil, corn snacks, soybean oil, halva, and mayonnaise (Suja *et al.* 2004; Nasirullah and Latha 2009; Elleuch *et al.* 2014; Li Y *et al.* 2014; Hashempour-Baltork *et al.* 2018; Hussain *et al.* 2018; Karshenas *et al.* 2018; Bord *et al.* 2019; El-roby *et al.* 2020). In consideration of all these aspects, the contents of both sesamin and sesamol are a critical factor in evaluating sesame seed quality (Kim *et al.* 2004). Sesame is cultivated only once a year, and its production is influenced by biotic and abiotic stresses (Kole 2019). Therefore, creating environmentally-stable sesame varieties containing high oil and lignans is the main purpose of sesame breeding.

Tiwari *et al.* (2011) reported the limitations of the conventional breeding approach in sesame, and noted that only genomic assisted-breeding techniques could

Table 1 Variations in the major antioxidant components in sesame seed

Component	Quantity	Reference
Total sesamin and sesamol	0.49–18.01 mg g ⁻¹	Wang <i>et al.</i> (2012); Ajit <i>et al.</i> (2019)
Sesamol	1.2 mg g ⁻¹	Pathak <i>et al.</i> (2014)
Sesaminol triglucoside	0.36–15.6 mg g ⁻¹	Moazzami <i>et al.</i> (2006)
Sesaminol diglucoside	0–4.93 mg g ⁻¹	Moazzami <i>et al.</i> (2006)
Tocopherol	50.9–211 µg g ⁻¹	Rangkadilok <i>et al.</i> (2010)
Melatonin	1.32 mg kg ⁻¹	Niu <i>et al.</i> (2018)
Total phenolics	3.56–7.86 g kg ⁻¹	Zhou <i>et al.</i> (2016); Lin <i>et al.</i> (2017)
Total flavonoids	5.8–13.55 g kg ⁻¹	Zhou <i>et al.</i> (2016); Lin <i>et al.</i> (2017)

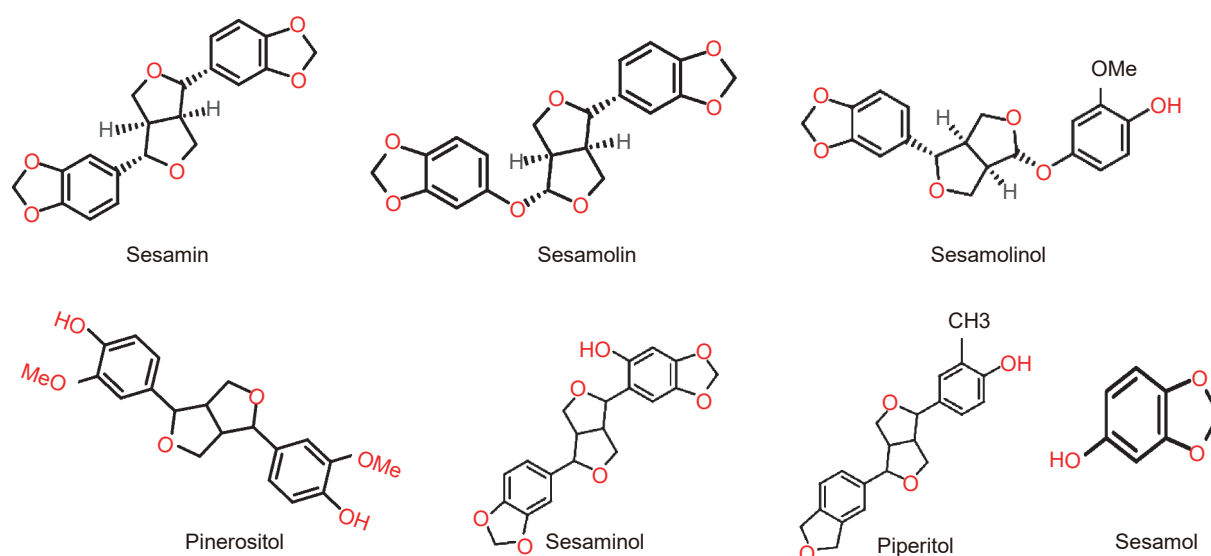


Fig. 1 Chemical structures of some lignans.

Table 2 Plants reported to content sesamin and sesamol

Family	Species	Organ	Sesamin and/or sesamol	Reference
Bignoniaceae	<i>Paulownia tomentosa</i> Staud.	Stem	Sesamin and sesamol	Bedigian et al. (1985)
Bignoniaceae	<i>Phyllanthus comorensis</i>	Root and stem	Sesamin	Bedigian et al. (1985)
Acanthaceae	<i>Justicia simplex</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Lamiaceae	<i>Hyptis tomentosa</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Anacyclus pyrethrum</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Artemisia absinthium</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Artemisia gorgonum</i>	Leaves	Sesamin	Martins et al. (2014)
Asteraceae	<i>Chrysanthemum cinerariaefolium</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Chrysanthemum frutescens</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Chrysanthemum indicum</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Diotis maritima</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Eupatorium ageratina</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Eupatorium ritonia</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Eupatorium fleischmannia</i>	Leaves	Sesamin	Bedigian et al. (1985)
Asteraceae	<i>Otanthus maritimus</i>	Leaves	Sesamin	Bedigian et al. (1985)
Scrophulariaceae	<i>Aptosimum spinescens</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Verbenaceae	<i>Gmelina arborea</i> Roxb.	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Araliaceae	<i>Acanthopanax senticosus</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Araliaceae	<i>Acanthopanax sessiliflorum</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Araliaceae	<i>Eleutherococcus senticosus</i>	Root and bark	Sesamin	Jin et al. (2020)
Araliaceae	<i>Eleutherococcus divaricatus</i>	Root	Sesamin	Zatuski et al. (2015)
Aristolochiaceae	<i>Asarum sieboldii</i>	Leaves	Sesamin	Bedigian et al. (1985)
Aristolochiaceae	<i>Aristolochia cymbifera</i>	Leaves	Sesamin	Sartorelli et al. (2010)
Betulaceae	<i>Alnus glutinosa</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Chenopodiaceae	<i>Salicornia europaea</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Cupressaceae	<i>Austrocedrus chilensis</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Rutaceae	<i>Evodia micrococca</i>	Leaves	Sesamin	Bedigian et al. (1985)
Rutaceae	<i>Fagara xanthoxyloides</i>	Bark	Sesamin	Bedigian et al. (1985)
Rutaceae	<i>Fagara tessmannii</i>	Bark	Sesamin	Mbaze et al. (2007)
Rutaceae	<i>Fagara heitzii</i>	Bark	Sesamin	Mbaze et al. (2009); Moussavi et al. (2015)
Rutaceae	<i>Micromelum minutum</i>	Bark	Sesamin	Kassim et al. (2018)
Rutaceae	<i>Melicope glabra</i>	Bark	Sesamin	Kartinee et al. (2013)
Rutaceae	<i>Spiranthera odoratissima</i>	Leaves	Sesamin	Albernaz et al. (2012)
Rutaceae	<i>Flindersia pubescens</i>	Leaves	Sesamin	Bedigian et al. (1985)
Rutaceae	<i>Zanthoxylum naranjillo</i>	Leaves	Sesamin	Henrique et al. (2016)
Rutaceae	<i>Zanthoxylum tingoassuiba</i>	Leaves	Sesamin	Henrique et al. (2016)
Rutaceae	<i>Zanthoxylum armatum</i>	Root and stem	Sesamin	Guo et al. (2015)
Rutaceae	<i>Zanthoxylum paracanthum</i>	Root bark and stem	Sesamin	Kaigongi et al. (2020)
Rutaceae	<i>Zanthoxylum piperitum</i>	Bark	Sesamin	Kim and Ahn (2017)
Rutaceae	<i>Zanthoxylum nitidum</i>	Root	Sesamin	Lu et al. (2019)
Rutaceae	<i>Zanthoxylum flavum</i>	Stems	Sesamin	Mohamed et al. (2020)
Rutaceae	<i>Zanthoxylum alatum</i> Roxb.	Stem bark	Sesamin	Mukhija et al. (2014)
Rutaceae	<i>Zanthoxylum bungeanum</i>	Leaves	Sesamin	Zhang et al. (2014)
Ginkgoaceae	<i>Ginkgo biloba</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Lauraceae	<i>Machilus glaucescens</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Lauraceae	<i>Ocotea usambarensis</i>	Leaves and bark	Sesamin and sesamol	Bedigian et al. (1985)
Lauraceae	<i>Aiouea trinervis</i> Meisn.	Leaves	Sesamin	Guterres et al. (2014)
Magnoliaceae	<i>Talauma hodgsonii</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Magnoliaceae	<i>Magnolia</i> spp	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Magnoliaceae	<i>Liriodendron tulipifera</i>	Leaves and twigs	Sesamin	Jeong et al. (2015)
Pinaceae	<i>Picea abies</i>	Leaves	Sesamin and sesamol	Bedigian et al. (1985)
Piperaceae	<i>Macropiper excelsum</i>	Leaves	Sesamin	Bedigian et al. (1985)
Piperaceae	<i>Piper sarmentosum</i>	Leaves	Sesamin	Pan et al. (2011)
Pedaliaceae	<i>Sesamum indicum</i>	Seed and leaves	Sesamin and sesamol	Bedigian et al. (1985); Shittu et al. (2007, 2008); Pathak et al. (2015)
Pedaliaceae	<i>Sesamum radiatum</i>	Seed and leaves	Sesamin and sesamol	Bedigian et al. (1985); Shittu et al. (2007, 2008); Pathak et al. (2015)
Pedaliaceae	<i>Sesamum mulayanum</i>	Seed	Sesamin and sesamol	Bedigian et al. (1985); Shittu et al. (2007, 2008); Pathak et al. (2015)

(Continued on next page)

Table 2 (Continued from preceding page)

Family	Species	Organ	Sesamin and/or sesamolins	Reference
Pedaliaceae	<i>Sesamum malabaricum</i>	Seed	Sesamin and sesamolins	Bedigian <i>et al.</i> (1985); Shittu <i>et al.</i> (2007, 2008); Pathak <i>et al.</i> (2015)
Pedaliaceae	<i>Sesamum laciniatum</i>	Seed	Sesamin and sesamolins	Bedigian <i>et al.</i> (1985); Shittu <i>et al.</i> (2007, 2008); Pathak <i>et al.</i> (2015)
Pedaliaceae	<i>Sesamum alatum</i>	Seed	Sesamin and sesamolins	Bedigian <i>et al.</i> (1985); Shittu <i>et al.</i> (2007, 2008); Pathak <i>et al.</i> (2015)
Pedaliaceae	<i>Sesamum angustifolium</i>	Seed	Sesamin and sesamolins	Bedigian <i>et al.</i> (1985); Shittu <i>et al.</i> (2007, 2008); Pathak <i>et al.</i> (2015)
Pedaliaceae	<i>Sesamum angolense</i>	Seed	Sesamin and sesamolins	Bedigian <i>et al.</i> (1985); Shittu <i>et al.</i> (2007, 2008); Pathak <i>et al.</i> (2015)
Pedaliaceae	<i>Sesamum calycinum</i>	Seed	Sesamin and sesamolins	Bedigian <i>et al.</i> (1985); Shittu <i>et al.</i> (2007, 2008); Pathak <i>et al.</i> (2015)
Saururaceae	<i>Anemopsis californica</i>	Root and leaves	Sesamin	Bussey III <i>et al.</i> (2014)
Fagaceae	<i>Quercus frainetto</i> Ten.	Wood galls	Sesamin	Cetera <i>et al.</i> (2018)
Euphorbiaceae	<i>Vernicia fordii</i>	Seed testa	Sesamin	Chen <i>et al.</i> (2020)
Euphorbiaceae	<i>Jatropha curcas</i>	Seed	Sesamin	Li X <i>et al.</i> (2014)
Zygophyllaceae	<i>Larrea tridentata</i>	Leaves	Sesamin	Garcia <i>et al.</i> (2018)
Rubiaceae	<i>Morinda citrifolia</i>	Fruits	Sesamin	Liu W <i>et al.</i> (2018)
Sterculiaceae	<i>Glossostemon bruguieri</i>	Root	Sesamin	Meselhy (2003)
Oleaceae	<i>Ligustrum japonicum</i>	Fruits	Sesamin	Ngo <i>et al.</i> (2017)
Menispermaceae	<i>Triclisia sacleuxii</i>	Aerial parts	Sesamin	Samita <i>et al.</i> (2016)

Table 3 Variations of sesamin and sesamolins in some species

Species	Plant material	Sesamin	Sesamolins	Reference
<i>Sesamum indicum</i>	Seed	0.05–11.05 mg g ⁻¹	0–10 mg g ⁻¹	Yasumoto and Katsuta (2006); Rangkadilok <i>et al.</i> (2010); Wang <i>et al.</i> (2012)
<i>S. malabaricum</i>	Seed	3.21–5.29 mg g ⁻¹	0.89 mg g ⁻¹	Akhila and Suhara Beevy (2015); Pathak <i>et al.</i> (2015)
<i>S. mulayanum</i>	Seed	2.04 mg g ⁻¹	0.37 mg g ⁻¹	Pathak <i>et al.</i> (2015)
<i>S. radiatum</i>	Seed	0.33–6.52 mg g ⁻¹	1.37 mg g ⁻¹	Akhila and Suhara Beevy (2015); Pathak <i>et al.</i> (2015)
<i>S. laciniatum</i>	Seed	0.28–2.05 mg g ⁻¹	0.97 mg g ⁻¹	Akhila and Suhara Beevy (2015); Pathak <i>et al.</i> (2015)
<i>S. alatum</i>	Seed	0–0.14 mg g ⁻¹	0.38 mg g ⁻¹	Akhila and Suhara Beevy (2015); Pathak <i>et al.</i> (2015)
<i>S. prostratum</i>	Seed	2.03 mg g ⁻¹	ND	Akhila and Suhara Beevy (2015)
<i>Zanthoxylum naranjillo</i>	Leave	8.69 µg mL ⁻¹	ND	Henrique <i>et al.</i> (2016)
<i>Z. tingoassuiba</i>	Leave	15.11 µg mL ⁻¹	ND	Henrique <i>et al.</i> (2016)
<i>Eleutherococcus senticosus</i>	Root	0.272 µg mg ⁻¹	ND	Jin <i>et al.</i> (2020)
<i>E. senticosus</i>	Bark	0.882 µg mg ⁻¹	ND	Jin <i>et al.</i> (2020)

ND, not determined.

be useful for the genetic improvement of sesame seed quality. Obtaining the information related to the lignan contents in sesame is an essential prerequisite for any breeder interested in meeting the current sesame breeding objectives. In this review, we present the current state of knowledge on sesamin and sesamolins in *S. indicum* L. Moreover, we propose and discuss some studies that are needed to pave the way for genomics-assisted breeding of sesame varieties with high lignan content.

2. Sesamin and sesamolins roles in plants and pharmacological attributes

2.1. Sesamin and sesamolins in planta functions

The potential biological roles of sesamin and sesamolins

related to human and animal health have been widely studied. Comparatively, their relevant biological functions in the sesame plant remain elusive. According to Bedigian *et al.* (1985), sesamin and sesamolins might be involved in seed maturation, germination, and seed protection during storage. They are associated with seed germination since their amounts in seeds decrease significantly during germination (Ha *et al.* 2017). In a recent study, Tera *et al.* (2019) discovered steroleosin B, a sesamin-binding protein, and characterized its roles in transgenic *Arabidopsis thaliana* plants. They found that sesamin in the presence of steroleosin B influenced *Arabidopsis* plant development by suppressing leaf expansion and root elongation. The studies by Miyake *et al.* (2005) and Radhakrishnan *et al.* (2013) showed that sesamin and sesamolins are involved in the plant's defense against diseases by inhibiting reactive

oxygen species (ROS) production and staving off oxidative damage in infected sesame plants. However, the molecular mechanisms remain unclear. Further experiments are needed to clarify the biological functions of sesamin and sesamol in during sesame plant development, and to analyze their potential antioxidant effects during osmotic stress.

2.2. Pharmacological attributes of sesamin and sesamol in

Sesamin and sesamol possess various pharmacological proprieties, such as antioxidative, anti-cancerogenic, anti-inflammatory, anti-proliferative, anti-hypertensive, and anti-melanogenesis effects. Majdalawieh *et al.* (2017, 2020), Wu *et al.* (2019), and Dar *et al.* (2013) have reviewed some pharmacological properties of sesamin and sesamol. These reviews reported the ability of sesamin to reduce oxidative stress, proliferation, inflammation, angiogenesis, and metastasis, and to induce apoptosis and autophagy in defective human and animal cells. They discussed the anti-hyperlipidemic properties of sesamin and sesamol. Moreover, they outlined the capacity of sesamin to inhibit fatty acid and cholesterol synthesis and absorption, cause fatty acid oxidation, maintain macrophage cholesterol homeostasis, and control circulating serum and liver lipid levels. In a recent study, Abe-Kanoh *et al.* (2019) have confirmed the anti-inflammatory effects of sesamin.

In addition to the above-reported functions, sesamin and sesamol have been associated with several other health-promoting abilities, including anti-hypertensive and anti-melanogenesis effects (Srisayam *et al.* 2017), prevention of brain damage (Cheng *et al.* 2006), improvement of cardiac

function (Fan *et al.* 2017; Thuy *et al.* 2017), auditory-protective effects (Kim Y H *et al.* 2020), suppression of aging phenotypes (Le *et al.* 2019), alleviation of blood-brain barrier disruption (Liu *et al.* 2017), anti-osteonecrosis and anti-osteoporosis effects (Deng *et al.* 2018; Ma *et al.* 2019), enhancement of habit learning memory deficits (Zhao *et al.* 2016), reduction of amyloid- β toxicity (Keowkase *et al.* 2018), anti-collagen and elastin fiber degradation (Kugo *et al.* 2019), influence on voltage-gated Na⁺ and K⁺ currents (Kuo *et al.* 2020), promotion of natural killer cell cytotoxicity and migration activity (Lee 2020), protection against lesion-induced degeneration (Li and Lv 2020), extension of lifespan (Nakatani *et al.* 2018), promotion of cartilage repair (Narakornsak *et al.* 2017) and anti-depression and memory loss improvement (Zhao *et al.* 2019).

3. Variability of sesamin and sesamol in sesame

3.1. Variations in sesame seeds

Information on the diversity of sesame cultivars regarding their sesamin and sesamol contents is a prerequisite for selecting and breeding lignan-rich sesame varieties. Accordingly, sesame cultivars have been collected worldwide, and the variability in sesamin and sesamol contents has been checked in many germplasms that are conserved in China, India, Korea, Japan, USA, and Thailand (Table 4). Sesame seed total sesamin and sesamol contents vary from one germplasm to another. The sesamin and sesamol contents in sesame seeds broadly range from 0.05 to 11.05 mg g⁻¹ and 0 to 10 mg g⁻¹, respectively

Table 4 Variations in sesamin and sesamol contents in sesame seeds

Population	Germplasm location	Method	Sesamin (mg g ⁻¹)	Sesamol (mg g ⁻¹)	Reference
650 accessions	Japan	HPLC	0.1–10	0–10	Yasumoto and Katsuta (2006)
403 accessions	Korea	HPLC/UV	0.38–5.12	0.46–4.41	Kim <i>et al.</i> (2006)
14 accessions	Europe	HPLC	1.67–8.04	0.48–2.79	Moazzami <i>et al.</i> (2007)
11 accessions	USA	HPLC-PAD	0.67–6.35	ND	Williamson <i>et al.</i> (2008)
58 lines	Thailand	HPLC	0.05–7.23	0–2.25	Rangkadilok <i>et al.</i> (2010)
215 lines	China	HPLC	0.88–11.05	0.93–6.96	Wang <i>et al.</i> (2012)
209 accessions	China	HPLC	1.32–5.00	ND	Mei <i>et al.</i> (2013)
20 accessions	Korea	HPLC	0.84–5.53	1.13–4.29	Kim J H <i>et al.</i> (2014)
143 accessions	Korea	HPLC	0.78–7.00	0.23–6.98	Kim S U <i>et al.</i> (2014)
15 accessions	India	HPLC	2.03–6.45	ND	Muthulakshmi <i>et al.</i> (2017)
224 RILs, F9	China	NIR	1.7–5.1	ND	Wu <i>et al.</i> (2017)
100 accessions	China	UV/VIS spectroscopy	1.11–9.41	0.2–3.35	Kai <i>et al.</i> (2017)
22 accessions	China	HPLC	2.16–7.37	1.09–3.73	Zhu <i>et al.</i> (2018)
43 accessions	India	HPLC	2.10–5.98	1.52–3.76	Dar <i>et al.</i> (2019)
40 accessions	India	HPLC	0.08–2.58	0.28–2.52	Ajit <i>et al.</i> (2019)
18 accessions	Greece	HPLC	1.13–2.83	0.59–1.48	Mikropoulou <i>et al.</i> (2019)
548 RILs, F8	China	HPLC	0.33–7.52	0.36–2.70	Xu <i>et al.</i> (2021)

ND, not determined.

(Yasumoto and Katsuta 2006; Rangkadilok *et al.* 2010; Wang *et al.* 2012; Ajit *et al.* 2019). In a core collection conserved in Korea, which included accessions from Russia, Japan, Turkey, Nepal, Afghanistan, Iran, Mexico, Pakistan, Korea, India, China, USA, Egypt, and Vietnam, the total sesamin and sesamol contents varied from 2.33 to 12.17 mg g⁻¹ with an average of 8.18 mg g⁻¹ (Kim S U *et al.* 2014). In China and India, the seed sesamin content mainly varied from 0.88 to 11.05 and 0.08 to 6.45 mg g⁻¹, respectively (Wang *et al.* 2012; Muthulakshmi *et al.* 2017; Ajit *et al.* 2019). In the same countries, the sesamol content in sesame seeds ranged from 0.2 to 6.98 mg g⁻¹ and 0.28 to 3.76 mg g⁻¹, respectively (Wang *et al.* 2012; Kai *et al.* 2017; Ajit *et al.* 2019; Dar *et al.* 2019). All the studies listed in Table 4 reported a significant positive correlation between the contents of sesamin and sesamol in sesame seeds. In addition to the seeds, sesamin has been detected in sesame leaves in a range of 0.5 to 2.6 µg g⁻¹ of dry weight (Hata *et al.* 2010). However, no more information is currently available on the variability of lignan contents in sesame leaves.

3.2. Influences of various factors

Reports on the variability of the sesamin and sesamol contents in sesame seeds indicated that these lignans are affected by genetics, cultivars, origin, agronomic conditions, environmental stresses, plant architecture, and other seed traits (Yasumoto *et al.* 2005; Kumazaki *et al.* 2009; Wang *et al.* 2012; Kim S U *et al.* 2014; Dar *et al.* 2019).

Seed coat color and seed biochemistry Seed coat color is a critical agronomic trait in sesame that significantly affects the phytochemical contents of seeds (Wang *et al.* 2012; Mei *et al.* 2013; Kim J H *et al.* 2014; Li C *et al.* 2014; Dossa *et al.* 2018b; Dar *et al.* 2019). Studies conducted on germplasms containing a higher number of accessions with different colors (white, yellow, brown, and black) revealed that white sesame seeds are generally richer in lignans than black, brown, and yellow sesame seeds (Wang *et al.* 2012; Kim S U *et al.* 2014; Kancharla and Arumugam 2020). In contrast, the studies of Shi *et al.* (2017), Dar *et al.* (2019), Muthulakshmi *et al.* (2017) and Ajit *et al.* (2019) on collections containing 6, 4, 2, and 6 accessions with a black seed coat, respectively, found that black sesame seeds were the richest in sesamin and sesamol. Some of the individual black and brown sesame lines exhibited higher contents of sesamin and sesamol. Among the 215 accessions evaluated by Wang *et al.* (2012), ZZM3495, a line with a brown seed coat, had the highest sesamin and sesamol contents of 11.05 and 6.96 mg g⁻¹, respectively. The sample 16NF378-1 (black seeds) had the highest contents of sesamin and sesamol (9.41 and 3.35 mg g⁻¹, respectively) among the cultivars tested by Kai *et al.* (2017).

Most of the precursors of sesamin and sesamol in the biosynthetic pathway are also involved in the biosynthesis of other seed components (Fig. 2). Therefore, there is a need to understand the correlations that exist between the contents of these lignans and other seed components for targeting improvements in sesame seed quality. Dar *et al.* (2019) reported a significant negative correlation between the sesamol content and the contents of sesamin and sesamol. They also found positive correlations between sesamol and oleic acid, stearic acid and sesamin, and a negative correlation between the sesamol and linoleic acid contents. Mei *et al.* (2013) and Wu *et al.* (2017) observed that the sesamin and protein contents were negatively correlated. Interestingly, the oil content in sesame seed was positively correlated with the content of sesamol, supporting the possibility of breeding high oil and high lignan sesame varieties in accordance with the sesame seed market demands (Mei *et al.* 2013; Wu *et al.* 2017; Kancharla and Arumugam 2020).

Plant architecture and growth conditions As mentioned above, in addition to genetics, the growing conditions and plant architecture affect the contents of sesamin and sesamol through the differences in seed weight (Yasumoto *et al.* 2005; Kumazaki *et al.* 2009). Sesamin and sesamol contents increase proportionally with the seed dry weight. Yasumoto *et al.* (2005) observed a variation in the sesamin and sesamol contents among seeds at different positions in the capsules. They suggested that for improving the selection of lignan-rich sesame varieties, it is necessary to sample seeds from capsules that flowered and were harvested on the same date as the variability analysis. The study of Kumazaki *et al.* (2009) revealed that in normal growing conditions, seeds from higher capsule positions on the stem are richer in sesamin and sesamol than those from capsules at lower positions. In addition, they observed that in contrast to a high air temperature (30/23°C) during ripening, a low air temperature (22/15°C) increased the amounts of sesamin and sesamol in seeds. With regard to the day length and soil temperature, they found no impact of high soil temperature or a short-day length (10 h) on the contents of these lignans.

To gain insight into the effect of the day length (light) on the content of lignans in sesame, Hata *et al.* (2012, 2013) performed several types of experiments. They showed that a continuous light (24 h) photoperiod increased sesame leaf sesamin levels to the 1/200th of that in seeds, while in normal agronomic conditions, the leaf sesamin content was the 1/5000th or less compared to that in seeds (Hata *et al.* 2010). Concerning the light type, they found that blue LED light increased the leaf sesamin content by 2.0- and 4.5-fold compared to white fluorescent and red LED light, respectively (Hata *et al.* 2013). However, the blue LED light caused unfavorable morphological changes and a reduction in growth.

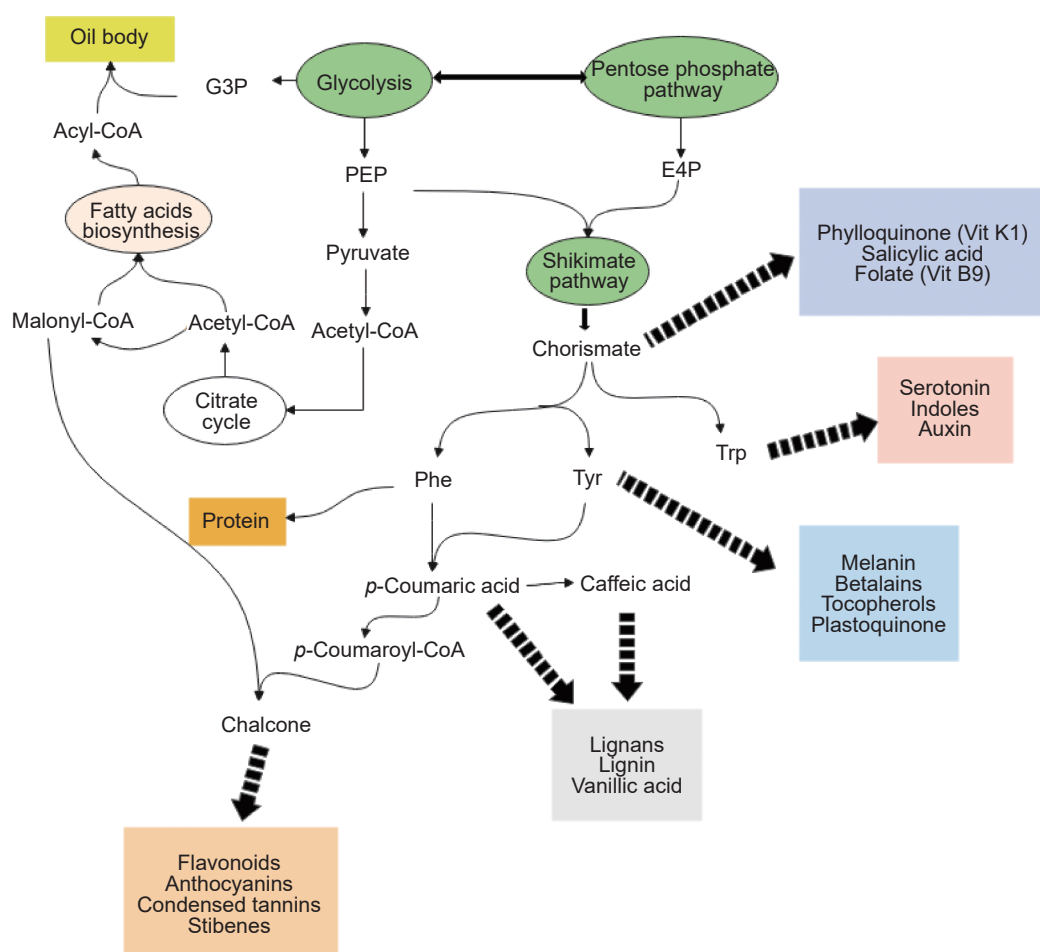


Fig. 2 Complexity of the metabolic pathways in *Sesamum indicum* L. PEP, phosphoenol pyruvate; E4P, erythrose-4-phosphate; G3P, glyceraldehyde-3-phosphate; Phe, phenylalanine; Tyr, tyrosine; Trp, tryptophan.

Abiotic stresses Drought, waterlogging, and salt stresses are the common adverse abiotic stresses that affect sesame yield and quality traits. The sesame plant responds to these stresses have been well studied at the genomic level (Wang *et al.* 2016, 2020; Mmadi *et al.* 2017; Dossa *et al.* 2018a, 2019a; Zhang *et al.* 2019). However, information related to the effects of these stresses on the sesamin and sesamolin contents is very limited, and only two contradictory reports on the impact of drought stress on the variations of these lignans are available. Kermani *et al.* (2019) examined the influence of drought stress on the contents of sesamin and sesamolin in 10 sesame cultivars. They found that the sesamin content decreased while the sesamolin content increased under drought stress. In contrast, Dossa *et al.* (2017b) reported a significant increase of sesamin in the seeds of five sesame varieties subjected to drought stress. Regarding the content of sesamolin, they found no significant difference between the stressed and unstressed seeds. Therefore, experiments involving large germplasm

collections are needed to elucidate the influences of these stresses on lignan biosynthesis in sesame, and to identify the environmentally stable lignan-rich sesame varieties.

Biotic stresses In contrast to abiotic stresses, biotic stresses were reported to have a clearly positive influence on the lignan content in sesame (Radhakrishnan *et al.* 2013, 2014; Horii and Ishii 2014). Radhakrishnan *et al.* (2013, 2014) found that infection by fungi *Penicillium* spp. (RDA01, NICS01, and DFC01) and *Fusarium* sp. increased the contents of sesamin, sesamolin, and amino acids in sesame, although the two species showed an antagonistic activity. Horii and Ishii (2014) discovered that arbuscular mycorrhizal fungi (AMF) and their partner bacteria could promote the growth and development of the sesame plant, and sesamin accumulation in seeds. In fact, sesame plants infected by *Glomus clarum* IK97 and *Pseudomonas* sp. (KCIGC01) NBRC-109613 contained higher sesamin levels than the control. No significant difference was observed regarding the sesamolin content.

4. Genetic basis and breeding of high sesamin and sesamolin content varieties

4.1. Genetic basis

The genetic basis of sesamin and sesamolin contents in sesame is poorly understood, with only some biosynthetic genes and loci discovered thus far. The sesamin and sesamolin contents in sesame are polygenic traits, controlled by additive, dominant, and environmental effects (Hata *et al.* 2010; Chandra *et al.* 2019; Usman *et al.* 2020). These two lignans are genetically very close and are biosynthesized from the same precursors (Kato *et al.* 1998).

Sesamin and sesamolin biosynthesis in *S. indicum* Deciphering the molecular mechanisms involved in the lignan pathway is a prerequisite for breeding lignan-rich sesame varieties. It will help to efficiently target the genes responsible for lignan variations among sesame germplasms. Sesamin ($C_{20}H_{18}O_6$) and sesamolin ($C_{20}H_{18}O_7$) are biosynthesized in developing sesame seeds, mainly between 10 and 30 days post-anthesis (DPA) (Suh *et al.* 2003; Ono *et al.* 2006; Ke *et al.* 2011; Wang *et al.* 2014b). The studies of Kato *et al.* (1998) and Jiao *et al.* (1998) revealed that these two nutraceuticals, sesamin and sesamolin, are biosynthesized in the phenylpropanoid pathway from tyrosine (Tyr) or

phenylalanine (Phe) (Fig. 3). As a reminder, the Phe and Tyr precursors are biosynthesized in plants *via* the shikimate pathway (Maeda and Dudareva 2012). First, these two amino acids are converted through a series of reactions into coniferyl alcohol, which then goes through a stereo-specific dimerization to yield pinoresinol, the basal lignan (Jiao *et al.* 1998; Kato *et al.* 1998; Suh *et al.* 2003). Then, pinoresinol is converted into sesamin *via* piperitol (Ono *et al.* 2006), and finally, sesamin is metabolized to sesamolin and sesaminol by a specific oxygenation reaction (Murata *et al.* 2017) (Fig. 3). Sesaminol is mostly accumulated in its triglucoside form (Ono *et al.* 2020). By comparing expressed sequence tags (ESTs) obtained from the cDNA libraries of *S. indicum* L. and *A. thaliana* developing seeds, Suh *et al.* (2003) shed light on some of the genes and metabolic pathways involved in sesame lignan biosynthesis. The biosynthesis of coniferol alcohol from Phe and Tyr still needs to be clarified, as only cinnamate-4-hydroxylase (C4H), caffeic acid O-methyltransferase (COMT), cinnamoyl-CoA reductase (CCR), 4-coumarate-CoA ligase (4CL), and cinnamyl alcohol dehydrogenase (CAD) have been identified by ESTs analysis (Suh *et al.* 2003; Ke *et al.* 2011). Likewise, the studies of Davin and Lewis (2000), Suh *et al.* (2003), Ono *et al.* (2006), Ke *et al.* (2011), Murata *et al.* (2017), and Chandra *et al.* (2019) revealed the importance of some key catalytic genes

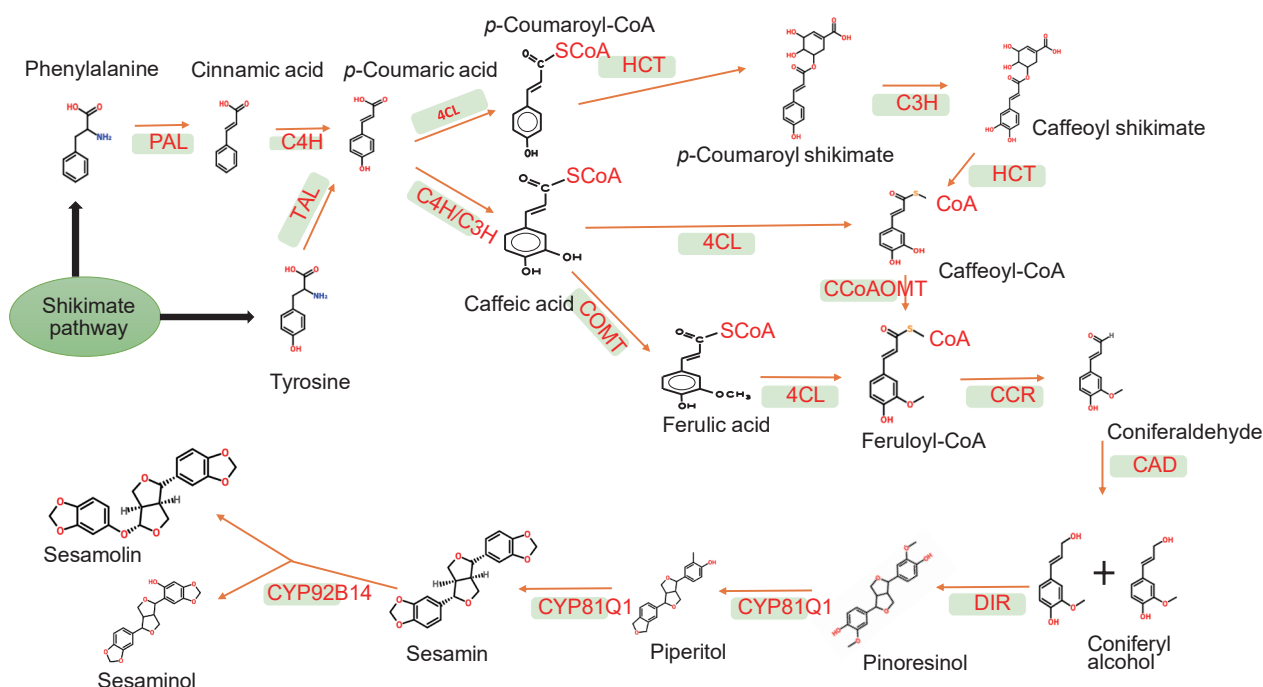


Fig. 3 The general biosynthetic pathway of major lignans in *Sesamum indicum* L. Key enzymes catalyzing some reactions: PAL, phenylalanine ammonia-lyase; C4H, cinnamate 4-hydroxylase; 4CL, 4 coumaroyl-coenzyme A ligase; TAL, tyrosine ammonia-lyase; C3H, *p*-coumarate 3-hydroxylase; CCR, cinnamoyl-CoA reductase; HCT, hydroxycinnamoyl-CoA shikimate/quinic acid hydroxycinnamoyltransferase; COMT, caffeic acid O-methyltransferase; CCoAOMT, caffeoyl-CoA O-methyltransferase; CAD, cinnamyl alcohol dehydrogenase; DIR, dirigent protein; CYP81Q1, piperitol/sesamin synthase (PSS) and CYP92B14, sesaminol and sesamolin synthase.

during the sesamin and sesamol biosynthetic process.

Caffeic acid O-methyltransferase (COMT): By competing with 4CL for the substrate, caffeic acid, COMT catalyzes the reaction leading to ferulic acid. Suh *et al.* (2003) and Ke *et al.* (2011) identified 20 and two ESTs associated with COMT, respectively. They suggested that a higher expression of COMT is needed in developing sesame seeds for coniferyl alcohol formation than caffeoyl-CoA O-methyltransferase (CCoAMT), which is involved in feruloyl-CoA synthesis from caffeoyl-CoA. None of the ESTs was linked to CCoAMT in the two studies. There are five copies of the COMT gene in sesame (Ke *et al.* 2011).

Cinnamyl-alcohol dehydrogenase (CAD): CAD is a committed enzyme for the biosynthesis of lignans and lignin in sesame and other plants (Ke *et al.* 2011; Liu Q *et al.* 2018). In the lignan pathway, this enzyme converts coniferaldehyde into coniferyl alcohol by competing with ferulate 5-hydroxylase (F5H). Twelve CAD-like genes are present in the sesame genome (Ke *et al.* 2011).

Dirigent protein (DIR): The first committed reaction leading to the sesame lignans is the coupling of two coniferyl alcohol molecules to yield pinoresinol (Kato *et al.* 1998; Satake *et al.* 2015). This reaction is catalyzed by DIR competing with laccase and peroxidase for the substrate coniferyl alcohol (Davin *et al.* 1997; Davin and Lewis 2000, 2005). The gene *SiDIR* (*SIN_1015471*) corresponds to DIR in the sesame genome (Wang *et al.* 2014 b).

Piperitol/sesamin synthase (PSS): PSS (*CYP81Q1/SIN_1025734*) is a committed NADPH-cytochrome P450 oxidoreductase in the biosynthesis of sesamin from pinoresinol *via* piperitol by the generation of two methylenedioxy bridges (Ono *et al.* 2006). Pathak *et al.* (2015) have analyzed the expression of PSS, coupled with sesamin content evaluation during seed development, and found that PSS was negatively favored during domestication. Wang *et al.* (2014b) examined the genome sequences of 29 sesame accessions and discovered that PSS was especially conserved. Thus, they suggested that sesamin content variation in sesame might be imputed to PSS regulatory genes. There are 25 *CYP81* genes in sesame (Wang *et al.* 2014b).

Sesamol/sesaminol synthase (*CYP92B14*): Sesamol is the second most abundant lignan in sesame seed and oil. *CYP92B14* is a cytochrome P450 enzyme that catalyzes the formation of sesamol and sesaminol from sesamin by an oxygenation scheme that is named the oxidative rearrangement of α -oxy-substituted aryl groups (ORA) (Murata *et al.* 2017; Harada *et al.* 2020). The same study revealed that a deletion of four C-terminal amino acids (Del4C) in *CYP92B14* was responsible for sesamol deficiency in sesame. Moreover, they demonstrated that *CYP81Q1* and *CYP92B14* operate in coordination in

developing sesame seeds (Murata *et al.* 2017).

CYP reductase1 (CPR1): CPR1 is a committed enzyme in sesamin biosynthesis. Its role is to facilitate the transfer of electrons from NADPH to *CYP81Q1* and *CYP92B14* (Murata *et al.* 2017; Chandra *et al.* 2019). Functional characterization demonstrated that in the absence of CPR1, the *CYP81Q1* enzyme was limited in converting pinoresinol to sesamin (Chandra *et al.* 2019).

Transcriptome analyses revealed that lignan biosynthesis in sesame seed is developmentally regulated (Suh *et al.* 2003; Ono *et al.* 2006; Ke *et al.* 2011; Wang *et al.* 2014b). However, the regulatory pathway of sesamin and sesamol biosynthesis in developing seeds is unclear. Wei *et al.* (2015) performed an association mapping using 705 global sesame accessions grown in four environments, and found that the *SiNST1* gene associated with lignification in the seed coat was strongly associated with the variations in sesamin, sesamol, oil, and protein contents in sesame. Recently, by combining QTL mapping and transcriptome profiling, we identified two candidate regulatory genes (*SIN_1005755* and *SIN_1005756*) associated with sesamin and sesamol biosynthesis in sesame (Xu *et al.* 2021). *SIN_1005755* encodes a NAC domain protein which might be the key regulatory gene of lignan biosynthesis in sesame by controlling lignin biosynthesis from coniferaldehyde or coniferyl alcohol. Functional characterization of these candidate regulatory genes using advanced genomics-editing tools is needed to shed light on the molecular mechanisms involved in lignan synthesis regulation in developing sesame seeds.

Molecular markers related to sesamin and sesamol

Molecular markers and QTLs have significantly enhanced the genetic gain in crop breeding. Various molecular markers have been developed for use in sesame breeding (Dossa *et al.* 2017a). To date, expressed sequence tags (ESTs) are the only class of molecular markers available for sesamin and sesamol (Table 5). Suh *et al.* (2003) have developed 3328 ESTs from a cDNA library of 5- to 25-day-old developing seeds, among which 58 were involved in the sesame lignan biosynthesis pathway. Ke *et al.* (2011) randomly sequenced a cDNA library constructed from 5 to 30 day-old immature seeds and generated 41 248 ESTs, among which 117 were associated with sesamin and sesamol biosynthesis. Quantitative trait loci (QTLs) are important genetic resources for studying key agronomic traits and implementing marker-assisted breeding of both model and non-model crops. In total, 34 and 26 loci for sesamin and sesamol have been detected by Lei *et al.* (2014) and Xu *et al.* (2021), respectively (Table 5). Lei *et al.* (2014) performed an association analysis using the general linear model (GLM) and identified 26 and eight significant loci associated with sesamin and sesamol, respectively. By coupling the mixed composite

Table 5 Markers and loci detected for sesamin and sesamolins

Methods	Population	Markers/Loci	Number of markers/loci	Reference
cDNA library, BLAST	Over 10 cultivars	ESTs	58	Suh <i>et al.</i> (2003)
cDNA library, KEGG blast	Two cultivars	ESTs	117	Ke <i>et al.</i> (2011)
Association analysis (GLM)	215 accessions	Loci	34	Lei <i>et al.</i> (2014)
QTL mapping	224 RILs, F9	QTL	6	Wu <i>et al.</i> (2017)
QTL mapping	548 RILs, F8	QTL	26	Xu <i>et al.</i> (2021)

interval mapping (MCIM) and the multiple interval mapping (MIM) methods, Wu *et al.* (2017) mapped six QTLs for sesamin content variation in sesame seed using 224 RILs (recombinant inbred lines) grown in three environments. In a recent study, we used composite interval mapping (CIM) in a 548 RILs population (Xu *et al.* 2021). We detected 16 QTLs for sesamin and 10 QTLs for sesamolins, including one pleiotropic QTL located on chromosome 11 in an interval of 127 to 127.21 cM. By analyzing the QTL interactions, we found that sesame lignan biosynthesis might be governed by a major gene with a large effect.

4.2. Breeding of sesame varieties with high lignan content

Despite the considerable repertoire of sesame germplasms, conventional and biotechnological methodologies have not been successful in developing high-quality cultivars (Pathak *et al.* 2014). The most widely used breeding techniques in sesame have been mutation induction and pedigree selection (Kole 2019). Sesame breeding programs are focused principally on the seed yield, disease resistance, plant architecture, and high oil content. To our knowledge, “Gomazou” is the most successful hybrid created that contains high sesamin and sesamolins levels. “Gomazou” was selected from the progeny of a cross between “Toyama 016”, a broad seed line from Peru, and “H65”, a high-lignan-content line from South China (Yasumoto and Katsuta 2006). The total sesamin and sesamolins content in “Gomazou” seed was 13.1 mg g⁻¹. Recently, by crossing different types of parents using the combining ability tool, Khuimphukhieo and Khaengkhan (2018) and Usman *et al.* (2020) created four and 21 hybrids, respectively, with variable sesamin and sesamolins contents. These crosses need further evaluation for the possible isolation of high yielding hybrids that have high sesamin and sesamolins contents. Sesame cultivars with higher lignan levels may allow farmers to produce sesame for various industries (Khuimphukhieo and Khaengkhan 2018). Taken together with the heritability found in a RIL population by Wu *et al.* (2017), it is clear that lignan-rich sesame lines can be selected from the crosses of the proper parents. However, to save time and labor, genomics-assisted breeding approaches might be used to restructure the sesame plant's ideotype and to increase its lignan level.

5. Future prospects

5.1. Genome-wide association studies of sesamin and sesamolins variation

The studies of Wang *et al.* (2014b) and Wei *et al.* (2015) made a great deal of genome-wide information available for use in GWAS to gain some insight into the genetic architecture of complex quantitative traits in sesame, such as the sesamin and sesamolins contents. This approach was useful in locating loci, SNPs, QTLs, and candidate genes of complex agronomic traits such as oil and protein contents, charcoal rot resistance, oleic acid and linoleic acid concentrations, and salinity and drought tolerance in sesame (Dossa *et al.* 2019a; Kole 2019). Therefore, GWAS could be harnessed to shed new light on the genetic basis of the sesamin and sesamolins contents in *S. indicum* L.

5.2. Functional characterization of sesamin and sesamolins candidate regulatory genes

Candidate genes are putative causative genes that require functional analysis to validate their effects and functional variants (Wei *et al.* 2015). Since the achievement of the greatest sesame transformation and regeneration efficiencies of 42.66 and 57.33%, respectively (Chowdhury *et al.* 2014), candidate sesamin and sesamolins regulatory genes should be thoroughly studied in mutant sesame and *Arabidopsis* plants to understand the molecular mechanisms involved in lignan biosynthesis and regulation.

5.3. Overexpression and knockout of PSS in sesame

Knocking out, over-expressing or down-regulating the sesamin synthase gene in sesame using advanced genomics tools may help to unveil the biological functions of lignans during sesame plant development.

5.4. Deciphering the influences of abiotic stresses (drought, waterlogging, and salt) on the sesamin and sesamolins contents in seeds through gene expression and quantification

Due to the adverse effects of climate change on crop

production, especially in sesame, there is an urgent need to screen large amounts of germplasm to identify drought, waterlogging, and salt-tolerant lignan-rich sesame varieties. Performing these experiments at the genomics level may help us to discover the potential roles of these lignans in osmotic stress tolerance, and to identify the possible correlations between the regulatory genes of lignans and the core abiotic stress-responsive genes (Dossa *et al.* 2019b).

5.5. Insight into the correlations between seed coat colors and lignan content variations at the genomics level

Tracking the expression of genes involved in the biosynthesis and regulation of flavonoids, anthocyanins, lignin, melanin, and lignans during sesame seed development may be useful for dissecting the influence of seed coat color on sesamin and sesamol variability.

5.6. Genome-wide analysis of the DIR family in sesame

Dirigent proteins play a critical role in lignan biosynthesis. Overexpression of *GmDir22*, the homologous gene of *AtDir21/AtDir23*, increased the lignan contents in soybean (Li *et al.* 2017). Therefore, a genome-wide analysis of the DIR family in sesame may help us to identify potential candidate DIR genes that contribute to high lignan accumulation in sesame.

5.7. Genomics-assisted breeding of lignan-rich sesame varieties

GWAS will provide numerous markers linked to variations in the sesamin and sesamol contents in sesame, as well as candidate genes. Functional analysis of those candidate genes will shed light on simple and effective markers that can be targeted for the breeding of high lignan content sesame varieties. Therefore, advanced genome-editing tools may be used to knock out or edit specific sequences of the sesamin and sesamol candidate genes together with other key genes. Overall, the efficient editing of these genes will generate various sesame materials with different levels of sesamin and sesamol that might be useful in the process of breeding high-quality knockout mutant sesame varieties. Molecular breeding methods have been developed in rice and maize (Ramstein *et al.* 2019; Wei *et al.* 2021), and a summary of our suggested ways to accelerate lignan breeding in sesame was shown in Fig. 4.

6. Conclusion

Sesamin and sesamol represent the principal lignans in sesame seeds. Human interest in these compounds is increasing due to their multiple biological proprieties. The production of these lignans is limited because sesame seed represents the sole primary source of these nutraceuticals. Besides, the development of nutritionally superior sesame varieties through conventional and biotechnological methodologies has not been successful.

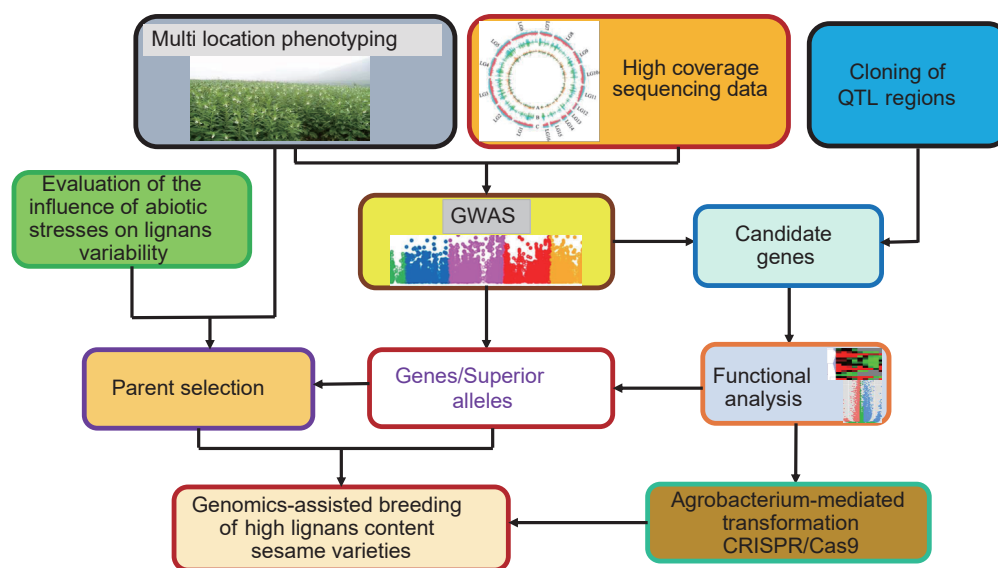


Fig. 4 Strategies for breeding high-lignan content sesame varieties. Integration of high-throughput sequencing and phenotyping, GWAS, functional analysis, parent selection, and genomic selection to enhance the development of high-quality sesame varieties in breeding.

Previous studies showed that the sesamin and sesamol contents in sesame are polygenic quantitative traits. With the availability of sesame genome sequence data and advanced techniques for functional genomic analysis, previously unknown candidate genes and markers linked to sesamin and sesamol can be identified by GWAS in a massive germplasm sample and multiple environments. These candidate genes will constitute valuable materials for further genomic studies that will lead to teasing out the molecular mechanisms involved in lignan content regulation in sesame and discovering the roles of sesamin and sesamol in sesame. The integration of high-efficiency genomic editing tools in sesame breeding programs will allow the improvement of sesame quality, especially its sesamin and sesamol contents. Sesame cultivars with higher lignan contents may also favor the production of sesame for various industries.

Acknowledgements

This study was supported by the Open Project of Key Laboratory of Biology and Genetic Improvement of Oil Crops, Ministry of Agriculture and Rural Affairs, China (KF2020004 and KF2022002), the Agricultural Science and Technology Innovation Project of the Chinese Academy of Agricultural Sciences (CAAS-ASTIP-2016-OCRI), the Key Research Projects of Hubei Province, China (2020BBA045 and 2020BHB028), the Science and Technology Innovation Project of Hubei Province, China (2021-620-000-001-035), the China Agriculture Research System of MOF and MARA (CARS-14), and the Fundamental Research Funds for Central Non-profit Scientific Institution, China (Y2022XK11).

Declaration of competing interest

The authors declare that they have no competing interests.

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