Review Article

A Comprehensive Review on Distribution, Pharmacological Properties, and Mechanisms of Action of Sesamin

Yao Zhang [ID],[1] **Fen Liu** [ID],[2] **Yan Lin** [ID],[3] **Linhai Li** [ID],[1] **Mingfeng Chen** [ID],[2] and **Lin Ni** [ID][1]

[1]*College of Plant Protection, Fujian Agriculture and Forestry University, Fuzhou 350002, China*
[2]*Fujian Provincial Hospital, Shengli Clinical Medical College of Fujian Medical University, Fuzhou 350122, China*
[3]*College of Animal Sciences (College of Bee Science), Fujian Agriculture and Forestry University, Fuzhou 350002, China*

Correspondence should be addressed to Lin Ni; nilin_fjau@126.com

Sesamin is a kind of fat-soluble lignan extracted from sesame seeds or other plants. It has attracted more and more attention because of its extensive pharmacological activities. In this study, we systematically summarized the pharmacological activities of sesamin including antioxidant, anti-inflammatory, anticancer, protection of liver and kidney, prevention of diabetes, hypertension, and atherosclerosis. Studies focus on the abilities of sesamin to attenuate oxidative stress by reducing the levels of ROS and MDA, to inhibit the release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, etc.), and to induce apoptosis and autophagy in cancer cells through a variety of signaling pathways such as NF-κB, JNK, p38 MAPK, PI3K/AKT, caspase-3, and p53. By inhibiting the production of ROS, sesamin can also enhance the biological activities of NO in blood vessels, improve endothelial dysfunction and hypertension, and change the process of atherosclerotic lesion formation. In line with this, the various pharmacological properties of sesamin have been discussed in this review so that we can have a deeper understanding of the pharmacological activities of sesamin and clear the future development direction of sesamin.

1. Introduction

Sesamin, which was first discovered in *Sesamum indicum* L, is a natural lignan component. *Sesamum indicum* is one of the most archaic crops, which is rich in nutrition and has been used as a nutritional product for a long history. It has been known to replenish liver and kidney, nourish blood, and moisten intestinal dryness. Previous studies found that sesamin is the most important ingredient to exert medicinal effects in this plant [1]. Nowadays, sesamin has always been a research hotspot for scientists and more and more pharmacological activities of sesamin have been reported.

As we all know, oxidative damage and inflammation can cause many diseases. However, sesamin was reported to have antioxidant and anti-inflammatory effects. It can increase the activities of antioxidant enzymes and reduce the production of reactive oxygen species and malondialdehyde. At the same time, it can also inhibit the release of pro-inflammatory cytokines to ensure the normal functions of liver, kidney, heart, and other organs [2–4]. In addition,

sesamin can also resist a variety of cancers such as liver cancer and lung cancer. It inhibits the growth of cancer cells by downregulating the expression of related proteins and inducing cell cycle arrest [5, 6]. What is more, sesamin also has certain preventive and therapeutic effects on some cardiovascular and cerebrovascular diseases such as diabetes, hypertension, and atherosclerosis [7]. Although there have been many reports on the activities of sesamin, no one has made a comprehensive and systematic summary. In this study, we systematically summarized the plant sources and pharmacological properties of sesamin (Figure 1) to understand the current research status and deficiencies of sesamin and define the future development direction.

2. Physicochemical Properties and Sources of Sesamin

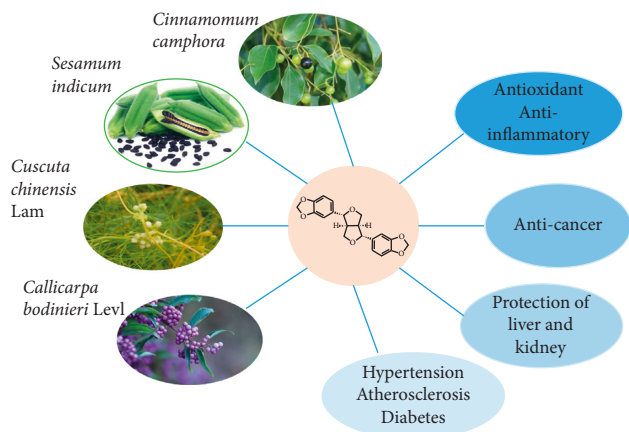*2.1. Physicochemical Properties of Sesamin.* Sesamin is a white needle crystal with a molecular formula of $C_{20}H_{18}O_6$

FIGURE 1: Main plant sources and pharmacological activities of sesamin.

FIGURE 2: Structure of sesamin.

and a melting point of 120-121°C. Its molecular structure is shown in Figure 2.

2.2. Sources of Sesamin.

Sesamin was first isolated from *Sesamum indicum* L in 1894 [8]. Since then, a new era of sesamin research has begun. Subsequently, more and more plants were reported to contain sesamin. Ye et al. separated five lignans from the petroleum ether and chloroform extraction of *Cuscuta chinensis* Lam. by silica gel column chromatography, including D-sesamin and 9 (*R*)-hydroxy-D-sesamin [9]. In 2004, the leaves of *Callicarpa bodinieri* Levl. were refluxed and extracted with 95% ethanol to obtain sesamin [10]. In addition, it has been reported that sesamin has been isolated from other plants such as *Zanthoxylum nitidum* (Roxb.) DC, *Zanthoxylum stenophyllum* Hemsl., *Eleutherococcus nodiflorus* (Dunn) S. Y. Hu, *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim, and *Asarum heterotropoides* Fr. var. *mandshuricum* (Maxim.) Kitag. [11, 12]. However, the sesamin content in these plants is much lower than that of sesame seeds. In 2003, Dai et al. evaluated the trace components from 42 kinds of sesame seeds collected from China, Colombia, Afghanistan, Mexico, and other places. The sesamin content in sesame oil was found to be 0.07%–0.61%, of which the black seeds with oil content of 44.5% had the lowest sesamin content, and the white seeds with oil content of 55.1% had the highest sesamin content of 0.44% [13, 14].

Although the content of sesamin in sesame seeds is relatively high, sesame is a precious oil crop, so it costs a lot to separate a large amount of sesamin from sesame. At present, it is urgent to develop a method for separating sesamin from plants with a simple process and low cost. Our research group has been committed to the research of the chemical constituents of *Cinnamomum camphora* var. linaloolifera. We were pleasantly surprised to find that the leaves of *Cinnamomum camphora* contain a large amount of sesamin and the content is equivalent to that of sesame. Through our continuous experiments, we developed a new method for recrystallization of sesamin with purity up to 92% in only three steps [15–17]. This greatly reduces the
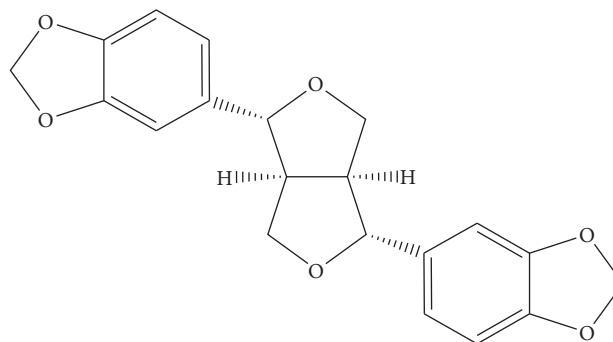
production cost and optimizes the preparation process. *Cinnamomum camphora* is expected to replace sesame as a new plant material for preparing sesamin.

3. Pharmacological Activities of Sesamin

3.1. Antioxidant Activity of Sesamin.

Under normal circumstances, the production and removal of free radicals in the organism are in a balanced state. However, when excessive free radicals are produced, this balance will be broken, showing oxidative stress damage and disruption to the normal function of cells and tissues. Studies have shown that sesamin can scavenge free radicals in the body and therefore exhibit antioxidant activity.

Oxidation is the most difficult problem in the process of oil preservation. The synthetic antioxidants have potential toxicity, so the antioxidant activity of sesamin can be used in oil preservation. The antioxidant activity of different dosages of sesamin in soybean oil has been reported and the results showed that sesamin shows significant antioxidant activity in soybean oil, with the activity increasing in a dose-dependent manner [18]. The peroxide value and conjugated diene value of soybean oil added with sesamin were both lower than those of the blank group, and within a certain range, the peroxide value and conjugated diene value decreased with the increase in sesamin addition, indicating that sesamin showed significant antioxidant activity [19]. Sesamin can also exert its antioxidant effect at high temperature. At a high temperature of 120°C, the peroxide value of lard and rapeseed oil added with sesamin was significantly lower than that of the control group, indicating that the antioxidant activity of sesamin has good thermal stability [20]. These studies have shown that sesamin can be used as a natural antioxidant in the process of oil preservation.

There have been some detailed reports on the mechanism of sesamin's antioxidant effect. Waralee et al. found that sesamin can inhibit the production of ROS and enhance the activities of CAT, SOD, and other enzymes to protect the body from oxidative damage [21]. Likewise, after spinal cord injury in rats, the production of MDA increased and the activities of protective enzymes such as SOD and CAT decreased significantly. However, this trend was obviously reversed after treatment with sesamin, which indicated that sesamin can effectively inhibit the oxidative stress response that occurs in rats with spinal cord injury [22]. The

antioxidant effect of sesamin had also been confirmed in hypertensive rats. The SOD activity decreased in the hippocampus and cortex tissues of hypertensive rats and the levels of MDA and H_2O_2 increased, showing a typical oxidative stress response. After treatment with sesamin, the levels of MDA and H_2O_2 were significantly reduced while the SOD activity was obviously increased, revealing that sesamin can reduce the oxidative stress damage in hippocampus and cortex tissues in hypertensive rats and improve the antioxidant capacity [23]. Furthermore, studies have found that sesamin showed antioxidant effects by activating certain signal transcription. When adult drosophila with high levels of ROS was fed with sesamin-containing feed, Nrf2/Cnc was strongly activated in neurons, and the transcription factor Nrf2 (Cnc in drosophila) was critical in reducing oxidative stress. Therefore, the antiaging effect of sesamin is to reduce the accumulation of oxidative stress in neurons by activating the Nrf2/Cnc pathway [24]. Sesamin can also reduce the oxidative stress damage in zebrafish head caused by fluoride stress and enhance the activities of immune enzymes such as ACP and AKP [25]. The above studies have shown that the antioxidant activity of sesamin is related to the regulation of the activity of protective enzymes and immune enzymes in the body and the inhibition of the production of ROS and MDA. Other relevant reports about the antioxidant effects of sesamin *in vivo* and *in vitro* are shown in Table 1.

3.2. Anti-Inflammatory Activity of Sesamin.

Inflammation is a part of defense mechanism in the body and is typically characterized by pain, swelling, and fever. Pathogen infection, chemical stimulation, physical injury, connective tissue disease, allergic reaction, and so on can all cause the occurrence of inflammatory reaction. Some uncontrolled chronic inflammation often leads to many diseases. Natural or synthetic anti-inflammatory drugs are currently considered as a treatment for the disease. It has been reported that sesamin can play an anti-inflammatory role *in vivo* and resist a variety of inflammations [34].

Ulcerative colitis (UC) is the main form of inflammatory bowel disease. Patients show clinical symptoms such as abdominal pain, diarrhea, and physical weakness. Bai et al. used dextran sodium sulfate (DSS)-induced ulcerative colitis mice as a model and found that sesamin can enhance Nrf2-mediated protection against H_2O_2-induced oxidative stress *in vitro* and alleviate colitis induced by DSS *in vivo*. The research also proved for the first time that sesamin can activate Nrf2-mediated oxidative stress protective signaling pathway in colitis via AKT and ERK activation [35]. Physical damage such as ultraviolet (UV) exposure can also cause skin inflammation. Studies have confirmed that sesamin treatment can reduce the production of reactive oxygen species in human dermal fibroblasts after UVB irradiation and prevent the overexpression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), thereby resisting UVB-induced skin inflammation [36].

In addition, some neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are occurring more and more frequently in our country. One of the causes of this disease is the activation of microglia mediated by neuroinflammation. Toll-like receptor (TLR4) is a key innate immune receptor involved in microglia activation and neuroinflammation. It was reported that sesamin reduced the expression of TLR4 by inhibiting the pathway of JNK and NF-κB. It also led to the downregulation of neurotoxicity in BV2 microglia and reduced the release of NO, prostaglandin E2 (PGE2), and pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in microglia [37]. As for airway inflammation, allergic asthma is a typical one, which is a chronic airway inflammatory disease. Lin et al. found that sesamin exerted a significant anti-inflammatory effect in ovalbumin (OVA)-induced asthma mice. The expression levels of interleukin-4 (IL-4), IL-5, IL-13, and serum IgE decreased in OVA-stimulated mice treated with sesamin, as did the number of total inflammatory cells and eosinophils in bronchoalveolar lavage fluid (BALF). These results indicated that sesamin exhibited a good therapeutic effect on OVA-induced allergic asthma in mice [30]. Other experiments on the anti-inflammatory activity of sesamin *in vivo* and *in vitro* are shown in Table 2.

However, studies have shown that it is not sesamin itself that really exerts antioxidant and anti-inflammatory effects, but the metabolites produced by sesamin in the body. The methylenedioxy groups of sesamin are catalyzed by cytochromes CYP450 and converted to catechol-type metabolites, S1 ((7α, $7'\alpha$, 8α, $8'\alpha$)-3′, 4′-methylenedioxy-7, 9′:7′, 9-diepoxylignane-3,4-diol) and S2 ((7α, $7'\alpha$, 8α, $8'\alpha$)-7, 9′:7′, 9-diepoxylignane-3, 3′, 4, 4′-tetraol) in the liver, respectively (Figure 3) [45]. Researchers found that S1 exhibited an anti-inflammatory effect dependent on ANX A1. The mechanism involved S1-induced phosphorylation of ANXA1 at serine 27, which promoted the release of extracellular ANXA1. Therefore, the ANX A1 is released into the extracellular space and inhibited the production of TNF-α (Figure 4) [46]. In another study, it was indicated that S1 can strongly inhibit the IFN-β/iNOS signaling in the LPS-induced macrophages while sesamin weakly inhibited [47]. There were studies that also confirmed that S2, which has two catechol moieties, showed much higher radical scavenging activities than any flavonoid reported to date [45]. These all suggested that the metabolites of sesamin exert the antioxidant and anti-inflammatory effects rather than sesamin itself and the catechol moieties play a major role.

3.3. Anticancer Activity of Sesamin.

Cancer has always been a major problem that humans need to overcome. Chemotherapy is still the main method of treating cancer at present. However, chemotherapy also has the disadvantages of low efficiency and large side effects. Therefore, the development of natural anticancer drugs should be a new research direction. Studies have shown that sesamin can effectively inhibit a variety of tumors, which provides a new idea for the development of anticancer drugs.

Liver cancer is a high-incidence and extremely harmful malignant tumor. According to the data released by the National Cancer Center in 2019, the incidence of liver cancer is the fourth highest in China and the mortality rate is as

Table 1: Antioxidant activity of sesamin.

Experimental model	Dosage	Administration mode	Mechanism of action	References
Drosophila senescence-accelerated model	0.35, 2.0 mg/ml	With diet	Sesamin upregulates the expression of several antioxidative and DNA repair genes	[22]
Drosophila adults	2.0 mg/ml	With diet	Sesamin protects drosophila adults against oxidative damage via stimulation of the Nrf2/Cnc-dependent transcription in the adult gut and brain	[24]
Spontaneously hypertensive rats	40, 80, 160 mg/kg/d	Orally	Sesamin improves arterial function in SHR through the upregulation of eNOS expression and downregulation of p22phox and p47ph	[23]
CCl4-induced rat model	100 mg/kg/d	Orally	Sesamin reduces the levels of liver enzymes (ALT, AST, and TBIL) and the levels of IL-6 and COX-2 in the liver by inhibition of NF-kB activation with improved SOD and GPx activities	[26]
Kainic acid-induced rat model	15, 30 mg/kg	Orally	Decrease in MDA, expression of ERK1/2, p38 mitogen-activated protein kinases, caspase-3, and COX-2	[27]
Pb and LPS-induced rat model	10 mg/kg	Orally	Reduction in the AST, ALT, CRP, TNF-α, IL-1, IL-6, NO, and ROS generation, liver tissue expressions of JNK, p38 MAPK, GADD45β, COX-2, and iNOS	[28]
6-OHDA-induced rat model	10, 20 mg/kg/d	Orally	The levels of MDA and ROS decreased; the activities of SOD increased	[29]
OVA-induced mice model	1, 10, 20 mg/kg	Intraperitoneally	Inhibition of expression levels of interleukin-4 (IL-4), IL-5, IL-13, and serum IgE with reduced numbers of total inflammatory cells and eosinophils in BALF	[30]
CCl4-induced mice model	10 mg/kg	Orally	Enhancement of the expression levels of JNK with diminished release of mitochondrial cytochrome c in liver	[31]
Human (clinical trial)	200 mg/d	With diet	Significant decrease in serum levels of MDA with increased TAC and HDL-C levels	[32]
Hepatic steatosis rat model	40, 80, 160 mg/kg	Intraperitoneally	Reduction in the serum levels of total cholesterol, triacylglycerols, low-density lipoprotein cholesterol, free fatty acid, malonaldehyde	[33]

Table 2: Anti-inflammatory activity of sesamin.

Experimental model		Dosage	Administration mode	Administration duration	Mechanism of action	References
Model *in vivo*	C57BL/6 mice	50, 100 mg/kg	Orally	0–9 d	Sesamin stimulates Nrf2-mediated protective defense against oxidative stress and inflammation in colitis via AKT and ERK activation	[35]
	Cecal ligation puncture (CLP) mouse model	25, 50, 100 mg/kg	Injection	7 d	Inhibition of sepsis inflammation through HMGB1/TLR4/IL-33 signaling pathway	[38]
	ONFH rat model	100 mg/kg	Injection	0, 1, 2, 3, 4 weeks	Inhibition of Akt-mediated apoptosis and ROS levels	[39]
	STZ-induced DR mouse model	30 mg/kg	Injection	4 weeks	Reduction in blood sugar, TNF-α, and ICAM-1; inhibition of microglia activation	[40]
	CUMS-induced mouse model	50 mg/kg/d	Orally	6 weeks	Sesamin inhibits the excessive activation of cortical microglia and the expression of iNOS, COX-2, TNF-α, and other inflammatory factors	[41]

TABLE 2: Continued.

| Experimental model		Dosage	Administration mode	Administration duration	Mechanism of action	References
Model *in vitro*	Caco-2 cells	5, 10, 20, 40, 80, 160, and 320 μM	Cell line	8, 16, 24 h	Sesamin protects Caco-2 cells from H_2O_2-induced oxidative stress injury via GSH-mediated scavenging of ROS	[35]
	Murine macrophages	100 μM	Cell line	12 h	Sesamin inhibits the ubiquitination of HO-1 protein and the release of NO in activated macrophages.	[42]
	Human umbilical vein endothelial cells	0, 12.5, 25, 50, 100 μM	Cell line	24 h	Sesamin inhibits the release of IL-8, ET-1, and the expression of adhesion molecules by blocking NF-κB activation	[43]
	Human articular chondrocyte	0.25, 0.5, 1.0 μM	Cell line	21 d	Promotes the synthesis of CSPGs by human chondrocytes and inhibits the expression of IL-1β	[44]
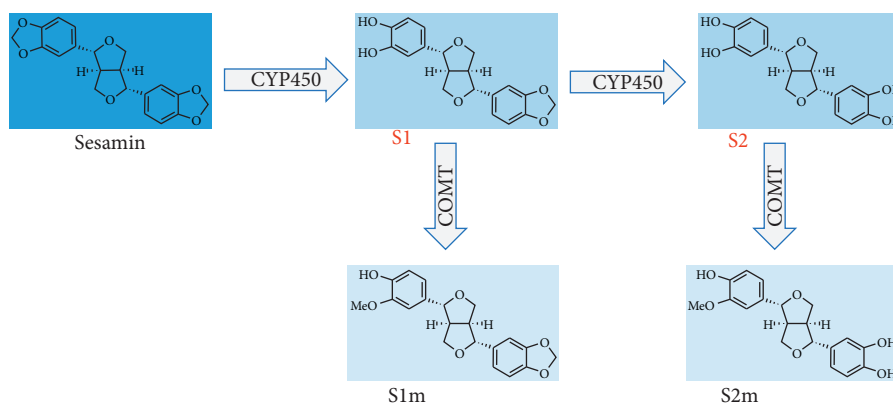
FIGURE 3: Scheme of sesamin metabolism in the liver.
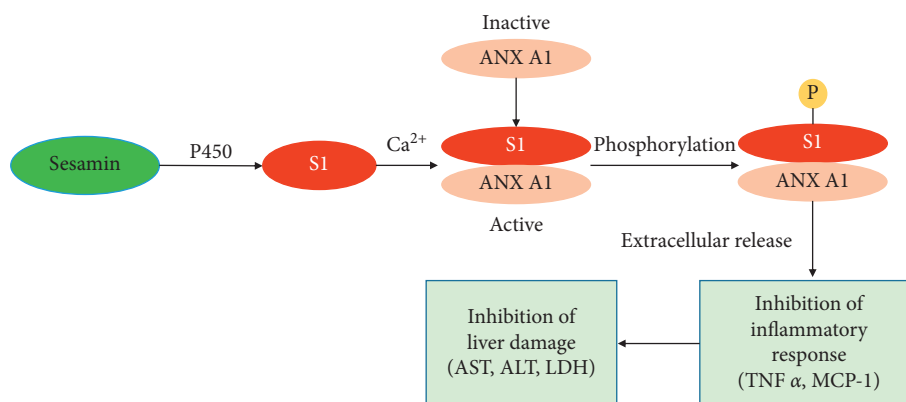
FIGURE 4: Schematic of the anti-inflammatory effect of S1 mediated by ANX A1 activation. S1 directly binds to the repeat 3 domain of ANX A1 in monocytes. Under stimulation, S1 promotes the phosphorylation of ANX A1 Ser27 and the subsequent extracellular release of ANX A1 and inhibits the production of TNF-α or MCP-1 to exert anti-inflammatory effect.

high as the second [48]. Studies have reported the antitumor effect of sesamin on H22 hepatocellular carcinoma-bearing mice. Experiments have found that low-dose sesamin had a certain inhibitory effect on H22 liver cancer cells, while high-dose sesamin had less inhibitory effect. Although the inhibiting effect was not as good as traditional anticancer drugs, sesamin was far less harmful to human body than traditional anticancer drugs. This suggests that there are more medicinal ingredients in natural plants to be developed. In the experiment of mice treated with sesamin and given diethylnitrosamine (DEN) intragastric administration, all mice in the model groups suffered from liver cancer, and

liver index, ALT, AST, and other liver function indexes were higher than those of the control groups. However, the liver index and various indicators of the sesamin treatment groups were normal, which indicated that sesamin had a protective effect on DEN-induced liver cancer in mice [49–51]. HepG2 cells are also a type of hepatocarcinoma cells that are currently studied. The study found that after treating human hepatoma HepG2 cells with sesamin for 48 hours, the inhibition rate can reach 41.8%, and the cell growth is obviously inhibited. However, the inhibition effect on normal liver cells L02 was significantly lower than that of HepG2 cells under the same conditions, indicating that sesamin had no significant toxicity to normal human cells [52]; at the same time, it was found that sesamin can induce early apoptosis of HepG2 cells, which indicated that sesamin can inhibit the proliferation of HepG2 cells by inducing apoptosis [53]. In addition, studies have found that the inhibiting effect of sesamin on the proliferation of HepG2 was related to the expression of related proteins. Sesamin could inhibit the proliferation of HepG2 cells to varying degrees at the concentration of 0–96 ug/mL, and the inhibiting effect became more obvious with the increase in concentration and the extension of time. The optimal treatment time was 48 h. HepG2 cells were reduced in G1 phase and increased in G2 phase after 48 hours of sesamin treatment, which was found to be related to the decrease in the expression of cyclin A and cyclin B1 proteins. It indicated that sesamin inhibited the proliferation of HepG2 cells by downregulating the expression of these two proteins [54].

Lung cancer is one of the most harmful malignant tumors with the fastest increasing morbidity and mortality. Numerous studies have found that sesamin also had good inhibitory activities on lung cancer. According to statistics, non-small cell lung cancer (NSCLC) accounts for about 85% of the total incidence of lung cancer. At present, there are many studies on the human non-small cell lung cancer cell line A549. A549 cells were treated with sesamin. The cell viability, migration ability, and cell cycle were detected by the CCK8 method, scratch method, and flow cytometer. The results showed that sesamin could inhibit the viability and migration ability of A549 cells and induce G0/G1 phase arrest. It can produce lethal effects on lung cancer cells by inducing autophagy and mitochondrial apoptosis [55]. In addition, the experiments *in vivo* and *in vitro* had shown that sesamin inhibited Akt activity and upregulated the expression of p53, indicating that sesamin induced the arrest of cell cycle in G1 phase through Akt/p53 signaling pathway and inhibited the proliferation of NSCLC cells [56]. Watanabe et al. used the MTT to determine the antiproliferative effect in human lung adenocarcinoma cell line A549 by sesamin, vinorelbine, and sesamin collaborative vinorelbine. When A549 cells were treated with sesamin in the range of 10–100 ug/mL for 48 hours, it is found that low concentrations of sesamin had an antiproliferative effect on A549 cells. The combination of sesamin and vinorelbine had a higher inhibitory rate on the growth of A549 cells than the two drugs used alone [57]. Studies have also found that the proliferation of A549 and H1792 cancer cells could be significantly inhibited by the treatment of sesamin within the concentration gradient of 10–40 μM for 24 or 48 hours. The apoptosis of A549 and H1792 cells was significantly induced at 10–30 μM for 24 hours in a dose-effect relationship. An in-depth study of its mechanism has found that sesamin upregulated the expression of p53 and downregulated the expression of cyclin D1 and CDK2, so that G1 phase was arrested and the proliferation of NSCLC cells was inhibited [58]. In addition to the study on A549 cells, Binaifer et al. explored the resistance of sesamin combined with cisplatin to lung cancer cell H460 through proliferation inhibition experiments and Western blot experiments. The results showed that sesamin combined with cisplatin synergistically suppressed the proliferation of H460 cells and this may be achieved by inhibiting the expression of p-Akt [59].

In addition, sesamin also has a certain inhibitory effect on other malignant tumors. Dou et al. studied the effect of sesamin on cervical cancer (HeLa) cells, and the results showed that in the sesamin treatment groups, the expressions of Bax, caspase-12, GRP78, GADD153, p-IRE1α, p-JNK, LC3I/II, and beclin-1 increased and the expression of Bcl-2 decreased. Further studies have confirmed that sesamin can also induce autophagy in HeLa cells and inhibit their proliferation and migration [60]. Sun et al. discussed the effect of sesamin on human colon cancer SW480 cells. After 48 hours of treatment with sesamin at 100 μM, the inhibition rate reached 49.95%, and the maximum inhibition rate reached 79.21%. Compared with the control group, the sesamin group's early apoptosis rate is statistically significant and the expression of caspase-3 and caspase-8 was more significant ($P < 0.01$), indicating that sesamin could inhibit the proliferation of SW480 through the activation of caspase family members [61].

Through the above studies, it is found that sesamin plays an anticancer effect mainly by regulating the expressions of related proteins, promoting cell cycle arrest in G1 phase, inhibiting the proliferation of cancer cells, and inducing apoptosis. There are many other reports on the effects of sesamin on other cancer cells in Table 3.

3.4. The Protection of Liver and Kidney.

With the changes in modern lifestyles, the incidence of various diseases such as fatty liver disease caused by dietary imbalance is getting higher and higher. The pathological changes in liver cells are often caused by lipid metabolism disorders and lipid peroxidation. Studies at home and abroad have found that sesamin has a good regulatory effect on lipid metabolism disorders and can effectively prevent the formation of fatty liver and protect the liver.

Zhao et al. used AlCl$_3$ gavage combined with D-galactose intraperitoneal injection to establish the rat model of liver injury to study the protective effect of sesamin on the liver. The results of the study showed that the rats in the liver injury model groups not only lost weight and eat less but also decreased the activities of SOD and other enzymes in the body indicating that the liver of rat had oxidative damage. After treatment with sesamin, the above symptoms were relieved to varying degrees, the activities of SOD and other protective enzymes increased, and the content of MDA

TABLE 3: Anticancer effects of sesamin.

Cancer type	Cell line	Dosage	Mechanism of action	References
Head and neck squamous cell carcinoma	FaDu, HSC-3, Ca9-22	0, 10, 20, 40 μM	Sesamin inhibits the migration and infection of HNSCC cells by regulating MMP-2	[62]
Breast cancer	TNBC cells	0, 50, 100, 150, 200 μM	Sesamin reduces the expression of PD-L1 by inhibiting the JAK/Stat signaling pathway; inhibits the proliferation and migration of MDA-MB231 breast cancer cells	[63]
	MCF-7 cells	12.5–100 μM	Sesamin causes a cell cycle arrest at the G1 phase by inducing RB dephosphorylation	[64]
	Athymic mice (MCF-7 cells)	1 g/kg/day	Sesamin decreases the levels of EGFR-2, EGFR, and downstream pMAPK	[65]
	MCF-7 cells, MDA-MB-231 cells	10–100 μM	Sesamin suppresses VGEF signaling via HIF-1α, NF-κB, AKT, and p38 MAPK	[66]
	MCF-7 cells, MDA-MB-231 cells	40–150 μM	Sesamin inhibits cell growth and viability of different cancer cell lines	[67]
Hematological malignancies	Molt 4B cells	20–100 μM	Sesamin forms apoptotic bodies and fragmentation of DNA into oligonucleosomal-sized fragments	[68]
	THP-1 cells	0.01–10 μM	Sesamin suppresses LPS-induced expression of IP-10/CXCL10 and inhibits LPS-induced activation of p38 MAPK and NF-κB signaling pathways	[69]
Gallbladder cancer	Side population cells	11–100 μM	Sesamin suppresses the carcinogenic potential of SP cells, tumor-sphere formation, colony formation, and Matrigel invasion	[70]
Cervical cancer	HeLa, SiHa, Hs68	15, 30, 75, 150, 300 μM	Sesamin (75, 150 μM) significantly inhibits the proliferation of HeLa and SiHa; the levels of PUMA, Bax, and PTEN increased	[71]
Prostate cancer	DU145, LNCaP	0–200 μM	Sesamin selectively inhibits TRPM8 in HEK293/TRPM8 cells and inhibits the proliferation of DU145 and LNCaP cells	[72]
	PC3 cells	10–100 μM	Sesamin inhibits LPS-induced expression of IL-6, TNF-α, MMP-9, ICAM-1, and VEGF	[73]
Malignant melanoma	SK-MEL2	0, 0.2, 0.4, 0.6, 0.8, 1.0 mg/ml	Sesamin inhibits the activities of mushroom tyrosinase and cell tyrosinase; absorbs ultraviolet	[74]

decreased. It is suggested that sesamin can improve the ability of antioxidative damage in rats with liver injury, which may be one of the mechanisms of sesamin to protect against liver injury [75]. Some studies have also shown that sesamin plays an antioxidant role by downregulating the expression of iNOS protein and has a protective effect on rat liver disease induced by AlCl$_3$ and D-galactose [76]. Fluoride exposure can also cause liver histological changes in animals. When determining the effect of sesamin on oxidative stress and immune damage in zebrafish liver under fluorine exposure, it was found that sesamin can regulate the activities of immune-related enzymes and the expressions of related gene. For example, it can increase the expression of LZM, ACP, AKP, and IL-10 and reduce the expression of TNF-α, INF, IL-11, M17, IL-1β, IL-6, and IL-12P40 mRNAs [77]. Some related experiments have been carried out in rabbits. Rabbits were fed with hyperlipidemic feed for 10 weeks to establish hyperlipidemia rabbit models. From the fifth week, they were fed with sesamin (25, 225 mg/kg) once a day. After 6 weeks of continuous feeding of sesamin, the levels of TC, LDL-C, and TG in the rabbits were significantly reduced and the expression of HDL-C increased, indicating that sesamin

had the effect of lowering blood lipids. At the same time, the AST, ALT, and other liver indexes were significantly reduced, which proved that sesamin also had a certain hepatoprotective effect [78].

The significant increase in blood pressure can also cause abnormal blood flow in the kidneys and cause damage to kidney function. Acute kidney injury (AKI) is a common comorbidity in critically ill patients, with an incidence of up to 30–60%. AKI not only affects the acute phase but can also develop into chronic kidney disease (CKD) in the later stage, affecting the prognosis of the disease and increasing the mortality rate. Researchers usually expose mouse to lipopolysaccharide (LPS) to make AKI mouse models. In the study of the protective effect of sesamin on LPS-induced acute renal injury, 25, 50, and 100 mg/kg of sesamin were injected one hour before the injection of LPS (10 mg/kg). Compared with the control groups, the level of blood urea nitrogen (BUN) in LPS groups increased significantly and the level of creatinine also increased one day later. In contrast, the levels of BUN and creatinine in 100 mg/kg sesamin groups decreased significantly. The measurement results of oxidative stress parameters showed that the levels

of MDA and nitrate increased and the levels of SOD, CAT, and GSH decreased significantly in LPS groups, while the 100 mg/kg sesamin could significantly reverse this trend. It indicated that sesamin can protect the kidneys from the damage of LPS by reducing oxidative stress and inflammation [79]. Xuan found that sesamin can reduce the levels of serum creatinine, urea nitrogen, and urinary microalbumin in spontaneously hypertensive rats and reduce the damage of renal fibrosis [80].

It can be seen that the protective effect of sesamin on liver and kidney is mainly achieved by reducing oxidative stress damage and regulating lipid metabolism. Sesamin can reduce the content of MDA, increase the activities of antioxidant enzymes, and therefore reduce the damage caused by oxidative stress. At the same time, it can reduce the levels of TC, LDL-C, and TG in the body, promote the expression of HDL-C, and improve lipid metabolism disorders and lipid peroxidation, to play a role in liver and kidney protection. Other related reports are shown in Table 4.

3.5. Prevention and Treatment of Cardiovascular and Cerebrovascular Diseases

3.5.1. The Effect of Sesamin on Hypertension.
Hypertension is the most common chronic disease and the most dangerous factor in inducing cardiovascular and cerebrovascular diseases. Long-term hypertension can lead to impaired heart function, cause hypertrophy and apoptosis of cardiomyocytes, and ultimately lead to heart failure. Maintaining good living habits, reducing the intake of salt and alcohol, and maintaining a healthy weight can effectively prevent the occurrence of high blood pressure. In addition to lifestyle changes, medical treatment is also an important way to prevent and treat hypertension. Natural compounds such as sesamin have been found to have good antihypertensive effects.

Li et al. found that right ventricular systolic pressure and mean pulmonary artery pressure significantly decreased after sesamin was applied to hypertensive rats induced by monocrotaline. The mechanism may be related to sesamin's inhibition of the production of NADPH and MDA [85]. Studies had also confirmed that the antihypertensive mechanism of sesamin was related to the increase in NO activities in the organism. Kong et al. confirmed that sesamin treatment reduced the systolic blood pressure, improved vascular relaxation induced by acetylcholine, and enhanced aortic NO bioactivities. The increase in NO biosynthesis was due to the upregulation of P-eNOS and the inhibition of eNOS uncoupling. In addition, sesamin also reduced the inactivation of NO and the production of superoxide anions by downregulating p47phox. A series of experiments have proved that sesamin can reduce hypertension and improve endothelial dysfunction by enhancing the biological activities of NO in the aorta of hypertensive rats [86].

The antihypertensive effect of sesamin is also attributed to the ability of its metabolites to scavenge free radicals. The systolic blood pressure is positively correlated with the production of superoxide in the aorta. Therefore, the antioxidant activities of sesamin may contribute to its antihypertensive effect [87]. Taking DOCA salt hypertensive rats as models, studies have confirmed that the ability of sesamin to inhibit superoxide production and improve vasodilation contributes to its antihypertensive effect [88–90].

Sesamin is also considered to be an inhibitor of 20-hydroxyeicosatetraenoic acid (20-HETE), which is the metabolite of arachidonic acid. 20-HETE can act on the renin-angiotensin system and change the regulation of blood pressure, leading to hypertension [91]. The experiments *in vitro* have shown that sesamin can prevent the synthesis of 20-HETE in human liver and kidney microsomes with $IC_{50} < 20\,\mu mol/L$. In a randomized controlled crossover trial, overweight men and women ($n = 33$) were given 25 g sesame (approximately 50 mg sesame lignan) daily for 5 weeks. The content of 20-HETE in plasma and urine decreased by 28% and 32%, respectively [92].

The above studies have shown that sesamin may reduce systolic blood pressure and mean arterial pressure, enhance aortic NO activities, and improve vascular endothelial function, thereby lowering blood pressure. Other reports on the antihypertensive effects of sesamin *in vivo* and *in vitro* are shown in Table 5.

3.5.2. The Effect of Sesamin on Atherosclerosis.
Atherosclerosis (As) is a chronic inflammatory disease. Under the influence of risk factors such as hyperlipidemia and high blood pressure, it is easy to cause lipid metabolism disorders in the body and result in a large amount of lipid accumulation under the intima of blood vessels, leading to chronic inflammation [97–99]. The proliferation of SMCs, lipid accumulation in blood vessels, the necrosis, apoptosis, and fibrosis of cells are the characteristics of atherosclerosis [100]. According to reports, there are 8 to 10 million people die every year from cardiovascular disease and stroke caused by atherosclerosis. Studies have confirmed that feeding low-density lipoprotein receptor defect mouse with feed containing sesame oil for 3 months can significantly inhibit the formation of atherosclerotic lesions in mouse and reduce the levels of plasma cholesterol, triglycerides, and low-density lipoprotein cholesterol [101]. To explore the mechanism by which sesame oil may regulate atherosclerosis, Narasimhulu et al. did relate research and found that there were at least three mechanisms by which sesame oil inhibited atherosclerosis: (a) lowering plasma cholesterol by accelerated catabolism through the oxidation of cholesterol; (b) enhancing reverse cholesterol transport mediated by SR-B1 and ABC transporters; and (c) controlling mediators of inflammation [102]. To clarify the role of lignans in this anti-inflammatory response, a more in-depth study was carried out on the mechanism of sesame oil against atherosclerosis, and it was found that sesamin can reduce the formation of atherosclerotic lesions in ApoE-deficient mice with the reduction of nearly 40%, although this was not statistically significant [103]. Related studies have found that in ApoE gene-deficient mice, whether fed with food or atherosclerotic food, the mice showed hypercholesterolemia and

TABLE 4: Effects of sesamin on protection liver and kidney.

Experimental model	Dosage	Administration mode	Administration duration	Mechanism of action	References
$AlCl_3$-induced hepatic injury in rats	160 mg/kg/d	Intraperitoneal injection	8 weeks	Sesamin downregulates the expression of iNOS and levels of MDA and NO and boosts T-AOC and SOD activities	[75]
Cardiac hypertrophy mouse models	100 mg/kg/d	Orally	3 weeks	Sesamin improves cardiac function and prevents the development of cardiac hypertrophy via Sirt3/ROS pathway	[76]
Fluoride-induced male juvenile zebrafish	1.0, 2.0 g/kg	With diet	45, 90 d	Sesamin inhibits the production of ROS and reverses the activities of antioxidant enzymes in liver	[77]
Cisplatin-induced rat kidney injury model	5 mg/kg/d	Orally	7 d	Sesamin reduces the nephrotoxic injury in rats by reversing the oxidative stress and inflammation induced by cisplatin	[81]
Alcohol-induced liver disease in rats	30 mg/kg/d	Intragastric administration	4, 12, 24 weeks	Significantly inhibits the levels of ALT, AST, and γ-GT in rat serum; increases the activities of SOD; and decreases the content of MDA	[82]
LPS/D-GalN-induced fulminant liver failure model in mice	10, 30, 100 mg/kg	Intraperitoneal injection	48 hours	Sesamin reduces the expression of TLR4 on the surface of macrophages and inhibits the activation of p38 MAPK and NF-κB, thereby reducing the production of inflammatory cytokine TNF-α	[83]
Spontaneously hypertensive rat model	80, 160 mg/kg	Intragastric administration	12 weeks	Decreases the diastolic blood pressure in SHR rats; inhibits over-activated PI3K/AKT/mTOR signaling pathway	[84]

TABLE 5: Effects of sesamin on hypertension.

Experimental model	Dosage	Administration mode	Administration duration	Mechanism of action	References
Pulmonary hypertensive rats	50, 100 mg/kg	Injection	4 weeks	The RVSP and mPAP of rats decreased significantly; the expressions of α-SMA and collagen I in pulmonary artery decreased	[93]
Spontaneously hypertensive rats	40, 80, 160 mg/kg	Intragastric administration	16 weeks	SBP, DBP, and MAP were significantly reduced; the content of NO in the aorta and the expression of eNOS mRNA increased	[94]
DOCA salt-sensitive hypertensive rats	10 g/kg	Orally	5 weeks	The systolic blood pressure and the expression of p22phox, gp91phox, and Nox1 decreased	[89]
Two-kidney one-clip hypertensive rats	60, 120 mg/kg	Orally	8 weeks	The systolic blood pressure decreased by 11% (60 mg/kg) and 17% (120 mg/kg)	[95]
Streptozotocin-induced diabetic rat model	50, 100, 200 mg/kg	Orally	4 weeks	Increased systolic and diastolic blood pressure: 50 mg (17/8.2 mmHg), 100 mg (37.8/14.7 mmHg), and 200 mg (38.6/17.5 mmHg)	[96]

atherosclerotic lesions [104], while in LDL receptor-deficient mice, hypercholesterolemia and atherosclerotic lesions will only appear after feeding foods that cause atherosclerosis [105]. The anti-atherosclerotic effect of sesamin is expected to be more pronounced in LDL-deficient mice than in ApoE gene-deficient mice. Therefore, it is recommended that LDL-deficient mice be used as a model to evaluate the anti-atherosclerotic effect of sesamin.

Studies have found that sesamin inhibited the growth and proliferation of vascular smooth muscle cells (VSMCs) in humans, mouse, and rat induced by PDGF-BB by inhibiting the activation of MAPK and PI3K pathways and reducing oxidative stress by inducing the expression of heme oxygenase-1 [106]. In fact, other studies have shown that sesamin (25–100 μM) upregulated the expression and transcriptional activities of PPARγ1 and LXRα in macrophages through MAPK signals and enhanced cholesterol efflux from macrophages. PPARγ1 and LXRα are important nuclear receptors involved in macrophage cholesterol homeostasis and inflammation. Therefore, another mechanism of sesamin's anti-atherosclerosis may be to promote the outflow of macrophage cholesterol and prevent the formation of foam cells [107].

Studying the effect of sesamin on the adhesion molecules of endothelial leukocytes can provide a more in-depth understanding of the anti-atherosclerotic mechanism of

TABLE 6: Effects of sesamin on atherosclerosis.

Experimental model	Dosage	Administration mode	Administration duration	Mechanism of action	References
Rabbit model of atherosclerosis	High-fat feed + sesamin (4 mg/d)	Intragastric administration	8 weeks	TC, TG, and LDL were significantly reduced; the level of MMP-13 in the sesamin group was significantly lower than that in the model group	[111]
Rabbit model of atherosclerosis	High-fat feed + sesamin (4 mg/d)	Intragastric administration	8 weeks	TC, TG, HDL, and LDL were significantly lower than the model group; SOD expression increased	[112]
Rabbit model of atherosclerosis	High-cholesterol feed + sesamin (4 mg/d)	Intragastric administration	0, 5, 8 weeks	LDL in serum is lower than the model group; MMP-2 and MMP-9 levels are significantly lower than the model group	[113]
ApoE gene deletion mouse	64 mg/kg	Orally	20 weeks	Reduce the formation of atherosclerotic lesion by 40%	[114]
ApoE gene deletion mouse	5 g/kg	Orally	11 weeks	Decreased expression of ICAM-1 protein; shrinkage of the aortic intima	[115]
Rabbit model of atherosclerosis	High-cholesterol feed (100 g/d) + sesamin (4 mg/d)	Intragastric administration	0, 5, 8 weeks	TC and LDL were significantly lower than the model group; the expression of vascular cell adhesion molecule-1 was downregulated by 42.9%	[116]
Renal hypertensive-hyperlipidemia rats	10, 33, 100 mg/kg	Intragastric administration	8 weeks	TC, TG, and LDL decreased; HDL-C increased; inhibited aortic intima thickening and the formation of inflammatory cells and foam cells	[117]

sesamin. Studies have shown that treatment of human aortic endothelial cells (HAECs) treated with tumor necrosis factor-alpha with sesamin ($10 \mu M$, $100 \mu M$) reduced the expression of intercellular adhesion molecule-1 by 35% and 70%, respectively [108]. The inhibitory effect of sesamin on ICAM-1 was also mediated by the downregulation of ERK1/2 and p38. In addition to ICAM-1, sesamin can also inhibit the expression of VCAM-1 in the rat aorta with an inhibition rate of 27.59% [109]. ICAM-1 and VCAM-1 play a role in the adhesion of monocytes to endothelial cells, and both participate in the formation of atherosclerotic lesions [110]. Other reports on the anti-atherosclerosis effect of sesamin are shown in Table 6.

3.5.3. The Effect of Sesamin on Diabetes. Diabetes is one of the leading causes of death in the world. There are approximately 2.2 million people die of diabetes worldwide each year. In fact, diabetes is a manifestation of metabolic disorders. High blood lipids and high blood sugar cause inflammation and oxidative stress damage. When the body cannot control blood sugar levels, it shows that insulin secretion or insulin response is blocked, leading to the occurrence of diabetes [118].

Studies have reported the effect of sesamin on diabetes and its complications. Sesamin treatment of spontaneous diabetic mice (KK-Ay) can significantly reduce the levels of fasting blood glucose, cholesterol, and triglycerides and improve the insulin-binding capacity to liver crude plasma membranes [119]. Some researchers have done experiments in humans. Patients with type 2 diabetes took 200 mg of sesamin daily for 8 weeks. The examination found that fasting blood glucose (FBS),

glycosylated hemoglobin (HbA1c), TNF-α, body adiposity index (BAI), and other indicators were significantly reduced [120]. All these indicate that sesamin can regulate blood sugar levels and reduce inflammation.

One of the causes of diabetes is the long-term excessive consumption of fat-rich foods. However, taking sesamin together with high-fat foods can reduce the occurrence of this adverse reaction. For example, after taking sesamin in high-fat diet rats, it can significantly improve the fasting blood glucose and white adipose tissue concentration in the body, and it can also reduce the level of glucose-6-phosphatase (G6Pase) [121]. The reduction of G6Pase reduced the conversion of glucose-6-phosphate to glucose, thereby reducing blood glucose concentration. In addition to regulating blood sugar concentration, sesamin can also prevent the damage of skeletal muscle mitochondria in diabetic patients and effectively improve the decline of their exercise capacity. Sesamin mainly achieved this goal by inhibiting the increase of NADPH oxidase activities and the production of superoxide anions [122]. What is more, sesamin has also been found to have a cardioprotective function. Taking sesamin (100, 200 mg/kg) for 4 weeks in STZ-induced type 1 diabetic rats can significantly reduce blood sugar levels and improve heart rate and blood pressure [100]. Other reports on the antidiabetic effect of sesamin are shown in Table 7.

At present, there are few studies on the effects of sesamin on type 1 and type 2 diabetes, and the existing studies are only at the stage of model experiments, which needs to be further strengthened in clinical trial research. Furthermore, in addition to the effect of sesamin on fasting blood glucose, whether it has an effect on postprandial blood glucose and the secretion of insulin and C peptide needs to be further studied.

TABLE 7: Effects of sesamin on diabetes.

| Experimental model	Dosage	Administration mode	Administration duration	Mechanism of action	References
Rats model of type 2 diabetes	60, 120 mg/kg/d	Intragastric administration	8 weeks	In the high-dose group, endothelium-dependent vasodilation was enhanced; NO activities increased; serum MDA content decreased; aortic eNOS protein expression increased	[123]
Adult male Wistar rats	30 mg/kg/d	Intraperitoneal injection	8 weeks	Prevent the loss of hippocampal CA1 neurons, regulate the expression of Bcl-2 family proteins, and reduce blood glucose levels	[124]
C57BL/6J mice	160 mg/kg	Intragastric administration	4 weeks	The content of liver glycogen was increased; the dysfunction and apoptosis of β-cell were improved	[86]
C57BL/6J mice	0.2 g/kg	Orally	8 weeks	Increased blood insulin and blood lipids caused by high-fat diet were improved	[125]
Hyperlipidemia SD rats	—	—	7 weeks	The levels of TC, TG, LDL, ApoB, and insulin decreased; the levels of HDL-C and ApoA increased	[126]
Type 2 diabetes patients	200 mg/d	Orally	8 weeks	FBS and HbA1c levels decreased; serum adiponectin levels increased	[120]
Type 1 diabetic rats induced by STZ	50, 100, 200 mg/kg	Orally	4 weeks	Blood sugar level decreased by 17% (50 mg/kg), 30% (100 mg/kg), and 26% (200 mg/kg)	[127]
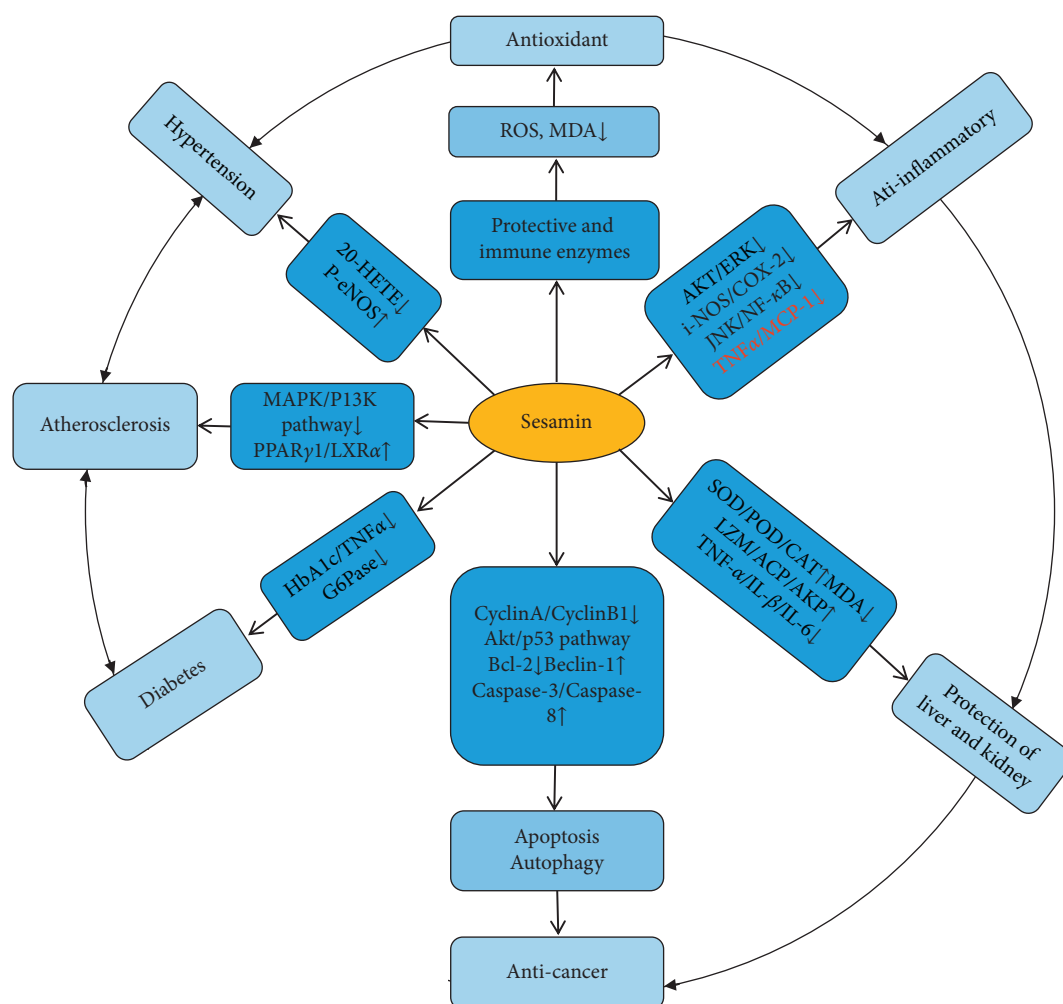
FIGURE 5: Schema of sesamin's various pharmacological properties and its mechanism of action.

4. Conclusion

Sesamin is a natural lignan compound mainly found in sesame seeds. At present, many studies have reported that it has rich medicinal value. This article systematically summarized its pharmacological activities and found that sesamin has obvious antioxidant and anti-inflammatory effects and multiorgan protection. The antioxidant effect of sesamin is achieved by reducing lipid peroxidation, reducing the levels of superoxide and nitric oxide, and improving the activities of antioxidase such as SOD, CAT, and GSH. Oxidative stress damage can also cause inflammation, sesamin can reduce COX and PEG2, and inhibit the release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, etc.) to alleviate the inflammatory response, which also has a certain protective and therapeutic effect on the damage of liver, kidney, lung, and other organs caused by oxidative stress and inflammation. However, research shows that the antioxidant and anti-inflammatory effects of sesamin depend on its metabolites containing the catechol moieties. Inflammation can also cause a variety of complications including various cancers. Studies have found that sesamin can inhibit the occurrence of liver cancer, lung cancer, colon cancer, breast cancer, and other cancers to varying degrees. Research studies *in vivo* and *in vitro* have shown that sesamin inhibits the growth of cancer cells by downregulating protein expression, inhibiting the production of gene products, and inducing cell cycle arrest. In addition, by inhibiting the production of ROS, sesamin enhances the biological activities of NO in blood vessels, improves endothelial dysfunction and hypertension, and changes the process of atherosclerotic lesion formation. Continuously taking sesamin can reduce the levels of fasting blood glucose concentration, glycosylated hemoglobin (HbA1c), and body adiposity index (BAI), regulate blood sugar levels, and reduce the occurrence of diabetes. The various pharmacological properties of sesamin and its mechanism of action can be seen in Figure 5.

Through the above research reports, we can find that the current research reports on the pharmacological effects of sesamin are relatively extensive, but few studies can clearly point out the link between the mechanism of sesamin and the disease. In particular, the influence of inflammation and oxidative damage on the existence of disease is worthy of in-depth study. In addition, the research on the structure-activity relationship of sesamin is rarely reported. The structure-activity relationship study can infer the relationship between the chemical structure and physiological activities of the biologically active substance and then infer the structure of the target active site and design a new active substance structure. Surprisingly, studies have found that the catechol groups in sesamin metabolites play an important role in antioxidant and anti-inflammatory effects. This provides a new direction for further research on the structure-activity relationship of sesamin, and it has certain reference significance for its better application in clinical and new drug design.

Abbreviations

ROS:	Reactive oxygen species
SOD:	Superoxide dismutase
MDA:	Malondialdehyde
AKT:	Protein kinase B
ERK:	Extracellular regulated protein kinases
COX-2:	Cyclooxygenase-2
JNK:	c-Jun *N*-terminal kinase
LCM:	Lysozyme
ACP:	Acyl carrier protein
AKP:	Alkaline phosphatase
TNF-α:	Tumor necrosis factor-α
IL-β:	Interleukin-β
IL-6:	Interleukin-6
Bcl-2:	B-Cell lymphoma-2
HbA1a:	Glycated hemoglobin
G6Pase:	Glucose-6-phosphatase
MAPK:	Mitogen-activated protein kinase
PPARγ1:	Peroxisome proliferator-activated receptors
LXRα:	Liver *X* receptor alpha
20-HETE:	20-Hydroxyeicosatetraenoic acid.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Y. Z. and F. L. conceptualized the review and drafted the initial version of the manuscript. Y. L and L. H. L. undertook the database search for the literature. M. F. C. and L. N. significantly contributed in the gathering of information and discussions of the manuscript. All authors read and approved the final manuscript. Yao Zhang and Fen Liu contributed equally to the article.

Acknowledgments

References

[1] M. Sayeh and A. Hassan, "A comprehensive mechanistic insight into the dietary and estrogenic lignans, arctigenin and sesamin as potential anticarcinogenic and anticancer agents. Current status, challenges, and future perspectives," *Critical Reviews in Food Science and Nutrition*, vol. 61, pp. 1–17, 2021.

[2] R. Joshi, M. S. Kumar, K. Satyamoorthy, M. K. Unnikrisnan, and T. Mukherjee, "Free radical reactions and antioxidant activities of sesamol: pulse radiolytic and biochemical

studies," *Journal of Agricultural and Food Chemistry*, vol. 53, no. 7, pp. 2696–2703, 2005.

[3] J. Xu, S.-B. Chen, and Q.-H. Hu, "Antioxidant activity of brown pigment and extracts from black sesame seed (Sesamum indicum L.)," *Food Chemistry*, vol. 91, no. 1, pp. 79–83, 2005.

[4] X.-P. Bai, X.-L. Gou, P.-H. Cai et al., "Sesamin enhances Nrf2-mediated protective defense against oxidative stress and inflammation in colitis via AKT and ERK activation," *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 2432416, 20 pages, 2019.

[5] H. Ye, L.-Y. Sun, J. Li et al., "Sesamin attenuates carrageenan-induced lung inflammation through upregulation of A20 and TAX1BP1 in rats," *International Immunopharmacology*, vol. 88, Article ID 107009, 2020.

[6] S. Dalibalta, A. F. Majdalawieh, and H. Manjikian, "Health benefits of sesamin on cardiovascular disease and its associated risk factors," *Saudi Pharmaceutical Journal*, vol. 28, no. 10, pp. 1276–1289, 2020.

[7] S.-Z. Ye, W. Wang, X.-Y. Chen, and Y.-B. Deng, "Sesamin promotes angiogenesis and accelerates wound healing in rats via alleviates TBHP-induced apoptosis in human umbilical vein endothelial cells," *Bioscience, Biotechnology, and Biochemistry*, vol. 84, no. 5, pp. 887–897, 2020.

[8] W. Adriani, "About sesame and sesame oil," *Journal of Food Studies*, vol. 56, no. 3, pp. 187–194, 1928.

[9] M. Ye, Y.-N. Yan, X.-M. Ni, and L. Qiao, "Study on the chemical constituents of the whole plant of Cuscuta," *Journal of Chinese Medicinal Materials*, vol. 5, pp. 339–341, 2001.

[10] F.-Z. Ren, B.-K. He, X.-H. Luan, and Y.-M. Zhao, "Study on chemical constituents of Callicarpa bodinieri," *Chinese Pharmaceutical Journal*, vol. 1, pp. 17–19, 2004.

[11] S. Lee, B. K. Kim, S. H. Cho, and K. H. Shin, "Phytochemical constituents from the fruits of Acanthopanax sessiliflorus," *Archives of Pharmacal Research*, vol. 25, no. 3, pp. 280–284, 2002.

[12] Y.-H. Liu, J.-X. Li, L.-X. Xin, N.-W. Zhao, and L.-T. Pan, "Chemical constituents of lsodn flavidus produced leishan," *Chinese Traditional and Herbal Drugs*, vol. 47, no. 10, pp. 1657–1660, 2016.

[13] H.-P. Dai, X.-G. Wang, and C.-T. Yu, "China oils and fats," *Research and exploitation of sesamin*, vol. 6, pp. 52–54, 2003.

[14] T. Tashiro, Y. Fukuda, and T. Osawa, "Oil contents of seeds and minor components in the oil of sesame, Sesamum indicum L., as affected by capsule position," *Japanese Journal of Crop Science*, vol. 60, no. 1, pp. 116–121, 1991.

[15] M.-T. Wu, S.-Y. Liu, D.-L. Huang et al., "Chemical constituents from the leaves of Cinnamomum camphora var. linaloolifera and their anti-inflammatory activities," *China Journal of Chinese Materia Medica*, vol. 46, no. 14, pp. 3592–3598, 2021.

[16] L. Ni, S.-Q. Zou, M.-T. Wu et al., "A new plant-derived raw material for preparing sesamin and its method," CN112661768A, 2021.

[17] L. Ni, S.-Q. Zou, and M.-T. Wu, "A new plant-derived raw material for preparing 4-hydroxysesamin and its method," CN111004247A, 2020.

[18] W.-H. Si, P.-F. Xie, K.-Y. Ma et al., "Antioxidant activity of sesamin in canola oil," *Journal of the American Oil Chemists' Society*, vol. 90, no. 4, pp. 511–516, 2013.

[19] Y. Wan, H.-X. Li, G.-M. Fu, X.-Y. Chen, F. Chen, and M.-Y. Xie, "The relationship of antioxidant components and antioxidant activity of sesame seed oil," *Journal of the Science of Food and Agriculture*, vol. 95, no. 13, pp. 2571–2578, 2015.

[20] M. Nadeem, C. Situ, A. Mahmud et al., "Antioxidant activity of sesame (Sesamum indicum L.) cake extract for the stabilization of olein based butter," *Journal of the American Oil Chemists' Society*, vol. 91, no. 6, pp. 967–977, 2014.

[21] W. Ruankham, W. Suwanjang, P. Wongchitrat, V. Prachayasittikul, S. Prachayasittikul, and K. Phopin, "Sesamin and sesamol attenuate H_2O_2-induced oxidative stress on human neuronal cells via the SIRT1-SIRT3-FOXO3a signaling pathway," *Nutritional Neuroscience*, vol. 24, no. 2, pp. 90–101, 2021.

[22] T. D. Le, Y. Nakahara, M. Ueda et al., "Sesamin suppresses aging phenotypes in adult muscular and nervous systems and intestines in a Drosophila senescence-accelerated model," *European Review for Medical and Pharmacological Sciences*, vol. 23, no. 4, pp. 1826–1839, 2019.

[23] J.-X. Zhang, J.-R. Yang, G.-X. Chen et al., "Sesamin ameliorates arterial dysfunction in spontaneously hypertensive rats via downregulation of NADPH oxidase subunits and upregulation of eNOS expression," *Acta Pharmacologica Sinica*, vol. 34, no. 7, pp. 912–920, 2013.

[24] T. D. Le and Y. H. Inoue, "Sesamin activates Nrf2/Cnc-dependent transcription in the absence of oxidative stress in drosophila adult brains," *Antioxidants*, vol. 10, no. 6, pp. 924–943, 2021.

[25] J.-L. Cao, J.-J. Chen, L.-T. Xie, J.-D. Wang, C.-P. Feng, and J. Song, "Protective properties of sesamin against fluoride-induced oxidative stress and apoptosis in kidney of carp (Cyprinus carpio) via JNK signaling pathway," *Aquatic Toxicology*, vol. 167, pp. 180–190, 2015.

[26] X.-W. Chen, X.-Z. Ying, L. Chen, W.-W. Zhang, and Y.-C. Zhang, "Protective effects of sesamin on liver fibrosis through antioxidative and anti-inflammatory activities in rats," *Immunopharmacology and Immunotoxicology*, vol. 37, no. 5, pp. 465–472, 2015.

[27] P. F. Hsieh, C. W. Hou, P. W. Yao et al., "Sesamin ameliorates oxidative stress and mortality in kainic acid-induced status epilepticus by inhibition of MAPK and COX-2 activation," *Journal of Neuroinflammation*, vol. 8, no. 1, p. 57, 2011.

[28] H.-M. Chiang, H. Chang, P.-W. Yao et al., "Sesamin reduces acute hepatic injury induced by lead coupled with lipopolysaccharide," *Journal of the Chinese Medical Association*, vol. 77, no. 5, pp. 227–233, 2014.

[29] T. Baluchnejadmojarad, M. Mansouri, J. Ghalami, Z. Mokhtari, and M. Roghani, "Sesamin imparts neuroprotection against intrastriatal 6-hydroxydopamine toxicity by inhibition of astroglial activation, apoptosis, and oxidative stress," *Biomedicine & Pharmacotherapy*, vol. 88, pp. 754–761, 2017.

[30] C.-H. Lin, M.-L. Shen, N. Zhou, C.-C. Lee, S.-T. Kao, and D.-C. Wu, "Protective effects of the polyphenol sesamin on allergen-induced T(H)2 responses and airway inflammation in mice," *PLoS One*, vol. 9, no. 4, Article ID e96091, 2014.

[31] J.-Q. Ma, J. Ding, L. Zhang, and C.-M. Liu, "Hepatoprotective properties of sesamin against CCl 4 induced oxidative stress-mediated apoptosis in mice via JNK pathway," *Food and Chemical Toxicology*, vol. 64, pp. 41–48, 2014.

[32] B. Helli, K. Mowla, M. Mohammadshahi, and M. T. Jalali, "Effect of sesamin supplementation on cardiovascular risk factors in women with rheumatoid arthritis," *Journal of the American College of Nutrition*, vol. 35, no. 4, pp. 300–307, 2016.

[33] R. Zhang, Y. Yu, S. Hu et al., "Sesamin ameliorates hepatic steatosis and inflammation in rats on a high-fat diet via LXRα

and PPARα," *Nutrition Research*, vol. 36, no. 9, pp. 1022–1030, 2016.

[34] A. Mohasana, K. Z. Neamul, S. J. Uddin et al., "A systematic review on antioxidant and antiinflammatory activities of Sesame (Sesamum indicum L.) oil and further confirmation of antiinflammatory activities by chemical profiling and molecular docking," *Phytotherapy Research*, vol. 33, no. 10, pp. 2585–2608, 2019.

[35] X.-P. Bai, X.-L. Gou, P.-H. Cai et al., "Sesamin enhances Nrf2-mediated protective defense against oxidative stress and inflammation in colitis via AKT and ERK activation," *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 2432416, 20 pages, 2019.

[36] T.-Y. Lin, P.-Y. Wu, C.-W. Hou et al., "Protective effects of sesamin against UVB-induced skin inflammation and photodamage in vitro and in vivo," *Biomolecules*, vol. 9, no. 9, pp. 479–502, 2019.

[37] S. Udomruk, C. Kaewmool, P. Pothacharoen, T. Phitak, and P. Kongtawelert, "Sesamin suppresses LPS-induced microglial activation via regulation of TLR4 expression," *Journal of Functional Foods*, vol. 49, pp. 32–43, 2018.

[38] Z.-L. Li, M. Gao, M.-S. Yang, X.-F. Xiao, J.-J. Liu, and B.-C. Yang, "Sesamin attenuates intestinal injury in sepsis via the HMGB1/TLR4/IL-33 signalling pathway," *Pharmaceutical Biology*, vol. 58, no. 1, pp. 898–904, 2020.

[39] S. Deng, J.-L. Zhou, H.-S. Fang, Z.-G. Nie, S. Chen, and H. Peng, "Sesamin protects the femoral head from osteonecrosis by inhibiting ROS-induced osteoblast apoptosis in rat model," *Frontiers in Physiology*, vol. 9, pp. 1787–1795, 2018.

[40] S. Ahmad, N. M. ElSherbiny, M. S. Jamal et al., "Anti-inflammatory role of sesamin in STZ induced mice model of diabetic retinopathy," *Journal of Neuroimmunology*, vol. 295-296, pp. 47–53, 2016.

[41] Y.-H. Zhao, Q.-X. Wang, M.-Z. Jia et al., "(+)-Sesamin attenuates chronic unpredictable mild stress-induced depressive-like behaviors and memory deficits via suppression of neuroinflammation," *The Journal of Nutritional Biochemistry*, vol. 64, pp. 61–71, 2019.

[42] M. Fukunaga, M. Ohnishi, A. Shiratsuchi et al., "Sesamin increases heme oxygenase-1 protein in RAW 264.7 macrophages through inhibiting its ubiquitination process," *European Journal of Pharmacology*, vol. 741, pp. 214–221, 2014.

[43] W. J. Lee, H. C. Ou, C. M. Wu et al., "Sesamin mitigates inflammation and oxidative stress in endothelial cells exposed to oxidized low-density lipoprotein," *Journal of Agricultural and Food Chemistry*, vol. 57, no. 23, pp. 11406–11417, 2009.

[44] W. Srisuthtayanont, D. Pruksakorn, P. Kongtawelert, and P. Pothacharoen, "Effects of sesamin on chondroitin sulfate proteoglycan synthesis induced by interleukin-1beta in human chondrocytes," *BMC Complementary and Alternative Medicine*, vol. 17, no. 1, pp. 286–311, 2017.

[45] M. Nakai, M. Harada, K. Nakahara et al., "Novel antioxidative metabolites in rat liver with ingested sesamin," *Journal of Agricultural and Food Chemistry*, vol. 51, no. 6, pp. 1666–1670, 2003.

[46] Y. Kabe, D. Takemoto, A. Kanai et al., "Annexin A1 accounts for an anti-inflammatory binding target of sesamin metabolites," *NPJ Science of Food*, vol. 4, no. 1, p. 4, 2020.

[47] N. Abe-Kanoh, Y. Kunimoto, D. Takemoto et al., "Sesamin catechol glucuronides exert anti-inflammatory effects by suppressing interferon β and inducible nitric oxide synthase expression through deconjugation in macrophage-like J774.1 cells," *Journal of Agricultural and Food Chemistry*, vol. 67, no. 27, pp. 7640–7649, 2019.

[48] C.-X. Li, H. Zhang, X.-F. Wu et al., "Clinical efficacy and prognostic factors analysis following curative hepatectomy for hepatocellular carcinoma patients with different China liver cancer staging," *Chinese Journal of Surgery*, vol. 59, no. 2, pp. 134–143, 2021.

[49] L.-D. Ma, Y. Zhang, S.-H. Wen et al., "Enhancing effect of matrine on the tumor-inhibition by TIM2 gene-modified hepatocarcinoma H22 cells in mice," *Chinese Journal of Oncology*, vol. 30, no. 4, pp. 255–258, 2008.

[50] L.-D. Ma, Y. Zhang, S.-H. Wen et al., "Effects of matrine on oncogenicity of H22 cells modified by TIM2 gene in vivo," *China Journal of Chinese Materia Medica*, vol. 33, no. 10, pp. 1175–1179, 2008.

[51] W. Cao, K. Mo, S.-J. Wei, X.-B. Lan, W.-J. Zhang, and W.-Z. Jiang, "Effects of rosmarinic acid on immunoregulatory activity and hepatocellular carcinoma cell apoptosis in H22 tumor-bearing mice," *Korean Journal of Physiology and Pharmacology*, vol. 23, no. 6, pp. 501–508, 2019.

[52] P.-Y. Deng, C. Wang, L.-L. Chen et al., "Sesamin induces cell cycle arrest and apoptosis through the inhibition of signal transducer and activator of transcription 3 signalling in human hepatocellular carcinoma cell line HepG2," *Biological and Pharmaceutical Bulletin*, vol. 36, no. 10, pp. 1540–1548, 2013.

[53] Y. Ono, N. Tomimori, H. Hori, Y. Kitagawa, and H. Shibata, "Mechanisms of chromosomal aberrations induced by sesamin metabolites in Chinese hamster lung cells," *Mutation Research, Genetic Toxicology and Environmental Mutagenesis*, vol. 822, pp. 19–26, 2017.

[54] Z.-G. Liu, Q. Xiang, L.-H. Du, G. Song, Y.-T. Wang, and X.-B. Liu, "The interaction of sesamol with DNA and cytotoxicity, apoptosis, and localization in HepG2 cells," *Food Chemistry*, vol. 141, no. 1, pp. 289–296, 2013.

[55] S.-S. Yang, X.-G. Li, H.-W. Dou, Y.-L. Hu, C.-G. Che, and D.-Y. Xu, "Sesamin induces A549 cell mitophagy and mitochondrial apoptosis via a reactive oxygen species-mediated reduction in mitochondrial membrane potential," *Korean Journal of Physiology and Pharmacology*, vol. 24, no. 3, pp. 223–232, 2020.

[56] Y.-M. Chen, H.-C. Li, W.-N. Zhang et al., "Sesamin suppresses NSCLC cell proliferation and induces apoptosis via Akt/p53 pathway," *Toxicology and Applied Pharmacology*, vol. 387, Article ID 114848, 2020.

[57] M. Watanabe, Y. Iizumi, M. Sukeno, M. Iizuka-Ohashi, Y. Sowa, and T. Sakai, "The pleiotropic regulation of cyclin D1 by newly identified sesaminol-binding protein ANT2," *Oncogenesis*, vol. 6, no. 4, p. e311, 2017.

[58] K. B. Harikumar, B. Sung, S. T. Tharakan et al., "Sesamin manifests chemopreventive effects through the suppression of NF-kappa B-regulated cell survival, proliferation, invasion, and angiogenic gene products," *Molecular Cancer Research*, vol. 8, no. 5, pp. 751–761, 2010.

[59] B. R. Balsara, J. M. Pei, R. Page et al., "Frequent activation of AKT in non-small cell lung carcinomas and preneoplastic bronchial lesions," *Carcinogenesis*, vol. 25, no. 11, pp. 2053–2059, 2004.

[60] H.-W. Dou, S.-S. Yang, Y.-L. Hu, D.-Y. Xu, L. Liu, and X.-D. Li, "Sesamin induces ER stress-mediated apoptosis and activates autophagy in cervical cancer cells," *Life Sciences*, vol. 200, pp. 87–93, 2018.

[61] F.-B. Sun, J.-Q. Bai, Y. Wang, B. Zhao, Y.-Y. Tong, and X.-X. Zhang, "The effect of sesamin on human's colon cancer

SW480 cells," *Journal of Jilin Medical College*, vol. 36, no. 5, pp. 324–327, 2015.

[62] J.-M. Chen, P.-Y. Chen, C.-C. Lin et al., "Antimetastatic effects of sesamin on human head and neck squamous cell carcinoma through regulation of matrix metalloproteinase-2," *Molecules*, vol. 25, no. 9, pp. 2248–2264, 2020.

[63] P. Kongtawelert, B. Wudtiwai, T. H. Shwe, P. Pothacharoen, and T. Phitak, "Inhibition of programmed death ligand 1 (PD-L1) expression in breast cancer cells by sesamin," *International Immunopharmacology*, vol. 86, Article ID 106759, 2020.

[64] T. Yokota, Y. Matsuzaki, M. Koyama et al., "Sesamin, a lignan of sesame, down-regulates cyclin D1 protein expression in human tumor cells," *Cancer Science*, vol. 98, no. 9, pp. 1447–1453, 2007.

[65] J. S. Truan, J. M. Chen, and L. U. Thompson, "Comparative effects of sesame seed lignan and flaxseed lignan in reducing the growth of human breast tumors (MCF-7) at high levels of circulating estrogen in athymic mice," *Nutrition and Cancer*, vol. 64, no. 1, pp. 65–71, 2012.

[66] C.-C. Lee, K.-J. Liu, Y.-C. Wu, S.-J. Lin, C.-C. Chang, and T.-S. Huang, "Sesamin inhibits macrophage-induced vascular endothelial growth factor and matrix metalloproteinase-9 expression and proangiogenic activity in breast cancer cells," *Inflammation*, vol. 34, no. 3, pp. 209–221, 2011.

[67] M. R. Akl, N. M. Ayoub, B. S. Abuasal, A. Kaddoumi, and P. W. Sylvester, "Sesamin synergistically potentiates the anticancer effects of γ-tocotrienol in mammary cancer cell lines," *Fitoterapia*, vol. 84, pp. 347–359, 2013.

[68] Y. Miyahara, T. Komiya, H. Katsuzaki et al., "Sesamin and episesamin induce apoptosis in human lymphoid leukemia Molt 4B cells," *International Journal of Molecular Medicine*, vol. 6, no. 1, pp. 43–46, 2000.

[69] C. C. Hsieh, C. H. Kuo, H. F. Kuo et al., "Sesamin suppresses macrophage-derived chemokine expression in human monocytes via epigenetic regulation," *Food & Function*, vol. 5, no. 10, pp. 2494–2500, 2014.

[70] X. Kong, M.-Z. Ma, Y. Zhang et al., "Differentiation therapy: sesamin as an effective agent in targeting cancer stem-like side population cells of human gallbladder carcinoma," *BMC Complementary and Alternative Medicine*, vol. 14, no. 1, p. 254, 2014.

[71] T.-N. Kuo, C.-S. Lin, G.-D. Li, C.-Y. Kuo, and S.-H. Kao, "Sesamin inhibits cervical cancer cell proliferation by promoting p53/PTEN-mediated apoptosis," *International Journal of Medical Sciences*, vol. 17, no. 15, pp. 2292–2298, 2020.

[72] Y.-T. Sui, S.-Y. Li, Y.-H. Zhao et al., "Identification of a natural compound, sesamin, as a novel TRPM8 antagonist with inhibitory effects on prostate adenocarcinoma," *Fitoterapia*, vol. 145, Article ID 104631, 2020.

[73] P.-Y. Xu, F. Cai, X.-F. Liu, and L.-L. Guo, "Sesamin inhibits lipopolysaccharide-induced proliferation and invasion through the p38-MAPK and NF-κB signaling pathways in prostate cancer cells," *Oncology Reports*, vol. 33, no. 6, pp. 3117–3123, 2015.

[74] M. Srisayam, N. Weerapreeyakul, and K. Kanokmedhakul, "Inhibition of two stages of melanin synthesis by sesamol, sesamin and sesamolin," *Asian Pacific Journal of Tropical Biomedicine*, vol. 7, no. 10, pp. 886–895, 2017.

[75] M.-Q. Zhao, S.-G. Zheng, J.-R. Yang et al., "Protective effect of sesamin on the hepatic injury of rats induced by $AlCl_3$ and

D-gal," *Acta Academiae Medicinae Wuhan*, vol. 33, no. 4, pp. 283–286, 2014.

[76] D. Fan, Z. Yang, F.-Y. Liu et al., "Sesamin protects against cardiac remodeling via Sirt3/ROS pathway," *Cellular Physiology and Biochemistry*, vol. 44, no. 6, pp. 2212–2227, 2017.

[77] J.-L. Cao, C.-P. Feng, L.-T. Xie et al., "Sesamin attenuates histological alterations, oxidative stress and expressions of immune-related genes in liver of zebrafish (*Danio rerio*) exposed to fluoride," *Fish & Shellfish Immunology*, vol. 106, pp. 715–723, 2020.

[78] M. B. Tekin and H. Toker, "The effect of hyperlipidemia on bone graft regeneration of peri-implantal created defects in rabbits," *International journal of implant dentistry*, vol. 5, no. 1, pp. 18–25, 2019.

[79] A. M. Rousta, S. M. S. Mirahmadi, A. Shahmohammadi et al., "Protective effect of sesamin in lipopolysaccharide-induced mouse model of acute kidney injury via attenuation of oxidative stress, inflammation, and apoptosis," *Immunopharmacology and Immunotoxicology*, vol. 40, no. 5, pp. 423–429, 2018.

[80] J.-L. Xuan, *Protective Effects of Sesamin on Renal Fibrosis in Spontaneoushypertensive Rats and its Related Mechanism*, Wannan Medical College, Wuhu, China, 2015.

[81] B. H. Ali, S. Al Salam, Y. Al Suleimani et al., "Ameliorative effect of sesamin in cisplatin-induced nephrotoxicity in rats by suppressing inflammation, oxidative/nitrosative stress, and cellular damage," *Physiological Research*, vol. 69, no. 1, pp. 61–72, 2020.

[82] T. S. Tai, N. Tien, H. Y. Shen et al., "Sesamin, a naturally occurring lignan, inhibits ligand-induced lipogenesis through interaction with liver *X* receptor alpha (LXR *α*) and pregnane *X* receptor (PXR)," *Evidence-based Complementary and Alternative Medicine*, vol. 2019, Article ID 9401648, 17 pages, 2019.

[83] L. Ma, *Sesamin Ameliorates Lipopolysaccharide/D-Galactosamine Induced Fulminant Hepatic Failure by Suppression of Toll-like Receptor 4 Signaling in Mice*, ChongQing Medical University, Chongqing, China, 2015.

[84] H.-R. Hu, J.-L. Xuan, J.-R. Yang, W. Li, M.-Q. Zhao, and J. Han, "Effects of sesamin on ameliorating kidney injury in spontaneously hypertensive rats and its relationship with PI3K/AKT/mTOR signaling pathway," *Chinese Journal of Pathophysiology*, vol. 32, no. 4, pp. 719–725, 2016.

[85] X.-W. Li, Y.-X. Gao, S. Li, and J.-R. Yang, "Effect of sesamin on pulmonary vascular remodeling in rats with monocrotaline-induced pulmonary hypertension," *China Journal of Chinese Materia Medica*, vol. 40, no. 7, pp. 1355–1361, 2015.

[86] X. Kong, W. Li, L.-Q. Guo et al., "Sesamin enhances nitric oxide bioactivity in aortas of spontaneously hypertensive rats," *Therapeutic Advances in Cardiovascular Disease*, vol. 9, no. 5, pp. 314–324, 2015.

[87] D. Nakano, C. J. Kwak, K. Fujii et al., "Sesamin metabolites induce an endothelial nitric oxide-dependent vasorelaxation through their antioxidative property-independent mechanisms: possible involvement of the metabolites in the antihypertensive effect of sesamin," *Journal of Pharmacology and Experimental Therapeutics*, vol. 318, no. 1, pp. 328–335, 2006.

[88] D. Nakano, C. Itoh, M. Takaoka, Y. Kiso, T. Tanaka, and Y. Matsumura, "Antihypertensive effect of sesamin. IV. Inhibition of vascular superoxide production by sesamin," *Biological and Pharmaceutical Bulletin*, vol. 25, no. 9, pp. 1247–1249, 2002.

[89] D. Nakano, D. Kurumazuka, Y. Nagai, A. Nishiyama, Y. Kiso, and Y. Matsumura, "Dietary sesamin suppresses aortic NADPH oxidase in DOCA salt hypertensive rats," *Clinical and Experimental Pharmacology and Physiology*, vol. 35, no. 3, pp. 324–326, 2008.

[90] M. Yasuo, K. Satomi, O. Rie, and O. Tomoko, "Effects of sesamin on altered vascular reactivities in aortic rings of deoxycorticosterone acetate-salt-induced hypertensive rat," *Biological and Pharmaceutical Bulletin*, vol. 23, no. 9, pp. 1041–1045, 2000.

[91] S. L. Hoopes, V. Garcia, M. L. Edin, M. L. Schwartzman, and D. C. Zeldin, "Vascular actions of 20-HETE," *Prostaglandins & Other Lipid Mediators*, vol. 120, pp. 9–16, 2015.

[92] J. H. Wu, J. M. Hodgson, M. W. Clarke et al., "Inhibition of 20-hydroxyeicosatetraenoic acid synthesis using specific plant lignans: in vitro and human studies," *Hypertension*, vol. 54, no. 5, pp. 1151–1158, 2009.

[93] X.-W. Li, Y.-X. Gao, S. Li, and J.-R. Yang, "Effect of sesamin on pulmonary vascular remodeling in rats with mono-crotaline-induced pulmonary hypertension," *China Journal of Chinese Materia Medica*, vol. 40, no. 7, pp. 1355–1361, 2015.

[94] N. Daisuke, I. Chie, I. Fumie et al., "Effects of sesamin on aortic oxidative stress and endothelial dysfunction in deoxycorticosterone acetate-salt hypertensive rats," *Biological and Pharmaceutical Bulletin*, vol. 26, no. 12, pp. 1071–1075, 2003.

[95] X. Kong, J.-R. Yang, L.-Q. Guo et al., "Sesamin improves endothelial dysfunction in renovascular hypertensive rats fed with a high-fat, high-sucrose diet," *European Journal of Pharmacology*, vol. 620, no. 1–3, pp. 84–89, 2009.

[96] T. D. Thuy, N. N. Phan, C. Y. Wang et al., "Novel therapeutic effects of sesamin on diabetes-induced cardiac dysfunction," *Molecular Medicine Reports*, vol. 15, no. 5, pp. 2949–2956, 2017.

[97] R. A. K. Srivastava, "Life-style-induced metabolic derangement and epigenetic changes promote diabetes and oxidative stress leading to NASH and atherosclerosis severity," *Journal of Diabetes and Metabolic Disorders*, vol. 17, no. 2, pp. 381–391, 2018.

[98] A. Aboonabi, R. R. Meyer, and I. Singh, "The association between metabolic syndrome components and the development of atherosclerosis," *Journal of Human Hypertension*, vol. 33, no. 12, pp. 844–855, 2019.

[99] H. Wang, K. Sugimoto, H. Lu et al., "HDAC1-mediated deacetylation of HIF1α prevents atherosclerosis progression by promoting miR-224-3p-mediated inhibition of FOSL2," *Molecular Therapy–Nucleic Acids*, vol. 23, pp. 577–591, 2021.

[100] R. B. Singh, S. A. Mengi, Y. J. Xu, A. S. Arneja, and N. S. Dhalla, "Pathogenesis of atherosclerosis: a multifactorial process," *Experimental and Clinical Cardiology*, vol. 7, no. 1, pp. 40–53, 2002.

[101] S. Bhaskaran, N. Santanam, M. Penumetcha, and S. Parthasarathy, "Inhibition of atherosclerosis in low-density lipoprotein receptor-negative mice by sesame oil," *Journal of Medicinal Food*, vol. 9, no. 4, pp. 487–490, 2006.

[102] C. A. Narasimhulu, K. Selvarajan, D. Litvinov, and S. Parthasarathy, "Anti-atherosclerotic and anti-inflammatory actions of sesame oil," *Journal of Medicinal Food*, vol. 18, no. 1, pp. 11–20, 2015.

[103] W. M. Loke, J. M. Proudfoot, J. M. Hodgson et al., "Specific dietary polyphenols attenuate atherosclerosis in apolipoprotein E-knockout mice by alleviating inflammation and

[104] A. S. Plump, J. D. Smith, T. Hayek et al., "Severe hyper-cholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells," *Cell*, vol. 71, no. 2, pp. 343–353, 1992.

[105] S. Ishibashi, J. L. Goldstein, M. S. Brown, J. Herz, and D. K. Burns, "Massive xanthomatosis and atherosclerosis in cholesterol-fed low density lipoprotein receptor-negative mice," *Journal of Clinical Investigation*, vol. 93, no. 5, pp. 1885–1893, 1994.

[106] C. Freise, K. Sommer, and U. Querfeld, "Protective effects of the polyphenols (+)-episesamin and sesamin against PDGF-BB-induced activation of vascular smooth muscle cells are mediated by induction of haem oxygenase-1 and inhibition of mitogenic signalling," *Journal of Functional Foods*, vol. 18, pp. 586–597, 2015.

[107] J. H. Han, S. G. Lee, S. H. Jung et al., "Sesamin inhibits PDGF-mediated proliferation of vascular smooth muscle cells by upregulating p21 and p27," *Journal of Agricultural and Food Chemistry*, vol. 63, no. 33, pp. 7317–7325, 2015.

[108] W.-H. Wu, S.-H. Wang, I.-I. Kuan et al., "Sesamin attenuates intercellular cell adhesion molecule-1 expression in vitro in TNF-alpha-treated human aortic endothelial cells and in vivo in apolipoprotein-E-deficient mice," *Molecular Nutrition & Food Research*, vol. 54, no. 9, pp. 1340–1350, 2010.

[109] A.-F. Cui, M. Xiang, M. Xu et al., "VCAM-1-mediated neutrophil infiltration exacerbates ambient fine particle-induced lung injury," *Toxicology Letters*, vol. 302, pp. 60–74, 2019.

[110] K. Kitagawa, M. Matsumoto, T. Sasaki et al., "Involvement of ICAM-1 in the progression of atherosclerosis in APOE-knockout mice," *Atherosclerosis*, vol. 160, no. 2, pp. 305–310, 2002.

[111] N. Liu, C.-M. Wu, L.-Z. Sun, J. Zheng, and P. Guo, "Sesamin enhances cholesterol efflux in RAW264.7 macrophages," *Molecules*, vol. 19, no. 6, pp. 7516–7527, 2014.

[112] D.-D. Yuan, *The Effect of Sesamin on Superoxide Dismutase in Atherosclerotic Rabbits Model*, Yanbian University, Jilin, China, 2012.

[113] C. Freise, W. Trowitzsch-Kienast, U. Erben et al., "(+)-Episesamin inhibits adipogenesis and exerts anti-inflammatory effects in 3T3-L1 (pre)adipocytes by sustained Wnt signaling, down-regulation of PPARγ and induction of iNOS," *The Journal of Nutritional Biochemistry*, vol. 24, no. 3, pp. 550–555, 2013.

[114] Z.-L. Yu, *The Effect of Sesamin on MMP-2 and MMP-9 in Atherosclertic Rabbits*, Yanbian University, Jilin, China, 2011.

[115] W. M. Loke, J. M. Proudfoot, J. M. Hodgson et al., "Specific dietary polyphenols attenuate atherosclerosis in apolipoprotein e-knockout mice by alleviating inflammation and endothelial dysfunction," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 4, pp. 749–757, 2010.

[116] L.-K. Guan and S.-L. Wang, "Effects of sesamin on the plaques formation and mRNA expression of VCAM-1 in experimental models of rabbit atherosclerosis," *Modern Preventive Medicine*, vol. 36, no. 15, pp. 2958–2960, 2009.

[117] X. Kong, J.-R. Yang, L.-Q. Guo, and Y. Zhou, "Effects of sesamin on myocardial hypertrophy in renal hypertensive-hyperlipidemia rats," *Chinese Journal of Experimental Traditional Medical Formulae*, vol. 14, no. 12, pp. 44–47, 2008.

[118] O. O. Oguntibeju, "Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links," *International*

endothelial dysfunction," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 4, pp. 749–757, 2010.

journal of physiology, pathophysiology and pharmacology, vol. 11, no. 3, pp. 45–63, 2019.

[119] L. Hong, W. Yi, C. Liangliang, H. Juncheng, W. Qin, and Z. Xiaoxiang, "Hypoglycaemic and hypolipidaemic activities of sesamin from sesame meal and its ability to ameliorate insulin resistance in KK-Ay mice," *Journal of the Science of Food and Agriculture*, vol. 93, no. 8, pp. 1833–1838, 2013.

[120] M. Mohammad Shahi, M. Zakerzadeh, M. Zakerkish, M. Zarei, and A. Saki, "Effect of sesamin supplementation on glycemic status, inflammatory markers, and adiponectin levels in patients with type 2 diabetes mellitus," *Journal of Dietary Supplements*, vol. 14, no. 1, pp. 65–75, 2017.

[121] Y. Fujiwara, Y. Okamura, M. Iwamura et al., "We-P14:485 Sesamin reduced blood glucose concentrations in Zucker fatty rat," *Atherosclerosis Supplements*, vol. 7, no. 3, p. 454, 2006.

[122] S. Takada, S. Kinugawa, S. Matsushima et al., "Sesamin prevents decline in exercise capacity and impairment of skeletal muscle mitochondrial function in mice with high-fat diet-induced diabetes," *Experimental Physiology*, vol. 100, no. 11, pp. 1319–1330, 2015.

[123] L.-Q. Guo, J.-R. Yang, and X. Kong, "Protective effect of Sesamin on endothelial function of type-2 diabetic rats," *Chinese Pharmacological Bulletin*, vol. 28, no. 3, pp. 392–396, 2012.

[124] Y. Farbood, S. Ghaderi, M. Rashno et al., "Sesamin: a promising protective agent against diabetes-associated cognitive decline in rats," *Life Sciences*, vol. 230, pp. 169–177, 2019.

[125] S. Takada, S. Kinugawa, S. Matsushima et al., "Sesamin prevents decline in exercise capacity and impairment of skeletal muscle mitochondrial function in mice with high-fat diet-induced diabetes," *Experimental Physiology*, vol. 100, no. 11, pp. 1319–1330, 2015.

[126] J.-B. An and R.-J. Zhang, "Effects of sesamin on lipid metabolism in hyperlipidemia rats," *Journal of Xi'an Jiaotong University*, vol. 31, no. 1, pp. 67–70, 2010.

[127] S.-G. Zheng, M.-Q. Zhao, Y.-N. Ren, Y.-J. Wu, and J.-R. Yang, "Sesamin suppresses STZ induced INS-1 cell apoptosis through inhibition of NF-κB activation and regulation of Bcl-2 family protein expression," *European Journal of Pharmacology*, vol. 750, pp. 52–58, 2015.