Sesamol and Health – A Comprehensive Review

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ABSTRACT

Antioxidant potential of sesamol has led to being studied extensively in recent decades for its beneficial role in vast aliments. There has been a renewed interest in this compound recently, due to its activities such as hepatoprotective, neuroprotective, chemopreventive, anti-inflammatory, cardioprotective, skin protective and antiaging properties which were established in various preclinical models. Further studies may be required to develop its underlying mechanisms and to investigate its various biological activities to develop an optimal dose range. Hence, a comprehensive review is necessary on in vivo and in vitro activities of sesamol. This review is to highlight the potential of sesamol as a potent therapeutic agent for humans.

Keywords: In vitro, in vivo studies, Pharmacokinetics, Sesamol, Synthesis.

INTRODUCTION

Recently, the attention has been increasing toward the natural compounds obtained from the dietary plants, with protective biological functions. These naturally obtained compounds have the potential for the protection against oxidative stress. Sesame seeds of the scientific name Sesamum indicum, Linn, Pedaliaceae are popular in India and other East Asian countries where they are used as health foods.¹ Several compounds such as sesaminol, sesamolinol and pinoresinol, which are lipid-soluble, antioxidant compounds, were isolated from sesame seeds.²

SYNTHESIS OF SESAMOL

A significant amount of sesamin and sesamolin, sesame lignans, are found to be contained within the sesame oil for up to 1.5%. The bleaching process in industries of unroasted sesame oil produces sesaminol from sesamolin [Figure 1]. In addition, under specific favorable conditions, the sesamolin, produced in the bleaching process, gets converted to sesamol readily.³

PHYSICOCHEMICAL PROPERTIES OF SESAMOL

Sesamol is found as crystalline needles with pale brown color in nature with a peculiar odor. Sesamol’s melting point was observed to be 64°C ± 1°C with no signs of hygroscopicity, while the solubility was found to be 38.8 ± 1.2 mg/ml in water at 37°C. Sesamol shows solubility of approximately 10 mg/ml at all the pH <9 and a sharp increase in solubility with more alkaline pH >10 and the value being 41.83 mg/ml at pH 13. The ionization constant (pKa) value of sesamol is 9.79 ± 0.06. The predicted and experimental log P values for sesamol are 1.29 ± 0.01 and 1.34, respectively. Distribution coefficient (log D), of sesamol and the value, is found to vary in the range of 1.0–2.0, though the pH-solubility profile of sesamol was found to be persistent between pH 1.0 and 7.0.⁴
PHARMACOKINETIC CHARACTERISTICS OF SESAMOL

Sesamol is almost entirely absorbed through the stomach (85%) with 65%–75% absorption in every intestinal segment. Such a high permeability of sesamol can be due to its high log D values at the acidic pH (at pH 2) corresponding to the stomach, rather than the intestine (pH 5–7). Statistical difference of sesamol's permeability through various segments of the intestinal regions, such as the duodenum, jejunum and ileum, was not observed. Sesamol may hold a promise in the oral delivery, taking into consideration the high permeability through various intestinal segments, high aqueous solubility (38.8 mg mL ± 1) and low molecular weight (138.34 g) with a small size. However, given its high permeability, a controlled release formulation may be feasible to ensure the slow and steady release of sesamol to maintain the optimum plasma levels for sustained times.

IN VITRO AND IN VIVO STUDIES OF SESAMOL

Antioxidant activity

Geetha et al. in in vitro studies reported that sesamol at a variety of doses and test systems such as \( \text{H}_2\text{O}_2 \) assay, 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, nitric oxide (NO) scavenging and lipid peroxidation in the brain and liver showed a wide spectrum of antioxidant activity. Sesamol's chemical structure contains a benzo-dioxole group which is responsible for scavenging the hydroxyl radicals. Dihydroxybenzene, an antioxidant, is produced by hydroxyl radical scavenging. Sesamol was also reported to scavenge other radicals such as DPPH, 2-imidazoquinoxaline-type radical, superoxide anions and singlet oxygen. It was reported to inhibit the deoxyribose degradation and DNA cleavage induced by hydroxyl radicals. Sesamol showed notable scavenging of superoxide and NO radicals, with a significant IC\(_{50}\) value of 130.4 nmol, greater than that of catechin, epicatechin and ascorbic acid whose IC\(_{50}\) values are 188.3, 212.8 and 326.4 nmol, respectively. It is a unique compound with solubility in both oil and aqueous phase and is expected to progress as a therapeutic agent.

Pulse-radiolytic and biochemical studies

Using a technique such as a nanosecond pulse-radiolysis technique and cyclic voltammetry, the free-radical quenching potential of SM (Sesamol) was evaluated. SM proficiently quenched hydroxyl, lipid peroxyl, one-electron oxidizing and tryptophanyl radicals. SM was found to inhibit lipid peroxidation, degradation of deoxyribose and DNA cleavage in biochemical studies.

Effect on oxymyoglobin oxidation

The radical quenching potential was discovered to be of the order ellagic acid > sesamol > olive leaf extract > lutein, in comparison with other compounds. These compounds do not exhibit iron-chelating activity. Lipid peroxidation was decreased in muscle systems of porcine and bovine. The antioxidant potential was in the sequence: sesamol > ellagic acid > olive leaf extract > lutein. Olive leaf extract as well as ellagic acid reduced the oxymyoglobin oxidation and on the other hand, the addition of sesamol increased the oxymyoglobin in both the systems.

Effect on the lipid peroxidation

The potential of sesamol and 20 related moieties was tested on ascorbate/Fe\(^{2+}\)-induced lipid peroxidation of mitochondria. Sesamol and its related compounds, such as isosafrole catechol, caffeic acid, hydroxyhydroquinone, 3,4-dimethoxyaniline, 3-methoxy-4-hydroxyquinone, isoeugenol, eugenol and 3,4-methylenedioxy aniline, have produced a notable inhibitory effect on lipid peroxidation, with isoeugenol producing the most potent inhibitory activity.

Free-radical scavenging activity

The Solvation Model based on Density (SMD) continuum model was used to free-radical reactions of sesamol, particularly in the aqueous and nonpolar medium. SM reacted efficiently in the aqueous medium rather than nonpolar medium. SM, in anionic form, was discovered to be mainly sensitive to peroxyl radicals. Hence, SM shows the exceptional potential of peroxyl radical quenching in an aqueous medium under physiological conditions.

Effect on endotoxin-induced oxidative stress

Sesamol showed a reduction in serum lipid peroxidation (LPO) in endotoxin-challenged rats’ dose dependently. It did not reduce superoxide anion counts but reduced hydroxyl and peroxynitrite radicals. In endotoxin-treated rats, the levels of superoxide dismutase (SOD), catalase and glutathione (GSH) were elevated by sesamol. SM decreased NO production and inducible NO synthase.
expression. SM decreased liver and kidney damages that may be resulted from endotoxin in rats. Thus, SM protects against the organ damage by reducing NO-associated lipid peroxidation in endotoxin-treated rats.\textsuperscript{10}

**Radioprotective activity**  
*Protection from γ-radiation-induced damages*

The plasmid DNA (circular) was prevented from gamma-radiation-induced degradation by sesamol in a concentration-dependent manner. *Ex vivo* alkaline comet assay studies demonstrated the protective effect of the sesamol on DNA of leukocytes, taken from mouse blood which was exposed to gamma-radiation. The DNA damage caused by radiations in leukocytes of the mouse, *ex vivo*, was decreased in a time-dependent manner by SM. Thus, SM could be enhancing DNA repair. SM protected radiation-induced biomembrane damage by lipid peroxidation. Hence, SM could be used as a radioprotective agent in biomembrane mentioned above and DNA damage caused by ionizing radiations.\textsuperscript{11}

**The radioprotective effect in cultured human lymphocytes**

Lymphocytes pretreated with sesamol were exposed to gamma-radiation (1, 2 and 4 Gray [Gy]). Cellular changes were assessed and found sesamol significantly reduced micronucleus, dicentric aberration frequencies and thiobarbituric acid reactive substance levels. It also seemed to increase the antioxidant levels such as SOD, GSH and catalase in a concentration-dependent fashion. Thus, gamma-radiation tempered cellular damage in cultured human lymphocytes was significantly prevented by sesamol by free radical scavenging mechanism.\textsuperscript{12}

**In vivo radioprotective activity**

The radioprotective activity was assessed in Swiss albino mice with seven different doses of sesamol, namely 0–100 mg/kg body weight (bw). The dose was administered half an hour before γ-irradiation (9.5 Gy) exposure to the whole body. The pretreatment of mice with SM (50 mg/kg bw) with radiation (15 Gy) reduced significantly dead, inflamed and goblet cells of the jejunum. The antioxidant enzymes were increased by SM (50 and 100 mg/kg bw) in radiation-treated tissues. SM pretreatment keeps the spleen index normal indicating hemopoietic protection. SM significantly reduced Malondialdehyde (MDA) formation, as well as a reduction in DNA damage. This impaired DNA is prevented from false signaling leading to apoptotic signaling. Therefore, quenching of free radicals and potentiating antioxidant systems, defending the blood tissues and reducing DNA damage significantly may be the possible mechanisms found for the radioprotective potential of SM.\textsuperscript{13}

**The photoprotective effect in human blood lymphocytes**

Sesamol increasing concentrations (1, 5 and 10 μg/ml) pretreatment to lymphocytes for half an hour were irradiated. Antioxidant activities and lipid peroxidation were examined. Photoprotective effect of sesamol was proved through the highest dose (10 μg/ml) by normalizing the ultraviolet (UV) B-induced lipid peroxidation.\textsuperscript{14}

**In vitro radioprotective activity**

Sesamol has produced substantial radioprotective effectiveness in plasmid DNA and DNA from calf thymus. The assays such as 2,2’-azino-di(3-ethylbenzothiazoline)-6-sulfonic acid (ABTS), 2-deoxyribose degradation and DPPH were conducted to measure the radical quenching potential of SM and melatonin (MLT). SM’s scavenging activity was found to be significant relative to MLT. SM was found to be 20 times potent than MLT in *in vitro* experiments on V79 (Hamster Chinese lung male) cells. It was found that SM was more effective than MLT due to its higher free radical quenching potential.\textsuperscript{15}

**Radioprotective potential of SM in mice**

SM was explored for its activity in the γ-radiation-induced blood tissue and gastrointestinal damage in mice. The mice of species C57BL/6 were treated with a dose of 100 or 50 mg/kg of SM by the i. p. route, 30 min before the study and exposed them to γ-radiation of 7.5 Gy and 5 Gy (sublethal dose). SM treatment inhibited lipid peroxidation and improved rejuvenation of crypt cells of the intestine Gastro-Intestinal Tract (GIT). In addition, SM was observed to reduce the expression of p53 and Bax proteins (apoptotic markers) in cells of the bone marrow, spleen and intestine induced by radiation. SM treatment improved antioxidant activity in the spleen and gastrointestinal system revealed by ABTS and DPPH assays. Hence, SM as a preventive dose can protect blood tissue and gastrointestinal tissues from exposure to γ-radiation which causes damages in mice organs.\textsuperscript{16}

**Effect on radiation-induced genotoxicity in the hematopoietic system**

Sesamol was investigated for radioprotective potential in bone marrow cells from mice and radiation-induced genotoxicity in the hematopoietic system. Either SM or MLT (10 and 20 mg/kg bw) was dosed to C57BL/6 mice, intraperitoneally, half an hour before irradiation (2 Gy). Then, mice were sacrificed a day after. SM (10 and
20 mg/kg doses) administered in irradiated mice showed the reduction in Tricarboxylic Acid (TCA) and micro-nucleated polychromatic erythrocyte occurrence in bone marrow cells by 57% and 50%, respectively, relative to radiation-only groups. SM showed the reduction in radiation causing apoptosis and facilitation of cell proliferation. Granulocyte populations were increased in peripheral blood by sesamol as MLT. Inclusively, sesamol was found to be effective the radioprotective as MLT. It was intensely suggested the significant radioprotective effectiveness of SM in the blood tissue of mice.17

**Cardioprotective effect**

**In cardiomyopathy**

The cardioprotective effect of SM in experimental rats against doxorubicin (DOX)-induced cardiomyopathy was evaluated. The six-divided dose of DOX for 2 weeks on the 8th, 10th, 14th, 16th, 18th and 21st day was dosed i. p. at a total collective dose of 15 mg/kg to rats. In the heart tissue homogenate, the endogenous antioxidants and lipid peroxidation were estimated, after the last dose administration. It is observed that the DOX significantly elevated the levels of triglyceride (TG), total cholesterol, low-density lipoprotein (LDL) and very LDL and decreased the levels of high-density lipoprotein. Pretreatment of SM significantly reverted the above-said lipid parameters near to normal which showed that sesamol lowered the lipids because of the prevention of cholesterol biosynthesis and enhancement in the absorption of LDL from blood in the liver. SM was found to be cardioprotective significantly in DOX-induced cardiomyopathy.18

**In myocardial infarction**

Myocardial infarction is associated with altered lipid metabolism. Isoproterenol (ISO)-induced cardiotoxicity is associated with an increased level of circulatory lipids. Elevated plasma TG and free fatty acid (FFA) concentrations also contribute directly to increase the risk of cardiovascular disease. Treatment with SM decreases the levels of plasma TG and FFA in ISO-treated rats. As a potent antioxidant in nature, sesamol prevented the degradation of membrane phospholipids. The increase in the phospholipid content in myocardium and liver might be due to free radical quenching mechanism. Increased LDLs and very LDLs and decreased high-density lipoprotein levels in the ISO-administered rat were reversed after the treatment with SM. Hence, SM has protection against myocardial infarction induced by ISO. The results indicate that SM could provide an antihyperlipidemic activity. The cardioprotective effect of SM may probably be credited to its effect to inhibit the lipid accumulation caused by ISO, by its hypolipidemic property.19

**In cardiometabolic syndrome**

The effect of SM was investigated for the cardiometabolic syndrome (CMedS) in rats caused by high-cholesterol/high-fat diet (HFD). Rats were fed with a diet containing high-fat content for 60 days to induce obesity, dyslipidemia, insulin resistance (IR), hepatic steatosis and hypertension. Rats with total cholesterol >150 mg/dl were considered hypercholesterolemic on the 30th day, and SM (2, 4 and 8 mg/kg/day) was administered for the following 30 days. SM treatment was observed to reduce IR, hyperinsulinemia, hyperglycemia and dyslipidemia, in a dose-dependent manner. Furthermore, hepatic peroxisome proliferator-activated receptor-gamma (PPAR-γ), PPAR-α and endothelial NO synthase (eNOS) protein expressions were upregulated, while nuclear factor-κB (NF-κB) expression was downregulated by SM treatment. Thus, SM was discovered to prevent CMedS by regulating the above-mentioned protein expressions in HFD-fed rats.20

**Effect on H9c2 cardiomyoblasts**

Cardiomyoblasts (H9c2) exposed to DOX were treated with sesamol in doses of 12.5, 25 and 50 μm. Cellular and genetic damage of DOX was by elevating the levels of intracellular reactive oxygen species (ROS), decreasing the cell viability and increased apoptosis. The administration of sesamol reversed these cytotoxic and genotoxic activity. Sesamol also reduced the proapoptotic proteins. Pretreatment of sesamol prevented ROS production and improved endogenous antioxidant enzyme levels. This reflects the importance of sesamol in improving the damaging effects related to cancer chemotherapy.21

**Effect on atherosclerosis**

SM activity against atherosclerosis development and levels of LDL in plasma of rodents was investigated. The study was found to show the effect of SM on L5, the subfraction of LDL-induced apoptosis in cultured vascular endothelial cells. For this purpose, Syrian hamsters were selected, since their LDL profile is close to that of human beings. The normal group animals were fed with chow diet, HFD group received food with high-fat content and another group received HFD along with 50 or 100 mg/kg SM orally for 16 weeks. At the end of the treatment, it was observed that HFD + sesamol had diminished L5 levels...
compared to the HFD-only group. The aortic arch of the animals was removed and subjected to oil red O staining, where the aortic arch of animals which received HFD plus SM treatment was observed to have reduced atherosclerotic lesions than that of HFD-only group. SM 0.3–3 μM hampered the apoptosis incited by L5 in human aortic ECs, in a dose-dependent manner. It was observed that SM inhibited lectin-like oxidized LDL receptor 1. It also leads to increased phosphorylation of eNOS, Akt. Hence, it was claimed that SM might protect against atherosclerosis by lowering the L5 levels.22

**Cardiovascular in vivo reactivity**

NO is an endothelium-derived factor that has a pivotal role in protecting the endothelium, by having an anti-thrombotic and antiatherosclerotic activity. The NO is synthesized by an enzyme eNOS, whose expression is controlled by the endothelial cells. SM effect on the release of NO release was investigated by Chen et al., where the SM effect on NO release and eNOS expression is examined in human umbilical vein endothelial cells. No release was measured 24 h after the treatment and SM-induced NO release was observed to be in a dose-dependent manner. The increased expression of NOS and NOS activity in endothelial cells was also observed due to the SM treatment. The confirmation for the activation of eNOS by SM was done through a signaling pathway of PI-3-kinase-Akt (protein kinase B) activation. This study establishes the sesamol’s activity in NO release and suggests its possible role in cardiovascular in vivo reactivity.23

**Effect on central nervous system**

**In Huntington’s disease**

SM was analyzed for the prophylactic activity in neurotoxicity induced by 3-nitropropionic acid (3-NP) in preclinical aspects. The toxicant, 3-NP (10 mg/kg), was administered for 14 days in male rats. Pretreatment with SM (5, 10 and 20 mg/kg) markedly increased bw, motor coordination and locomotion. SM also reduced oxidative damage in tissues of rat brain as well as brain regions were found to rich in mitochondrial enzymes. Hence, SM was discovered to be a novel treatment approach for Huntington’s disease management.24

**In menopause-associated cognitive and emotional/central nervous system disturbances**

SM has enhanced tissue distribution as its log P is 1.29 and the solubility is 38.8 mg/ml. This reduces the SM's delivery to the brain. For this reason, solid lipid nanoparticles loaded with SM were prepared with entrapment efficiency of 75.9% ± 2.91% and an average particle size of 122 nm. These formulations efficiently deliver SM to the brain and are shown to possess a positive effect on memory and anxiety that are monitored centrally through in vivo antioxidant mechanism. The delivery of these formulations to the brain is by apolipoprotein E (ApoE). The ApoE is adsorbed on to the surface of this Sesamol-loaded solid lipid nanoparticles (S-SLN) and then taken up by ApoE receptors located on the blood–brain barrier. The potency of S-SLN in improving cognitive deficits and anxiety is established in ovariectomized rats. Hence, these S-SLN formulations may be a possible treatment for neuron-damaging diseases in geriatric patients and menopausal women.25

**Neuron protective potential of SM individually and solid lipid nanoparticles loaded with SM**

The SM loaded into the solid lipid nanoparticles (S-SLN) are tested in the intracerebroventricular streptozotocin (ICV-STZ)-induced cognitive deficit model. Solid lipid nanoparticles loaded with SM, with 122–200 nm as mean particle size and 75.9% ± 2.91% as entrapment efficiency. The rat’s cognitive deficits were evaluated using Morris water maze and elevated plus maze where the ICV-STZ rats produced significant memory impairment, which is also established by a marked increase in the nitrosative stress, altered acetylcholinesterase in the brain and increased tumor necrosis factor-alpha (TNF-α) levels. Chronic treatment of SLNs loaded with SM produced a dose-dependent improvement of cognitive function in ICV-STZ rats. SM has reduced the nitrosative stress, cytokine release. Administration of SM and S-SLNs at a dose at 8 and 16 mg/kg can be attributed to the significant drop in TNF-α levels in ICV-STZ group. S-SLN at 16 mg/kg was observed to be more efficacious as compared to direct SM administration, producing effects almost like that of rivastigmine (RIV). S-SLN is an effective therapeutic strategy for cognitive dysfunction.26

**In epilepsy**

The potential of SM as an anticonvulsant is evaluated against the pentylenetetrazol-induced seizures, cognitive impairment and oxidative stress. The doses of SM 10, 20 and 30 mg/kg (i.p) were used in the study and of all the doses 30 mg/kg notably delayed the development of kindling and protected against the seizure-induced cognitive impairment and oxidative stress. The antioxidant and anti-seizure activity of SM may partly be involved in SM’s effect against cognitive impairment. SM down-regulates the apoptotic markers, reduces mitochondrial dysfunction and lipid peroxidation and exerts high NO and superoxide scavenging activity; kindled seizures lead to the damage of parts of the brain responsible for the
memory. In addition, it can also lead to increased glutamnergic transmission leading to excitotoxicity. Hence, it is possible that SM may reduce such elevated neurotransmission and along with antioxidant effect prevents memory decline.\textsuperscript{27}

**In stress-induced anxiety**

Kumar \textit{et al.} investigated the protective action of SM, buspirone (BUS) and their combination of behavioral alterations and oxidative damage induced by immobilization stress. SM (5 and 10 mg/kg) and BUS (5 and 10 mg/kg) were used for the study. Pretreatment with SM and BUS for 5 days markedly reduced the bw loss and enhanced the locomotor activity. The SM and BUS were co-administered resulted in a further significant reduction in the bw loss and enhanced the locomotor activity in comparison with disease control group. Immobilization stress significantly impaired the antioxidant defense mechanism and oxidative stress. SM and BUS pretreatment markedly reduced behavioral and biochemical variations caused by the stress of immobilization. The antioxidant potential of SM is claimed to be the reason for the betterment bw and locomotion. The synergistic anxiolytic activity of SM and BUS suggests their therapeutic potential for anxiety caused by immobilization stress.\textsuperscript{28}

**Monoamine oxidase inhibitors**

Derivatives of SM and benzodioxane (BDO), eight of each, were synthesized and assessed as monoamine oxidase (MAO-recombinant human) A and B inhibitors. The SM and BDO derivatives are similar to phthalide derivatives structurally. SM derivatives were found to 0.164–7.29-μM IC\textsubscript{50} values for MAO-B inhibition while 13.2 to >100-μM IC\textsubscript{50} values for MAO-A inhibition.\textsuperscript{29}

**Parkinson’s disease rat model**

SM and naringenin (NAR) independently were tested for their potential of neuroprotection in Parkinson’s disease (PD). Male Wistar rats were administered with rotenone for 11 days to induce PD. Then, from the next day onward, SM (15 mg/kg p. o.) and NAR (10 mg/kg p. o.) were administered individually for a further 10 days. Both treatment groups noticeably enhanced the motor skills, bw, expression of parkin, DJ1, tyrosine hydroxylase and COOH terminus of heat shock protein 70-interacting protein (CHIP) in the striatum and substantia nigra region in comparison with a diseased group (rotenone treated only). Moreover, the reduction in caspase and ubiquitin levels by immunostaining and immunoblotting further established the active potential of SM and NAR against PD. SM and NAR had significantly enhanced morphology and survivability of neuronal cells. The effect of these biomolecules in muscles leads to muscle morphology restoration, parkin was increased and cell death was decreased. Therefore, SM and NAR act at different sites in the central nervous system (CNS) and peripheral regions. Thus, they have the potential of neuroprotection as well as neuronal restoration.\textsuperscript{30}

**In aluminum chloride-induced behavioral and biochemical alterations**

Aluminum, a highly neurotoxic metal, is responsible for the progression of Alzheimer’s disease and PD. The anti-dementia effect of SM in aluminum chloride (AlCl\textsubscript{3}) caused neurocognitive disorders specifically in the hippocampus and frontal cortex regions. Wistar rats (male) were administered AlCl\textsubscript{3} of dose strength 175 mg/kg p. o. for 60 days. Sesamol (10 and 20 mg/kg) and standard drug Rivastigmine (1mg/kg) was administered orally 45 min prior to the aluminum chloride treatment. The duration of the treatment was 60 days. Morris water maze was used to assess spatial memory. SM activity was found to be significant in preventing behavioral impairments caused by aluminum in rats. SM significantly improved the acetylcholinesterase levels may be due to the ability of SM to re-establish the acetylcholine release and protecting cholinergic neurons. Both RIV and SM treatment normalized the altered levels of nitrite, MDA levels and antioxidant enzyme such as catalase. GSH revealed the antioxidant role as well as inhibition of NO synthase activity of SM. SM reversed the elevated NO indicating its protective role in neuroinflammation. Thus, it was found to be the potent neuroprotective in action.\textsuperscript{31}

**Anticancer activity**

**Gastric cancer**

Sesamol-floating beads (S-FBs) were prepared using calcium carbonate, sodium alginate and hydroxypropyl methylcellulose and were characterized and evaluated for \textit{in vivo} in N-methyl-N-nitro-N-nitroguanidine-induced gastric cancer in male Wistar rats. Single oral dose plasma pharmacokinetic study was also performed for free SM and S-FBs. Restraining SM in floating beads significantly lowered the release (diffusion controlled) rate, increased the time required for 50\% drug release (t\textsubscript{50/\%}) 31 times and reduced its \textit{in vivo} clearance >1.5 times than free SM. The preclinical evaluation showed that S-FBs (10 mg/kg) were found to be more potent than free SM and better/equivalent to the standard drug methotrexate (2 mg/kg). Hence, prepared and recognized S-FBs were found to sustained therapeutic effect against gastric cancer.\textsuperscript{32}
**Apoptosis and steroidogenesis in Leydig tumor cells of the mouse**

The apoptotic and steroidogenic activity of SM on Leydig tumor cells of the mouse (MA-10 cells) was studied. SM was found to induce apoptosis by the caspase-activation pathway and StAR protein was expressed, which confirmed the steroidogenesis in MA-10 cells. This interpretation suggests that SM might be an excellent chemotherapeutic agent.\(^{33}\)

**Activity in human liver cancer cell line (HepG2)**

Sesamol is responsible for the induction of apoptosis in HepG2 cells (human liver cancer cell) by disturbing membrane potential and subsequent mitochondrial dysfunction possibly due to Akt (serine/threonine-specific protein kinase) and Mitogen Activated Protein Kinase (MAPK) redox signaling pathway. In addition, in a xenograft model of nude mice, SM was found to be antihepatoma. Hence, it was concluded mitochondria as the target of SM which leads to cell death in HepG2 cells. Therefore, various favorable anticancer characteristics of SM support in designing anticancer drug design.\(^{34,35}\)

**Liver protective**

**In cyclophosphamide-induced hepatotoxicity**

The protective role of sesamol against cyclophosphamide (CP) induced organ toxicity. CP at a dose of 150 mg/kg, i. p., was administered after that SM was given orally from day 2 to rats. On completion of 8 days, rats were sacrificed to investigate the oxidative stress in blood and tissue homogenate. In disease control group, only CP treated showed a high level of ROS, TNF-α, interleukin-1 (IL-1), IL-6 and COX-2 and altered liver function markers as well as organ toxicity. SM (50 mg/kg) restored the oxidative stress and reduction in inflammatory-mediated toxic effect to the normal level suggesting its antioxidant, anti-inflammatory and protective to liver potential and adjuvant in stress-related diseases as well as cancer.\(^{36}\)

**In acetaminophen-overdosed hepatic injury**

Acetaminophen (APAP) (1 g/kg) was given to Wistar rats, orally, to induce hepatic injury which is associated with the oxidative stress of mitochondria. SM (10 mg/kg) injected, i. p., immediately after APAP intoxicated administration to evaluate its prophylactic effects. APAP-treated rats showed significant enhancement in the levels of liver function markers, centrilobular necrosis and an increase in a free radical activity in the liver tissue after 24 h of administration. SM had marked protective effect in APAP-treated rats. It is said to be due to maintaining centrilobular necrosis, an increase in a free radical activity in the liver tissue and hepatic injury.\(^{37}\)

In another study, SM and N-acetylcysteine were studied to know hepatoprotective action in mice caused by APAP. SM and N-acetylcysteine in an equal amount of dose 1 mmol/kg were administered along with APAP (300 mg/kg) and after 6 h, liver function markers were found to be decreased. Both drugs helped in maintaining GSH level and reduced LPO activity in liver tissue. Hence, indicating the hepatoprotective role of SM is comparable to N-acetylcysteine.\(^{38}\)

**In acutely iron-intoxicated hepatic dysfunction**

Hsu et al. investigated the effect of sesamol on systemic oxidative stress and hepatic function in acutely iron-intoxicated mice. Sesamol reduced the levels of lipid peroxidation, hydroxyl radical, iron production and superoxide anion generation and xanthine oxidase activity in iron-intoxicated mice. Furthermore, sesamol decreased the serum levels of aspartate aminotransferase and alanine aminotransferase and ameliorated iron-intoxication-induced histological changes in the liver. In summary, sesamol might be protective improving hepatic function in iron-intoxicated mice.\(^{39}\)

**In carbon tetrachloride-induced liver injury**

Ohta et al. described the protective action of SM in liver injury caused by carbon tetrachloride (CCL\(_4\)) in rats. The SM along with methylenedioxybenzene and isosafrole was found to be protective against CCl\(_4\)-induced cholestasis.\(^{40}\)

Oral administration of Sesamol has limitations as less bioavailability, rapid elimination and gastric irritation in the forestomach. SM and silymarin were studied in comparison to solid lipid nanoparticles of SM (S-SLN), postinduction for hepatic injury caused by CCl\(_4\) in rats. S-SLN (8 mg/kg) resulted in significant hepatoprotection in comparison to SM. The hepatoprotection achieved with silymarin (25 mg/kg) was approximately like S-SLN-treated group. The postinduction hepatic injury can be treated by S-SLN; thus, these nanoparticles are said to be a promising formulation for liver ailments.\(^{41}\)

S-SLN were also investigated for the subchronic hepatic damage by CCl\(_4\); S-SLN (8 mg/kg) were found to be effective hepatoprotective in comparison to SM and silymarin (25 mg/kg). Thus, by formulating a dosage form of SM in a delivery system increases the biopharmaceutical potential and acts as potent hepatoprotective in action.\(^{42}\)

**In liver damage induced by cecal ligation and puncture**

SM was investigated for mortality and hepatic damage caused by cecal ligation and puncture (CLP) which leads to sepsis in Wistar rats. CLP procedure was performed on rats; then, they were treated with SM (10 mg/kg) by
subcutaneous route at seven-time points with a gap of 6 h. At an eightieth-time point, mortality was examined. The SM treatment delayed the mortality rate due to reduced oxidative stress. In addition, SM prevented the formation of nitrite and the activity of NO synthase in the hepatic cells. This may be the reason for its protective action in rats against sepsis.\textsuperscript{43}

**Skin-protective effect of SM**

**Skin cancer**

The apoptotic potential of SM was confirmed by \textit{in vitro} in HL 60 cells by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and DNA fragmentation studies. S-SLN formulation was developed and particle size and entrapment efficiency were found to be 127.9 nm and 88.21\%, respectively. \textit{Ex vivo} experiments on skin permeability and retention indicated the significant retention in the skin and therefore, SM may be available in the systemic circulation on topical application. The animal studies in mice showed the significant anticancer activity of S-SLN. The results from the study indicated that incorporation of SM into solid lipid nanoparticles not only increased the bioavailability of SM in the skin but enhanced the anticancer potential of it in skin cancer.\textsuperscript{44}

**Anti-melanogenic and skin-protective**

The anti-melanogenic and skin-protective action of SM was evaluated alone with other compounds. SM, as known, showed good antioxidant effects in DPPH and lipid peroxidation studies. SM also inhibited mushroom tyrosinase and cellular tyrosinase claiming its whitening effects. Therefore, SM could be used as an alternative to cosmeceutical purpose.\textsuperscript{45}

**Anti-melanogenesis activity**

SM and kojic acid, the known anti-melanogenic agent, showed a delay in melanogenesis because of inhibition of tyrosinase and the total melanin content was reduced. The human melanoma cells (SK-MEL2) were investigated by Fourier-transform infrared spectroscopy and microspectroscopy, to examine vibrational characteristic related to melanogenesis in untreated cells versus SM- and kojic acid-treated cells. SM and kojic acid were found to inhibit mushroom tyrosinase and cellular tyrosinase in SK-MEL2 cells. Hence, SM and kojic acid resulted in the same pattern but at a different degree.\textsuperscript{46}

**Anti-inflammatory potential**

**In lipopolysaccharide-induced inflammatory response**

The inflammation induced by lipopolysaccharide (LPS) was evaluated for SM potential as an inflammatory agent. The animal model using mice treated with LPS was performed to show the activity of SM. Serum parameters such as TNF-\(\alpha\), IL-1\(\beta\) and nitrite production were inhibited by SM in said \textit{in vivo} model. In leukocytes of the mouse, the NO synthase, which is induced by LPS, was inhibited as well by SM. Results revealed from the blood biochemistry, creatinine clearance analysis and histopathology studies, SM inhibited lipid peroxidation in kidney and prevent acute renal injury through inhibiting free radical mechanism. Along with it, SM showed the inhibitory action against LPS-exhibited NF-\(\kappa\)B translocation in RAW 264.7 cells. Thus, SM reduced the inflammatory response induced by LPS through inhibiting serum parameters as above and preventing NF-\(\kappa\)B pathway.\textsuperscript{47}

**Lipopolysaccharide- and lipopolysaccharide-binding protein interaction**

During the progression of sepsis, LPS binds to the LPS-binding protein; after that, LPS is moved to CD14 further to the MD2-Toll-like receptor 4 complex that eventually causes the release of different pro-inflammatory cytokines as TNF-\(\alpha\) and IL-1\(\beta\). SM blocked LPS binding with LPS-binding protein in a dose-dependent manner. The inflammatory cytokines were inhibited in LPS-treated macrophages and serum of rats (LPS treated) by SM. SM was also found to reduce the mortality due to endotoxemia.\textsuperscript{48}

**On metabolic organ**

**In acute renal injury**

The protective action of SM was accessed in ferric nitritolactetate (Fe-NTA)-treated mice which caused renal damage. A high-performance chemiluminescence analyzer examined free radical production, i.e., hydroxyl ion and superoxide levels. Xanthine oxidase levels and activities in the kidney were also monitored. Therefore, SM showed potential to protected mice in Fe-NTA causing acute renal injury through inhibiting the free radicals.\textsuperscript{49}

**In stress-mediated acute pancreatitis**

The \textit{in vitro} and \textit{in vivo} potential of Sesamol was tested in Pancreatitis model. The effect of SM was investigated in cerulein-induced apoptosis in the culture of pancreatic AR42J cell and caerulein-induced acute pancreatitis in rats model. SM inhibited lipid peroxidation, 8-hydroxydeoxyguanosine in the cell lines compared to the cells which were added only with cerulein. In the rat model, SM was found to inhibit the amylase and lipase levels, lipid peroxidation and pancreatic edema, while elevating the levels of GSH and NO. Hence, SM shows the protective activity of pancreatic acinar cells by inhibiting oxidative stress in rats.\textsuperscript{50}
**Forestomach neoplasm induction**

The dietary level of 2% of SM was analyzed in 30 rats and mice of both sexes, particularly F344/DuCrj and B6C3F1, respectively, for the duration of 104 (rats) and 96 (mice) weeks. Male rats showed higher toxicity (31%), whereas female only 10% in the form of carcinomas of squamous cells in forestomach. Whereas, papillomata were observed in both male (34%) and female (47%) rats but not observed in mice. SM treated rats and mice developed hyperplasia.51

**In diabetic neuropathy**

Neuropathy associated with diabetes was observed in hyperglycemic rats which had hyperalgesia and increased levels of nitrosative stress and inflammatory mediators alone with caspase-3. SM was administered at three different doses (2, 4 and 8 mg/kg, orally); this chronic treatment was started after the 4th week of STZ administration and continued till 4 weeks further. The treatment of SM significantly changed the parameters concerned with diabetic neuropathy. In addition, SM was administered with insulin and observed that combination was more effective than insulin alone. Hyperglycemia and pain response due to diabetes were inhibited by insulin in rats, but the combination of SM and insulin was found to be effective in diabetic condition and inhibited neuropathic pain by antioxidant activity, decreasing cytokine release and expression of caspase-3. Therefore, SM can be explored for clinical use to treat neuropathic pain associated with diabetes.52

**In diabetic nephropathy**

SM chronic dosing was done in diabetic rats (STZ treated) with three different doses (2, 4 and 8 mg/kg, orally, for 4 weeks) after 4 weeks' completion of STZ treatment. The diabetic rats develop nephropathy after 8 weeks of STZ treatment. SM was observed to be effective significantly and dose-dependent manner in preventing biochemical and molecular alterations caused due to diabetes. The combination of SM with insulin was found to be more effective in comparison to a single treatment. The results suggest that SM showed significant renal protection in diabetic rats.53

**In acute gastric mucosal injury induced by diclofenac**

The protective action of SM was investigated on gastric mucosal damage by diclofenac-tempted gastric mucosal injury in rodents. It was observed that neither diclofenac nor SM has any effect on superoxide anion. SM was observed to reduce hydroxyl radical levels and reduction in lipid peroxidation. SM did not possess any effect on mucosal production but maintained GSH levels and inhibited diclofenac-induced Cox pathway and decreased prostaglandin E2-generation. This study provides evidence for the SM’s potential in the protection of gastric mucosa without effecting Cox pathway.54

**Effect on blood**

**Antiplatelet activity**

SM was evaluated for in vitro and in vivo activities of SM in inhibiting platelet activation. Washed platelets were treated with SM at a dose of 2.5–5 μM and were observed the inhibition of platelet activation, thromboxane A(2) formation and phosphorylation of Mitogen-Activated Protein Kinase (MAPK). In an animal model of mice, SM was investigated at a dose of 5 mg/kg and that resulted in significant prolongation of platelet plug formation. Hence, SM can be said to have antiplatelet activity at such a low dose and SM can be a newer approach for improving the functionality of thromboembolism condition.55

**Apoptosis induction in platelets of human**

Chang et al., 2010, had described the inhibitory effects of sesamol on aggregation of platelet at doses below 100 μM. Therefore, another experiment was carried out by Thushara et al. in the year 2013 that had discovered the toxicity of SM on platelets of a human. Platelet apoptosis was observed on treatment with SM at the dose of 0.25 mM. SM at higher concentration was found to be proapoptotic as it caused depolarization of mitochondrial membrane and increased expression of caspase. Consequently, this study warrants the importance of appropriate dose when sesamol is used as the therapeutic agent.56

**Ex vivo effect on hemolysis**

Hou et al. studied the metabolic profile of SM after intravenous and oral administration in rats. It was concluded that sesameol is immediately converted into its sulfate and glucuronide conjugates in either intravenous or oral administration. Ex vivo experimentation suggested that SM showed the potential against 2,2'-azo-bis(2-amidinopropane) dihydrochloride causing hemolysis.57

**Effect on the fibrinolytic system**

In atherosclerosis disease, the plasminogen activator (PA) and its adjustment factor, PA inhibitor-1 (PAI-1), plays an important role. The in vitro study was undertaken to demonstrate the efficacy of SM on PA and PAI-1, and comparison was made with potent antioxidants such as Vitamins C and E; the study was performed on human umbilical vein endothelial cells. SM and Vitamin C and E were dosed at a dose level of 100 μmol/L. Culture medium alone with cells was collected after 24 h for the analysis. Enzymatic immunity method was used to
determine the levels of PA and PAI-1. The PA levels were found to be increased significantly and the regulation of mRNA expression was also increased; these conclusions were made by the northern blot analysis. While Vitamins C and E could partially increase the levels of PA, sesamol and Vitamins C and E did not affect the expression of PAI-1. Therefore, in conclusion, SM may increase the vascular fibrinolytic potential to regulate PA gene expression.38

Miscellaneous

Chondroprotective activity

Osteoarthritis (OA) characterized by cartilage destruction is governed by matrix metalloproteinases (MMPs) over-expression. SM was found to significantly diminish TNF-α and expression of MMP-9 in chondrosarcoma cell lines (SW1353 cells) in a dose-dependent fashion. In *in vitro* studies, joint cartilage of rats was subjected to estimate MMP expression after treatment with monosodium iodoacetate to induce OA, which was found to regulate MMP-1 and MMP-9 expressions down. Therefore, SM resulted in inhibition of cytokine or MMPs by NF-κB or ERK/p38 MAP kinases suppression. Hence, SM can be used as an adjuvant for chondroprotection.39

In adjuvant-induced arthritis disease

SM protects in inflammation and oxidative stress induced during arthritis (AR). The protective action was evaluated by cytokine (pro-inflammatory) levels and markers of oxidative stress. Wistar rats were administered Freund’s complete adjuvant (FCA), subcutaneous (100 IL) to induce AR. SM at doses, 25 and 50 mg/kg, resulted in the lessening of AR which developed degradation of cartilage by diminishing increased blood concentration of MMPs 13, 3 and 9 and hyaluronidase. SM reduced the bone resorption markers and inflammatory mediators. Furthermore, SM counterbalances oxidative stress caused by AR. The antioxidant potential of SM is the reason for a counterbalance of stress by ROS. Therefore, SM could be an active molecule in AR and AR associated with cardiovascular disorders and diabetes complications.40

Effect on melanin synthesis

Synthesis of melanin takes place in melanocytes and the rate-limiting step involved an enzyme, mushroom tyrosinase. This tyrosinase has activities such as monophenolase and diphenolase, which was considered as a model in the inhibition of melanin synthesis. The activities such as monophenolase and diphenolase were inhibited by SM with IC₅₀ of 1.9 μM and 3.2 μM, respectively. SM was found to inhibit melanin synthesis in B16F10 (mouse melanoma cells) in a dose-dependent fashion. Furthermore, SM (100 μg/mL) resulted in a 63% decrease in some cells. Thus, SM can be developed as an anti-browning agent.51

Fluorescent derivative for fluorometric assay

The estimation of NO *in vitro*, particularly in cells and tissues, is found to be very tedious, as NO reacts very fast with other molecules. The measurement of NO radical in case of pharmaceutical becomes a matter of concern and very important for their potential to be potent. Thus, Abe et al. developed an assay for NO estimation by fluorometry using SM as a substrate. SM dimerizes to form fluorescent derivative in the NO presence. The NO levels can be measured to 400 fmol by this method and pharmaceuticals, generating NO, can be analyzed by this developed assay.62

In the pathophysiological changes induced by surgical menopause

The widely used ovariectomized rat menopausal model was in this study. Kaur et al. studied SM’s activity in the oxidative stress-induced alterations in the main organ systems such as the cardiovascular system, skeletal system and CNS. SM doses (2, 4 and 8 mg/kg p. o.) were administered to the animals for 7 weeks. Sesamol attenuated brain oxidative stress, TNF-α, serum lipid levels in dose dependent manner as compared to ovariectomised control rats leads to the improvement of the memory. In the case of a skeletal system, it was found that animals treated with sesamol showed an increase in bone ash content and mechanical stress. This is evident of sesamol’s activity in pathologies of menopause.63

SM as an antiaging agent

SM was evaluated against UV-induced oxidative stress in lacca strain mouse skin. The UV lamp (300 W) was used as a radiation source. Wrinkles are produced due to cross-linking of collagen and elastin which is further lead by free radicals. Thus, SM which is potent antioxidant resulted in attenuating injuries by radiation because of chronic exposure of UV radiation. Histopathology and biochemical experiments made the confirmation to above. Therefore, SM can be considered as an effective antiaging molecule.64

Suppression of cyclooxygenase-2 promoter-dependent transcriptional activities

Sesamol blocked COX2 gene transcriptional activity in human colon cancer cells. In addition, sesamol significantly blocked NADPH oxidase 1 (NOX1) mRNA levels in a dose-dependent manner. It is proven that knockdown of NOX1 successfully blocks COX2 transcriptional activity, thus inhibiting the NADPH
oxidase, specifically NOX1, which may be involved in the suppression of COX2 transcriptional activity by sesamol. Therefore, sesamol downregulating the NOX1 could be another approach against β-catenin signaling-dependent cancers. NOX1 mRNA was significantly suppressed by sesamol. Thus, we next shifted the focus on the role of NOX1. NOX1-specific siRNAs effectively inhibited COX-2 transcriptional activity. These data demonstrate the pivotal role of NOX1 in the control of COX-2 transcription. Results from the studies clearly indicate that, sesamol inhibits the COX-2 transcriptional activity.65

**Anticandidal potential**

Ansari et al. investigated the antifungal effects of SM in *Candida albicans*, a human fungal pathogen. Results from the studies reveal that the antifungal effect of SM neither affects the MDR efflux transporter activity nor the passive diffusion of the drug. In mechanistic studies, it was revealed that *C. albicans* treated with SM copies the phenotype displayed by cells having a defect in calcineurin signaling and therefore, the anticandidal potential of SM may be due to the disruption of calcineurin signaling pathway. Furthermore, the ergosterol levels were significantly decreased by 63% confirming membrane disruption in the presence of SM. Therefore, SM can be considered as an effective antifungal agent and used in the treatment of *Candida* infections.66

**Derivatives of sesamol and its therapeutic potentials**

Synthetic derivatives of sesamol have been evaluated for its potential in atherosclerosis (rabbit model), insect chemosterilant, insecticidal, insect control and so on. The derivatives synthesized showed effective and patentable results [Table 1]. The structure and name of derivatives are quoted in Table 1.

**CONCLUSION**

Sesamol has been investigated for many indications and proven to be active in most studies. The pharmacokinetic profile showed it to be a good candidate for the oral formulation. On the other hand, it is a potent antioxidant, thus, indicated in diabetic complications, liver diseases, radiation protective, neuroprotective, to some extent anticancer and many more. These activities make this molecule a unique candidate to write a review and provide the useful information to researchers. This review will open new doors for this molecule to be explored further in the form of formulation and clinical trials studies.

<table>
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<tr>
<th>Sr. No.</th>
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<tr>
<td>1</td>
<td>3,4-methylenedioxy-6-nitro phenyl acetate</td>
<td><img src="image1" alt="Structure" /></td>
<td>Rabbit Model of Atherosclerosis</td>
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<td>sesamol, 3-aminopropane phosphoric acid diester</td>
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<td>3</td>
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<td><img src="image3" alt="Structure" /></td>
<td>Insect Chemosterilants</td>
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<td></td>
<td>B. 2-Alkoxy-4,5-methylenedioxy- cinnamylbenzenes</td>
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<td>Polyethylene Oxide Sesamol Derivatives</td>
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<td>Novel inhibitors of arachidonic acid formation</td>
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<td>B. 5-(3-Chlorobenzyloxy)benzo[1,3]dioxole</td>
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<td>C. 5-(3-Bromobenzyloxy)benzo[1,3]dioxole</td>
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<td>D. 5-Phenethylbenzox-benzo[1,3]dioxole</td>
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<td>E. 5-(3-Phenylpropoxy)benzo[1,3]dioxole</td>
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<td>G. 5-(2-(4-Chlorophenoxy)ethoxy)benzo[1,3]dioxole</td>
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<td>H. 5-(2-(4-Bromophenoxy)ethoxy)benzo[1,3]dioxole</td>
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<td>6</td>
<td>A. 6-Chloro(Chrysanthemumates)</td>
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<td>B. 6-bromochrysanthemumates</td>
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**CONFLICT OF INTEREST**

The authors declare no conflicts of interest.

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SUMMARY

• Sesamol, a molecule derived from the Sesame seeds, has been explored widely in the scientific community for the treatment of various diseases and disorders.

• In this review, we have explored a compressive review on different in vitro and in vivo pharmacological activities with various mechanistic pathways.

• This review provides a brief outline on sesamol for its possible clinical utility and development of formulation.