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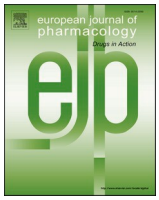

Sesamol: A lignan in sesame seeds with potent anti-inflammatory and immunomodulatory properties

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ABSTRACT

Inflammation is associated with the development and progression of a plethora of diseases including joint, metabolic, neurological, hepatic, and renal disorders. Sesamol, derived from the seeds of *Sesamum indicum* L., has received considerable attention due to its well-documented multipotent phytotherapeutic effects, including its anti-inflammatory and immunomodulatory properties. However, to date, no comprehensive review has been established to highlight or summarize the anti-inflammatory and immunomodulatory properties of sesamol. Herein, we aim to address this gap in the literature by presenting a thorough review encapsulating evidence surrounding the range of inflammatory mediators and cytokines shown to be targeted by sesamol in modulating its anti-inflammatory actions against a range of inflammatory disorders. Additionally, evidence highlighting the role that sesamol has in modulating components of adaptive immunity including cellular immune responses and Th1/Th2 balance is underscored. Moreover, the molecular mechanisms and the signaling pathways underlying such effects are also highlighted. Findings indicate that this seemingly potent lignan mediates its anti-inflammatory actions, at least in part, via suppression of various pro-inflammatory cytokines like IL-1β and TNFα, and downregulation of a multitude of signaling pathways including NF-κB and MAPK. In conclusion, we anticipate that sesamol may be employed in future therapeutic regimens to aid in more effective drug development to alleviate immune-related and inflammatory conditions.

1. Introduction

Inflammation is considered as one of the most central processes required in the defense against certain injuries and microbial infections (Isailovic et al., 2015). This process involves a series of coordinated dynamic reactions involving cellular and vascular regulatory processes and particular humoral secretions (Uccella et al., 2023). Immune cells release a multitude of secreted mediators and other signaling molecules including cytokines, histamine, prostaglandins, leukotrienes, and oxygen- and nitrogen-derived free radicals, all of which contribute towards inflammation (Abdulkhaleq et al., 2018; Anwikar and Bhitre, 2010). Thus, immune system modification has been regarded as a crucial strategy for the avoidance and potential treatment of inflammatory illnesses (Majdalawieh et al., 2022). Anti-inflammatory medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), are frequently used to regulate inflammation, and have been shown to be effective in treating a variety of inflammatory illnesses (Majdalawieh et al., 2022; Moore et al., 2006; Scheiman and Fendrick, 2005). Nevertheless, chronic use of NSAIDs often lead to adverse effects developing gastrointestinal ulcers, hypertension, acute renal failure, and worsening of preexisting heart failure (Vonkeman and van de Laar, 2010), suggesting such drugs may not be preferable for long-term use. Consequently, the use of natural products with known safety profiles may be a promising source for the discovery of new drug leads for the prevention and potential amelioration of inflammatory diseases (Majdalawieh et al., 2022; Wu et al., 2022). In this regard, phytochemicals are known to possess a variety of therapeutic properties and have been used since ancient times as traditional medicine for their health benefits (Ahmed et al., 2022;

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Jang and Lee, 2023). These naturally-occurring phytochemicals have been shown to possess a wide range of pharmacological and biological properties, with less safety concerns, making them ideal blueprints for novel pharmaceutical drug development. Berberine (in *Berberidaceae*) (Majdalawieh et al., 2022), sesamin (in *Sesamum indicum*) (Majdalawieh et al., 2021), and thymoquinone (in *Nigella sativa*) (Majdalawieh and Fayyad, 2015), are all examples of known phytochemicals commonly studied for their pluripotent health benefits. Sesamol, another lignan isolated from *S. indicum* seeds and sesame seed oil, has also recently emerged as a promising agent with potentially potent anti-inflammatory and immunomodulatory effects against myriads of diseases. Sesamol has a molecular formula of $C_7H_6O_3$ and a molar mass of 138.12 g/mol (Majdalawieh and Mansour, 2019). Numerous studies have been conducted on the bioactivity potential of sesamol. This lignan has been shown to possess promising anti-carcinogenic (Majdalawieh and Mansour, 2019), anti-atherogenic (Majdalawieh and Ro, 2014), anti-hyperlipidemic (Majdalawieh et al., 2023), and most relevant to this review, anti-inflammatory and immunomodulatory therapeutic properties both *in vivo* and *in vitro*. Despite its well-documented role as an anti-inflammatory and immunomodulatory agent in the literature, no review has been conducted outlining the molecular mechanisms and signal transduction pathways found underlying such effects. Herein, this comprehensive review aims to outline the available evidence regarding the anti-inflammatory and immunomodulatory role that sesamol plays both *in vivo* and *in vitro*. Particularly, we highlight the involvement of major cytokines and other inflammatory and immunologically-relevant mediators and their suggested mechanisms of action through associated signaling pathways. Additionally, we expand on the anti-inflammatory scores and effects on certain disorders and outline the role that sesamol may play on adaptive immunity, particularly cell-mediated and humoral immunity. Identifying these pathways of action pharmacologically will aid in the investigation of the potential use of a natural substance like sesamol for the treatment of inflammatory disorders to increase the efficacy of the therapy and dampen the side effects commonly associated with the use of popular synthetic anti-inflammatory medicines.

2. Search methodology

The literature search was conducted using a variety of online databases, such as PubMed, Cochrane Library, Elsevier (Science Direct), and Google Scholar. To ensure the identification of relevant studies, the word "sesamol" was used along with keywords including "inflammation", "Th1/Th2 balance", "cytokines", "antibodies", and "immunomodulation". Articles were screened and selected, with no restriction on publication dates, the experimental subjects/models used, mode and duration of sesamol administration, or other experimental details.

3. Effects of sesamol on inflammation

As indicated previously, inflammation is a biological response to a variety of stimuli including the immune system that can be triggered by a variety of stimuli. Research exploring the cellular and molecular processes that initiate and modulate the interactions among the different key players in the inflammatory process is still ongoing (Germolec et al., 2018). Acute inflammation is known to aid in tissue homeostasis restoration via defending the host against the threat of pathogenic infection or injury (Serhan, 2017). This is facilitated by the release of a plethora of immunomodulatory agents including cytokines, chemokines, leukotrienes (LT), eicosanoids, and reactive oxygen species (ROS), to name a few (Majdalawieh et al., 2022). Although critical for fighting infections, inflammation that lingers long-term, and is therefore chronic, may result in permanent organ malfunction as it may lead to tissue damage and fibrogenesis (Guo and Friedman, 2010; Kawanishi et al., 2013; Radak et al., 2019). Chronic inflammation is also a major contributor to the cardiovascular complications of both types of diabetes mellitus and glycemic and lipidemic-driven atherosclerosis (Girard and Vandiedonck, 2022). In this regard, an increasing body of research suggests that sesamol may help dampen excessive inflammatory reactions by targeting multiple inflammatory mediators in various *in vivo* and *in vitro* models. Acute-phase inflammation is triggered by the synthesis of cytokines, most notably including the secretions of interleukin-1β (IL-1β), IL-8, IL-6, IL-12, and tumor necrosis factor α (TNFα) (Rubin and Reisner, 2009). In one study for example, the ways in which sesamol influences the binding of lipopolysaccharide (LPS), LPS-binding protein (LBP), and the release of pro-inflammatory cytokines in male Sprague Dawley rats and their peritoneal macrophages was examined (Hsu et al., 2009). LPS, which is secreted from the outer membrane of the bacterium, was found to be the main cause of inflammation and sepsis induced by gram-negative bacteria. Sesamol (0, 30, 100, and 300 μM) was found to reduce the binding of LPS to LBP in a concentration-dependent manner, even after being introduced 30 min into their co-incubation. To further confirm this finding, the rat peritoneal macrophages were tested for their pro-inflammatory cytokine levels 24 h after sesamol (0, 30, 100, and 300 μM) treatment. In comparison to the LPS-alone groups, sesamol downregulated the LPS-induced production of IL-1β and TNFα in a dose- and time-dependent manner. Additionally, serum IL-1β and TNFα levels were found to be significantly higher in the LPS (5 mg/kg) group compared with saline (1 ml/kg); whereas after 3 h of sesamol (0, 1, 3, and 10 mg/kg) treatment, serum IL-1β and TNFα levels were dose-dependently downregulated. These findings suggest that the inhibition of pro-inflammatory cytokines by sesamol may be mediated, at least in part, via modulating LPS-LBP binding. Furthermore, with regards to the protective effects of sesamol against endotoxemia, sesamol (10 mg/kg) treatment of rats injected with lethal LPS (80 mg/kg) injections for 12, 18, and 24 h significantly attenuated the lethal effects of the injections and was found to increase the survival rate of the rats. Taken together, these findings suggest that sesamol may be employed for the treatment of LPS-induced inflammation and sepsis induced by LPS in rats (Hsu et al., 2009). In another study, the effects of sesamol on modulating mitochondrial protection against inflammation was studied in LPS-exposed RAW 264.7 cell line (Duarte et al., 2018). With regards to cell viability, sesamol was not found to cause any significant changes on its own, however, pretreatment of the cell line with sesamol for 1 h at 50–100 μM was found to reduce the LPS-induced (1 μg/ml) loss in viability. The anti-apoptotic role of sesamol (100 μM) showed successful inhibition of the LPS-induced rise in the Bcl-2 associated X protein/B-cell lymphoma 2 (BAX/Bcl-2) ratio, reduced effects of LPS on the activation of pro-apoptotic caspase-3 and caspase-9, and relieved cytochrome *c* loss in the mitochondria and cytoplasm of LPS-treated RAW 264.7 macrophages. In addition, DNA fragmentation levels, a telltale indication of apoptosis, were also significantly reduced after sesamol pretreatment. The antioxidant effects of sesamol also decreased the quantities of $O_2\bullet$ in the mitochondria and the NO• that LPS-treated macrophages produced. Additionally, the anti-inflammatory modulation of sesamol was marked by how this lignan was able to diminish the activity of nuclear factor-kappa B (NF-κB), suppress secretions of the pro-inflammatory cytokines IL-1β, IL-6, and TNFα, and decrease the levels of cyclooxygenase-2 (COX-2) and high mobility group box-1 (HMGB1) proteins in cells following LPS stimulation (Duarte et al., 2018). Another study investigated the molecular mechanisms underlying the anti-inflammatory potential of sesamol using LPS-stimulated RAW 264.7 macrophages (Wu et al., 2015). Sesamol (3, 10, 30, and 100 μM) treatment for 1 h was found to dramatically reduce the COX-2-mediated synthesis of prostaglandin E2 (PGE2) from arachidonic acids (AAs), as well as ROS and nitrite in a dose-dependent manner after LPS (1 μg/ml) stimulation in macrophages. Moreover, iNOS and COX-2 mRNA and protein expression in macrophages were considerably reduced dose-dependently by sesamol pretreatment for 1 h, when compared to LPS stimulation. Additionally, the production of pro-inflammatory cytokines IL-1β, IL-6, and TNFα were all significantly

suppressed by sesamol (3, 10, 30, and 100 μM) when compared to the LPS control (Wu et al., 2015). In another study, consumption of a sesamol-supplemented safflower oil (SO) diet, a source of linoleic acid, affected the fatty acid content of the liver membrane phospholipids and the LPS-induced generation of eicosanoids and cytokines in female BALB/c mice (Chavali and Forse, 1999). Specifically, mice given a SO diet supplemented with sesamol (1% wt) for 2 weeks had considerably greater levels of the anti-inflammatory dihomo–γ-linolenic acid (DGLA) than the control group; whose buildup may compete with AAs for binding to COX enzymes, thus reducing levels of pro-inflammatory dienoic eicosanoids. Additionally, sesamol treatment was shown to significantly reduce the levels of docosapentaenoic acid (DPA) and the Δ5 desaturation index for v6 polyunsaturated fatty acids (PUFAs), compared to the SO alone and control groups. Moreover, the production of pro-inflammatory AA metabolites like PGs may be reduced if DGLA builds up in the membrane phospholipids as a result of the sesamol diet; sesamol-supplemented SO diet-fed mice had considerably lower LPS (20 mg/kg)-induced levels of PGE1 and PGE2 than mice kept on SO alone. Furthermore, in comparison to groups of mice fed SO alone meals, those provided sesamol-supplemented SO diets had significantly lower levels of IL-6. Interestingly, however, Chavali and Forse (1999) found that sesamol (1% wt) supplementation had no effect on the levels of IL-10, IL-12, and TNFα, as the levels were not found to be significantly different in mice fed sesamol-supplemented SO diets compared to the controls, which is an interesting finding that requires further exploration. Notwithstanding, results from this study suggest the potential employment of sesamol as an anti-inflammatory agent. Studies confirming these effects in humans are still missing and therefore warrant further research. Multiple studies have indicated the pivotal role that reactive oxygen or nitrogen species have in inducing the expression of multiple genes implicated in inflammation (Ďuračková, 2010; Hussain et al., 2016). The inflammatory processes, which result in the production and release of pro-inflammatory cytokines, have been shown to be triggered by a variety of inflammatory stimuli, including excessive ROS created during the process of oxidative metabolism and some natural or manufactured substances (Hussain et al., 2016). For example, it has been shown that the generation of TNFα and activation of NF-κB play crucial roles in the inflammatory process leading to many chronic diseases (Hussain et al., 2016). In fact, excessive ROS or nitrogen species production has the potential to bring about cell death through necrotic and apoptotic processes by causing irreparable damage (Wang et al., 2004) Furthermore, the effectiveness of pretreating the human neuroblastoma SH-SY5Y cell line with sesamol to stop the mitochondrial breakdown induced by hydrogen peroxide was examined *in vitro* (da Silva Navarro et al., 2022). Apoptosis, inflammation, and a loss in bioenergetics are all linked to an increase in ROS production in the mitochondria, while, sesamol (25 μM) pretreatment for 24 h decreased the amount of O_2•• produced by the mitochondria and the amount of NO• present in the SH-SY5Y cells after H_2O_2 exposure. Additionally, they found that sesamol (25 μM) pretreatment stopped the increase in the levels of pro-apoptotic BAX in the H_2O_2 (300 μM)-exposed cells as well as the decrease in anti-apoptotic Bcl-2 in the cells exposed to H_2O_2. Furthermore, in the H_2O_2-induced cells, pretreatment with sesamol also prevented the release of cytochrome *c* into the cytosol, effectively suppressing the effects of H_2O_2 on the mitochondrial content of this molecule, while also reducing the pro-apoptotic activity of caspase-3 and caspase-9. Moreover, sesamol pretreatment downregulated the levels of IL-1β and TNFα. Overall, findings of this study showed that although further research is required to precisely determine the mechanism by which sesamol improves mitochondrial protection against redox disturbances, sesamol (25 μM) regulated not only the redox-related pro-inflammatory stimuli induced by the cells' exposure to H_2O_2, but also the primary modulator of an inflammatory response in this cell type (da Silva Navarro et al., 2022). In another study, the effects of sesamol on LPS-induced inflammatory responses were studied in male Institute of Cancer Research (ICR) mice and in the RAW 264.7 cell line (Chu et al., 2010b). *In vivo,* Western blot analyses revealed that sesamol (10 mg/kg) dramatically decreased serum levels of IL-1β, TNFα, and nitrite, as well as leukocyte inducible nitric oxide synthase (iNOS) expression in LPS (5 mg/kg)-treated mice. Furthermore, sesamol (100–300 μM) significantly and concentration-dependently suppressed the release of LPS-induced IL-1β and TNFα, as well as the synthesis of nitrite and the expression of the iNOS protein (Chu et al., 2010b). The results of this study suggest that sesamol may dampen the inflammatory response induced by LPS as evident by the decrease in the levels of TNFα, IL-1β, and nitrite in mice. In another study, Yashaswini et al. (2017a) investigated the bioavailability and anti-inflammatory effects of sesamol in human colon adenocarcinoma (Caco-2) and RAW 264.7 cell lines (Yashaswini et al., 2017a). In Caco-2 cell-line, phosphatidylcholine-encapsulated sesamol (PCS) (33.6 μM) and free sesamol (FS) (51.9 μM) both showed 50% loss in LOX activity, thus highlighting the superior anti-inflammatory effects of PCS in Caco-2 cells. Similarly, stimulating RAW 264.7 cells with LPS (1 μg/ml) and further treating them with FS and PCS (100 μM) resulted in a 42.6% and 74.8% suppression of ROS generation, which further confirms that PCS-encapsulation of sesamol enhances its anti-inflammatory potential. Additionally, the PCS group was also more effective in decreasing iNOS protein expression in LPS-stimulated macrophages by 2-folds (Yashaswini et al., 2017a). Taken together, these findings demonstrate that micelle encapsulation of sesamol with PCS enhances its bioaccessibility, and therefore, improves its anti-inflammatory propensity. The findings thus far reported point to the promising role that sesamol might play in boosting immune functions, which is critical for the alleviation of a plethora of inflammatory disorders, which will be discussed in details the following sections.

3.1. Joint disorders

Several studies reported that sesamol exerts anti-inflammatory effects that may be beneficial to patients with arthritis. In one study, the anti-arthritic, anti-inflammatory and anti-stress effects of sesamol in Freund's complete adjuvant-induced arthritic Wistar rats were investigated (Hemshekhar et al., 2013). As far as physical parameters are concerned, treating arthritis rats with sesamol (50 mg/kg) resulted in a substantial reduction of paw volume, edema, and bone cartilage damage, as indicated in radiographs taken every 4 days for 2 weeks. Moreover, analysis from immunoblots revealed that sesamol (50 mg/kg) demonstrated promising effects against serum matrix metalloproteinase (MMP) levels, including MMP-3, MMP-9, and MMP-13, all of which play a significant role in inducing inflammation and tissue remodeling. Specifically, sesamol (50 mg/kg) was shown to be superior to ibuprofen (10 mg/kg) in treating the increased serum MMP levels in comparison to the arthritis alone group. Furthermore, compared to the saline control, it was shown that arthritis-induced rats had considerably higher levels of IL-1β, IL-6, TNFα, COX-2, and PGE2 in sera, all of which indicate elevated inflammatory levels. Sesamol injections (50 mg/kg) were found to significantly dampen all of the above-mentioned inflammatory mediators. Interestingly, in comparison to the arthritic group, treating arthritis-induced rats with sesamol (50 mg/kg) was even found to suppress the endogenous formation of ROS, which as indicated earlier, is highly implicated in inflammation. Further analysis also revealed a significant improvement in serum, liver and spleen H_2O_2 elimination levels in the sesamol-treated group (50 mg/kg), as compared to the ibuprofen-treated and arthritis alone groups. In line with these finding, sesamol (50 mg/kg) also restored both the decrease in splenic and the increase in hepatic antioxidant superoxide dismutase (SOD) levels (Hemshekhar et al., 2013). Taken together, results from this study demonstrate that sesamol has the potential to alleviate and/or treat arthritis as well as its secondary complications like diabetes and cardiovascular diseases (CVDs). In another study, sesamol treatment (5, 10, and 20 μM) of SW1353 chondrosarcoma cell lines for 15 min was shown to downregulate cytokine-induced gelatinolysis and inhibit MMP-9

activation in a concentration-dependent manner, further reinforcing the inhibitory role that sesamol may have on MMP levels (Lu et al., 2011). Similarly, sesamol (5, 10, and 20 μM) treatment of the phorbol myristate acetate (PMA) (10 ng/ml)-stimulated chondrocyte culture significantly inhibited MMP-1 activation and MMP-13 expression in a concentration-dependent manner. Further analysis from western blots revealed that sesamol significantly and effectively reversed both TNFα and PMA-induced rates of degradation of SW1353 cells. Additionally, sesamol (30 mg/kg) treatment was found to inhibit the average expression cartilage levels of MMP-1 and MMP-9 back to normal levels in the rat model, suggesting its anti-inflammatory abilities (Lu et al., 2011). These results suggest that sesamol may be employed as a promising chondroprotective agent capable of treating arthritis by alleviating cartilage destruction. Future studies should aim to investigate the chondroprotective effects of sesamol in humans to confirm its anti-arthritic potential clinically. Fig. 1 Summarizes the reported mediators targeted by sesamol in joint disorders.

3.2. Neurological disorders

The anti-inflammatory properties of sesamol were demonstrated to be beneficial in ameliorating several types of neuroinflammatory conditions. In one study, sesamol administration (10 mg/kg) was found to significantly restore spinal cord injury (SCI)-enhanced caspase-3 cleavage and BAX protein expression and the decreased Bcl-2 protein levels in excised spinal tissues, indicating inhibition of apoptosis (Feng et al., 2022). Sesamol treatment (10 μM) of LPS-induced BV-2 cells for 28 days was also shown to ameliorate the damage caused by SCI by significantly

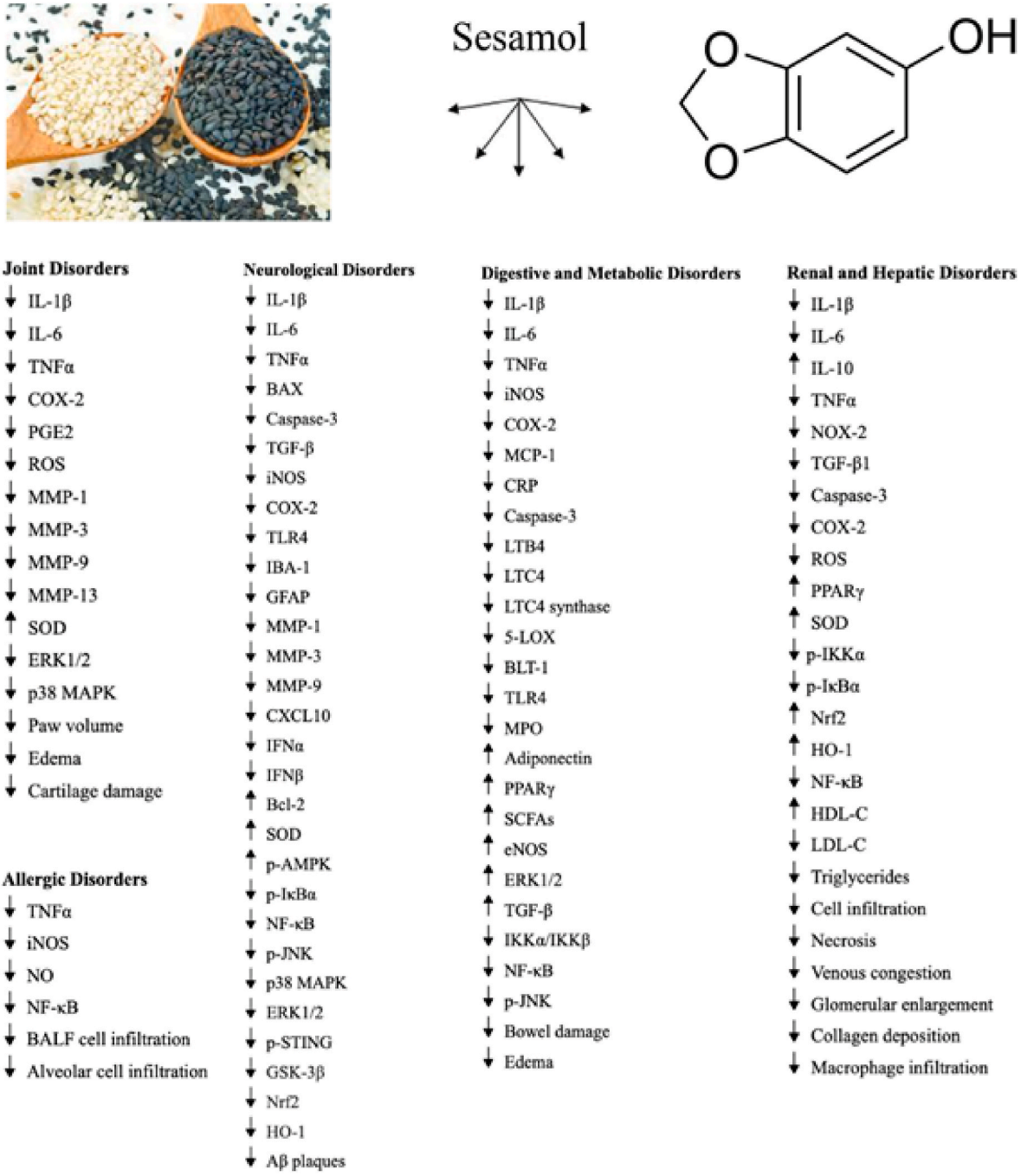

Fig. 1. Signaling mediators responsible for the reported anti-inflammatory and immunomodulatory effects of sesamol in different disorders.

reducing the levels of IL-6 and TNFα, both of which are known to be implicated in neuroinflammation and in the pathogenesis of SCI (Feng et al., 2022). In another study, sesamol (0.1%, w/w) administration significantly reversed the aging-induced elevation in the levels of IL-1β and TNFα in serum, and hippocampal mRNA expression of IL-1β, IL-6, and TNFα in male ICR mice, indicating the important role of sesamol as a potent anti-inflammatory agent (Ren et al., 2020). In addition, sesamol treatment in the same concentration (0.1%, w/w) also significantly improved the serum and hippocampal SOD enzyme activities that are induced by aging, demonstrating its abilities to reduce inflammation during the aging process in mice (Ren et al., 2020). In another study, the effectiveness of sesamol in treating middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia/reperfusion (I/R) injury in male Sprague Dawley rats was investigated (Gao et al., 2017). Results indicated a significant suppression of caspase-3 and BAX protein expression and an elevation of anti-apoptotic Bcl-2 protein expression with sesamol treatment (25 mg/kg) of MCAO alone rats, as compared to MCAO-induced rats not treated with sesamol. Additionally, sesamol treatment (25 mg/kg) of MCAO-induced rats markedly downregulated the mRNA expression and protein levels of IL-6 and TNFα, indicating reduced inflammation. Sesamol was also successful in upregulating the suppressed cortical SOD levels in MCAO alone rats, which could contribute to the catalysis of ROS generated during cerebral ischemia. This implies that the neuroprotective effects of sesamol (25 mg/kg) on brain tissue subjected to MCAO-reperfusion and ischemia damage in rats may be explained by the suppression of inflammatory and apoptotic responses (Gao et al., 2017). Collectively, these results indicate that sesamol supplementation may serve as a potent adjuvant therapy for focal I/R injury due to its above-mentioned neuroprotective effects. In another study, sesamol treatment (2, 4, and 8 mg/kg) of diabetic male Wistar rats for four weeks was shown to be associated with significant and concentration-dependent inhibition in streptozotocin (STZ)-induced rise in plasma NO, IL-1β, TNFα, tumor growth factor-beta (TGF-β), and sciatic pro-apoptotic caspase-3 levels, indicating reduced inflammation (Chopra et al., 2010). Interestingly, combining sesamol and insulin (10 mg/kg) was found to further dampen the levels of these inflammatory mediators, which is an interesting finding that warrants further research. Additionally, diabetic rats had significantly higher plasma levels of IL-1β, TNFα, and TGF-β than control rats, while dose-dependent sesamol treatment decreased the levels of all of these inflammatory mediators (Chopra et al., 2010). Overall, findings from this study suggest that sesamol may be employed in therapeutic settings to ameliorate neuropathic pain in diabetes via modulation of oxidative stress and pro-inflammatory mediator levels. Future studies exploring such effects in patients are certainly warranted to confirm the protective effects of sesamol against neuropathic pain in diabetes patients. In another study, sesamol administration (2, 4, and 8 mg/kg) in STZ-induced diabetic male Wistar rats was found to significantly and dose-dependently decrease nitrite levels and elevate cerebral SOD enzymatic activity in several brain regions of STZ (65 mg/kg)-induced rats after 10 weeks, indicating that inflammation due to ROS was suppressed (Kuhad and Chopra, 2008). Additionally, sesamol treatment (2, 4, and 8 mg/kg) was also found to significantly reduce serum TNFα levels in diabetic rats, highlighting the potential role of sesamol in treating inflammation-induced neurological abnormalities in diabetic rats. Interestingly, the use of sesamol in the control group, not subjected to diabetes, did not result in any of the above-mentioned beneficial effects, indicating that sesamol may have the potential to target diabetes-induced inflammation and neurological abnormalities. Furthermore, sesamol also markedly and dose-dependently increased cortical and hippocampal STZ-induced suppression of SOD enzymatic activity (Kuhad and Chopra, 2008). Results imply that sesamol may have therapeutic effects for treating diabetes patients suffering from neurological abnormalities. In another study, treatment of C57BL/6 J mice with sesamol (0.05%) was found to result in a significant reduction of LPS-induced neurodegeneration (Liu et al., 2017). Interestingly, sesamol (0.05%) was also found to slow down the process of amyloidogenesis in the brain via decreasing the accumulation of hippocampal and cortical Aβ plaques, which are typically induced by inflammation. Sesamol (0.05%) supplementation was also found to significantly dampen the mRNA expression levels of the inflammatory endogenous enzymes MMP-1, MMP-3, and MMP-9 and the serum and mRNA expression levels of IL-1β, IL-6, TNFα, while keeping the levels of IL-10 remained unchanged. Additionally, western blots and RT-qPCR proved sesamol treatment inhibited protein and mRNA expression of iNOS, COX-2, and toll-like receptor-4 (TLR4), respectively. Results from BV-2 microglia also showed similar results whereby sesamol (5, 12.5, 25 μM) treatment for 15 min concentration-dependently suppressed the LPS-induced COX-2 and iNOS protein levels. Collectively, these results suggest that sesamol has the potential to prevent neuronal injury, inhibit glia activation, and downregulate inflammatory responses in the central nervous system to reduce inflammation-induced amyloidogenesis and cognitive impairments (Liu et al., 2017). In another study, Western blot analyses and RT-qPCR tests revealed that sesamol (0.05%) was capable of dampening manganese (Mn)-upregulated neuroinflammatory hippocampal responses, including that of TNFα, chemokine CXC ligand-10 (CXCL10) mRNA expression, and iNOS mRNA and protein expression (Wu et al., 2023). Sesamol (25 μM) decreased the mRNA expression of TNFα, but not iNOS, and even exacerbated the rise in CXCL10 expression. Following sesamol treatment at 5 and 12.5 μM, with the former having more pronounced effects, the elevated expression of these pro-inflammatory cytokines after Mn exposure dramatically diminished, which may be noteworthy for future studies or evaluation. In addition, Mn exposure increased the *in vivo* mRNA expression of the antiviral agents, interferon α (IFNα) and IFNβ, and their transcriptional levels in BV-2 cells, both of which were significantly reduced upon treatment with sesamol (0.05% and 5 μM, respectively) (Wu et al., 2023). Collectively, these results indicate that sesamol may serve as an effective therapeutic treatment against Mn-induced neurotoxicity and its associated cognitive impairment. In another study, sesamol, thymol, wheatgrass and coenzyme Q10 (CoQ10) were all examined for their anti-inflammatory, antioxidant and anti-apoptotic properties against Mn-induced Parkinson's disease in male Sprague Dawley rats (Abu-Elfotuh et al., 2022). Daily sesamol (15 mg/kg) oral monotherapy for 5 weeks was found to significantly reverse the $MnCl_2$-induced brain inflammatory biomarker levels including those of IL-1β, TNFα, COX-2, TLR4, caspase-1, and NOD-like receptor protein 3 (NLRP3), more than the other treatment groups. Moreover, combination therapy using all four nutraceuticals was found to significantly reverse the levels of all the above-mentioned mediators more effectively compared to monotherapy, with the exception of NLRP3, which is an interesting finding that requires further research (Abu-Elfotuh et al., 2022). Taken together, results from this study support the role that sesamol may have in providing protection against Mn-induced neuronal degeneration and highlight the synergistic effects possible using combination therapy, which is a promising arena for effective drug development. In another study, sesamol (20 mg/kg) treatment in male Wistar rats for 8 weeks was found to significantly reduce chronic intermittent hypoxia (CIH)-induced elevation of IL-1β and TNFα in rat hippocampus, indicating reduced neuroinflammation (Zhang et al., 2021). Moreover, and as reported by other researchers, sesamol (20 mg/kg) treatment in the CIH-exposed rats was also found to significantly elevate the enzymatic activity of hippocampal SOD by week 2, proving to decrease oxidative stress and its associated chain of inflammatory reactions (Zhang et al., 2021). Data from this study highlight that sesamol is capable of alleviating cognitive impairments in CIH-exposed rats and may even possess neuroprotective effects via inhibiting oxidative stress and inflammation. Fig. 1 summarizes the reported mediators targeted by sesamol in neurological disorders.

3.3. Digestive and metabolic disorders

Inflammation is known to play a significant role in the pathogenesis of obesity, diabetes, and CVDs as it helps induce insulin resistance. Sesamol possesses promising anti-inflammatory effects which may prove to be useful for the mitigation of several digestive and metabolic conditions. In one study, sesamol supplementation (100 mg/kg) of male C57BL/6 mice for 6 weeks was found to significantly ameliorate dextran sulfate sodium (DSS)-induced colitis via inhibiting the protein expression of iNOS and COX-2, in comparison to mice exposed to DSS (2.5% w/v) alone (Zhao et al., 2020). These findings were supported by the observation that sesamol (100 mg/kg) treatment significantly reduced the DSS-induced rise in the mRNA expression of IL-1β, IL-6, TNFα, iNOS, COX-2, and TLR4, suggesting the successful attenuation of various inflammatory responses. Additionally, gut microbiome composition, structure, and relative abundance of beneficial bacteria in sesamol-supplemented mice was also found to be effectively regulated, indicating improved protective gut barrier with sesamol supplementation. Interestingly, sesamol treatment (100 mg/kg) was also found to significantly elevate the levels of butyrate, a fecal short-chain fatty acid (SCFA) that plays an important role in intestinal homeostasis (Zhao et al., 2020). Taken together, these results indicate the potential role of sesamol in mitigating inflammation in DSS-induced colitis in mice. Research confirming similar effects in humans is certainly warranted. In another study, sesamol (97% 100 mg/kg) supplementation of neonatal Wistar albino rats, both peritoneally and orally, for 3 days was found to alleviate the severity of necrotizing enterocolitis (NEC) via significantly attenuating bowel damage severity, edema, and fragility, as compared to rats in the control group (Cigsar et al., 2018). Additionally, sesamol treatment was also found to elevate SOD activity and reduce the number of Bcl-2 and caspase-3 positive cells, indicating reduced risk of NEC pathogenesis by preventing epithelial apoptosis (Cigsar et al., 2018). In another study, treatment of albino male Wistar rats with sesamol (100 mg/kg) for 7 days was found to have promising modulatory effects against dinitrochlorobenzene (DNCB)-induced inflammatory bowel syndrome (IBS) as it significantly decreased the DNCB-induced rise in the granulocytic enzyme, myeloperoxidase (MPO), and tissue nitrite levels, indicating reduced ROS and inflammation (Kondamudi et al., 2013). Interestingly, however, and contrary to findings reported by the other studies reported in this section thus far, results from this study did not reveal an inhibitory effect for sesamol on the levels of pro-inflammatory markers. Specifically, sesamol (100 mg/kg) supplementation was found to elevate IL-6 and TNFα levels in DNCB-induced rats. Although peculiar, Kondamudi et al. (2013) speculated that sesamol may actually induce the production of certain cytokines including adhesion molecules, arachidonic acid metabolites, and immune and non-immune cells in the context of IBS therapy, which is an interesting observation that warrants further research (Kondamudi et al., 2013).

The promising anti-inflammatory properties of sesamol are also believed to extend to various metabolic conditions. For example, Gourishetti et al. (2020) examined the effects of sesamol-polylactic-*co*-glycolic acid (SM-PLGA), a sesamol-containing drug-delivery nano formulation, on the various phases of the wound healing process in high fat diet (HFD)-induced diabetic foot ulcers (DFU) in male Wistar rats (Gourishetti et al., 2020). When compared to sesamol alone, the SM-PLGA nanosuspension (50 mg/kg) treatment for 15 days was found to significantly elevate the expression of growth factors like VEGF and PDGF, both of which are known to be involved in angiogenesis. Additionally, sesamol (50 and 100 mg/kg) and SM-PLGA nanosuspension (50 mg/kg) were both shown to significantly reduce TNFα level, after its level was elevated following HFD induction. Interestingly, SM-PLGA nanosuspension was shown to exhibit superior inhibitory effects on TNFα, as compared to sesamol alone, highlighting the importance of using nanoparticles to enhance the bioavailability of this potent lignan. Histological scores were used to observe the acceleration of wound healing with the treatments. The SM-PLGA nanosuspension group also showed a high number of cells positive for the protein cluster of differentiation 31 (CD31), also known as platelet endothelial cell adhesion molecule (PECAM-1), a major angiogenesis marker (Gourishetti et al., 2020). Collectively, results from this study identify the SM-PLGA nanoformulation (50 mg/kg) as a promising healing agent for use in the treatment of non-healing chronic wounds in diabetes as it promotes the acceleration of wound healing by restoring altered wound healing processes. Future research could certainly benefit from exploring the use of nanoparticles to aid in improving sesamol delivery and absorption for maximal benefits. To create more effective ways of sesamol delivery systems, Liu et al. (2020) investigated the efficacy of a sesamol-loaded cellulose acetate (CA) composite nanofiber membrane on the wound healing process in STZ-induced diabetes in male 57 B L/6 J mice (Liu et al., 2020). Backside wound healing rates were found to be significantly increased in STZ (50 mg/kg)-induced diabetic mice after sesamol-CA/zein composite (2% and 5% (w/v) treatment for 9 days, indicating enhanced wound healing rates due to improved efficiency in regulated and extended release of sesamol at the target side. The researchers stated that a particularly high concentration of sesamol is expected to cause thrombocyte coagulation and hinder wound healing despite the fact that both dosages used in this study were equally effective at accelerating wound healing. Therefore, future studies should potentially investigate the optimal sesamol dosage capable of delivering maximal beneficial effects. Furthermore, Liu and colleagues found that the sesamol-CA/zein composite (2% and 5%) caused a significant downregulation in IL-1β mRNA levels, but not TNFα. In the case of nitric oxide synthase-2 (NOS2), an inducible enzymatic product of macrophages, downregulation of mRNA expression was thought to be associated with the structure of the nanofiber membrane itself that provided better bioavailability of sesamol. Additionally, sesamol-CA/zein composite treatment groups (2% and 5%) was found to influence the expression of two keratinocyte-secreted cytokines, IL-6 and IL-10, whereby it upregulated the epidermal growth-promoting IL-6 expression and downregulated IL-10 expression, an anti-inflammatory cytokine thought to promote immunosuppression (Liu et al., 2020). These results operated synergistically to encourage keratinocyte proliferation and quicken wound healing. In another investigation, treatment of LPS-stimulated male Wistar rats with sesamol, sesamin or a combination of both (10 mg/kg) for 15 days was found to significantly reduce the LPS-induced rise in IL-1β, TNFα, and c-reactive protein (CRP) serum levels, indicating reduced inflammation (Yashaswini et al., 2017b). Sesamol was also found to exhibit superior effects in downregulating the levels of other inflammatory mediators compared to sesamin, however, the difference between the two lignans did not reach statistical significance. For IL-1β and CRP levels, a combination of the two lignans showed superior downregulation. Additionally, sesamol and sesamin (10 mg/kg) were both found to be equally effective in significantly reducing the serum levels of LTC4 and the expression of LTC4 synthase, indicating reduced leukotriene synthesis and serum levels. For LTB4, sesamin showed a more superior downregulation in LTB4 levels compared to sesamin. Interestingly, besides the promising anti-inflammatory effects reported for both lignans, sesamol was also demonstrated to exert exceptional inhibitory effects on NO production and even recovered the depleted SOD catalytic levels and activity, highlighting its important role as both an anti-inflammatory and antioxidant agent (Yashaswini et al., 2017b). In another study, sesamol (2, 4 and 8 mg/kg) treatment of male Wistar albino rats for 30 days was shown to ameliorate HFD-induced cardiometabolic syndrome (CMetS) as it concentration-dependently increased SOD antioxidant enzymatic activity and successfully returned the HFD-induced decrease in serum NO levels back to normal (at 8 mg/kg) (Sharma et al., 2012). Additionally, in terms of pro-inflammatory mediator levels, sesamol treatment dose-dependently suppressed the HFD-induced levels of TNFα and high sensitivity-CRP (hs-CRP), while lower doses (2 and 4 mg/kg) did the same for IL-6. Additionally, sesamol (2, 4, and 8 mg/kg) dose-dependent treatment restored the serum levels of adiponectin, a

hormone implicated in insulin sensitivity and inflammation, after its levels have been suppressed following HFD induction. Interestingly, the suppressed anti-inflammatory peroxisome proliferator-activated receptor γ (PPARγ) expression in the HFD control were significantly upregulated by sesamol (4 and 8 mg/kg) treatment, indicating attenuation of inflammation. Furthermore, sesamol (4 and 8 mg/kg) also significantly reversed the HFD-induced decrease in endothelial nitric oxide synthase (eNOS) expression and elevated the accumulation of nitrotyrosine (NT), an inactivation product of NO, in the treated rats. Histopathological analysis of the rat liver tissues revealed that sesamol (8 mg/kg) reversed the HFD-induced severe swelling of hepatocytes, fat accumulation and loss of nucleus and inflammatory cells, ameliorating the indicated hepatic steatosis (Sharma et al., 2012). Fig. 1 summarizes the reported mediators targeted by sesamol in digestive and metabolic disorders.

3.4. Renal and hepatic disorders

The documented anti-inflammatory effects of sesamol may also be influential against various types of renal and hepatic conditions. For example, sesamol administration (10 mg/kg) in male Wistar rats for 6 h was found to alleviate cecal ligation and puncture (CLP)-induced acute kidney injury (AKI) as it significantly reduced the CLP-induced rise in IL-1β and IL-6 levels in rats (Periasamy et al., 2015). Sesamol (3 mg/kg) also had similar effects against LPS-induced hypotension, in which it significantly reduced the LPS-induced rise in IL-1β and TNFα and increased IL-10 serum levels, indicating enhanced anti-inflammatory activity. LPS-elevated nitrite levels however were not significantly affected by sesamol supplementation, which is an interesting finding that requires further investigation. Additionally, the same study revealed that, when compared to the control group, sesamol treatment (3, 30, or 300 μM) significantly boosted PPARγ activation of rat LPS-treated primary peritoneal macrophages and leukocytes with no effects on viabilities of cells, after 24 h (Periasamy et al., 2015). Collectively, these results highlight the ability of sesamol to inhibit LPS-induced hypotension in rats by controlling the systemic inflammatory response through a PPARγ-related mechanism. In another study, daily treatment of male C57BL/6 mice with sesamol (100 mg/kg) for 8 weeks was found to alleviate HFD-induced hepatic inflammation as it dramatically decreased the activity and the hepatic mRNA expression levels of NADPH oxidase-2 (NOX2), an enzyme known to control phagocytic activity and inflammation (Zheng et al., 2021; Singel and Segal, 2016). Additionally, sesamol treatment (100 mg/kg) was found to significantly reduce the HFD-induced rise in hepatic NF-κB and TNFα protein and mRNA expression levels and even restored hepatic SOD levels (Zheng et al., 2021). These findings point to the potentially promising role that sesamol might play in alleviating hepatic inflammation and oxidative stress. In another study, sesamol administration (2, 4, and 8 mg/kg) of STZ-induced diabetic male Wistar rats was found to significantly and dose-dependently reduce the STZ-induced rise in the levels of the pro-inflammatory cytokines TNFα and TGF-β1, with this reduction being even more prominent when using a sesamol-insulin combination (Kuhad et al., 2009). Additionally, sesamol (2, 4, and 8 mg/kg) was shown to dose-dependently reduce the STZ-induced rise in caspase-3 levels, indicating reduced renal apoptosis, inflammation, and fibrosis (Yang et al., 2001). Similar to results observed with TNFα and TGF-β1, the decrease in caspase-3 levels was also shown to be more pronounced with the sesamol-insulin combination, which is an interesting finding that requires further research. Further analysis also revealed a significant reduction of the STZ-induced rise in NO levels, with this reduction again being more prominent with the sesamol-insulin combination. Furthermore, rats treated with the insulin-sesamol combination showed a more substantial reduction of pro-apoptotic caspase-3 expression (Kuhad et al., 2009). Results from this study highlight the role that sesamol can play in treating renal dysfunction in diabetic rats. Research focusing on testing whether these effects apply to humans is certainly warranted and should be investigated in the future. In another study, treating Al_2O_3-induced Sprague-Dawley rats with sesamol (100 mg/kg/day) for 28 days were found to exhibit promising protective effects on the hepatorenal system as it considerably downregulated the mRNA expression levels of hepatic and renal TNFα and caspase-3 protein, as compared to rats treated with Al_2O_3-NPs alone (El-Borai et al., 2022). Additionally, sesamol treatment of Al_2O_3-induced rats was also shown to reduce the Al_2O_3-induced decline in SOD, indicating enhanced endogenous defense against inflammation (El-Borai et al., 2022). Another study investigated the attenuating effects of sesamol on induced renal inflammation in female apolipoprotein-E-deficient ($ApoE^{-/-}$) mice and the human leukemia monocytic (THP-1) cell line (Tseng et al., 2022). Having been subjected to $^5/_6$ nephrectomy (5/6 Nx) and developing chronic kidney disease (CKD), mice models showed suppressed inflammation in terms of aggravation of nucleated cell count after sesamol (25 and 50 mg/kg) treatment. Sesamol also dose-dependently alleviated CKD-induced glomerular enlargement, proximal tubule apoptosis, and fibrosis-related collagen deposition in renal tissues. In addition, compared to the group with 5/6 Nx alone, renal macrophage infiltration, IκB kinase alpha (IKKα) and ROS-induced IL-1β protein expression were significantly reduced following sesamol dose-dependent treatment, with similar effects reported for H_2O_2 (5 μM)-treated THP-1 cells and macrophages regarding reduced IL-1β transcriptional (mRNA) expression with sesamol (2 μM) treatment. Moreover, sesamol dose-dependent treatment suppressed blood triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) levels, while elevating high-density lipoprotein cholesterol (HDL-C) levels. These results reflect on the inhibitory ability of sesamol in blocking CKD-induced ROS production due to elevated blood lipids (Tseng et al., 2022). In another study, examination of male Wistar rat livers and kidneys revealed that sesamol (50 mg/kg) may be therapeutic against cyclophosphamide (CP)-induced organ toxicity as it significantly reduced the serum levels of the pro-inflammatory mediators like IL-1β, IL-6, TNFα, and COX-2 (Jnaneshwari et al., 2014). Additionally, sesamol treatment (50 mg/kg) of CP-induced rats for one week was found to significantly restore decreased SOD levels, signifying enhanced anti-oxidant and anti-inflammatory potential (Jnaneshwari et al., 2014). Interestingly, western blotting data from another study conducted on the hepatic tissue of Kunming (KM) mice following their treatment with a synthetic compound, produced by combining sesamol pharmacophores with clofibric acid (CF) (412 mg/kg), showcased a significant downregulation in IL-6 and TNFα protein levels, as compared to mice treated with CF alone, suggesting potential hepatoprotective effects (Xie et al., 2021). Furthermore, and as indicated in various other studies reported in this review, a significant elevation of SOD levels was observed in the CF-sesamol combination (412 mg/kg) group, indicating increased ROS catalysis and enhanced anti-inflammatory activity (Xie et al., 2021). Fig. 1 summarizes the reported mediators targeted by sesamol in renal and hepatic disorders.

3.5. Allergic disorders

The anti-inflammatory effects of sesamol may also ameliorate allergic disorders. For example, in a one study, histological investigations of the bronchoalveolar lavage fluid (BALF) in male Sprague-Dawley rats revealed that sesamol administration (1 and 3 mg/kg) resulted in a significant reduction of nitrite and TNFα expression levels in LPS-induced rats, suggesting potential protective effects against acute lung inflammation (Chu et al., 2010a). Results also indicated a significant and dose-dependent decrease in the LPS-induced rise in the levels of the pro-inflammatory mediators TNFα, iNOS, and nitrite in the rat lung tissue following sesamol (1 and 3 mg/kg) treatment (Chu et al., 2010a). These results are indicative of the potentially promising role that sesamol might play in the amelioration of pulmonary diseases characterized by lung tissue inflammation. Nevertheless, compelling experimental evidence suggesting that sesamol may fight against other

allergic disorders is largely lacking. Future studies should be directed at examining the potential efficacy and feasibility of sesamol-containing natural nutraceuticals against different types of allergic ailments. Fig. 1 summarizes the reported mediators targeted by sesamol in allergic disorders. Additionally, a summary of the reported *in vitro* and *in vivo* findings of sesamol on inflammation is presented in Table 1.

4. Effects of sesamol on immunomodulation

The anti-inflammatory effects of sesamol thus far reported lend support to the role this lignan may have in promoting innate immunity. Research suggests that the immune-strengthening effects of sesamol may also extend to encompass aspects of adaptive immunity, mainly cell-mediated immunity. As will be seen in the next sections, although promising, research published in this area is rather scarce and warrants further *in vitro* and *in vivo* investigation. Notwithstanding, evidence supporting the potentially promising role of sesamol in adaptive immunity will be outlined here. In one study, treating polyhydroxyalkanoate (PHA)-stimulated splenocytes (T cells) with sesame seed oil (1, 10, and 100 g/ml) or sesamol (1–100 μg/ml) for 40 h was found to exert immunoprotective effects as it was shown to inhibit the proliferation of T cells, as compared to untreated phosphate buffered saline (PBS) cells (Khorrami et al., 2018). Interestingly, these inhibitory effects were specific to T cells, but not B cells, as neither sesame seed oil nor sesamol were found to inhibit LPS-stimulated splenocytes, as compared to unstimulated cells. B cells are believed to play a significant role in humoral immunity, a type of adaptive immunity responsible for producing antigen-specific antibodies (Sebina and Pepper, 2018). The finding that sesamol was found to exert inhibitory effects on T cells, but not B cells, suggests that the immunomodulatory potential of sesamol may be specific to cell-mediated but not humoral immunity. Further studies exploring this possibility may be necessary to support this assumption. In the same study, it was revealed that sesame seed oil and sesamol were found to prevent IFNγ production from splenocytes, hence contributing to suppressed T-helper cell type I (Th1) proliferation. Additionally, sesamol (1–100 μg/ml) was found to induce a Th2 cytokine shift, as evident by IL-4 secretion. Th1 and Th2 cells are believed to be the most prolific cytokine producers, with Th1 cells believed to be involved in activating macrophages and promoting cell-mediated responses and Th2 cells believed to be involved in eosinophil activation and strong antibody production (Romagnani, 1999). This observation further supports the previous finding from the study that suggests that sesamol was found to exert inhibitory effects only on cell-mediated immunity (Khorrami et al., 2018). Finally, and to further corroborate the findings from this study, analysis on LPS-stimulated dendritic cells (DCs) revealed that sesame seed oil and sesamol (1–100 μg/ml) reduced the proportion and expression levels of CD40, CD86, and major histocompatibility complex II (MHC-II), all of which are markers upstream of Th1/Th2 responses and is therefore indicative of the multiple pathways, genes, and proteins targeted by sesamol in its regulation of immune functions (Khorrami et al., 2018). Other studies reported similar regulatory effects on various other markers involved in immunomodulation. These include a decrease in the M1 microglia-related protein (CD86) and an elevation of the protein levels of the M2 microglial mediators, including mannose receptor (CD206) and arginase 1 (ARG-1) in male C57BL/6 mice after treatment with sesamol (10 mg/kg) for 28 days (Feng et al., 2022). Additionally, another study by Liu et al. (2017) reported a significant reduction of the microglial activation marker (IBA-1) and the astrocyte activation marker glial fibrillary acidic proteins (GFAPs) after sesamol treatment (0.05% (w/v)) of C57BL/6 mice for 4 h (Liu et al., 2017). In line with these findings, sesamol (100 mg/kg and 0.05%) treatment was reported to decrease hippocampal microglial activation through suppressing IBA-1 overexpression compared to scopolamine (SCOP)-treated mice (Yun et al., 2022) and in C57BL/6 mice (Wu et al., 2023). In another study, sesamol (0.05%) treatment was also found to suppress immune cell activation through reduced expression of hippocampal leukocyte-specific receptor (CD11b) in Mn-treated mice. Similar results were found *in vitro*, wherein sesamol (5 μM) reduced the fluorescence intensity of IBA-1 and CD68 in BV-2 cells (Wu et al., 2023). Furthermore, two studies reported suppressed LPS-induced monocyte chemoattractant protein-1 (MCP-1) with sesamol treatment (3, 10, 30, 100 μM and 10 mg/kg), respectively in RAW 264.7 macrophages (Wu et al., 2015). And in Wistar rats (Yashaswini et al., 2017b). Interestingly, the study by Yashaswini et al. (2017b) also found that sesamol (10 mg/kg) suppressed the levels of 5-lipoxygenase (5-LOX) and block lipid transport-1 (BLT-1), which play critical roles in the biosynthesis of LTs and chemotaxis of leukocytes, respectively Yashaswini et al., 2017b). These findings were further corroborated in another study, whereby histological results proved that sesamol (1 and 3 mg/kg) was successful in dose-dependently inhibiting the infiltration of LPS (10 mg/kg)-induced inflammatory cells in the alveolar spaces of rat lungs. Further assessments of the BALF revealed suppressed inflammatory cell infiltration and reduced protein leakage following sesamol (1 and 3 mg/kg) administration (Chu et al., 2010a). Taken together, these findings suggest reduced exaggerated chemotaxis of leukocytes to infection sites, hence contributing to more balanced and coordinated immune responses. Related to such findings, a recent study investigated the effects of hydrogel-containing sesamol-loaded nanocapsules (NC SES) on croton oil-induced contact dermatitis in male Swiss mice (Prado et al., 2023). Researchers found that treating male Swiss mice with hydrogel containing NC SES (1 mg/g) was found to inhibit croton oil-induced polymorphonuclear (PMN) cell infiltration after hydrogel NC SES treatment by about 74.6% (Prado et al., 2023). As the case with exaggerated chemotaxis, improperly guided cell infiltration can be linked with various pathological inflammatory conditions (Jin et al., 2008). In another study, sesamol and sesamin were found to suppress adhesion molecule expression in human aortic endothelial cells (HAECs) (Wu et al., 2010). Precisely, sesamin or sesamol (10, 25, 50, and 100 μM) treatment for 24 h was found to suppress the TNFα-induced increase in the intracellular adhesion molecule-1 (ICAM-1) protein and its mRNA expression by 70% and 30% by sesamol and sesamin, respectively. Furthermore, sesamol (100 μM) or sesamin were found to reduce the leukocyte interaction and adhesion of monocytic U937 cells to TNFα-stimulated HAECs by 70% and 42%, respectively. The researchers speculated that these inhibitory effects could be mediated, at least in part, via the inhibition of the ubiquitous HuR protein translocation and HuR-ICAM-1 mRNA interaction (Wu et al., 2010). According to findings from this study, sesame lignan may have untapped therapeutic potential in the treatment of inflammation and atherosclerosis as monocyte recruitment into the arterial wall after their adherence to endothelial cells is a critical stage in the pathophysiology of atherosclerosis. In another study involving Wistar rats, SM-PLGA nanosuspension (50 mg/kg) treatment was followed by matured granulation tissue, collagen deposition and angiogenesis by day 10 (Gourishetti et al., 2020). Less inflammatory cell infiltration was observed in all treatment groups by day 10 and 15, which correlates with the reduced TNFα levels on the respective days, and increased proliferation of fibroblast cells and collagen deposition at wound sites (Gourishetti et al., 2020). In another study, histopathological examination of KM mice liver tissue showed that inflammatory cell infiltration that resulted in central venous congestion and necrosis in the CF group was ameliorated after CF-sesamol (412 mg/kg) administration, however, hepatocyte swelling still remained (Xie et al., 2021). Although promising, as indicated at the start of this section, evidence pointing to the immunomodulatory potential of sesamol is scarce and warrants further research. Precisely, the effects of sesamol on humoral immunity, including immunoglobulins, eicosanoid production, and B cell function should be explored. Additionally, further *in vitro* and *in vivo* studies exploring the potential role of sesamol on Th1/Th2 responses and on macrophage and other leukocyte expression, production, and cell count levels should be conducted. The reported *in vitro* and *in vivo* effects of sesamin on cell-mediated immunity are summarized in Table 2.

Table 1
Main anti-inflammatory effects of sesamol.

Main Effects	Experimental Model	Dosage	Administration Mode	Administration Duration	References
-Downregulation of LPS-induced IL-1β and TNFα production in macrophages and in serum -Elevation of survival rate after lethal LPS injection -Reduction of LPS ability to bind to LBP in macrophages	Male Sprague Dawley rats (LPS-induced inflammation) Peritoneal macrophages (LPS-induced inflammation)	1, 3, and 10 mg/kg 30, 100 and 300 μM	Subcutaneous administration N/A	Treatment for 3 h Treatment for 24 h	Hsu et al. (2009)
-Decreased LPS-induced mitochondrial production of O2• and macrophage production of NO• -inhibition of LPS-induced activity of NF-κB -Inhibition of LPS-induced rise in BAX/Bcl-2 ratio and cytochrome *c* loss -Reduction of LPS-induced loss of cell viability -Reduction of LPS-induced activation of caspase-3 and caspase-9 -Reduction of LPS-induced DNA fragmentation levels -Suppression of LPS-induced secretions of IL-1β, IL-6, and TNFα, COX-2 and HMGB1 in RAW 264.7 cells	RAW 264.7 cell line (LPS-induced inflammation)	1–100 μM	N/A	Pretreatment for 1 h	Duarte et al. (2018)
-Reduction of PGE2, nitrite and ROS production -Suppression of iNOS and COX-2 mRNA and protein expression after LPS induction -Suppression of IL-1β, IL-6, and TNFα after LPS induction	RAW 264.7 cell line (LPS-induced inflammation)	3, 10, 30, and 100 μM	N/A	Pretreatment for 1 h and treatment for up to 24 h	Wu et al. (2015)
-Elevation of DGLA levels -Suppression of DPA levels and the Δ5 desaturation index for PUFAs -Suppression of LPS-induced levels of PGE1 and PGE2 -Suppression of LPS-induced levels of IL-6	Female BALB/c mice (LPS-induced inflammation)	1% wt	Oral administration	Treatment for 2 weeks	Chavali and Forse (1999)
-Downregulation in levels of IL-1β and TNFα -Reduction of mitochondrial $O_{2\cdot}$ production and NO levels in the SH-SY5Y cells after H_2O_2 induction -Reduction of caspase-3 and caspase-9 activity after H_2O_2 induction -Suppression of Bcl-2 levels after H_2O_2 induction -Inhibition of cytochrome *c* release after H_2O_2 induction -Elevation of BAX levels after H_2O_2 induction	Human neuroblastoma SH-SY5Y cell line (H_2O_2-induced inflammation)	12.5–50 μM	N/A	Pretreatment for 24 h	Da Silva Navarro et al. (2022)
-Reduction of IL-1β, TNFα, and nitrite levels in serum -Reduction of iNOS expression after LPS induction in mice and RAW 264.7 macrophages	Male ICR mice (LPS-induced inflammation) RAW 264.7 cell line (LPS-induced inflammation)	10 mg/kg 100 and 300 μM	Subcutaneous administration N/A	Treatment 1, 3, and 6 h after LPS induction Treatment for 24 h	Chu et al. (2010b)
-Suppression of LOX activity in Caco-2 cells -Suppression LPS-stimulated iNOS protein expression in RAW 264.7 macrophages -Suppression of LPS-stimulated ROS production in RAW 264.7 macrophages	Caco-2 cell line RAW 264.7 cell line (LPS-induced inflammation & PC-encapsulated sesamol)	300 μg/ml 100 μM	N/A N/A	Treatment for 48 h	Yashaswini et al. (2017a)
-Reduction of paw volume and prevention of edema and bone cartilage damage -Suppression of IL-1β, IL-6, TNFα, COX-2, and PGE2 levels after adjuvant-arthritis induction -Suppression of endogenous formation of ROS -Suppressed in adjuvant-induced MMP-3, MMP-9, and MMP-13 serum levels -Restoration in adjuvant-induced suppression splenic SOD levels and elevation of hepatic SOD levels	Wistar rats (Freund's complete adjuvant-induced arthritis)	25 and 50 mg/kg	Oral administration	Treatment for 14 days (daily)	Hemshekhar et al. (2013)
-Inhibition of MMP-9 activation through downregulation of cytokine-induced gelatinolysis in SW1353 cells -Inhibition of PMA-stimulated MMP-1 activation and MMP-13 expression in chondrocytes -Reversal of TNFα and PMA-stimulated rate of degradation of SW1353 cells -Suppression of MIA-induced expression of MMP-1 and MMP-9 *in vivo*	SW1353 Chondrosarcoma cell line (PMA-induced osteoarthritis) Male Wistar rats (PMA-induced osteoarthritis)	5−20 μM 30 mg/kg	N/A Oral administration	Treatment for 15 min Treatment for 2 weeks	Lu et al. (2011)

(*continued on next page*)

Table 1 (*continued*)

Main Effects	Experimental Model	Dosage	Administration Mode	Administration Duration	References
-Suppression of SCI-induced caspase-3 and BAX and elevation of Bcl-2 protein levels -Suppression of SCI-induced IL-6 and TNFα protein levels in mice and BV-2 cells	Male C57BL/6 mice (SCI-induced inflammation) BV-2 cells (SCI-induced inflammation)	10 mg/kg 10 μM	Intraperitoneal administration N/A	Treatment for 28 days	Feng et al. (2022)
-Reduction of expression of IL-1β and TNFα in the hippocampus and in serum -Suppression of hippocampal mRNA expression of IL-1β, IL-6, and TNFα -Elevation of serum and hippocampal of SOD enzymatic activity	Male CD-1 mice (Age-induced inflammation)	0.1%, w/w	Oral administration	Treatment for 12 weeks	Ren et al. (2020)
-Suppression of MCAO-induced caspase-3 and BAX protein expression levels -Reduction of MCAO-induced mRNA and protein expression of IL-6 and TNFα -Elevation of MCAO-induced Bcl-2 protein expression -Upregulation of MCAO-suppressed cortical SOD levels	Male Sprague Dawley rats (MCAO-related cerebral I/R)	25 mg/kg	Oral administration	Treatment for 7 days (daily)	Gao et al. (2017)
-Inhibition of STZ-induced NO plasma levels -Inhibition of STZ-induced caspase-3 activity -Suppression of STZ-induced IL-1β, TNFα, and TGF-β plasma levels	Male Wistar rats (STZ-induced, diabetes related neuropathy)	2, 4, and 8 mg/kg	Oral administration	Treatment for 4 weeks	Chopra et al. (2010)
-Suppression of nitrite levels in the cortex and hippocampus after STZ induction -Suppression of serum TNFα levels after STZ induction -Elevation of cortical and hippocampal SOD enzymatic activity	Male Wistar rats (STZ-induced neuroinflammation)	2, 4, and 8 mg/kg	Oral administration	Treatment for 10 weeks (daily)	Kuhad and Chopra (2008)
-Reduction of accumulation of cortical Aβ plaques -Inhibition of LPS-stimulated mRNA expression of iNOS, COX-2 and TLR4 in BV-2 microglia and in serum -Suppression of LPS-stimulated IL-1β, IL-6 and TNFα mRNA and protein expression -Suppression of LPS-stimulated MMP-1, MMP-3, and MMP-9 mRNA expression	C57BL/6 J mice (LPS-induced neuroinflammation) BV-2 cells (LPS-induced neuroinflammation)	0.05% (w/v) 0, 5, 12.5, 25 μM	Oral administration N/A	Treatment for 7 weeks Treatment for 4 h	Liu et al. (2017)
-Suppression of Mn-induced TNFα and CXCL10 mRNA expression in mice and BV-2 cells -Suppression of Mn-induced iNOS mRNA and protein expression -Suppression of Mn-induced IFNα and IFNβ mRNA expression in mice and transcriptional expression in BV-2 cells	Male C57BL/6 mice (Mn-induced neurotoxicity) BV-2 microglia (Mn-induced neurotoxicity)	0.05% sesamol (w/v) 5, 12.5, 25 μM	Oral administration N/A	Treatment for 7 weeks Treatment for 4 h	Wu et al. (2023)
-Suppression of Mn-induced brain levels of IL-1β, TNFα, COX-2, TLR4, caspase-1, and NLRP3	Male Sprague Dawley rats (Mn-induced Parkinson's disease)	15 mg/kg	Oral administration	Treatment for 5 weeks (daily)	Abu-Elfotuh et al. (2022)
-Suppression of CIH-stimulated IL-1β and TNFα hippocampal levels -Elevation of CIH-induced activity of hippocampal SOD	Male Wistar rats (CIH-induced inflammation)	20 mg/kg	Intraperitoneal administration	Treatment for 8 weeks (daily)	Zhang et al. (2021)
-Inhibition of DSS-induced iNOS and COX-2 protein levels -Suppression of DSS-induced IL-1β, IL-6, TNFα, iNOS, COX-2, and TLR4 mRNA expression via inhibiting the NF-κB pathway -Elevation of anti-inflammatory fecal SCFAs	Male C57BL/6 mice (DSS-induced colitis)	100 mg/kg	Oral administration	Treatment for 6 weeks (daily)	Zhao et al. (2020)
-Suppression of NEC-induced bowel damage, edema and fragility -Reduction of the number of intestinal Bcl-2 and caspase-3 positive cells -Elevation of intestinal SOD activity	Newborn Wistar albino rats (NEC-induced inflammation)	97% (100 mg/kg)	Intraperitoneal and oral administration	Treatment for 3 days twice daily	Cigsar et al., 2018
-Reduction of tissue nitrite levels after DNCB induction -Suppression of MPO levels after DNCB induction -Elevation of IL-6 and TNFα levels after DNCB induction	Male albino Wistar rats (DNCB-induced IBS)	100 mg/kg	Oral administration	Treatment for 7 days (daily)	Kondamudi et al. (2013)
-Inhibition of production of TNFα induced by HFD -Elevation of expression of CD31 cells through SM-PLGA treatment -Elevation of VEGF and PDGF levels	Male Wistar rats (HFD-induced DFU)	50 and 100 mg/kg 0.25% (w/v)	Oral administration	Treatment for 15 days	Gourishetti et al. (2020)
-Elevation of STZ-induced diabetic wound healing rates -Downregulation of mRNA expression of IL-1β	Male C57BL/6 J mice (STZ-induced diabetes)	2% and 5% (w/v)	CA/zein nanofiber membranes (transdermal)	Treatment 9 days (daily)	Liu et al. (2020)

(*continued on next page*)

Table 1 (*continued*)

Main Effects	Experimental Model	Dosage	Administration Mode	Administration Duration	References
-Downregulation of IL-10 expression associated with keratinocytes -Upregulation of IL-6 expression associated with keratinocytes -Suppression of LPS-stimulated serum IL-1β, TNFα, and CRP levels -Suppression of LPS-elevated serum LTB4, LTC4 levels and LTC4 synthase expression -Suppression of LPS-stimulated serum NO levels as well as its production -Elevation of LPS-stimulated SOD activity and levels	Male Wistar rats (LPS-induced inflammation)	10 mg/kg	Oral administration	Treatment for 15 days (daily)	Yashaswini et al. (2017b)
-Elevation of SOD enzymatic activity -Elevation of HFD-induced serum adiponectin levels -Restoration of HFD-induced drop in serum NO levels -Reversal of HFD-induced decrease in eNOS expression and increase in NT accumulation -Reversal of HFD-induced hepatocytic swelling, fat accumulation and nucleus loss in liver tissue -Suppression of HFD-induced serum levels of IL-6, TNFα, and hs-CRP -Upregulation of PPARγ expression	Male Wistar albino rats (HFD-induced CMetS)	2, 4 and 8 mg/kg	Oral administration	Treatment for 30 days (daily)	Sharma et al. (2012)
-Suppression of CLP and LPS-induced serum IL-1β, IL-6, and TNFα levels -Elevation of LPS-induced serum IL-10 levels -Elevation of LPS-influenced PPARγ activation levels in rat peritoneal macrophages and leukocytes	Male Wistar rats Rat peritoneal macrophages (CLP- & LPS-induced AKI)	3 and 10 mg/kg 3, 30 or 300 μM	Subcutaneous administration N/A	Treatment 0 and 6 h after LPS induction Treatment for 24 h	Periasamy et al. (2015)
-Suppression of NOX2 activity and its encoding mRNA -Restoration of HFD-induced hepatic protein and mRNA expression of NF-κB and TNFα -Restoration of hepatic SOD levels	Male C57BL/6 mice (HDF-induced inflammation)	100 mg/kg	Oral administration	Treatment for 8 weeks (daily)	Zheng et al. (2021)
-Suppression of STZ-induced total renal NO levels -Reduction of STZ-induced renal TNFα and TGF-β1 levels -Reduction of STZ-induced renal caspase-3 levels	Male Wistar rats (STZ-induced diabetes)	2, 4, and 8 mg/kg	Oral administration	Treatment for 3 weeks (daily)	Kuhad et al. (2009)
-Downregulation of hepatic and renal TNFα and caspase-3 mRNA expression after Al_2O_3-NPs induction -Reduction of decline of Al_2O_3-NPs-induced hepatic SOD levels	Male Sprague Dawley rats (Al_2O_3-NP-induced inflammation)	100 mg/kg	Oral administration	Treatment for 28 days (daily)	El-Borai et al. (2022)
-Suppressed aggravation of nucleated cell count -Alleviation of renal glomerular enlargement, proximal tubule apoptosis, and fibrosis-related collagen deposition -Reduction of renal macrophage infiltration, p-IKKα and ROS-induced IL-1β protein expression -Reduction of IL-1β mRNA expression in THP-1 cells and macrophages -Reduction of blood triglycerides, total cholesterol and LDL-C -Elevation of blood HDL-C	Female ApoE$^{-/-}$ mice (5/6 Nx-induced CKD) THP-1 cell line (5/6 Nx-induced CKD)	25 or 50 mg/kg 2 μM	Oral administration N/A	Treatment thrice per week for 8 weeks Pretreatment for 1 h	Tseng et al. (2022)
-Restoration of CP-induced elevated hepatic and renal ROS levels and suppressed SOD levels -Suppression of CP-induced serum levels of IL-1β, IL-6, TNFα, and COX-2	Male Wistar rats (CP-induced organ toxicity)	50 mg/kg	Oral administration	Treatment for a week (daily)	Jnaneshwari et al. (2014)
-Elevation of plasma SOD levels -Downregulation of IL-6 and TNFα protein levels	KM mice (Tyloxapol-induced hyperlipidemia)	412 mg/kg	Intragastrical administration	Treatment for 7 days (daily)	Xie et al. (2021)
-Inhibition of LPS-induced protein expression of TNFα and iNOS in rat lung tissue -Inhibition of LPS-induced NO production in rat lung tissue	Male Sprague Dawley rats (LPS-induced inflammation) Rat alveolar macrophages (LPS-induced inflammation)	0.3, 1 and 3 mg/kg 30, 100, 300, 1000 μM	Subcutaneous administration N/A	Treatment for 4 h Treatment for 24 h	Chu et al. (2010a)

Table 2
Main immunomodulatory effects of sesamol.

Main Effects	Experimental Model	Dosage	Administration Mode	Administration Duration	References
-Inhibition of proliferation of PHA-stimulated splenocytes (T cells) -Inhibition of IFNγ production by splenocytes -Induction of Th2 cytokine shift through IL-4 secretion -Suppressed expression of CD40, CD86, and MHC-II in DCs	Male BALB/c mice (PHA-induced inflammation) splenocyte subsets, dendritic cells & peritoneal macrophages (PHA-induced inflammation)	1–100 μg/ml	N/A	Treatment for 24 or 40 h	Khorrami et al. (2018)
-Elevation of M2 microglial mediators (CD 206 and Arg 1) -Suppression of M1 microglial mediators (CD86)	Male C57BL/6 mice (SCI-induced inflammation)	10 mg/kg	Intraperitoneal administration	Treatment for 28 days	Feng et al. (2022)
-Suppression of LPS-stimulated IBA-1 and GFAP proteins	C57BL/6 J mice (LPS-induced neuroinflammation)	0.05% (w/v)	Oral administration	Treatment for 4 h	Liu et al. (2017)
-Suppression of SCOP-induced IBA-1 hippocampal overexpression	C57BL/6 mice (SCOP-induced inflammation)	100 mg/kg	Oral administration	Pretreatment for 30 days (daily)	Yun et al. (2022)
-Suppression of Mn-induced microglial activation -Suppression of Mn-induced IBA-1 and CD68 expression in mice and BV-2 cells -Suppression of Mn-induced CD11b expression in mice	Male C57BL/6 mice (Mn-induced neurotoxicity) BV-2 microglia (Mn-induced neurotoxicity)	0.05% sesamol (w/v) 5,12.5, 25 μM	Oral administration N/A	Treatment for 7 weeks Treatment for 4 h	Wu et al. (2023)
-Suppression of LPS-induced rise in MCP-1 levels	RAW 264.7 macrophages (LPS-induced inflammation)	3, 10, 30, 100 μM	N/A	Pretreatment for 1 h and treatment for up to 24 h	Wu et al. (2015)
-Suppression of LPS-stimulated 5-LOX and BLT-1 serum levels -Suppression of LPS-induced rise in MCP-1 levels	Male Wistar rats (LPS-induced inflammation)	10 mg/kg	Oral administration	Treatment for 15 days (daily)	Yashaswini et al. (2017b)
-Inhibition of LPS-induced inflammatory cell infiltration in rat alveolar spaces -Suppression of LPS-induced BALF inflammatory cell infiltration, protein leakage	Male Sprague Dawley rats (LPS-induced inflammation)	0.3, 1 and 3 mg/kg	Subcutaneous administration	Treatment for 4 h	Chu et al. (2010a)
-Inhibition of croton oil-induced PMN cell infiltration	Male Swiss mice (Croton oil-induced inflammation)	1 mg/g	Topical administration	Treatment for 6 h	Prado et al. (2023)
-Suppression of TNFα, induced ICAM-1 protein and mRNA expression in HAECs -Decreased adhesion of U937 monocytes to TNFα-stimulated HAECs	HAEC culture (TNFα-induced inflammation)	10, 25, 50, 100 μM	N/A	Pretreatment for 24 h	Wu et al. (2010)
-Elevated proliferation of fibroblast cells and collagen deposition at wound sites -Matured granulation tissue, collagen deposition and angiogenesis -Suppressed inflammatory cell infiltration	Male Wistar rats (HFD-induced DFU)	50 and 100 mg/kg 0.25% (w/v)	Oral administration	Treatment for 15 days	Gourishetti et al. (2020)
-Amelioration of inflammatory cell infiltration, necrosis and venous congestion	KM mice (Tyloxapol-induced hyperlipidemia)	412 mg/kg	Intragastrical administration	Treatment for 7 days (daily)	Xie et al. (2021)

5. Signaling pathways underlying the immunomodulatory and anti-inflammatory effects of sesamol

Several studies have been conducted to shed more light on the signaling mechanisms underlying the reported anti-inflammatory and immunomodulatory actions of sesamol. Majority of studies identified key signaling pathways like NF-κB and members of the mitogen-activated protein kinase (MAPK) family, such as extracellular signal-regulated kinase (ERK), p38 MAPK, and jun N-terminal kinase (JNK), as well as the inflammatory oxidative-stress associated nuclear factor-erythroid factor 2-related factor 2 (Nrf2) pathway, as crucial for mediating the protective effects of sesamol against many inflammatory disorders. Other relevant, yet less common pathways, were also identified, including adenosine monophosphate-activated kinase (AMPK) and the TGF-β pathway. These pathways are also thought to mediate some of the reported anti-inflammatory and immunomodulatory effects of sesamol. For example, sesamol was found to exert immunomodulatory effects against platelet activation mainly via targeting the NF-κB signaling cascade (Chang et al., 2011). Precisely, collagen (1 μg/ml)-stimulated IκB kinase beta (IKKβ), p65 phosphorylation, and IκBα protein degradation in the platelets were found to be concentration-dependently attenuated with sesamol (2.5–25 μM) pretreatment for 3 min, indicating that sesamol interferes with the IKK-IκBα cascade and NF-κB signaling pathway in platelets. Noteworthy, researchers from the same study previously found that sesamol increases the levels of cyclic nucleotides like cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). They suggested NO production and eNOS activity were boosted by increased cAMP, which was followed by a rise in cGMP formation. This highlighted how cAMP functions as an upstream regulator of the eNOS–NO–cGMP cascade in the antiplatelet actions of sesamol. In the current study, cyclic nucleotide inhibitors like SQ22536 (100 μM) and ODQ (20 μM) were used to explain the inhibition of NF-κB signaling by sesamol; both inhibitors reversed the sesamol (25 μM)-mediated inhibition of IKKβ, NF-κB-p65 phosphorylation, and IκBα

degradation in the platelets. Moreover, the effects of adding an NF-κB inhibitor, like BAY11-7082, which is used to study [Ca^{2+}] immobilization and platelet aggregation, were further investigated in this study. At low concentrations of the NF-κB inhibitor (10 μM), both collagen-stimulated measures were considerably attenuated. Sesamol pretreatment (25 μM) with subsequent addition of the cAMP or kinase inhibitors was found to dramatically reverse the inhibition of the two measures. Collectively, results from this study indicate that the anti-platelet potential of sesamol seems to be mediated, at least in part, via the suppression of NF-κB (Chang et al., 2011). Sesamol treatment (3, 10, 30, and 100 μM) of LPS-stimulated RAW 264.7 macrophages was found to inhibit the LPS-induced rise in IκBα phosphorylation, decreasing nuclear translocation of p65, as compared to the LPS control (Wu et al., 2015). In addition, the MAPK pathway that promotes inflammatory mediators was suppressed after sesamol treatment through inhibition of ERK1/2, p38 and JNK protein phosphorylation. On the contrary, sesamol increased LPS-stimulated AMPK phosphorylation in macrophages in a concentration-dependent manner, while simultaneously restoring AMPK activity and reducing TNFα production when macrophages were treated with compound C, an AMPK inhibitor, promoting cellular homeostasis restoration. Furthermore, sesamol was also shown to exert potent antioxidant effects via enhancing HO-1 production and Nrf2 expression in macrophages before and after LPS induction (Wu et al., 2015). Results indicate that sesamol demonstrates antioxidant effects mainly via activating the Nrf2/HO-1 pathway and suppressing the production of pro-inflammatory cytokines by inhibiting the activation of NF-κB and MAPK pathways and promoting AMPK activation. The ability of sesamol to enhance the HO-1 pathway is of particular importance as the enhancement of such pathway correlates with reduced oxidative damage and inflammation (Alcaraz et al., 2003). Sesamol (10 mg/kg) administration was found to reverse the SCI-induced drop in Sirtuin-1 (SIRT1) protein expression and the ratio of p-AMPK/AMPK and the SCI-induced rise in p-p65/p65 ratio, implying that sesamol may activate AMPK/SIRT1 and decrease activation of NF-κB pathways in strained mice (Feng et al., 2022). Sesamol (5 μM) decreased the Mn-induced protein expression of p-STING and p–NF–κB-p65 in BV-2 microglia, while the protein expression of cyclic GMP-AMP synthase (cGAS) did not change significantly. This suggests that sesamol may have lowered the pro-inflammatory response to Mn by blocking the microglial cGAS-STING/NF-κB pathway (Wu et al., 2023). In another study, Abu-Elfotuh et al. (2022) found that sesamol monotherapy (15 mg/kg) decreased Mn-induced microglial neuroinflammation in Sprague Dawley rats via suppressing elevated brain activation levels of NF-κB and glycogen synthase kinase-3 beta (GSK-3B) (Abu-Elfotuh et al., 2022) Interestingly, combining sesamol with thymol, wheatgrass and CoQ10 was found to exert superior effects on the above-mentioned signaling pathways, indicating potential alleviation in PD symptoms in Mn-exposed Sprague Dawley rats. Furthermore, sesamol (15 mg/kg) monotherapy provided significant increments in brain levels of anti-inflammatory and antioxidant markers like Nrf2 and HO-1, with better results shown in combination therapy. Altogether, findings suggest a relation between sesamol, the inhibition of GSK-3β, and the activation of the Nrf2/HO-1 pathway. (Abu-Elfotuh et al., 2022; Yang et al., 2022). GSK-3 is one of Nrf2 upstream factors that can function as crucial mediators for the Nrf2/NF-κB pathway, highlighting the crucial role that GSK-3 pathway may play in mediating the anti-inflammatory effects of sesamol (Yan et al., 2020). In another study involving the neuroblastoma SH-SY5Y cell line by da Silva Navarro et al. (2022), sesamol (25 μM) pretreatment downregulated the levels of IL-1β and TNFα via reducing the activity of NF-κB in cells exposed to H_2O_2. Interestingly, the anti-inflammatory effect of sesamol on the activity of NF-κB was eliminated when the transcription factor, Nrf2, was silenced using siRNA, suggesting that the mitochondrial protective mechanisms of sesamol depended on Nrf2 activity (da Silva Navarro et al., 2022). Studies suggest that Nrf2 plays a role in regulating oxidative stress and inflammation, hence it may be useful for future studies to specifically look at deciphering the mechanisms by which sesamol may influence Nrf2 activity. In a study by Zheng et al. (2021), sesamol (100 mg/kg) treatment dramatically increased the levels of Nrf2 protein in HFD mice, demonstrating that sesamol activates Nrf2 in the presence of hepatic steatosis generated by HFD in male C57BL/6 mice (Zheng et al., 2021) Nrf2 along with HO-1 was also found by Xie et al. (2021) to be targeted by sesamol in its anti-inflammatory and hepatoprotective effects in KM mice (Xie et al., 2021). Additionally, the inflammatory expression of p–NF–κB-p65 protein was markedly suppressed by CF-sesamol (412 mg/kg) treatment, compared to the upregulation in the CF group (Xie et al., 2021). Collectively, these results indicate that sesamol helps reduce oxidative stress and hepatic inflammatory response, at least in part, via activating the Nrf2/NF-κB signaling pathway in the mouse liver. Tseng et al. (2022) found that sesamol (2 μM) suppressed renal inflammation in THP-1 cell line via downregulating the H_2O_2-induced phosphorylation levels of IKKα, IκBα, and NF-κB-p65, hence blocking IL-1β expression in THP-1 cells (Tseng et al., 2022). Additionally, HO-1 transcription was increased after sesamol (2 μM) administration, also resulting in decreased levels of p-IKKα. These results were further proved by the HO-1 inhibitor, tin protoporphyrin (SnPP), abolishing these anti-inflammatory effects on THP-1 cells (Tseng et al., 2022). In another study, Western blots analyses revealed that sesamol 0.05% (w/v) treatment of C57BL/6 mice inhibited the increased LPS-induced ratios of p-IκBα/IκBα, p–NF–κB/NF-κB and the MAPK transcription factors JNK, p38 and ERK1/2 (Liu et al., 2017). Similarly, studies on BV-2 microglia from the same study also showed similar results whereby sesamol (0, 5, 12.5, 25 μM) treatment for 15 min inhibited NF-κB by decreasing the p-IκB/IκB ratio and expression of p50 in the nucleus while also blocking the LPS-induced NF-κB DNA-binding activity, in a concentration-dependent manner (Liu et al., 2017). In a study by Chu et al. (2010b) exploring LPS-induced inflammatory responses in male ICR mice, sesamol (10 mg/kg) strongly decreased LPS-induced IκB phosphorylation and NF-κB release and translocation in macrophages without affecting their viability, which is an interesting finding as it sheds light on the mechanisms behind the association of sesamol with suppression of pro-inflammatory mediator release (Chu et al., 2010b). Acute lung inflammation and damage induced by systemic endotoxin in male Sprague Dawley rats as well as their alveolar macrophages were also examined by Chu and colleagues. Macrophages were cultured and examined for NF-κB activation; sesamol (30, 100, 300, and 1000 μM) treatment for 24 h was found to markedly and concentration-dependently suppress NF-κB activation along with other inflammatory parameters, suggesting the role of NF-κB in mediating acute lung inflammation and the potential role of sesamol in regulating the expression of this pathway (Chu et al., 2010a). In another study involving neuroinflammation in CD-1 male mice, Ren et al. (2020) found that a critical component of controlling the expression of associated genes is played by the NF-κB. Specifically, daily sesamol (0.1%, w/w) treatment for 12 weeks prevented the significant rise in p–NF–κB/NF-κB in the hippocampus that was observed in aging mice (Ren et al., 2020). These results were further corroborated in the renal NF-κB-p65 subunit, whereby treatment with sesamol (2, 4, and 8 mg/kg) substantially and dose-dependently reduced the expression of the NF-κB-p65 subunit caused by ROS in the nuclear fraction of STZ-treated Wistar rats (Kuhad et al., 2009). In another study, sesamol supplementation (100 mg/kg) in DSS-treated C57BL/6 colitis mice was shown to attenuate inflammatory responses mainly via inhibiting the NF-κB pathway (Zhao et al., 2020). These findings were further corroborated in another study whereby sesamol (100 μM) and sesamin were both found to significantly inhibit NF-κB activation by 20% and 95%, respectively, after 24 h of treatment in TNFα-induced HAECs (Wu et al., 2010). Further investigations from the same study were carried out to ascertain whether this inhibition of activation was associated with the pretranslational effects of the two lignans. For that, the NF-κB-p65 protein levels in the nucleus of TNFα-treated HAECs were examined. Both lignan-treated cells showed a weaker nuclear but a stronger cytoplasmic protein expression. However,

the phosphorylation of MAPK transcription factors ERK1/2, JNK, and p38 stimulated by TNFα in HAECs, was not inhibited by sesamol (10 and 100 μM) pretreatment, a finding that warrants further research (Wu et al., 2010). In contrast, Lu et al. (2011) found that sesamol (5, 10, and 20 μM) treatment concentration-dependently inhibited PMA- and IL-1β-induced rise in the MAPK transcription factors, p-ERK1/2 and p38, but not c-JNK levels, in chondrosarcoma cell lines (Lu et al., 2011). Collectively, the majority of the findings reported above highlight the imperative role NF-κB and MAPK signaling pathways play in mediating the anti-inflammatory and immunomodulatory effects of sesamol. A couple of other studies also point to the potentially promising role that other pathway, like Nrf2, may play in mediating the anti-inflammatory and immunomodulatory effects of sesamol. Nevertheless, these require further research for their role to be fully elucidated and confirmed. Fig. 1

Table 3
Main signaling pathways involved in mechanisms of sesamol.

Main Effects	Experimental Model	Dosage	Administration Mode	Administration Duration	References
-Attenuation of collagen-stimulated IKKβ and NF-κB-p65 phosphorylation and IκBα protein degradation -Inhibition of collagen-stimulated [Ca^{2+}] immobilization and platelet aggregation	Human platelet suspensions (Collagen-induced inflammation)	2.5–25 μM	N/A	Pretreatment for 3 min	Chang et al. (2011)
-Suppression of IκBα phosphorylation and NF-κB translocation after LPS induction -Suppression of MAPK pathway through inhibition of ERK1/2, p38 and JNK protein phosphorylation -Elevation of AMPK phosphorylation and restoration of its activity -Upregulation of HO-1 production and Nrf2 expression before and after LPS induction	RAW 264.7 cell line (LPS-induced inflammation)	3, 10, 30, and 100 μM	N/A	Pretreatment for 1 h and treatment for up to 24 h	Wu et al. (2015)
-Suppression of SCI-induced p-p65/p65 ratio *in vivo* and *in vitro* -Elevation of p-AMPK/AMPK ratio and SIRT1 expression *in vivo* and *in vitro*	Male C57BL/6 mice (SCI-induced inflammation) BV-2 cells (SCI-induced inflammation)	10 mg/kg 10 μM	Intraperitoneal administration N/A	Treatment for 28 days	Feng et al. (2022)
-Suppression of protein expression of p-STING and p–NF–κB-p65 in BV-2 cells	BV-2 microglia (Mn-induced neurotoxicity)	5, 12.5, 25 μM	N/A	Treatment for 4 h	Wu et al. (2023)
-Suppression of Mn-induced activation levels of NF-κB and GSK-3β. -Elevation of brain levels of Nrf2, HO-1, and SOD activity. -Suppression of iNOS activity	Male Sprague Dawley rats (Mn-induced Parkinson's disease)	15 mg/kg	Oral administration	Treatment for 5 weeks (daily)	Abu-Elfotuh et al. (2022)
-Downregulation of NF-κB transcription factor after H_2O_2 induction -Downregulation of IL-1β and TNFα levels after H_2O_2 induction	Human neuroblastoma SH-SY5Y cell line (H_2O_2 -induced inflammation)	12.5–50 μM	N/A	Pretreatment for 24 h	da Silva Navarro et al. (2022)
-Elevation of hepatic Nrf2 levels	Male C57BL/6 mice (HDF-induced inflammation)	100 mg/kg	Oral administration	Treatment for 8 weeks (daily)	Zheng et al. (2021)
-Downregulation of p–NF–κB-p65 protein expression -Upregulation of expression Nrf2 and HO-1 protein expression	KM mice (Tyloxapol-induced hyperlipidemia)	412 mg/kg	Intragastrical administration	Treatment for 7 days (daily)	Xie et al. (2021)
-Downregulation in H_2O_2-induced phosphorylation levels of IKKα, IκBα, and NF-κB-p65 -Elevation of HO-1 transcription resulting in downregulation of p-IKKα	THP-1 cell line (H_2O_2-induced inflammation)	2 μM	N/A	Pretreatment for 1 h	Tseng et al. (2022)
-Inhibition of LPS-stimulated serum ratios of p-IκB/IκB and p–NF–κB/NF-κB in BV-2 microglia and in serum -Inhibition of LPS-stimulated expression of JNK, p38, and ERK1/2	C57BL/6 J mice (LPS-induced inflammation) BV-2 cells (LPS-induced inflammation)	0.05% (w/v) 5, 12.5, 25 μM	Oral administration N/A	Treatment for 7 weeks Treatment for 4 h	Liu et al. (2017)
-Suppression of IκB phosphorylation and NF-κB release and translocation after LPS induction in macrophages	Male ICR mice (LPS-induced inflammation) RAW 264.7 cell line (LPS-induced inflammation)	10 mg/kg 100 and 300 μM	Subcutaneous administration N/A	Treatment 1, 3, and 6 h after LPS induction Treatment for 24 h	Chu et al. (2010b)
-Suppression of LPS-induced iNOS mRNA expression and NF-κB activation	Rat alveolar macrophages (LPS-induced inflammation)	30, 100, 300 and 1000 μM	N/A	Treatment for 24 h	Chu et al. (2010a)
-Inhibition of rise in p–NF–κB/NF-κB ratio	Male CD-1 mice (Age-induced inflammation)	0.1%, w/w	Oral administration	Treatment for 12 weeks	Ren et al. (2020)
-Reduction of expression of the renal NF-κB-p65 subunit caused by ROS	Male Wistar rats (STZ-induced Diabetes)	2, 4, and 8 mg/kg	Oral administration	Treatment for 3 weeks (daily)	Kuhad et al. (2009)
-Suppression of DSS-induced p–NF–κB/NF-κB ratio	Male C57BL/6 mice (DSS-induced colitis)	100 mg/kg	Oral administration	Treatment for 6 weeks (daily)	Zhao et al. (2020)
-Inhibition of TNFα induced NF-κB activation and nuclear NF-κB-p65 protein expression	HAEC culture (TNFα-induced inflammation)	10, 25, 50, 100 μM	N/A	Pretreatment for 24 h	Wu et al. (2010)
-Inhibition of IL-1β and PMA-stimulated phosphorylated forms of ERK1/2 and p38	SW1353 Chondrosarcoma cell line (PMA-induced osteoarthritis)	5−20 μM	N/A	Treatment for 15 min	Lu et al. (2011)

summarizes the reported signaling pathways targeted by sesamol in various disorders. Additionally, a summary of the signaling pathways underlying the anti-inflammatory and immunomodulatory effects of sesamol are presented in Table 3.

6. Conclusion

In light of the discussed findings, future interventions could benefit from the use of sesamol to prevent and/or treat various types of inflammatory and immune-related diseases. Ample evidence supports the regulatory role that sesamol has against a plethora of inflammatory cytokines, the most important being IL-1β and TNFα. The exhibited anti-inflammatory actions of sesamol are believed to be most commonly mediated via NF-κB and MAPK signaling pathways and their associated transcription factors. Although evidence supporting the role that sesamol may play in adaptive immunity is scarce, the evidence in the literature thus far reported on this topic points towards a promising direction. Particularly, it seems plausible to suggest that sesamol may play a role in suppressing T cell over-proliferation, Th1 responses, inflammatory cell infiltration, and chemotaxis. Noteworthy, the minor discrepancies regarding the anti-inflammatory and immunomodulatory effects reported in studies outlined in this review could be attributed to the different experimental conditions employed in various studies, including, but not limited to, dosage, cell types, animal models, incubation time, mode of administration, and detection methods. Future experimental studies published on this topic should therefore have a more carefully planned experimental design to address the raised discrepancies related to experimental variables. This will help shed more light on the mechanisms of action underlying such effects. It remains to be clarified whether sesamol could influence B cell function, antibody production, humoral immunity, and Th1/Th2 balance. These are examples of research arenas that should be further investigated in future studies. Additionally, in terms of innate immunity, although ample research has been reported on the possible mediators targeted by sesamol in various inflammatory conditions, research on the role of sesamol on natural killer (NK) cell cytotoxic activity is yet to be explored. Once investigated, we anticipate that future studies can help confirm the seemingly potent role that this lignan may play in developing effective drugs with the potential of alleviating various types of inflammatory and immune-related conditions.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Amin F. Majdalawieh: Writing – original draft, Conceptualization, Investigation, literature analysis, Figure and tables generation, Critical revision. **Sogand H. Ahari:** Writing – original draft, Conceptualization, Investigation, literature analysis, Figure and tables generation. **Sarah M. Yousef:** Writing – original draft, Conceptualization, Investigation, literature analysis, Figure and tables generation. **Gheyath K. Nasrallah:** Writing – original draft, Conceptualization, Investigation, literature analysis, Critical revision, All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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List of Abbreviations

AA	Arachidonic acid
AKI	Acute kidney injury
Al_2O_3-NPs	Aluminum-oxide nanoparticles
AMPK	Adenosine monophosphate-activated kinase
ARG	Arginase
BALF	Bronchoalveolar lavage fluid
BLT	Block lipid transport
CA	Cellulose acetate
Caco-2	Human colon adenocarcinoma cell line
cAMP	Cyclic adenosine monophosphate
CD	Cluster of differentiation
CF	Clofibric acid
cGAS	Cyclic GMP-AMP synthase
CIH	Chronic intermittent hypoxia
CKD	Chronic kidney disease
CMetS	Cardiometabolic syndrome
CoQ	Coenzyme Q
COX	Cyclooxygenases
CP	Cyclophosphamide
CRP	C-reactive protein
CVDs	Cardiovascular diseases
CXCL	Chemokine CXC ligand
DCs	Dendritic cells
DFU	Diabetic foot ulcers
DGLA	Dihomo–γ-linolenic acid
DNCB	Dinitrochlorobenzene
DPA	Docosapentaenoic acid
DSS	Dextran sulfate sodium
eNOS	Endothelial nitric oxide synthase
ERK	Extracellular signal-regulated kinase
FS	Free sesamol
GFAPs	Glial fibrillary acidic proteins
GSK	Glycogen synthase kinase
HAECs	Human aortic endothelial cells
HDL	High density lipoprotein
HFD	High fat diet
HMGB1	High mobility group box 1
HO	Heme oxygenase
hs-CRP	High sensitivity-CRP
HuR	Human antigen R
I/R	Ischemia/reperfusion
IBA	Ionized calcium binding adaptor protein
IBS	Inflammatory bowel syndrome
ICAM	Intercellular adhesion molecule

ICR	Institute of Cancer Research
IFN	Interferon
ILs	Interleukins
iNOS	Inducible nitric oxide synthase
IκB	kinase IKK
JNK	Jun N-terminal kinase
KM	Kunming mice
LBP	LPS-binding protein
LDL	Low density lipoprotein
LOX	Lipoxygenase
LPS	Lipopolysaccharide
LT	Leukotrienes
MAPK	Mitogen-activated protein kinase
MCAO	Middle cerebral artery occlusion
MCP	Monocyte chemoattractant protein
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
MPO	Myeloperoxidase
NC SES	Sesamol-loaded nanocapsules
NEC	Necrotizing enterocolitis
NF-κB	Nuclear factor-kappa B
NK	Natural killer
NLRP	Nod-like receptor
NOS	Nitric oxide synthase
NOX	NADPH oxidase
Nrf2	Nuclear factor-erythroid factor 2
NSAIDs	Non-steroidal anti-inflammatory medicines
NT	Nitrotyrosine
Nx	Nephrectomy
OA	Osteoarthritis
PCS	Phosphatidylcholine-encapsulated sesamol
PD	Parkinson's disease
PECAM	Platelet endothelial cell adhesion molecule
PGE	Prostaglandin E
PHA	Polyhydroxyalkanoate
PMA	Phorbol myristate acetate
PMN	Polymorphonuclear
PPAR	Peroxisome proliferator-activated receptor
PUFAs	Polyunsaturated fatty acids
ROS/RNS	Reactive oxygen/nitrogen species
SCFAs	Short-chain fatty acids
SCI	Spinal cord injury
SCOP	Scopolamine
SIRT	Sirtuin
SM-PLGA	Sesamol-polylactic-*co*-glycolic acid
SnPP	Tin protoporphyrin
SO	Safflower oil
SOD	Superoxide dismutase
STZ	Streptozotocin
TGF-β	Tumor growth factor-beta
Th	Helper T cell
TLR	Toll-like receptor
TNFα	Tumor necrosis factor alpha
W/v	Weight percentage by volume
Wt	(w/w) Weight percentage

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