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A systematic review on antioxidant and anti-inflammatory activity of Sesame (Sesamum indicum L.) oil and further confirmation of anti-inflammatory activity by chemical profiling and molecular docking

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Running Head: A systematic review on antioxidant and anti-inflammatory activity of Sesame (*Sesamum indicum* L.)oil

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ABSTRACT

Traditionally sesame oil has been used as a popular food and medicine. The review aims to summarize the antioxidant and anti-inflammatory effects of sesame oil (SO) and its identified compounds as well as further fatty acid profiling and molecular docking study to correlate the interaction of its identified constituents with COX-2. For this, a literature study was made using Google Scholar, Pubmed and SciFinder databases. Literature study demonstrated that SO has potential antioxidant and anti-inflammatory effects in various test systems, including humans, animals and cultured cells through various pathways such as inhibition of COX, non-enzymatic defense mechanism, inhibition of pro-inflammatory cytokines, NF-kB or MAPK signaling and prostaglandin synthesis pathway. Fatty acidanalysis of SO using gas chromatography identified known 9 fatty acids.*In-silico* study revealed thatsesamin, sesaminol, sesamolin, stigmasterol, Δ5-avenasterol, and Δ7-avenasterol(-9.6 to -10.7 kcal/mol) were the most efficient ligand for interaction and binding with COX-2. The known fatty acid were also showed binding efficiency with COX-2 to some extent (-6.0 to -8.4 kcal/mol).In summary, it is evident that sesame oil may be one of promising traditional medicine that we could use in the prevention and management of diseases associated with oxidative stress and inflammation.

Key words:*Sesamum indicum, sesame oil, anti-inflammatory activity, antioxidant activity, molecular docking*

1. INTRODUCTION

Sesame (*Sesamum indicum* L., Family: Pedaliaceae) is one of the most archaic crops cultivated since the civilizations of Indus valley, 2500 BC, Babylonia,1750 BC, in Syria and Palestine around 3000 BC(Bedigian, 2004; Ricci, Groth, & Lago, 1999). From the ancient time sesame oil, derived from sesame seed, is used in various purposes including food, salve and medicine. The Assyrians community used sesame oil as food and medicine whereas it was a popular ingredient of massage in Ayurvedic medicine and interestingly in India it has been used as sacred oil(Shah, 2016). Ethnomedicinally sesame oil has been used against a number of ailment including pain, fever, inflammation, constipation, diuretic, healing burns and wounds and others **(Table 1)**.

Sesame seed contains about 50% oil of its weight and has a distinguishable nutty taste and aroma. Literature study found that sesame oil consists of saturated and unsaturated fatty acids, lignans, phytosterols, tocopherols and vitamins. It is reported that sesame oil contains linoleic (39 to 59%), oleic acid (35 to 54%),palmitic acid(10%) and stearic acid(5%) (Gunstone, 2006).It also reported some antioxidant compounds such as tocopherol and lignans like sesamolin,sesamin and sesamol(Hwang, 2005; Namiki, 1995)(**Figure 1 (a-d) and Table 1**). Several studies have been reported that sesame oil contributes to prevent a number of disorders including hypertension, hypercholesterolemia, cancer and aging (Kanu, Bahsoon, Kanu, & Kandeh, 2010). Moreover, sesame oil exhibits multiple physiological functions such as decreasing plasma triacylglycerol and arachidonic acid levels, imparting anti-inflammatory and estrogenic activities (Hemalatha, 2007; Shahidi, Wanasundara, & Wanasundara, 1997). Sesame oil showed an exceptionally high oxidative stability compared to soybean, corn and most other popular vegetable oils (Carrasco-Pancorbo et al., 2005; Minioti & Georgiou, 2010; Shahidi et al., 1997). Some studies have shown that sesame seeds can reduce oxidative stress by modulating the concentration of antioxidant enzymes [superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT)], as well as of oxidative stress markers [thiobarbituric acid reactive substance (TBARS) and malondialdehyde (MDA)] (Alipoor, Haghighian, Sadat, & Asghari, 2012; Chen et al., 2005; Sankar, Ali, Sambandam, & Rao, 2011; Sankar, Rao, Sambandam, & Pugalendi, 2006a, 2006b; Sankar, Sambandam, Rao, & Pugalendi, 2005; Wichitsranoi et al., 2011). However, there is no chemical profiling and further interaction docking study of sesame oil constituents to COX enzyme to correlate its ethnopharmacological

and reported anti-inflammatory activity. As a part of our continuous search for natural lead molecules for antioxidant and anti-inflammatory activity(Rahman, Khatun, Uddin, & Shilpi, 2016; Uddin, Grice, & Tiralongo, 2011; Zihad et al., 2018; Zilani et al., 2018), here the aim of this review is to draw antioxidant and anti-inflammatory mechanisms of sesame oil on the basis of literature findings using the above-mentioned databases and further molecular docking study of its identified constituents with CoX-2 enzyme to confirm its anti-inflammatory activity.

2.MATERIALS AND METHODS

2.1 Literature review

2.1.1 Search strategy

To begin this review, a comprehensive literature search was conducted by using several database platforms such as PubMed, Google Scholar and SciFinder with the term ‘sesame oil’ with ‘antioxidant’, ‘oxidative stress’, ‘inflammation’ and ‘anti-inflammation’. We focused on reports that were only in English due to the language barrier,time efficiency and non-feasible costs of translation.

2.1.2 Selection of studies for inclusion in the systematic review

The following types of studies and investigations were included in this review:a) *in-vivo* animal studies, b) *in-vitro* studies, c)clinical studies,d) studies that include the effects of sesame oil or aqueous extract of sesame oil or isolated compounds of sesame oil on oxidation and inflammation, e) studies that indicate the concentrations or doses employed and the form of administration and f) studies that point out to themechanisms of action associated with the sesame oil treatment and its isolated derivatives.

2.1.3 Data extraction

All the searched articles were assessed for the information according to surname of first author, year of publication, sesame oil and its isolated compound, test system, observation, result, suggested mechanism of action, concentrations tested and molecular mechanism involved. The general steps of the data search, the exclusion-inclusion data and other relevant information are presented in **Figure 2**.

2.2 Chemical profiling of sesame oil using gas chromatography

2.2.1 Extraction of sesame oil

The fresh sesame seedswere collected from local markets of Khulna, Bangladesh and identified by the expert of Forestry Discipline, Khulna University. A sample specimen of sesame seeds were deposited in Pharmacy Discipline, Khulna University for future reference. The collected samples were washed by water to remove any dust materials and shed dried. Finally the sesame oil was extractedusing expeller pressing (also called oil pressing) method under mild conditions to preserve the natural characteristics of the fresh oil.

2.2.2 Preparation of methyl ester (FAMEs)

The fatty acid composition was determined by analysis of their methyl esters. The fatty acid methyl esters (FAMEs) were prepared by esterification reaction using BF_3-MeOH complex according to an established method(Wirasnita et al., 2013). Briefly, sesame oil was taken in a screw capped glass tube and 1 mL of BF_3-MeOH complex was added. The oil mixture was heated at 100˚C for 1 hr in a water bath and then cooled at room temperature. 1 mL of deionized water and 2 mL of hexane were added in the cooled mixture and vortexand centrifuged at low RPM for two minutes. The upper layer was collected by means of syringe and kept in refrigerator with air tight glass vial. The prepared FAMEs were ready to analyze.

2.2.3 Gas Cromatography (GC) analysis of sesame oil

GC analysis of the fatty acids of sesame oil was carried out on Agilent 7890 system that equipped with flame ionization detector and split less injection system. The GC was fitted with a HP-5MS capillary column (60 m × 0.25 mm). The temperature program was as follows: initial oven temperature at 50˚C, then increased at 25˚C/rpm to 175˚C for 6 min., then 4˚C/rpmto 230˚C for 10 min and total run time was for 30 min.Helium was used as the carrier gas at 17.69 psi pressure with flow 0.6 mL/min. Samples were dissolved in methanol and 1 μL aliquot was injected automatically.

2.3 Molecular docking study of identified compounds in sesame oil

Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex (Lengauer & Rarey, 1996). It's a popular method to perform virtual screening on large libraries of compounds and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization (Grouleff, Irudayam, Skeby, & Schiøtt, 2015). The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Therefore, further confirmation of binding efficiency of identified 31 constituents in sesame oil with the COX-2 enzyme, a key protein responsible for inflammatory pain, a docking study was conducted.

2.3.1Computational Study

Computational studies of the identified compounds in sesame oil were conducted against human COX-2 enzyme, which is the inducible enzyme in human body contributing to inflammatory pain. Human COX-2 or Prostaglandin G/H Synthase 2 (PGH2) is a homodimer protein comprising 604 amino acids in each monomeric unit (UniProtKB ID: P35354). Homology model of single monomeric unit of the human COX-2 was built using Modeller 9.19(Zihad et al., 2018) taking three reported models as templates (PDB ID: 5F1A_A, 5IKQ_A, and 5F19_A) and dimeric structure predicted using Galaxy Gemini(Shin, Lee, Heo, Lee, & Seok, 2014)following energy minimization step. The initial model was selected based on dope (Discrete Optimized Protein Energy) score and further validated by analyzing Ramachandran plot (Using procheck and rampage) (Lovell et al., 2003). Knowledge based energy calculation was performed in ProSA (Wiederstein & Sippl, 2007). All the selected ligands were prepared using Autodock tools and the binding site in the enzyme was predicted through ProBiS server (Konc & Janežič, 2014) and further arachidonic acid was re-docked using Autodock Vina. Initial docking grid (40×40×40, 0.8 Å) enclosing the active binding site was generated depending on the binding of arachidonic acid. Finally all the prepared ligands were docked into the predicted binding pocket of the validated homology model of COX-2 utilizing Autodock Vina(Trott & Olson, 2010).

3. RESULTS AND DISCUSSION

3.1 LITERATURE REVIEW

The databases searched for antioxidant and anti-inflammatory activity of sesame oil were revealed 5039 records from PubMed (2096), Google Scholar (2000) and SciFinder (943)in which 87 studies were meeting the inclusion criteria.The exclusion of 4952documents were due to absence of sesame oil mentioning in the title or the abstract,duplication of information and non-relevance of the study.

3.1.1 Antioxidant effect of sesame oil and its isolated compounds

Sesame is a popular ethnomedicinal plant and its oil has been reported to use against a number of diseases including oxidative induced different ailments. Experimental studies have been reported that sesame seeds and its oil can reduce oxidative stress by modulating the antioxidant enzymes as well as of oxidative stress markers. **Table 2** and **4** summarized the anti-oxidative effects of sesame oil and its reported constituents either *in-vivo*, *in-vitro* or in clinical test model. A number of possible mechanisms for antioxidant effect of sesame oil has been highlighted in different reports (**Figure3**). One of the most common antioxidant effects of SO is to reduce oxidative stress in lipopolysaccharide (LPS) induced oxidative stress ratmodels(Chiang et al., 2014; Hsu, Chiang, Chien, Huang, & Liu, 2004a; Hsu & Liu, 2004b).Hsuet al., (2004) reported that the level of, lipid peroxidation, hydroxyl radical and nitrite levels reduced while the antioxidant enzyme superoxide dismutase (SOD) and catalase increased in SO treated LPS induced oxidative stress rat models(Hsu et al., 2004a). In addition, parenterally SO-treated animal groups showed attenuation ofhepatic disorder, although the symptoms were different when the SO was given orally(Ahmad et al., 2006; Hsu et al., 2004a; Saleem, Chetty, & Kavimani, 2013). However, superoxide anion decreased and glutathione increased in the oral SO groups(Ahmad et al., 2006; Saleem et al., 2013). Ahmad S. et al. (2006) showed that dietary SO behave as an antioxidant, resulting in increased enzymatic and non-enzymatic antioxidants activity in the middle cerebral artery occlusion (MCAO rat model against MCAO-induced cerebral ischemia injury(Ahmad et al., 2006). Furthermore, giving SO orally could reduce oxidative myocardial damage induced by isoproterenolin rat model(Saleem et al., 2013). According to Abdou et al., (2012), 5 mL/kg b.w, orally given sesame oil plays a protective role on cypermethrin-induced oxidative stress, biochemical changes, histopathological damage and genomic DNA fragmentation(Abdou, Hussien, & Yousef, 2012).SO not only protect rats from oxidative stress induced by chemical but also showed its protective effect against oxidative stress induced by chronic exposure to

electromagnetic radiation (EMR)(Marzook, El Moneim, & Elhadary, 2014). Majority of the reported protective effects of crude SO demonstrated in oxidative induced rat model within the dose of oral 5-10 mL/kg b.w**(Table 2)**. However, only one clinical trial was conducted by Sankar et al., (2006) to investigate the effect of SO in 40 hypertensive patients (32 male and 18 female, aged 35-60 yrs) who were on antihypertensive therapy either with diuretics (hydrochlorothiazide) or Beta-blockers (atenolol) and the results demonstrated that sesame oil as edible oil lowered blood pressure, decreased lipid peroxidation, and increased antioxidant status (increased SOD, CAT and GSH activity) without changing lipid profile of the hypertensive patients(Sankar et al., 2006a).

Phytochemical constituents from SO have also been evaluated for their protective effects against oxidative stress both *in-vivo* and *in-vitro*. Among these sesamol, sesamin sesamolin, sesaminol, ligning and their derivatives are the prominent constituents that reported for antioxidant effects **(Table 4)**.Sesamol is one the main constituent that has been reported to have antioxidant effect (in both *in-vivo* and *in-vitro* model) through reduction of lipid peroxidation, superoxide and nitric oxide production as well as increased antioxidative enzyme (SOD, CAT, GSH) level at a different doses ranging 10-50 mg/kg b.w.(Chiang et al., 2014; Kang, Naito, Sakai, Uchida, & Osawa, 1999; Khamphio, Barusrux, & Weerapreeyakul, 2016; Lv, Zhu, & Liu, 2015; Yashaswini, Sadashivaiah, Ramaprasad, & Singh, 2017b). Its antioxidant effect has a strong correlation with its anti-inflammatory action. Sesamin another prominent compound reported in SO that possesses significant protective effects against oxidative stress in animal model including through ameliorate SOD, GPx, reduction of malondialdehyde and elevated different liver marker, TBARS and lipid peroxidation as well as reduction of superoxide production(Ahmad et al., 2016; Chen, Ying, Chen, Zhang, & Zhang, 2015; Hou, Chang, & Jeng, 2015; Hsieh et al., 2011; Jeng & Hou, 2005; Jnaneshwari et al., 2014; Nakai et al., 2003; Tian & Guo, 2017a; Zhang et al., 2016b). *In-vitro* studies of sesamin especially in neuronal cell line (PC12), it showed reduction of ROS generation especially NO production(Cao et al., 2013; Duarte, Chenet, de Almeida, Andrade, & de Oliveira, 2018; Lee et al., 2009; Yashaswini, Rao, & Singh, 2017a). However, Hou et al., (2015) reported that 10 µM sesamin derivative, 3-bis (3-methoxybenzyl) butane-1, 4-diol inhibits LDH, lipid peroxidation and apoptosis as well as increases ACh release and also prevents cell damage, scavenges ROS, and attenuates the elevation of intracellular free Ca ion on Aβ-stressed PC12 cells(Hou et al., 2015).Both the

compounds sesamolin and sesaminol reported to exert their antioxidant effect through the reduction of nitric oxide production and inhibit peroxidation although there is only anoxygen bridge difference **(Figure 1)** in their structure(Hou, Chen, Tzen, & Jeng, 2003; Kong et al., 2016; Lee et al., 2009). However, there is another report stated that sesaminol has the ability to increase antioxidant enzyme (such as SOD, CAT, GSH) in H_2O_2 exposed cell line(Wu et al., 2015).

3.1.3 Anti-inflammatory effect of sesame oil and its isolated compounds

Inflammation is a biological protective response induced by tissue injury or infection by harmful stimuli (microorganisms, damaged cell, irritants and non-self cells) involving an increase of permeability of endothelial lining cells, influxes of blood leukocytes into the interstitium, oxidative burst, release of kinins or cytokines, activation of several enzymes (oxygenases, nitric oxide synthases, peroxidases) as well as thearachidonic acid metabolism(Miguel, 2010). Uncontrolled chronic inflammation may causes a number of diseases and therefore anti-inflammatory agents either from natural source or synthetic are considered as therapeutic agents to prevent these ailments. Sesame oil has been reported to use against a number of diseases including inflammation and a number of reports have been published on its anti-inflammatory action with highlighting a number of possible mechanism for anti-inflammatory effects (**Figure3**). **Table 3 and 4** summarized the anti-inflammatory effects of sesame oil and its reported constituents either *in-vivo*, *in-vitro* or in clinical test model. A number of reported showed that the anti-inflammatory activity of SO is associated with the reduction of pro-inflammatory cytokines and related factors in animal model **(Table 3)**. A number of reports stated that SO showed the anti-inflammatory effect through reduction of pro-inflammatory cytokines (TNF-α, IL-6, IL-1α, IL-1β) as well as anti-oxidative effect either reduction of ROS or induction of anti-oxidative enzymes (GSH, NADPH oxidase, GPx) (Hsu, Chu, & Jou, 2016c; Hsu, Chu, Li, & Liu, 2008b; Kang, Naito, Tsujihara, & Osawa, 1998; Nakano et al., 2002; Narasimhulu, Riad, & Parthasarathy, 2018b; Narasimhulu et al., 2016)**(Figure3)**.Ali et al. (2017) showed that SO significantly decreased the levels of inflammatory mediator TNF-α and IL-6, althoughthe levels of anti-inflammatory mediator IL-10 were significantly amplified in groups treated with combination of SO with MTX (first line anti-arthritis agent) compared to group treated with SO only or MTX onlyin adjuvant-induced arthritis rat model(Ali, Atia, El Allawy, & Alla, 2017).Later, Ismail et al., (2018) reported that daily oral administration of Δ9-THC/sesame

oil combination, over a period of 21 days, attenuated erythrocyte sedimentation rate (ESR) scores and pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 levels, to normal values and MTX treated values on adjuvant-induced arthritis (AIA) rat model(Ismail, Hasan, El-Orfali, Ismail, & Khawaja, 2018).Some *in-vitro* studies also showed that SO has potent anti-inflammatory properties by down regulating inflammatory markers as seen with LPS-induced inflammation in RAW macrophages or mouse peritoneal macrophages(Deme, Narasimhulu, & Parthasarathy, 2018; Narasimhulu, Burge, Doomra, Riad, & Parthasarathy, 2018a; Selvarajan, Narasimhulu, Bapputty, & Parthasarathy, 2015). The atherosclerosis PCR array revealed down regulation of a number of inflammatory markers such as Ccl2 or MCP-1, Ccl5 or RANTES, IL-1α, IL-1β, and TNF in the presence of SO(Selvarajan et al., 2015). Selvarajan et al., (2015) proved that sesame oil play a role in the prevention of atherosclerotic disease by suppression of colony stimulating factor 2 (Csf2), NF-kB1, an important pro-inflammatory transcription factor(Selvarajan et al., 2015). Other reports also demonstrated that SO reduced inflammatory gene expression and induced genes involved in cholesterol metabolism(Narasimhulu et al., 2018b; Narasimhulu et al., 2016). Independent analysis revealed significant inhibition of IL-6 expression in the presence of SO(Selvarajan et al., 2015).

Phytochemical constituents mainly sesamol, sesamin sesamolin, sesaminol, and their derivatives from SO have been reported for anti-inflammatory activity both *in-vivo* and *in-vitro* model**(Table 4)**.A number of constituents (sesamol, sesamolin, sesamin, sesamin derivative and sesaminol) identified from SO showed their anti-inflammatory activity by down regulating the COX-2 activity or PGE2 synthesis(Chen et al., 2015; Hemshekhar et al., 2013; Hsieh et al., 2011; Hsu et al., 2008b; Hung, Chen, & Hou, 2017; Jeng & Hou, 2005; Kong et al., 2016; Monteiro et al., 2014; Yashaswini et al., 2017b). Other reports also demonstrated that some of these constituents (sesamol, sesamolin, sesamin, sesaminol) inhibit the pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and NF-kB either *in-vivo* rat(Bournival, Plouffe, Renaud, Provencher, & Martinoli, 2012; Chen et al., 2015; Hemshekhar et al., 2013; Hsu, Chu, Chandrasekaran, & Liu, 2009a; Jeng & Hou, 2005; Yashaswini et al., 2017b)or *in-vitro* cell culture model(Bournival et al., 2012). Sesamol, sesamolin and sesamin also suppress the inflammatory cascade by down regulating the expression of caspase-3(Baluchnejadmojarad, Mansouri, Ghalami, Mokhtari, & Roghani, 2017; Chopra, Tiwari, Arora, & Kuhad, 2010; Hsieh et al., 2011; Hung et al., 2017; Jeng & Hou, 2005). A recent clinical trial was reported on

sesamin supplementation on cardiovascular risk factors in women with rheumatoid arthritis and the results found that sesamin research had been conducted and evaluated by Helli et al., (2016), showed protective effect of sesame oil(Helli, Mowla, Mohammadshahi, & Jalali, 2016).

3.2 CHEMICAL PROFILING OF SESAME OIL USING GAS CHROMATOGRAPHY

Sesame oil is an edible vegetable oil derived from sesame seeds. The presence of saturated and unsaturated fatty acids justifies the use of this oil to treat inflammation and other diseases. However, many researches have been carried out on sesame (*Sesamum indicum*), but no report on their fatty acid profiling FAME analysis using GC. Fatty acid has a strong inhibitory effect on the production of NO (Ren & Chung, 2007). They inhibit inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and tumor necrosis factor-alpha (TNF-alpha) gene expressions induced by LPS (Chavali, Zhong, & Forse, 1998).Fatty acids reduce a translocation of NF-kappaB subunit and NF-kappaB-dependent transcriptional activity. The activation of NF-kappaB is inhibited by prevention of the degradation of inhibitory factor-kappa B alpha (Simopoulos, 2002). They also inhibit LPS-induced phosphorylation of mitogen-activated protein kinases (MAPKs). Sesame oil (SO) is rich in both polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA), and has been shown to reduce high blood pressure and lower the amount of medication required to control hypertension (Narasimhulu et al., 2018a; Sankar et al., 2005) in humans. Therefore, the present study was undertaken for the first time with an objective to carry out a complete investigation of the compositions of fatty acids of sesame oil and correlate their role in its reported antioxidant and anti-inflammatory activity. The chromatogram of FAME analysis of sesame oil is shown on the **Supplementary Figure S1**and **Supplementary Table S1**includes the identified constituents with their retention time, quantity, peak height, area(%) of each constituent identified of the collected Bangladeshi sesame oil. The results demonstrated that a total of 9 major fatty acid components (namely octanoic acid, decanoic acid, lauric acid, myristic acid, palmitic acid, oleatic acid, linoleatic acid, arachidonic acid and behenic acid)were identified in FAME analysis from the samples by using GC. Among the identified constituents all were reported before from SO of Indian sample (Crews et al., 2006; Mondal, Bhat, & Srivastava, 2010; Sengupta & Roychoudhury, 1976; Shah, 2016).

3.3 MOLECULAR DOCKING STUDY OF IDENTIFIED COMPOUNDS IN SESAME OIL

3.3.1 Role of COX-2 in molecular docking

Cyclooxygenase (COX), officially known as prostaglandin-endoperoxide synthase (PTGS), is an enzyme that is responsible for formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin, from arachidonic acid (Litalien & Beaulieu, 2011).The two isozymes of COX involved in prostaglandin biosynthesis are COX-1 and COX-2. Arachidonic acid (AA) Pathway is a major component of inflammatory pathway (Kuehl & Egan, 1980). COX-2 is increasingly expressed during inflammatory conditions by pro-inflammatory molecules such as IL-1, TNF-α, LPS (Beuck, 1999; Kumar, Aggarwal, Saini, Kaushik, & Prakash, 2016; Ryn, Trummlitz, & Pairet, 2000) and its expression is absent or low in healthy individuals(Dinarello, 2010; Zhang et al., 2015).The target for anti-inflammatory drugs is cyclooxygenase (COX), a rate-limiting enzyme involved in the conversion of arachidonic acid into inflammatory prostaglandins. Literature study of SO showed that the anti-inflammatory activity of SO and it's identified constituents via a number of molecular mechanism including inhibiting the COX-2. However, there is no report found on the role of each identified constituents of SO in the molecular binding with COX-2.

3.3.2 Analysis and visualization of docking study of sesame oil compounds against COX-2

The initial homology model of human COX-2 enzyme was selected based on the lowest dope profile and used for the docking showed on **Figure 4**. The sequence alignment is given in the **Supplementary Figure S2**. The Ramachandran plot analysis, Z-score and knowledge based energy are presented in**Supplementary Figure S3**. The homo-dimer model of COX-2 was generated from its monomeric units using GalaxyGemini following energy minimization step.

The arachidonic acid binding pocket was identified with the following amino acid residues: Ala513, Val335, Gly512, Ser516, Tyr341, Phe343, Val102, Met99, Leu103, Val509, Leu338, Tyr371, and Ser339 presented in **Supplementary Figure S4**. Nine ligands obtained from GC analysis and other twenty one ligands were docked into the active site of the human COX-2 homology model and analyzed in the **Supplementary Figures S5-S32**and the results are presented in **Table 5.** Nineteen out of thirty one compounds showed higher affinity for COX-2 than that of arachidonic acid (-6.8 kcal/mol).

Molecular docking studies with the identified ligands against human COX-2 enzyme revealed that Stigmasterol, Δ5-Avenasterol and Δ7-Avenasterol shows the best binding affinity -10.7kcal/mol for COX-2 presented in **Figure 5 - 6**.

Among the 30 phytoconstituents, 12 compounds interacted with a number of amino acid residues (Ala513, Val335, Gly512, Ser516, Tyr341, Phe343, Val102, Met99, Leu103, Val509, Leu338, Tyr371, Ser339) associated with the binding of COX-2 at the catalytic site, with binding affinity ranging between -5.4 and -9.6 kcal/mol. Among these 12 compounds, Behenic acid showed lower binding affinity (-6.2 kcal/mol) than that of sesamolinol, pinoresinol and vitamin K phylloquinone, but with greater number (13) of interaction with the amino acid residues involved in the binding of COX-2 through hydrophobic interactions. Vitamin K (phylloquinone) interacted with Phe343, Ser339,Leu517,Val102, Leu103, Met99 and Val335 with an affinity of -9.6 kcal/mol. Eicosenoic acid interacted with 12 amino acid residues with an affinity of -6.2 kcal/mol. Pinoresinol also exhibited promising results in this computational study due to its binding with considerable interactions with amino acid residues (11 amino acids) around the catalytic site as well as with significant binding affinity (8.4 kcal/mol). Stearic acid (Binding affinity: -5.9 kcal/mol), Palmitic acid (Binding affinity: -5.4kcal/mol), Tocopherol (Binding affinity: -7.1 kcal/mol) and Vitamin A (Retinol) (Binding affinity: -7.4 kcal/mol) showed interaction with ten, nine,six and five amino acid residues, respectively.The other 18 compounds also showed high affinity for COX-2 enzyme but the amino acid residues were not involved in the binding of COX-2. Among the 18 compounds Sesaminol, Campesterol, Δ7-Stigmasterol, Beta-sitosterol, Sesamin and sesamolin showed binding affinity -10.6 kcal/mol, -10.5 kcal/mol, -10.5 kcal/mol, -10.2 kcal/mol, -10.4 Kcal/mol and -9.6 Kcal/mol respectively.In this study, all values are negative meaning binding will be spontaneous.The results of this docking study confirmed that the binding potential of the reported constituents of sesame oil with their reported significant COX-2 inhibition activity and have a major role in their anti-inflammatory activity. The reported components of sesame oil were the competitive inhibitors of cyclooxygenase (COX), the enzyme which mediates the bioconversion of arachidonic acid to inflammatory prostaglandins (PGs).

4.CONCLUSION

In this review we have considered antioxidant and anti-inflammatory research on SO over the last decade and a total of 87 studies were found which reported that sesame oil possesses prominent antioxidant and anti-inflammatory effect on various test systems. The antioxidant effect of SO and its constituents were exert through reduction of lipid peroxidation, superoxide and nitric oxide production as well as increased antioxidative enzyme (SOD, CAT, GSH) level which has strong correlation with its anti-inflammatory action. The anti-inflammatory action of SO and its constituents were due to their down regulation of COX and PGE2 as well as inhibition of pro-inflammatory cytokines. COX inhibition was a major pathway for its anti-inflammatory activity which further confirmed through the molecular docking study. Fatty acid profiling of SO identified known 9 fatty acid which also showed molecular binding with COX-2 to some extent as a confirmation of its contribution in anti-inflammatory activity of SO. However, sesamol, sesamin, sesaminol and sesamolin are the main active principle of SO that are responsible for its antioxidant and anti-inflammatory activity as we have showed in this review. Overall findings suggests that although a number of research on SO and its constituents have conducted over the last decade are mainly *in-vitro* and *in-vivo* studies and data related preclinical and clinical trials remain very low. Therefore, more clinical and pharmacokinetic investigation on SO will be needed for future use as a therapeutic agent. In summary, this review reveals that SO can be an important traditional medicine in the treatment of different inflammation.

CONFLICT OF INTEREST

None

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Table 1.Reported traditional uses, isolated compounds and pharmacological properties of Sesame oil (*Sesamum indicum* L.)

Scientific name	Family	Traditional uses	Isolated compounds	Reported pharmacological activities	References
***Sesamum indicum* L.**	Pedaliaceae	➢ Reduce body heat ➢ Relief pain ➢ Flavor enhanchers ➢ Laxative ➢ Swish strong teeth and gums ➢ Healthy vaginal balance ➢ Emollient ➢ Tonic ➢ Diuretic ➢ Emmenagogue ➢ Aphrodisiac ➢ Amenorrhoea ➢ Dysmenorrhea ➢ Piles ➢ Demulcent ➢ Dysentary ➢ Urinary complaints ➢ Solvent for injection	**1)Fatty acids** **a)Saturated-** Palmitic acid, Stearic acid, Arachidic acid, Myristic acid, Behenic acid, Octanoic acid, Decanoic acid, Lauric acid **b)Monounsaturated-** Oleic acid, Eicosenoic acid **c)Polyunsaturated-** Linoleic acid, Linolenic acid **2)Lignans** Sesamin, Sesamolin, Sesamol,Sesaminol,Sesamolinol, Pinoresinol, Lariciresinol, Asarinin **3)Phytosterols** Campesterol, Stigmasterol, Beta-sitosterol, Δ5-Avenasterol, Δ7-Stigmasterol and Δ7-Avenasterol **4)Vitamins** Alpha tocopherol, Beta tocopherol, Gamma tocopherol**,** Vitamin A,Vitamin B,Vitamin K	➢ Antioxidant ➢ Anti-inflammatory ➢ Antinociceptive ➢ Hepatoprotective ➢ Anti-arthritic ➢ Anti-hypertensive ➢ Chemo-protective ➢ Anti-cancer	(Ahmad et al., 2006; Azab, 2014; Balkrishna, 2008; Burdock, 2016; Cengiz et al., 2013; Chopra & Nayar, 1956; Ghani, 1998; Gharby et al., 2017; Guimarães et al., 2013; Hsu, Chen, Chu, & Liu, 2013; Jamieson & Baughman, 1924; Kapadia et al., 2002; Kuo, Lin, Chen, Yiu, & Tzen, 2011; Lahorkar, Ramitha, Bansal, & Narayana, 2009; Ma, Ding, Zhang, & Liu, 2014; Matsumura et al., 1995; Milder, Arts, van de Putte, Venema, & Hollman, 2005; Monteiro et al., 2014; Pole, 2006; Ramesh, Saravanan, & Pugalendi, 2005; Ricci et al., 1999; Saleem et al., 2011; Sankar et al., 2006b; Shafipour, Mosayebi, Asgari, Atrkarroushan, & Pasdaran, 2017; Simon, Chadwick, & Craker, 1984; Smith & Salerno, 1992; Sotnikova et al., 2009; Wan et al., 2015)

Table 2. Antioxidant activity of sesame oil

Test model	Dose/concentration	Route of administration	Mechanism of action	References
Myocardial injury rat model	5 and 10 mL/kg b.w	Orally	Reduction of thiobarbituric acid reactive substance (TBARS) andenhancement ofendogenous antioxidant enzymes,lactate dehydrogenase (LDH), creatine kinase (CK) and aspartate transaminase (AST).	(Saleem et al., 2013)
Doxorubicin-induced rat model	5 and 10 mL/kg b.w	Orally	Enhancementof cardiac endogenous antioxidants and reduction ofmyocardial TNF-α expression.	(Saleem, Chetty, & Kavimani, 2014)
Streptozotocin (STZ) induced rat model	2% oil supplemented with 6%	With diet	Reduction ofthe levels of blood glucose, glycosylated hemoglobin, TBARS, lipid hydroperoxides and glucose-6-phosphatase, fructose-1,6-bisphosphatase activities; and elevation of the levels of hemoglobin, vitamin E, GSH and hexokinase activity.	(Ramesh et al., 2005)
Lipopolysaccharide-induced rat model	8 mL/kg	Parenterally	Reduction of lipid peroxidation, hydroxyl radical and nitrite level; and a boost in superoxide dismutase and catalase activity.	(Hsu et al., 2004a)
Rat(cecal ligation and puncture) model	4 mL/kg	Orally	Depletion oflipid peroxidation and serum nitrite levels.	(Hsu, Li, Chien, & Liu, 2004b)
Iron-induced rat model	0.4 g/kg sesame oil	With diet	Attenuation of the level of hepatic thiobarbituric acid-reactive substances, serum glutamate:oxaloacetate transaminase activities and serum glutamate pyruvate transaminase activities.	(Hemalatha & Raghunath, 2004)
Lipopolysaccharide induced rat model	8 mL/kg	Orally	Reduction oflipid peroxidation and superoxide anion counts; andincrease in glutathione levels, and activities of superoxide dismutase and catalase.	(Hsu & Liu, 2004a)
Fenvalerate-induced rat	10% sesame oil	With diet	Reduction of lipid peroxidation; andelevation ofGSH levels and antioxidant enzymes.	(Prasanthi & Rajini,

model				2005)
(MCAO)-induced rat model	20% SO	With diet	Reduction ofglutathione (GSH), glutathione-S-transferase (GST), glutathione peroxide (GPx), glutathione reductase (GR), catalase (CAT), superoxide dismutase (SOD), thiobarbituric acid reactive substance (TBARS) and lipid peroxidation (LPO).	(Ahmad et al., 2006)
Mice model	4mL /kg/day	Intraperitoneally	Significant increase in TAC, but non-significant elevation of serum nitrite production.	(Mosayebi, Ghazavi, Salehi, Payani, & Khazae, 2007)
Acetaminophen-induced rat model	8 mL/kg	orally	Significant depletion of glutathione levels and mitochondrial aconitase activity; but contradictory increase in superoxide anion, hydroxyl radical, and lipid peroxidation levels.	(Chandrasekaran, Chien, Hsu, Chang, & Liu, 2010).
Gentamicin-plus-iodinated contrast-induced rat model	0.5 mL/kg	Orally	Prevention of renal lipid peroxidation, myeloperoxidase, hydroxyl radicals, superoxide anion, nitrite/nitrate, and inducible nitric oxide synthase.	(Hsu, Li, Chu, Periasamy, & Liu, 2011)
Lipopolysaccharide-induced rat model	8 mL/kg	Subcutaneously	Reductionof lipid peroxidation, hydroxyl radical, nitric oxide, TNF-α, and IL-1β along with considerable increase in the activities of superoxide dismutase, catalase and glutathione peroxidase in LPS intoxication.	(Hsu et al., 2005)
Cypermethrin-induced rat model	5 mL/kg b.w	Orallygavaged	Elevation of the level of glutathione (GSH) and the activities of the antioxidant enzymes along with a decrease inthe level of TBARS.	(Abdou et al., 2012)
Monocrotaline-induced rat model	0.5, 1, 2, or 4 mL/kg	Orally gavaged	Protection against SOS by down-regulation of MMP-9 expression, up-regulation of TIMP-1 expression, and inhibition of oxidative stress.	(Periasamy, Yang, Chen, Chang, & Liu, 2013)
Cyclosporine-A induced rat	1mL/kg	Orally gavaged	. Significant restoration ofthe level of MDA, GSH, SOD and CATcompared to CsA group, but changes in the IL-1α,IL-1β levels	(Gülcan, BÜLBÜL,

model			were insignificant	ÖZDEMİR, & EROL, 2015)
Streptozotocin-induced rat model	100 mg/kg b.w	Intraperitoneally.	Up-regulation of testosterone, LH, and FSH.	(Khaneshi, Nasrolahi, Azizi, & Nejati, 2013)
Mice model	0.5, 1 and 2 mL/kg	Ingestion	Reduction oflipid peroxidation alon with increased nuclear factor erythroid 2-related factor 2 and GAP43 expression in sciatic nerve.	(Hsu, Huang, Wu, Tai, & Jou, 2016a)
Rat model	0.5 or 1 mL/kg/day	Orally gavaged	Down-regulation the expression of angiotensin type 1 receptor, JNK and p38 MAPK and apoptosis signal regulating kinase 1, c-Fos and c-Jun withdiminishedproduction of superoxide anion, hydroxyl radical and lipid peroxidation.	(Liu & Liu, 2017)
Adjuvant arthritis rat model	1mL/kg	Orally	Decreased plasma TBARS and GGT activity in the joint and spleen tissues.	(Sotnikova et al., 2009)
(4-NQO) - induced rat model	1, 2, 4, and 8 mL/kg	Orally	Reduction of LPO and DNA damage from 4-NQO.	(Arumugam & Ramesh, 2011)
Septic rat model	4 mL/kg/day	Orally	Significant declinein hepatic lipid peroxidation, hydroxyl radical, superoxide anion, nitrite levels, xanthine oxidase activity and inducible nitric oxide synthase expression.	(Hsu et al., 2008a)
LPS induced rat model	8 mL/kg	Orally	Reduction of lipid peroxidation with increasedactivities of superoxide dismutase (SOD) and catalase (CAT).	(Hsu & Liu, 2004b)
Ethanol induced rat model	8 mL/kg	Orally	Reductio of mucosal lipid peroxidation, glutathione and nitric oxide production.	(Hsu, Chu, & Liu, 2009b)
Diazinon induced rat model	5 mL/kg body weight	Orally	Improvement in hematology and serum parameters, endogenous antioxidant status, and reduction oflipid peroxidation.	(Abdel-Daim, Taha, Ghazy, &

				El-Sayed, 2015)
Osteoarthritis rat model	1, 2, 4 mL/kg	Ingestion	Reduction oflipid peroxidation, muscular superoxide anion and peroxynitrite generations along with increased muscular glutathione and glutathione peroxidase levels, nuclear factor erythroid-2-related factor (Nrf2) expression	(Hsu, Chu, & Jou, 2016b)
EMR induced rat	1.5-3 mL	Orally	Reduction of cholesterol level with elevated SOD and CAT activities.	(Marzook et al., 2014)
DPPH and ABTS radical scavenging assays and β-carotene/linoleate model system.	0.1 – 0.5 g	*In-vitro*	Neutralization of DPPH and ABTS radical and the degradation of β-carotene.	(Bopitiya & Madhujith, 2013)
Human(clinical trial)	Use sesame oil as the only edible oil for 45 days.	With diet	Enhancement of superoxide dismutase (SOD), catalase (CAT), and the levels of vitamin C, vitamin E, beta-carotene, and reduced glutathione (GSH) along with decreased lipid peroxidation.	(Sankar et al., 2006a)

Table 3. Anti-inflammatory activity of sesame oil

Test model	Dose/concentration	Route of administration	Mechanism of action	References
LDLR -/- mice model	17% sesame oil	With diet	Reduction of plasma cholesterol, triglyceride, and LDL cholesterol levels in LDLR -/- mice.	(Bhaskaran, Santanam, Penumetcha, & Parthasarathy, 2006)
Mice (cecal ligation and puncture) model	5wt% SSO	With diet	Inhibition of delta-5 desaturase activity, resulting in an increase in the accumulation of dihomo-gamma-linolenic acid and subsequent decrease in the production of pro-inflammatory dienoic eicosanoids.	(Chavali, Utsunomiya, & Forse, 2001)
2,4,6-tri-nitro benzene sulfonic acid-induced rat model.	4 mL/kg	Orally gavaged	Reduction ofthe degree of inflammation, fibrosis, and acidic mucin with increased neutral mucin.	(Periasamy, Hsu, Chandrasekaran, & Liu, 2013)
(MSU) crystal-induced rat model.	0, 1, 2, or 4 mL/kg	Orally	Reduction ofMSU crystal-induced total cell counts, tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 levels in lavage and pouch tissue.	(Hsu et al., 2013)
Osteoarthritis Rat model	0, 1, 2, or 4 mL/kg/day	Orally	Significant decrease inmuscular interleukin-6, muscular lipid peroxidation, nuclear Nrf2 protein expression, and reactive oxygen species generations with increased citrate synthase activity and myosin heavy chain IL mRNA expression, glutathione production and glutathione peroxidase activity.	(Hsu et al., 2016c)
Both *in-vitro* and *in-vivo*(Atherosclerosis mice model)	340 mg/kg	With diet	Reduction of atherosclerotic lesions, plasma cholesterol, gene expression involved in inflammation and induction of genes involved in cholesterol metabolism and reverse cholesterol transport.	(Narasimhulu et al., 2016).
Adjuvant-	2.5mg/kg/day	Orally	Attenuation of erythrocyte sedimentation rate (ESR) scores and pro-	(Ismail et

induced arthritis (AIA) rat model			inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin 1-beta (IL-1β), and interleukin-6 (IL-6) levels.	al., 2018)
Rat model	10 wt% of GNO, RBO, and Sesame oil	With diet	Significant reduction in serum and liver lipids, 8-hydroxy-2-deoxyguanosine, cytokines in liver, and eicosanoids in leukocytesalong with an up-regulation of sterol regulatory element-binding protein (SREBP)-2 and peroxisome proliferator-activated receptor gamma (PPARγ) and down-regulation of nuclear factor-kappa B (NF-κB) p65.	(Yalagala, Sugasini, Ramaprasad, & Lokesh, 2017).
Atherosclerosis Mice model	.75 mg/day	With diet	Reduction of the expression of inflammatory genesand induction of genes involved in cholesterol metabolism and RCT.	(Narasimhulu et al., 2018b)
Rheumatoid arthritis rat model	1mL/kg	Orally	Significantly decrease in the levels of TNF-α, IL-6 with an increase inthe levels of IL-10 in groups treated with combination of SO and MTX compared to group treated with SO only or MTX only.	(Ali et al., 2017)
6-OHDA induced mice model	200 mL SO (20%)	With diet	Inhibition of activation of NADPH oxidase dependent inflammatory mechanism along with decreasedTBARS level and increased GSH activity.	(Ahmad et al., 2012)
RAW 264.7 macrophages (*in-vitro*)& mice(*in-vivo*)	50 and 250 µg/mL	Cell line and with diet(*in-vivo*)	Prevention of Ox-LDL uptake by RAW macrophages and further inflammation *in-vitro* withreductioin in plasma levels of TNF-α, IL-6, MCP-1 and VCAM1 in the SOAE pre-treated animals.	(Narasimhulu et al., 2018a)
Mice model and RAW 264.7 macrophage cell.	10 µg/mL-500 µg/mL	Injected intraperitoneally	Down-regulation of the number of inflammatory markers such as Ccl2 or MCP-1, Ccl5 or RANTES, IL-1alpha, IL-1beta,TNF, colony stimulating factor 2 (Csf2), Nfkb1 and matrix metallo-proteinase 3 (Mmp3).	(Selvarajan et al., 2015)
MDMs /RAW 264.7 cells	50 and 250 µg/mL for MDMs, 5 and 25 µg/mL for RAW macrophages	Cell line	Inhibition of IL-6 expression,TNF alpha or TLR4 or NFkB signaling pathways.	(Deme et al., 2018)

Table 4. Antioxidant and anti-inflammatory activity of pure compound

Isolated compound	Test model	Dose/conc.	Route of administration	Proposed mechanism	References
	DLF-induced gastric rat model	0, 1, 3, or 10mg/kg	Subcutaneously.	Reduction of mucosal lipid peroxidation, hydroxyl radical levels, DLF induced mucosal prostaglandin E2 generation and cyclo-oxygenase activity.	(Hsu et al., 2008b)
	Aspirin induced rat model	0 to 30 mg/kg/day	Orally	Reduction of gastric mucosal lipid peroxidation, nitric oxide production, gastric mucosal proinflammatory cytokines (tumor necrosis factor-α and interleukin 1-β levels), and the activity of gastric mucosal myeloperoxidase.	(Hsu et al., 2009a)
	Cyclophosphamide-induced rat model	50 mg/kg	Orally	Attenuation ofthe levels of endogenous reactive oxygen species, lipid peroxidation, tumor necrosis factor - α, interleukin (IL)-1β, IL-6 and cyclooxygenase-2 as wll as increase in the levels of glutathione, total thiols, superoxide dismutase, catalase, glutathione-transferase and glutathione peroxidase.	(Jnaneshwari et al., 2014)
Sesamol	M I/R injured Rat model	50 mg/kg b.wt	Orally	Diminishedinfarct size, resorted the cardiac markers, reduces the lipid peroxidn., neutrophil infiltration and increases the antioxidants level. Downregulates inflammatory genes, Bax, Caspase-3 apoptotic proteins and upregulates anti-apoptotic Bcl-2 protein.	(Tian & Guo, 2017b)
	Blood lymphocytes (*in-vitro*)	1, 5 and 10 µg/mL	Cell line	Reduction of lipid peroxidation marker, thiobarbituric acid reactive substances and elevation ofglutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase.	(Prasad, Mahesh, Menon, Jeevanram, &Pugalendi, 2005)

Sesamol	*In-vitro* colorectal carcinoma cells (HCT116).	Low (0.05 and 0.25 mM) and high (0.5, 2, 5, and 10 mM) concentrations	Cell line	Suppression of cell viability via disruption of cell cycle progression at high concentrations.	(Khamphio et al., 2016)
	STZ-induced rat model	2, 4, and 8 mg/kg body weight	Orally	Attenuation of release of inflammatory mediators (TNF-α, IL-1β, TGF-1β), and caspase 3.	(Chopra et al., 2010)
	Mice model	2, 4, and 8 mg/kg	Orally gavaged	Reduction of immobility period, lipid peroxidation and nitrite levels and elevation of sucrose preference, glutathione levels, superoxide dismutase and catalase activities.	(Saleem et al., 2011)
	Adjuvant-induced arthritis rat model	25 and 50 mg/kg	Orally	Reduction of the non-enzymatic inflammatory markers (TNF, IL-1β, IL-6, COX-2, PGE2, ROS, and H_2O_2,) withincreasedsuperoxide dismutase, catalase and glutathione-s-transferase activity.	(Hemshekhar et al., 2013)
	RAW 264.7 cells	1–100 µM	Cell line	Reduction of the levels of lipid peroxidation,protein nitration in the membranes of mitochondria,production of superoxide anion radical ($O_2^{-\bullet}$) and nitric oxide ($NO^{\bullet}$).	(Duarte et al., 2018)
	RAW 264.7 cells	3, 10, 30, 100 µM	Cell line	Inhibition of production of nitric oxide, prostaglandin E2 (PGE2), pro-inflammatory cytokines,the epression of iNOS and COX-2 and NF-κB and MAPK signaling pathwaysas wll as Upregulation of AMPK activation and Nrf2 signalling pathway..	(Wu et al., 2015)
	In-vitro	0-60 Mm	*In-vitro* strain	Inhibition ofCOX-1 andprolongation of the lag phase.	(Yashaswini et al., 2017a)
	Various strains of salmonella typhimurium	100 µg/plate dose		Neutralization ofoxygen free radicals and inhibition of the mutagenicity of H_2O_2.	(Kaur & Saini, 2000)

Modified form of Sesamol (INV-403)	Rabbit and *in-vitro*(endothelial cell)	20 mg/kg per day, Dietary supplementation and 100 µmol/L	With diet and cell line	Improvement of vascular function (decreases constriction to angiotensin II and increases relaxation to acetylcholine), attenuation ofsystemic and plaque oxidative stress, and inhibition of nuclear factor–κB activation.	(Ying et al., 2011)
Sesamin	(DOCA)-salt induced rat model.	0.1% and 1% sesamin	With diet	Inhibition of enhanced vascular O^{2-} production.	(Nakano et al., 2002)
	Middle cerebral artery occlusion (MCAO) rat model	30 mg/kg	Orally	Reduction of TBARS and protein carbonyl (PC) maintenance of healthylevel of glutathione and its dependent enzymes (glutathione peroxidase [GPx] and glutathione reductase [GR]) in MCAO group.	(Khan et al., 2010)
	Lipid-induced rat model	40, 80, or 160 mg/(kg/day)	Orally	Improvement of the serum total cholesterol, triglyceride, low-density lipoprotein cholesterol, apolipoprotein-B, oxidized-low-density lipoprotein, and serum creatinine as well asamelioration of the superoxide dismutase activity and reduction of malondialdehyde levels in kidney tissue.	(Zhang et al., 2016a)
	6-OHDA-lesioned rat model	10 or 20 mg/kg/day	Orally	Attenuation of motor imbalance in narrow beam test, striatal level of malondialdehyde (MDA) and reactive oxygen species (ROS), striatal caspase 3 activity and α-synuclein expression and improvement in superoxide dismutase (SOD) activity.	(Baluchnejadmojarad et al., 2017)
	(CCl_4)-induced rat model	100 mg/kg/day	Orally	Reduction ofthe release of liver enzymes (ALT, AST, and TBIL), protein carbonyls andthe levels IL-6 and COX-2 in the liver by inhibition of NF-kB activation withimprovedSOD and GSH-Px activities.	(Chen et al., 2015)
	Kainic acid-induced rat model	(15 mg/kg or 30 mg/kg) and (0.1, 0.5,	Orally gavagd and cell	Significant decreasein the release of Ca^{2+}, reactive oxygen species, and MDA from PC12 cells, expression of ERK1/2, p38 mitogen-activated protein kinases, Caspase-3, and COX-2	(Hsieh et al., 2011)

	and PC12 cell and BV-2 cell	1.0, or 2.0 μM) in cell model.	line	in BV-2 cells and PGE_2 production.	
	CCl_4 induced rat model	5 and 10 mL/kg bw	Intraperitoneally	Reduction of the elevated serum liver marker enzymes,TBARS andimprovementof GSH, SOD and catalase activities.	(Lv et al., 2015)
	STZ induced mice model	30 mg/kg BW	Intraperitoneally	Diminishedprogression of diabetic retinal injury by: 1) decreasing blood glucose level, 2) suppressing microglia activation, 3) reducing retinal TNF-α and ICAM-1 levels and 4) quenching iNOS expression.	(Ahmad et al., 2016)
	Pb and LPS induced rat model	10 mg/kg	Orally	Reduction ofthe serum levels of AST, ALT, CRP, TNF-α, IL-1, IL-6, NO, ROS generation, liver tissue expressions of c-Jun N-terminal kinase (JNK), p38 MAPK, GADD45β, COX-2, and iNOS.	(Chiang et al., 2014)
	Ovalbumin (OVA)-induced mice model	1 mg/kg, 10 mg/kg, and 20 mg/kg body weight	Intraperitoneally	Inhibition ofexpression levels of interleukin-4 (IL-4), IL-5, IL-13, and serum IgE with reduced numbers of total inflammatory cells and eosinophils in BALF.	(Lin et al., 2014)
	In-vitro and *in-vivo* mice model	1μmol and 1 mg/kg	Cell line and orally	Significant decrease in lipid peroxidation and neutralization offree radicals.	(Nakai et al., 2003)
	DOCA-salt induced rat model	0.1% sesamin	With diet	Inhibition of the enhancement of aortic O^{2-}production.	(Nakano et al., 2003)
Sesamin	CCl_4 induced mice model	10 mg/kg	Orally	Enhancement of theexpression levels of phosphorylated Jun N-terminal kinases (JNK) withdiminished release of mitochondrial cytochrome c in liver.	(Ma et al., 2014)
	Hepatic steatosis rat model	40, 80, and 160 mg/kg bw	Intragastrically	Reduction of the serum levels of total cholesterol, triacylglycerols, low-density lipoprotein cholesterol, free fatty acid, malonaldehyde and cytochrome P450 2E1 as well aspotentiation ofhepatic glutathione peroxidase and superoxide dismutase activities.	(Zhang et al., 2016b)
	Neuronal	1 Pm	Cell line	Significant depletion ofMPP+-Induced IL-6, IL-1β, and TNF-α	(Bournival

	PC12 cells cocultured with N9 microglial cells			mRNA and protein concentrations.	et al., 2012)
	Primary chondrocytes (cultured cell)	2.5 and 5μM	Cell line	Inhibition ofIL-1β induced production of PGE_2 and NO, production of MMP1, MMP3 and MMP13 in IL-1β-stimulated chondrocytes, and IL-1β-induced phosphorylation of NF-κB p65 and IκBa.	(Kong et al., 2016)
	Human (clinical trial)	200 mg/day	With diet	Significant decrease in serum levels of MDA withincreased TAC and high-density lipoprotein cholesterol (HDL-c) levels.	(Helli et al., 2016)
Sesamin	Neuronal PC12 cells	1 pM	Cell line	Reduction of intracellular ROS production andmodulation of tyrosine hydroxylase, superoxide dismutase, catalase, inducible NO synthase and interleukin-6 expression.	(Lahaie-Collins, Bournival, Plouffe, Carange, & Martinoli, 2008)
	Endothelial cell	12.5-100 μM	Cell line	Amelioration of oxLDL-induced ROS generation, SOD-1 inactivation, and activation of NF-κB.	(Lee et al., 2009)
Sesamin derivative-1, 2-bis(3-methoxybenzyl) ethane-1, 2-dicaroxylic acid (MMEDA)	Rat model,BV-2 microglia or PC12 cell	10 mg/kg, and 1, 10, 50 μM	Intraperitoneally and cell line	Attenuation of ROS, PGE_2 release, hypoxia-induced JNK and caspase-3.	(Hung et al., 2017)
Sesamin derivative,	PC12 cells	10 μM	Cell line	Inhibition of LDH, lipid peroxidation, cell damage, ROS, elevation of intracellular free Ca ion and apoptosis activity	(Hou et al., 2015)

3-bis (3-methoxybenzyl) butane-1, 4-diol				with increased ACh release.	
Sesamin and sesame oil	Paw edema mice model	sesame oil (100, 200, and 400 mg/kg) and sesamin (50, 100, and 200 mg/kg)	Orally	Inhibition of prostaglandin synthesis, pleural exudate formation and the leucocyte migration.	(Monteiro et al., 2014)
Sesamin and sesamolin	Mice model	(0%, 0.1%, 0.2%, and 0.5%)	With diet	Inhibition ofcaspase-3 and MAPK activation,IL-6, PGE2, tumor necrosis factor (TNF)-α and nitric oxide (NO) productions from microglia as well as elevation of IL-10..	(Jeng & Hou, 2005)
	BV-2 microglial cell line	50–100μM	Cell line	Inhibition of NO production, iNOS, mRNA and protein expression.	(Hou et al., 2003)
Sesamin and sesamol	LPS inducedrat model	Oral supplementation of sesamol and sesamin	Orally	Lowers LPS induced expression of $cPLA_2$, 5-LOX, BLT-1and LTC_4 synthase. The serum levels of TNF-α, MCP-1 and IL-1β are found to be reduced in sesamol and sesamin group,	(Yashaswini et al., 2017b)
Sesamolin	Rat model	1% sesamolin	With diet	Reduction of lipid peroxidation, measured as 2-thiobarbituric acid reactive substances.	(Kang et al., 1998)
Sesaminol	Cultured rat astrocytes	sesaminol glucosides (10–100 μg/ml)	Cell line	Inhibition of LPS-induced generation of nitric oxide (NO), reactive oxygen species (ROS) and expression ofcytosolic phospholipase A_2 ($cPLA_2$), cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS)as well as prevention of LPS-induced DNA binding and transcriptional activity of nuclear factor KappaB (NF)-κB.	(Lee et al., 2006)
	PC12 cells	25, 50 and 100μmol	Cell line	Elevatation of cell survival rate and, SOD, CAT and GSH-Px activity with significant decline in the secreted LDH level,	(Cao et al., 2013)

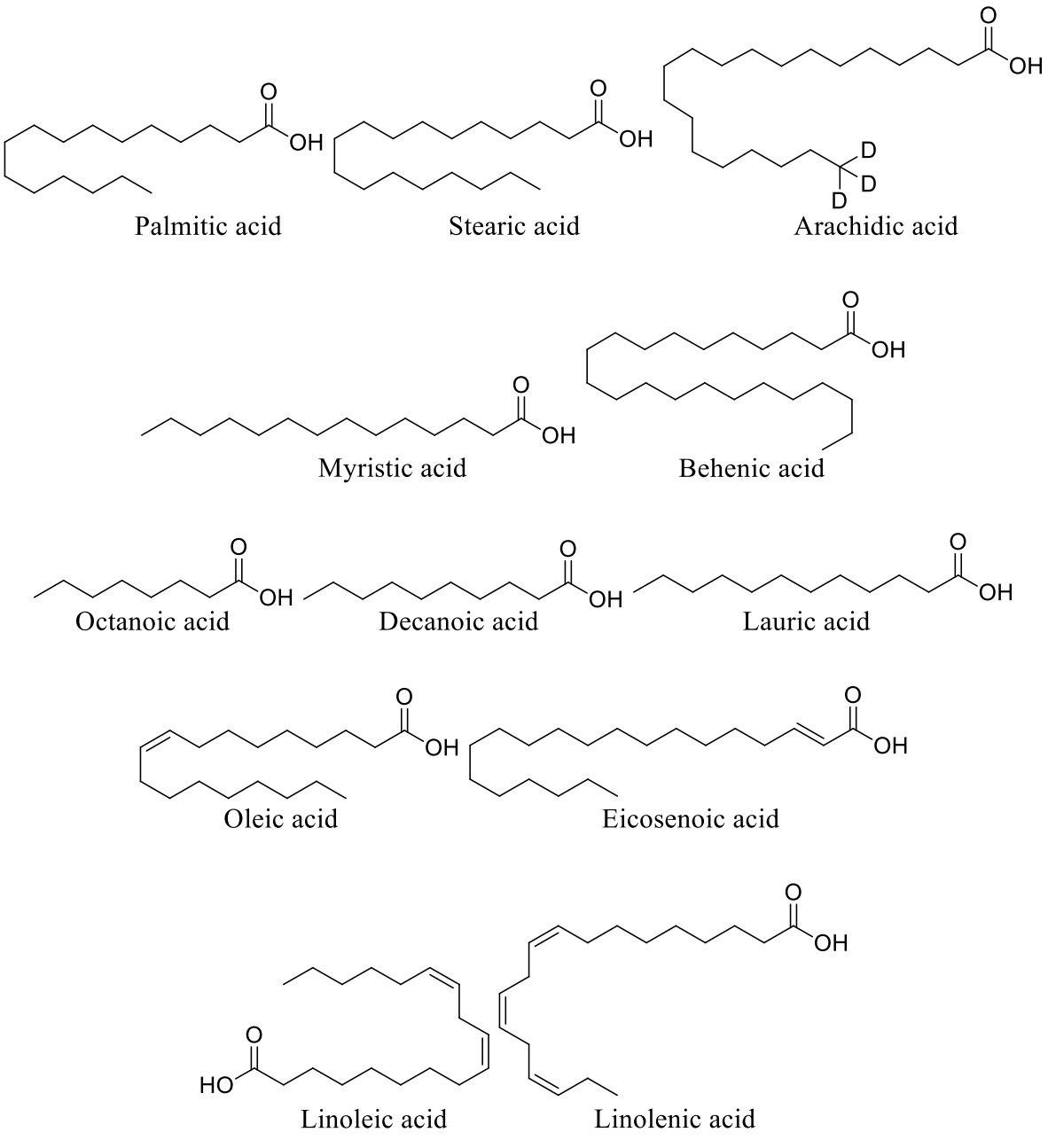
				apoptosis rate and ROS level of H_2O_2 exposed cells.	
Sesame lignans and tocopherols	DM rat model	0.5% sesame lignin + 0.25% alpha tocopherol	With diet	Amelioration of the alteration in lipid profile and the adverse free radical generation.	(Dhar et al., 2007)
Sesame lignans	*In-vitro*	0.1 µM	Cell line	Inhibition of TBARS formation.	(Kang et al., 1999)

Table 5. Binding affinity and interaction of sesame oil ligands with COX-2 after docking.

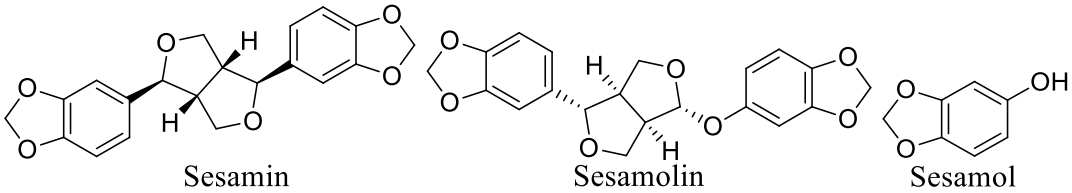
Compounds	Binding affinity to COX2 (kcal/mol)	Interacting Amino acid
Linoleic Acid	-7.0	Pro528, Lys346, Ile331, Gly324, Met99, Phe347, Leu352, Leu351, Asp348, Ile327, Leu103, Pro349, Lys328, Cys526, Trp531
Linolenic Acid	-7.3	Phe353, Phe347, Ile331, Asp348, Lys346, Ile327, Leu352, Cys526, Lys328, Pro528, Pro349, Trp531
Oleic Acid	-6.5	Ile331, Arg46, Leu352, Phe347, Ile327, Cys526, Pro528, Lys328, Pro349, Trp531
Palmitic Acid	-5.4	Gln336, Val102, Leu517, Ala513, Leu345, Val335, Val509, Leu338, Phe343, Ser339, Tyr341
Pinoresinol	-8.4	Ser339, Tyr371, Leu517, Ala513, Gly512, Val335, Met99, Met508, Val509, Phe343, Tyr341, Ser516,Val102
Sesamin	-10.4	Val524, Asn523, Arg362, Arg362, Phe128, Gln360, Asp215, Gly211, Asn361
Sesaminol	-10.6	Arg362, Asp215, Gly211, Ser129, Phe128, Gln360, Phe128, Arg362, Asn361
Sesamol	-6.4	Tyr359, Gln356, Pro528, Leu352, Ser527, Gln358, Phe357
Sesamolin	-9.6	Ser527, Lys355, Leu352, Phe357, Lys355, Ser112, Tyr359, Phe357, Phe353, Pro528, Thr104, Ser107, Gln358, Gln356

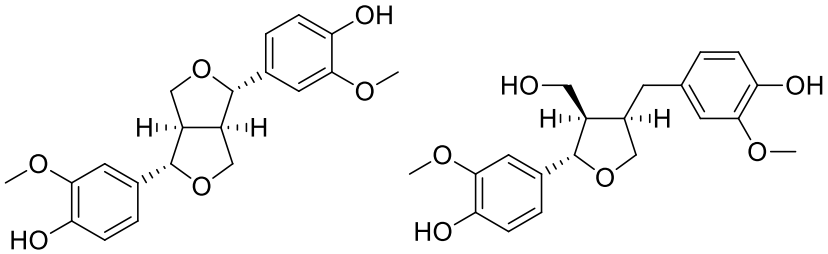
Sesamolinol	-8.8	Lys518, Lys355, Leu352, Pro528, Gln358, Thr104, Phe357, Gln356, Ser112, Leu103, Ser107
Stearic Acid	-5.9	Met508, Leu345, Phe343, Val335, Ala513, Gly512, Val102, Phe504, Leu338, Leu517, Val509, Ser339, Tyr341
Tocopherol	-7.1	Ser105, Ala513, Leu345, Phe343, Arg106, Ile98, Trp85, Phe84, Ile77, Leu517, Met99, Val74, Leu78, Val102, Tyr341
Vitamin A Retinol	-7.4	Ser339, Ser105, Tyr101, Leu78, Pro69, Lys68, Ala513, Val335, Glu510, Arg106, Val74, Val102, Pro71, Tyr341
Vitamin K Phylloquinone	-9.6	Cys526, Leu352, Asp348, Lys346, Gly324, Met521, Phe343, Ser339, Val335, Leu345, Ile327, Val102, Tyr341, Trp531, Leu103, Met99, Leu517, Ile331, Lys328
Arachidic acid	-6.5	Met521, Asp348, Gly324, Met99, Phe346, Lys346Leu352, Ile3278, Pro528, Phe351, Ile331, Cys526, Lys328, Trp531, Pro349
Myristic acid	-6.2	Cys526, Lys346, Gly324, Phe347, Leu352, Pro349, Ile331, Ile327, Lys328, Trp531
Behenic acid	-6.2	Gly512, Tyr371, Leu345, Leu103, Met99, Phe343, Val102, Leu517, Leu338, Ser516, Ala513, Tyr341, Ser339, Val335, Val509
Octanoic acid	-5.2	Asp348, Ile327, Trp531, Lys346, Phe347, Lys328
Decanoic acid	-5.8	Phe347, Gly324, Leu352, Ile327, Pro528, Cys526, Lys328, Pro349, Trp531
Lauric acid	-5.8	Cys526, Leu352, Pro349, Met99, Asp348, Lys346, le327, Ile331, Phe347, Lys328, Trp531
Eicosenoic acid	-6.2	Phe343, Gly512, Leu338, Leu103, Val335, Leu517, Ala513, Leu345, Met99, Val509, Tyr341, Val102, Ser516, Ser339
Lariciresinol	-8.8	Asp215, Tyr359, Gly211, Leu210, Trp125, Val524, Arg362, Gly211, Phe128, Gln360, Phe128, Arg362, Asn523, Asn361
Asarinin	-10.4	Val524, Asn523, Arg362, Asp215, Arg362, Phe128, Gly211, Phe128, Gln360, Asn361
Campesterol	-10.5	Asn523, Gly211, Trp125, Val524, Val524, Asn361, Leu131, Arg362, Gln360, Phe128, Trp125, Arg362, Gly211, Asn523, Asp215
Stigmasterol	-10.7	Val524, Gly211, Gln360, Leu210, Val524, Asn361, Leu131, Phe128, Arg362, Phe128, Trp125, Arg362, Gly211, Asn523, Asp215
Beta-sitosterol	-10.2	Val524, Arg362, Asn361, Phe128, Val524, Asn361, Leu131, Ser129, Gln360, Phe128, Trp125, Arg362, Gly211, Asn523, Asp215

Δ5-Avenasterol	-10.7	Val524, Gly211, Leu210, Ser129, Gln360, Val524, Asn361, Leu131, Phe128, Arg362, Phe128, Trp125, Arg362, Gly211, Asn523, Asp215
Δ7-Stigmasterol	-10.5	Val524, Leu131, Gln360, Gly211, Leu210, Asn361, Phe128, Trp125, Phe128, Gly211, Trp125, Val524, Gln360, Arg362, Asn523, Asp215
Δ7-Avenasterol	-10.7	Arg362, Leu210, Asn361, Leu131, Trp125, Val524, Asn523, Gln360, Phe128, Val524, Ser129, Phe128. Gly211, Trp125, Gly211, Arg362, Asp215, Asn523
Vitamin B(Riboflavin)	-8.5	Arg362, Trp125, Asn523, Asp215, Leu131, Ser129, Leu210, Arg362, Gln360, Gly211, Asn361
Control		
Arachidonic Acid	-6.8	Met99, Gly512, Tyr371, Val335, Leu103, Leu517, Ala513, Phe343, Ser339, Leu338, Val102, Val509, Tyr341


Palmitic acid
Stearic acid
Arachidic acid
Myristic acid
Behenic acid
Octanoic acid
Decanoic acid
Lauric acid
Oleic acid
Eicosenoic acid
Linoleic acid
Linolenic acid

(a)


Sesamin
Sesamolin
Sesamol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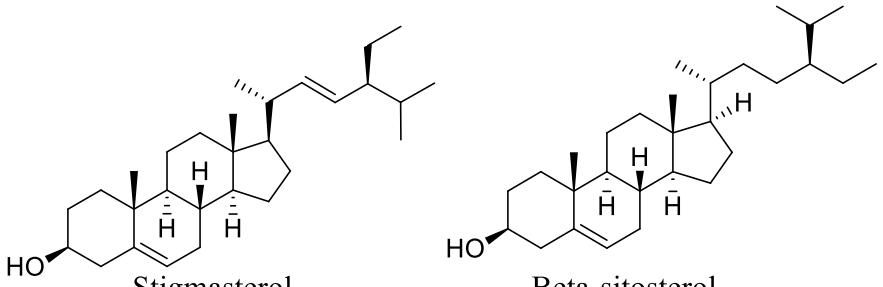
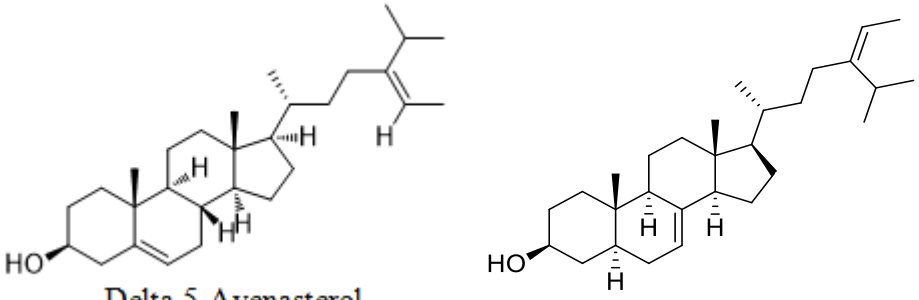
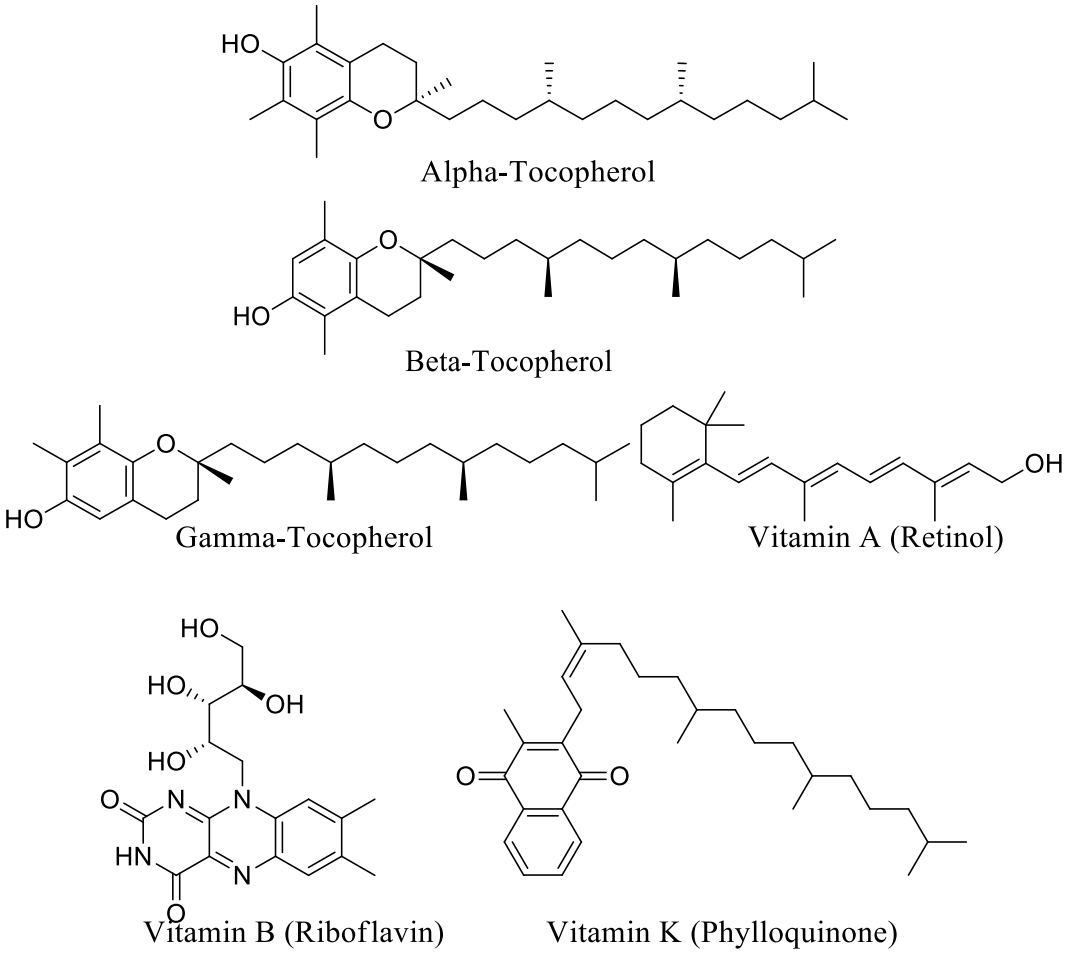
Lariciresinol

(b)


Stigmasterol
Beta-sitosterol


Delta 5-Avenasterol
Delta 7-Avenasterol

(c)



(d)

Figure 1: Structures of constituents reported in sesame oil. (a) Structures of fatty acids; (b) Structures of lignans; (c) Structures of phytosterols; (d) Structure of vitamins

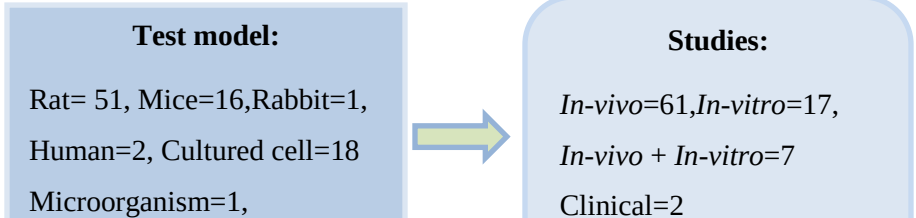


Figure 2: Workflow of database searches with literature inclusion and exclusion criteria.

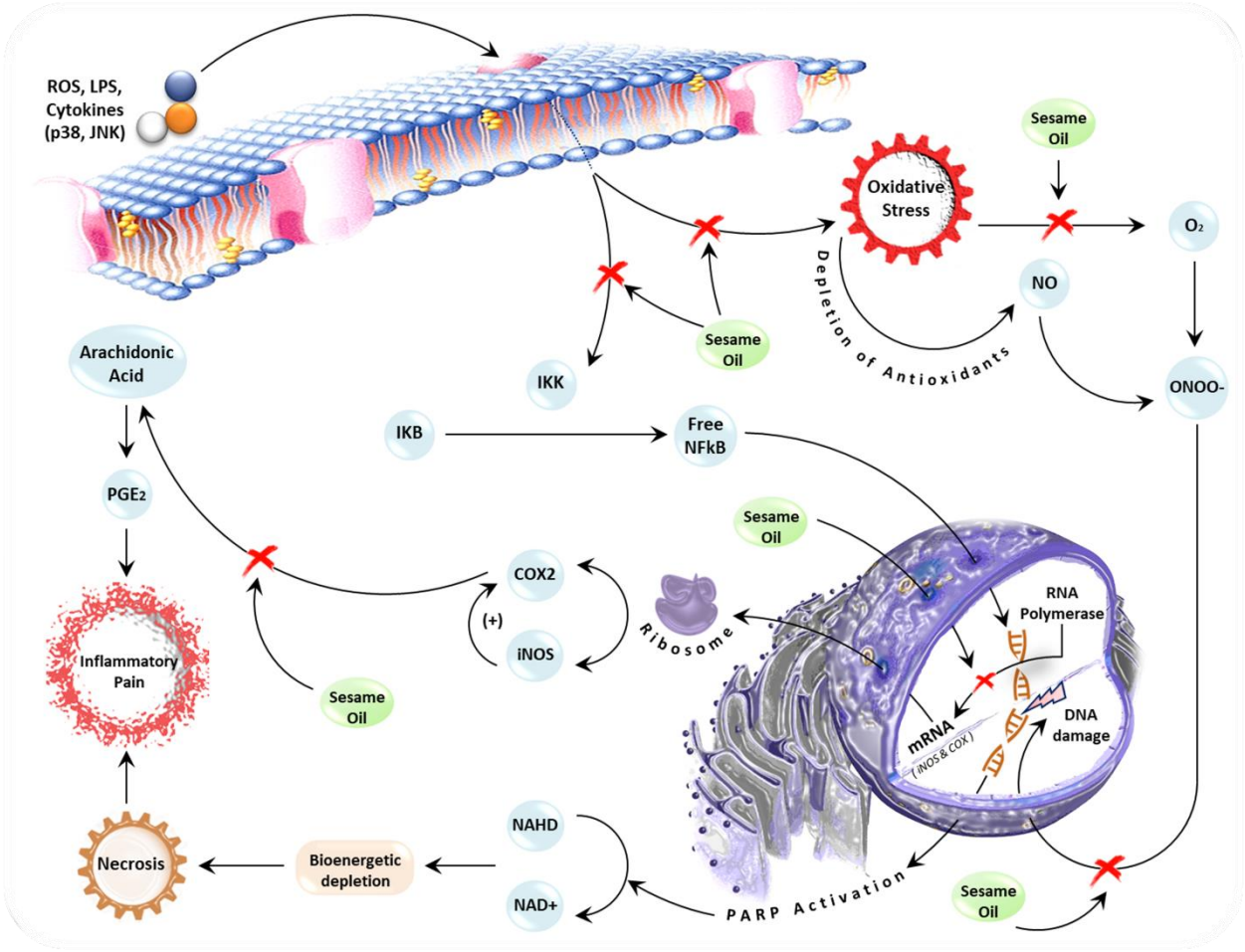


Figure3: Proposed mechanism of antioxidant and anti-inflammatory activity of sesame oil

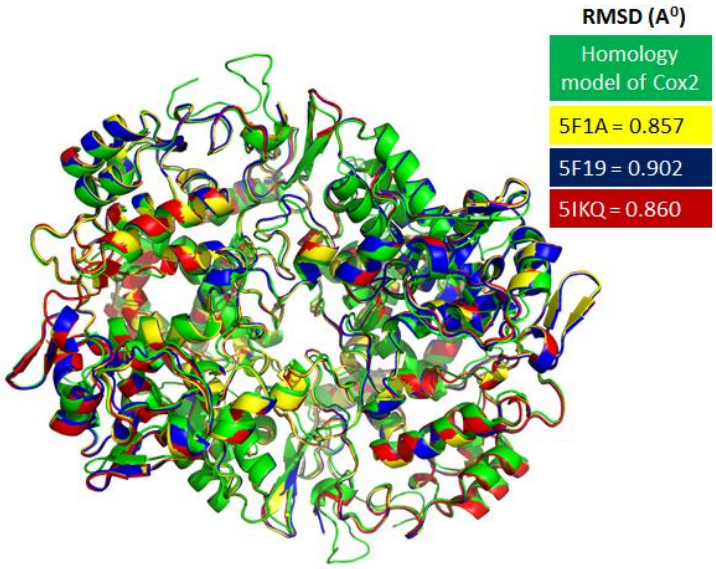


Figure 4: Homology model of Human COX-2 enzyme.

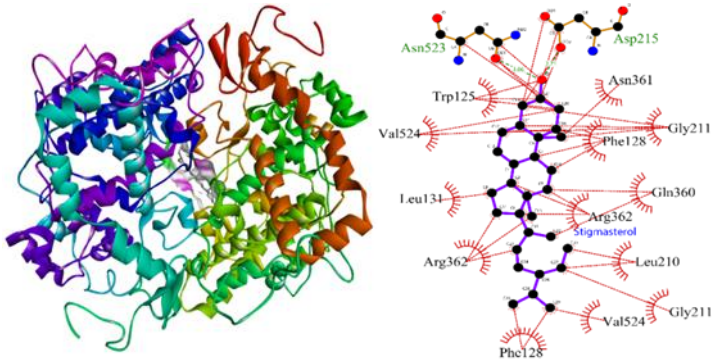


Figure 5: Docking of Stigmasterol with human COX-2 enzyme

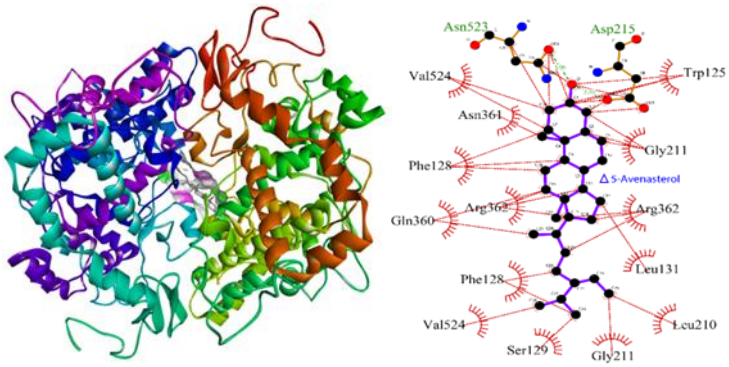


Figure 6: Docking of Δ5 Avenasterol with human COX-2 enzyme