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SESAMOL & ITS DERIVATIVES: A COMPREHENSIVE REVIEW ON PHYTOCHEMISTRY, PHARMACOLOGY, AND ADVANCED FORMULATION STRATEGIES FOR ENHANCED BIOLOGICAL ACTIVITIES

Puneet Sudan[1*], Sachin Kumar Sharma[2], Anju Goyal[3], Ramica Sharma[4], Gauri[5], Sukhbir Singh Tamber[6]

[1]Associate Professor, University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali, Punjab, India
Email ID: puneetsudan22@gmail.com Orcid- 0000-0002-5110-2512
[2]Research Scholar & Assistant Professor, University School of Pharmaceutical Sciences, Rayat Bahra University- Kharar (Mohali), Punjab,
Email ID: sachin.19568@rayatbahrauniversity.edu.in
[3]Professor, University School of Pharmaceutical Sciences, Rayat Bahra University- Kharar (Mohali), Punjab
Email ID: anju_goyal2003@rediffmail.com
[4]Associate Professor, University School of Pharmaceutical Sciences, Rayat Bahra University- Kharar (Mohali) Punjab
Email ID: ramica.17740@rayatbahrauniversity.edu.in
[5]Assistant Professor, University School of Pharmaceutical Sciences, Rayat Bahra University- Kharar (Mohali) Punjab
Email ID: gauri.17697@rayatbahrauniversity.edu.in
[6]Assistant Professor, University School of Pharmaceutical Sciences, Rayat Bahra University- Kharar (Mohali) Punjab
Email ID: sukhbir.19391@rayatbahrauniversity.edu.in
*Corresponding Author: Puneet Sudan, Email ID: puneetsudan22@gmail.com

ABSTRACT
Sesame-derived phytoconstituents have long been recognized as valuable bioactive agents in both nutritional and therapeutic applications. Among these, sesamol—one of the principal phenolic lignans present in sesame oil—has garnered significant scientific interest due to its broad-spectrum pharmacological potential. Empirical evidence from preclinical and clinical studies underscores sesamol's efficacy in the prevention and management of multiple pathological conditions, including oncological, hepatic, cardiovascular, and neurodegenerative disorders. The compound exhibits a diverse pharmacodynamic profile encompassing antioxidant, anti-inflammatory, anticancer, and antimicrobial properties, which contribute to its therapeutic relevance. However, the clinical translation of sesamol remains constrained due to inherent limitations such as poor aqueous solubility, chemical instability, low oral bioavailability, and rapid systemic elimination. To address these biopharmaceutical challenges, various advanced drug delivery strategies have been developed, including nano formulations, lipid-based carriers, and polymeric systems, aimed at enhancing its pharmacokinetic and therapeutic profiles. This comprehensive review delineates the recent advances in the pharmacological characterization of sesamol, with a particular focus on its mechanism of action across different disease models. Additionally, the manuscript explores the formulation-based interventions designed to overcome the physicochemical limitations of sesamol, thereby proposing novel carrier systems as viable platforms to augment its clinical efficacy. The insights provided herein aim to facilitate the rational design of sesamol-based therapeutics for potential use as frontline interventions in chronic and degenerative diseases.

INTRODUCTION
A substantial body of scientific literature has demonstrated the pivotal role of bioactive compounds in advancing human health and well-being. These naturally occurring molecules, recognized for their potent nutraceutical attributes, exhibit significant potential for integration into both food and pharmaceutical formulations. Owing to their ability to modulate diverse molecular targets, bioactives have historically contributed to the prevention and management of a wide spectrum of chronic and life-threatening diseases. Their global acceptance and multifaceted therapeutic efficacy underscore their relevance in contemporary biomedical and nutraceutical research [1]. Sesamol (3, 4-methylenedioxyphenol), a naturally occurring phenolic derivative, is a prominent antioxidant constituent isolated from sesame oil, which is derived from the lignans present in the seeds of *Sesamum* species. [2]. Sesame (*Sesamum indicum* L.) is a widely cultivated oilseed crop, predominantly grown in tropical and subtropical regions, with major production centers in countries such as Myanmar, India, China, and Sudan. [3]. Sesame seeds are widely incorporated into various culinary applications globally, commonly used as toppings on bread, biscuits, and crackers, as well as a flavor-enhancing seasoning in diverse traditional and modern food preparations [4]. Sesame seeds serve as a valuable nutritional resource, offering a rich composition of oil, high-quality protein, carbohydrates, and essential minerals, thereby contributing significantly to human dietary requirements [5]. Sesame (*Sesamum indicum* L.) has emerged as a promising nutraceutical resource, primarily due to its rich antioxidant profile, which contributes significantly to the management and prevention of various pathological conditions. It contains a diverse array of bioactive lignans, including sesamin, sesamolin, sesaminol, and sesamol. Among these, sesamol (SES) is recognized as the most potent and pharmacologically active constituent, with its therapeutic potential largely attributed to its robust free radical-scavenging and antioxidative capabilities [6]. Sesamol, a lipophilic lignan derived from sesame

seeds, is chemically identified by several synonyms, including 1, 3-benzodioxol-5-ol, 3, 4-methylenedioxyphenol, 3,4-(methylenedioxy) phenol, oxyhydroquinone methylene ether, and 5-hydroxy-1,3-benzodioxole. These nomenclatures reflect its structural features as a methylenedioxy-substituted phenolic compound [7]. Sesamol can also be synthesized via organic synthesis pathways, with heliotropin (piperonal) serving as a key precursor. The broad-spectrum pharmacological efficacy of this bioactive compound is primarily attributed to its ability to modulate a diverse array of cellular signaling pathways and molecular targets. These include nuclear factor kappa B (NF-κB) activator protein-1 (AP-1), permeability glycoprotein (P-gp), multidrug resistance-associated proteins (MRP-1 and MRP-2), glutathione-dependent mechanisms, protein kinase C, ATPase activity, receptor tyrosine-protein kinase ErbB-2, alpha-1-acid glycoprotein (AGP), cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), and cyclin D1. Through the regulation of these critical pathways, the compound exerts its therapeutic effects across various disease models [8]. Previous studies have highlighted that the therapeutic efficacy, safety, and pharmaceutical applicability of sesamol are significantly constrained by its inherent limitations, including poor aqueous solubility, low bioavailability, rapid systemic clearance, and chemical instability. In light of these challenges, recent research efforts have been increasingly directed toward developing innovative strategies to overcome the limitations associated with conventional sesamol delivery systems [9]. To address the aforementioned limitations, the development of novel drug delivery systems has emerged as a promising approach to enhance the pharmacokinetic and therapeutic profile of sesamol. Advanced formulation strategies facilitate the passive absorption of phenolic compounds and antioxidants across the intestinal epithelium into systemic and lymphatic circulation, thereby significantly improving their bioavailability [10]. In this context, a wide range of innovative carrier platforms—such as polymeric nanoparticles, lipid-based vesicles, solid lipid nanoparticles, nanoemulsions, inclusion complexes, and nanosponges—are being actively explored. These advanced delivery systems hold the potential to overcome the physicochemical and biopharmaceutical barriers associated with sesamol and other sesame-derived bioactives. Consequently, formulation of sesame-based bioactives using state-of-the-art technologies has demonstrated enhanced therapeutic efficacy in the management of various pathological conditions [11]. In light of the aforementioned findings, this review aims to comprehensively explore the critical attributes and advancements related to sesamol (SES)-loaded novel drug delivery systems. Additionally, it provides an in-depth overview of the pharmacological background of sesamol, including its mechanisms of action and therapeutic potential across a broad spectrum of disease conditions. The article is structured into three main sections: the first outlines the molecular mechanisms by which sesamol exerts its effects in various pathological states; the second highlights its diverse therapeutic applications; and the final section focuses on the design, development, and applicability of advanced delivery platforms intended to overcome sesamol's inherent biopharmaceutical limitations. Furthermore, this review discusses the multifunctional bioactivities of sesamol and elaborates on emerging strategies to enhance its bioavailability, including nanotechnology-based systems and molecular complexation approaches.

MECHANISTIC INSIGHTS INTO THE MODE OF ACTION

In recent years, experimental research focusing on oxidative stress has witnessed substantial growth, primarily due to the pivotal role of antioxidant defense mechanisms in the pathogenesis and progression of various disorders, including cancer, neurodegenerative and cardiovascular diseases, atherosclerosis, aging, and other oxidative stress-related conditions [12]. The excessive generation of reactive oxygen species (ROS) imposes a significant oxidative burden that surpasses the body's endogenous antioxidant defenses. This overproduction, particularly of superoxide anions (O_2^-), a byproduct of cellular metabolism, and peroxyl radicals (RO_2^-), primarily generated during lipid peroxidation, results in oxidative damage to essential biomolecules such as proteins, lipids, and DNA. Such molecular damage is closely associated with the onset and progression of several pathological conditions, including cancer, neurodegenerative, and cardiovascular diseases [13]. In this context, the potent antioxidant properties of sesamol (SES) have garnered considerable scientific interest. Numerous studies have demonstrated that SES effectively inhibits radical-mediated reactions and neutralizes various reactive oxygen species. Its antioxidant activity is predominantly attributed to redox-based mechanisms, involving the donation of a hydrogen atom or an electron to stabilize free radicals [14]. This bioactive compound has demonstrated significant efficacy in inhibiting hydroxyl radical-induced DNA strand cleavage and deoxyribose degradation [15]. Furthermore, this bioactive compound exhibits a broad spectrum of biological activities, including potent inhibition of lipid peroxidation and enhanced free radical scavenging capacity. It contributes to the upregulation of endogenous antioxidant enzymes and down regulation of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). Additionally, it suppresses the activation of nuclear factor-kappa B (NF-κB) and modulates key signaling pathways such as extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK). The compound also inhibits the activities of 5-lipoxygenase (5-LOX) and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1). Notably, it attenuates phorbol 12-myristate 13-acetate (PMA)-induced expression of matrix metalloproteinases MMP-1 and MMP-13, promotes apoptosis in tumor cells, induces cell cycle arrest at various phases, and modulates the expression of key regulatory proteins including p53, caspase-3, Bcl-2, and Bax. Moreover, it significantly reduces the levels of myeloperoxidase (MPO) and nitrite, further affirming its anti-inflammatory and antioxidative potential [15-16]. Collectively, the multifaceted modulatory effects of sesamol on diverse molecular pathways (as illustrated in Figure 1) underscore its potential as a promising therapeutic candidate for the management of various pathological conditions.

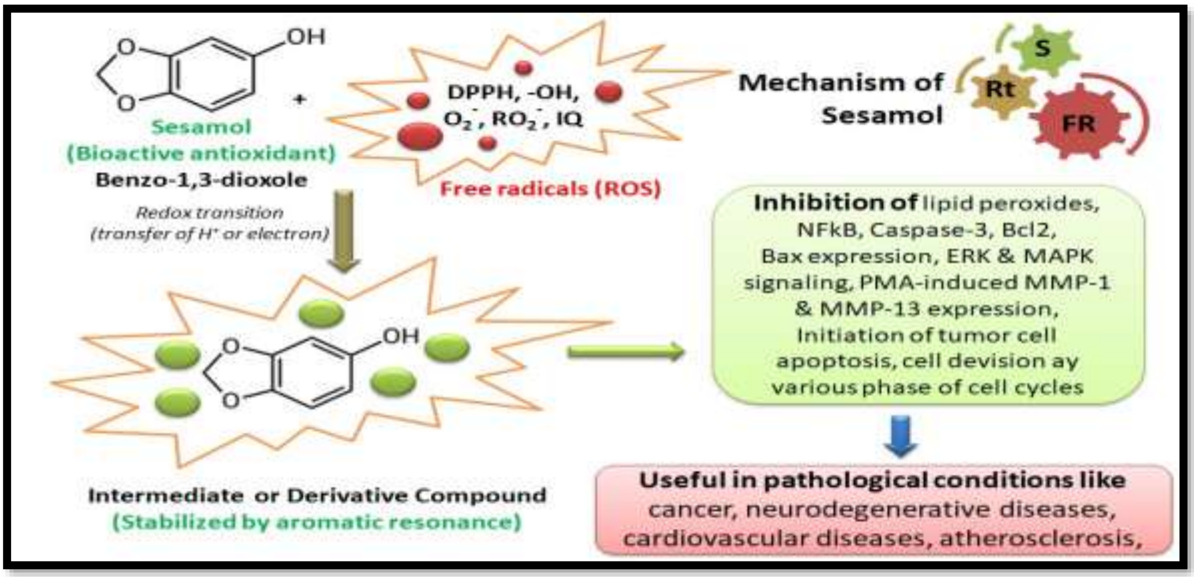


Figure: 1 Mechanistic Overview of Sesamol's Bioactivity: Antioxidant Enhancement, Anti-inflammatory Action, and Apoptotic Regulation through Key Molecular Targets

Sesamol occurrence and extraction procedure

Plants serve as prolific reservoirs of novel bioactive compounds and represent a valuable source for the development of therapeutic agents against a wide array of diseases. Sesamol is a naturally occurring phenolic compound present in sesame (Sesamum indicum L.) seeds and their oil. It is primarily formed and extracted from roasted sesame seeds as a degradation product of sesamolin [18]. Sesame seeds are widely utilized as nutritional ingredients in various culinary applications and are recognized for their distinctive flavor, crunchy texture, and health-promoting properties. Sesame (Sesamum indicum L.) seeds and their cold-pressed oil are particularly rich in bioactive phytochemicals, notably sesame lignans such as sesamin, sesamolin, sesamol, and pinoresinol—classified as methylene dioxyphenyl derivatives [19]. These lignans have been extensively reported to contribute significantly to the health-promoting properties of sesame. Among them, sesamol is present only in trace amounts in raw seeds but is formed through the thermal degradation of sesamolin during the roasting process. The process of sesamol formation and extraction of associated bioactives from sesame seeds is depicted in Figure 2. Sesamol exhibits a broad spectrum of biological activities, including modulation of fatty acid metabolism, inhibition of cholesterol absorption and biosynthesis, potent antioxidant effects with vitamin E-sparing properties, hypotensive activity, hepatoprotective effects against alcohol-induced damage, anti-aging properties, induction of cell cycle arrest and apoptosis in cancer and cardiovascular cells, and enhancement of vascular fibrinolytic activity. Moreover, sesamol is considered cost-effective relative to other natural antioxidants and is well-recognized for its strong antioxidant potential and diverse therapeutic benefits. [20].

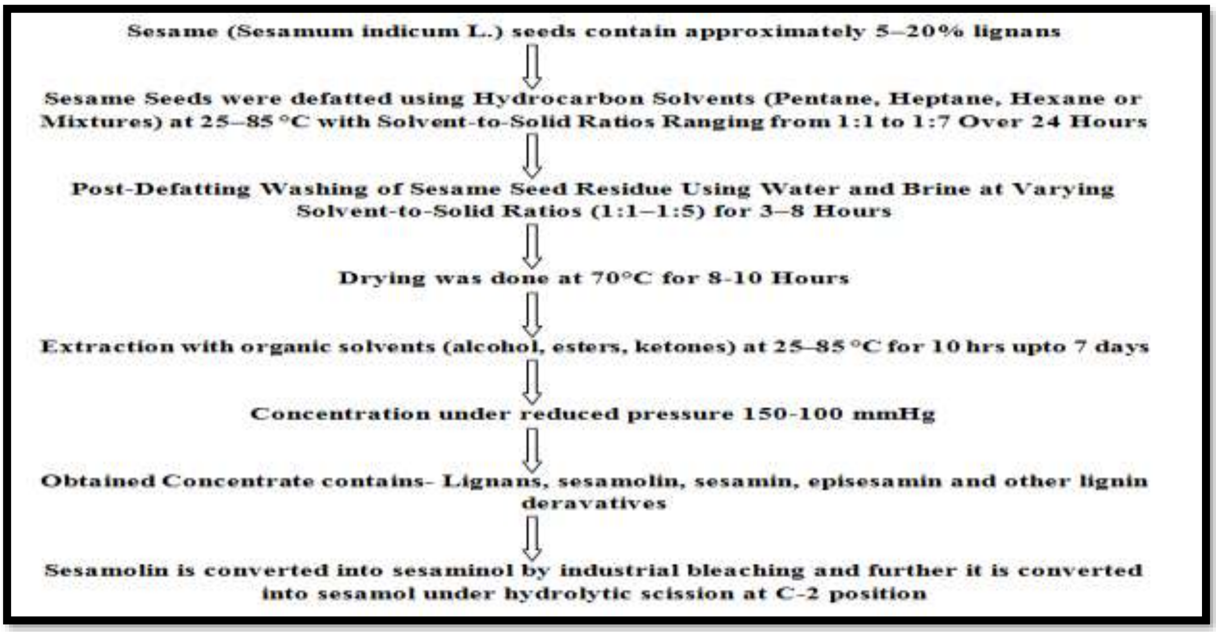


Figure: 2 Extraction of sesamol and other bioactives from sesame seed

Pharmacology of sesamol

Sesame seeds and their oil have long been recognized for their diverse health-promoting properties. These therapeutic effects are largely attributed to the bioactive constituents present in sesame, particularly sesamol. Owing to its multifaceted biological activities, sesamol holds significant potential in the prevention and management of various pathological conditions, as outlined below

- Anti-cancer
- Antifungal
- Anti-inflammatory
- Anti-ageing
- Anti-ulcer
- Anti-oxidant
- Antiadipogenic
- Anti-melanogenesis
- Cardioprotective
- Neuroprotective
- Hepatoprotective
- Wound-healing

Anticancer activity

Cancer remains one of the leading life-threatening disorders affecting the human population. Although chemotherapy is a commonly employed treatment strategy, it is often associated with severe and intolerable side effects. In contrast, plant-derived compounds are generally considered safer, more cost-effective, less toxic, and environmentally friendly alternatives to conventional therapies [21]. A substantial body of evidence indicates that diets rich in fruits and vegetables are correlated with a reduced risk of cancer, largely due to their abundance of polyphenolic compounds with potent anticancer properties. These polyphenols exert their effects through multiple mechanisms, including induction of cell cycle arrest and apoptosis, inhibition of growth factor receptor (GFR)-mediated signaling, suppression of protein kinase activity, and down regulation of NF-κB activation [22]. Sesamol has been extensively reported to possess significant anticancer potential. Numerous studies have highlighted its efficacy in the prevention and treatment of various types of carcinomas, suggesting its promising role as a therapeutic agent in oncology. [23].

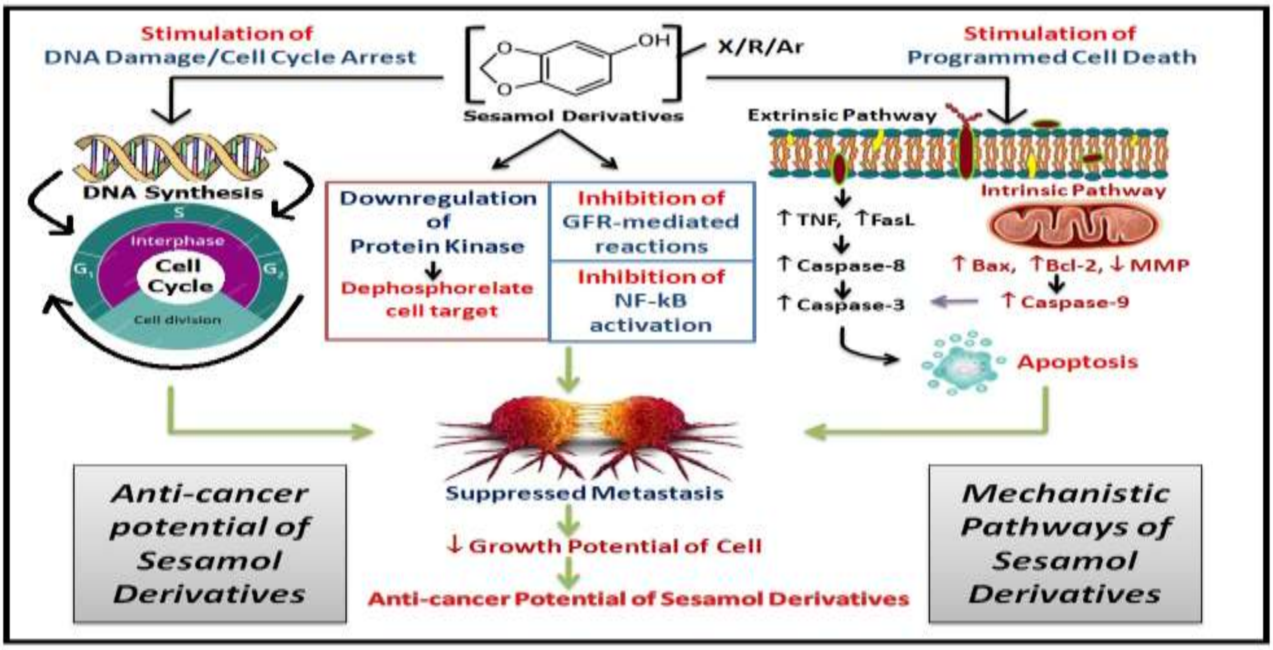


Figure: 3 Anti-cancer activity of sesamol derivatives through multiple mechanistic pathways

The antineoplastic efficacy of sesamol has been rigorously evaluated in human hepatocellular carcinoma (HepG2) cell models. Experimental findings revealed that sesamol administration markedly suppressed clonogenic potential and induced S phase cell cycle arrest, indicating a disruption of DNA synthesis and cell proliferation. Furthermore, sesamol activated both the intrinsic (mitochondria-mediated) and extrinsic (death receptor-mediated) apoptotic cascades in a concentration-dependent manner. Mitochondrial dysfunction was evident through depolarization of the mitochondrial membrane potential, accompanied by excessive intracellular accumulation of hydrogen peroxide (H_2O_2), which subsequently perturbed redox-sensitive signaling networks. Notably, sesamol attenuated the phosphorylation and activity of key oncogenic mediators such as protein kinase B (Akt) and mitogen-activated protein kinases (MAPKs). In parallel, a significant down regulation of mitochondrial biogenesis was observed, as indicated by reduced expression of mitochondrial complex I subunit NADH dehydrogenase 1 (ND1) and its upstream regulatory axis, including AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma co activator 1-alpha (PGC-1α). Importantly, sesamol also impaired mitophagy and macroautophagy processes by inhibiting the phosphoinositide 3-kinase (PI3K) class III/Beclin-1 signaling pathway. These multifaceted molecular perturbations underscore sesamol's robust anti-hepatocarcinogenic potential, further validated in vivo using a HepG2 xenograft model in immunodeficient (nude) mice [24].

The anti-gastric carcinogenic efficacy of sesamol has been further substantiated through the development and in vivo evaluation of a novel gastro retentive drug delivery system. Sesamol-loaded floating beads (S-FBs) were fabricated employing ionotropic gelation using calcium carbonate as a gas-generating agent, in combination with sodium alginate and hydroxypropyl methylcellulose (HPMC) as polymeric matrices. These beads were systematically characterized for their physicochemical properties, floating behavior, and drug release kinetics. The in vivo pharmacodynamic performance of S-FBs was assessed in a rat model of gastric carcinoma induced by N-methyl-N-nitro-N-nitrosoguanidine (MNNG). Pharmacokinetic analysis following a single oral administration revealed that S-FBs significantly modified sesamol's release profile, exhibiting a sustained, diffusion-controlled release pattern, a 31-fold increase in the time required for 50% drug release (t_{50}%), and a marked reduction in systemic clearance by over 1.5-fold, compared to free sesamol. Notably, the S-FBs demonstrated comparable or superior chemotherapeutic efficacy to methotrexate in preclinical evaluation, highlighting their potential as a targeted, gastro retentive delivery system for effective management of gastric malignancies [25].

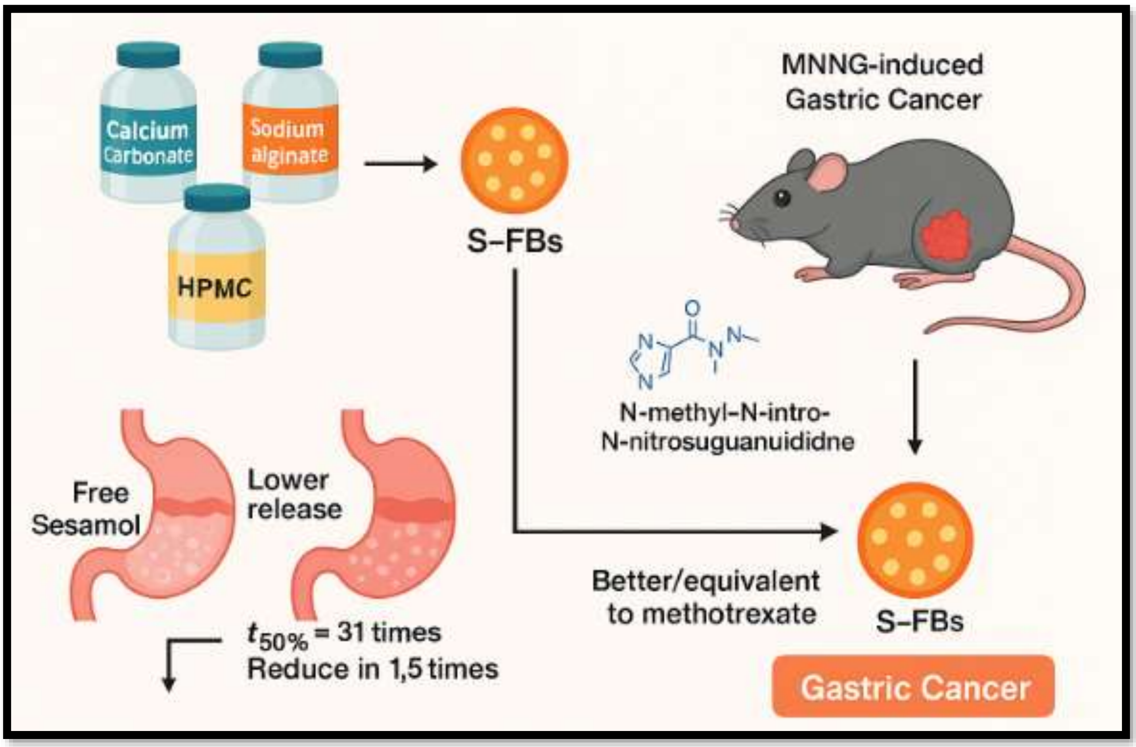


Figure: 4 Sesamol floating beads (S-FBs) in gastric carcinoma

Previous investigations have elucidated the anticancer efficacy of sesamol, particularly its pro-apoptotic mechanisms in SK-LU-1 human lung adenocarcinoma cells. The apoptotic effects were evidenced by both biochemical alterations, such as caspase-3/7 activation, and morphological changes, including the formation of apoptotic bodies. Sesamol treatment resulted in significant induction of cell death in a dose-dependent manner. Mechanistic analysis revealed elevated activities of caspase-8 and caspase-9, indicating that sesamol triggers apoptosis through both the extrinsic (death receptor-mediated) and intrinsic (mitochondria-mediated) pathways. A schematic representation of these findings is provided below to illustrate the dual-pathway activation induced by sesamol in SK-LU-1 cells [26].

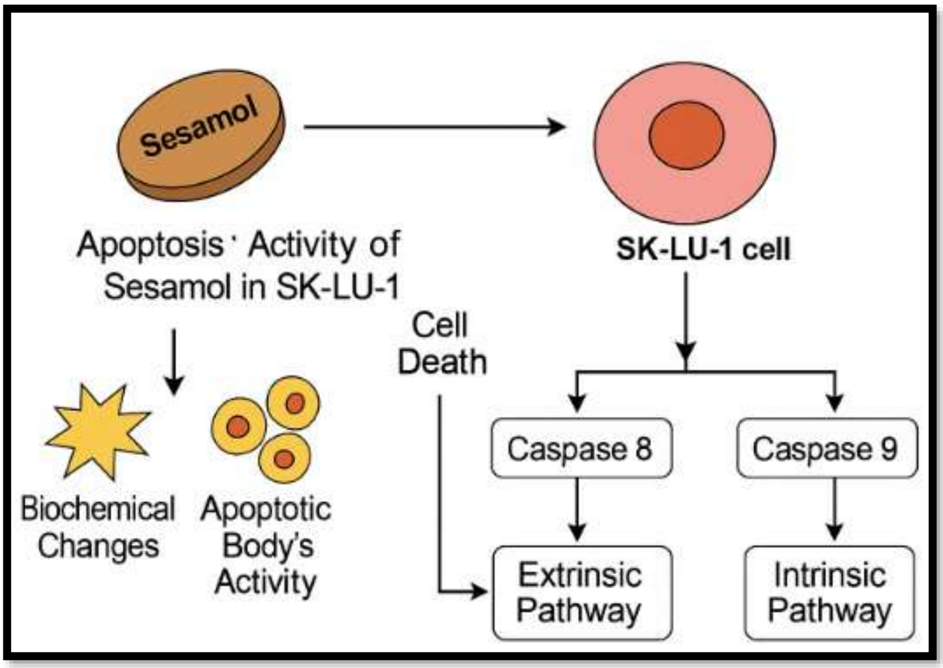


Figure: 5 Dual-pathway activation induced by sesamol in SK-LU-1 cells in lung carcinoma

Sesamol, owing to its potent antioxidant properties, has demonstrated promising potential in the management of skin cancers. In vitro studies using HL-60 human promyelocytic leukemia cells confirmed the antiproliferative and pro-apoptotic effects of sesamol, as evidenced by MTT assay and DNA fragmentation analysis. For topical delivery, sesamol-loaded solid lipid nanoparticles (S-SLNs) were formulated in a cream base. The formulation exhibited enhanced dermal retention with minimal transdermal flux, as demonstrated by in vivo skin retention and ex vivo skin permeation studies. Furthermore, in vivo anticancer evaluations revealed histological normalization of skin architecture following carcinogen-induced skin cancer, confirming the therapeutic efficacy of the S-SLN formulation in cutaneous malignancies [27].

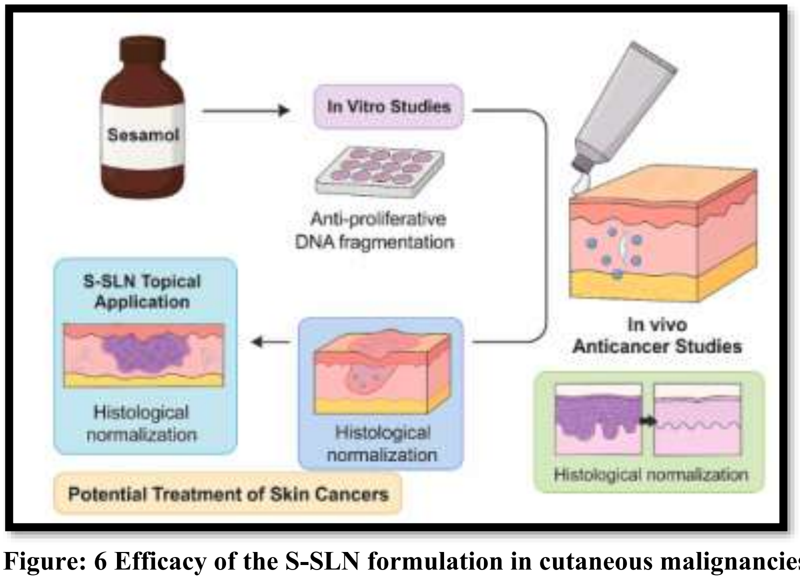


Figure: 6 Efficacy of the S-SLN formulation in cutaneous malignancies

From previous research, the estrogenic activity of sesame lignans and their metabolites was evaluated using an estrogen-responsive element (ERE)-driven luciferase reporter assay in T47D-KBluc cells, a T47D breast cancer cell line stably transfected with the ERE-luciferase construct. Additionally, the expression levels of estrogen-responsive genes, *pS2* and *progesterone receptor* (PR), were quantified in the T47D cell line to further validate the estrogenic potential. Co-incubation of sesamol (1–100 μM) with 1 nM 17β-estradiol (E2) demonstrated a concentration-dependent inhibitory effect on E2-mediated responses. Among the tested compounds, sesamin, sesamol, and enterolactone (EL) significantly upregulated *pS2* gene expression; however, only sesamol elicited a statistically significant induction of *progesterone receptor* gene expression [28]. Previous studies have investigated the chemosensitizing potential of sesamol in cervical cancer cells, demonstrating its ability to enhance the cytotoxic efficacy of paclitaxel. The combinatorial treatment resulted in increased reactive oxygen species (ROS) generation, augmented DNA damage, and a significant reduction in cell proliferation, thereby improving the overall therapeutic impact of paclitaxel [29].

Antifungal activity

Sesamol has demonstrated potent antifungal activity against *Candida albicans*, primarily through the disruption of membrane integrity via a calcineurin-independent pathway. It significantly impairs morphogenetic switching from yeast to hyphal form, suppresses biofilm architecture and adhesion capabilities, and perturbs cellular iron homeostasis and mitochondrial bioenergetics. Furthermore, sesamol interferes with the deoxyribonucleic acid (DNA) repair machinery, thereby compromising genomic stability, although it does not exert measurable modulation of cell cycle progression. In 2016, a detailed mechanistic study by the same research group elucidated the antifungal mode of action of sesamol against *Candida albicans*. The compound was found to significantly impair critical virulence determinants, including hyphal morphogenesis, biofilm development, and epithelial cell adhesion. Disruption of iron homeostasis was evidenced by ferroxidase activity assays, which revealed diminished intracellular iron levels, enhanced susceptibility under iron-limited conditions, and marked transcriptional upregulation of the high-affinity iron permease gene *FTR2*. Furthermore, sesamol induced mitochondrial dysfunction, likely through impairment of oxidative phosphorylation, and promoted genotoxic stress, as indicated by altered DNA integrity. These findings suggest that sesamol exerts multifaceted antifungal effects by targeting virulence regulation, iron metabolism, mitochondrial homeostasis, and genome stability. [30].

Anti-inflammatory activity

Recent investigations have demonstrated the potential of sesamol in attenuating lipopolysaccharide (LPS)-induced lung inflammation and injury. In this study, murine macrophage RAW 264.7 cells were pre-treated with sesamol prior to LPS stimulation to mimic an inflammatory response. The levels of pro-inflammatory cytokines were quantified using enzyme-linked immunosorbent assay (ELISA). Additionally, the gene and protein expression levels of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and nuclear factor erythroid 2–related factor 2 (Nrf2) were assessed by real-time quantitative PCR and Western blotting, respectively. The involvement of key inflammatory signaling pathways, including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), was also investigated. Sesamol significantly inhibited the production of nitric oxide (NO), prostaglandin E2 (PGE2), and pro-inflammatory cytokines. Furthermore, it markedly down regulated the mRNA and protein expression of iNOS and COX-2. Concurrently, sesamol activated the antioxidant defense mechanism via upregulation of Nrf2 and heam oxygenase-1 (HO-1). Notably, sesamol impeded the nuclear translocation of NF-κB and suppressed MAPK phosphorylation, while concurrently enhancing the activation of AMP-activated protein kinase (AMPK). These findings suggest that sesamol exerts anti-inflammatory and antioxidant effects through modulation of multiple signaling pathways, highlighting its therapeutic potential in managing acute lung injury[31-32].

Antiaging activity

Aging is intrinsically associated with a progressive increase in biological entropy, resulting in the deterioration of cellular and systemic homeostatic mechanisms, ultimately leading to organism senescence and death. The free radical theory of aging postulates that an imbalance in the redox homeostasis—favoring pro-oxidants over antioxidant defenses—leads to persistent oxidative stress, which drives cumulative macromolecular damage, mitochondrial dysfunction, and cellular senescence. Among exogenous factors, chronic ultraviolet (UV) radiation exposure is a predominant inducer of reactive oxygen species (ROS), contributing to oxidative modification of nucleic acids, lipids, and proteins, particularly within cutaneous tissues. This pathological cascade culminates in photoaging, a phenotype characterized by epidermal thinning, wrinkle formation, collagen degradation, and loss of dermal elasticity. Sesamol, a naturally occurring lignan and phenolic antioxidant derived from *Sesamum indicum*, has demonstrated potent photo protective properties in various experimental models. It effectively attenuates UV-induced oxidative stress by scavenging ROS, modulating redox-sensitive signaling pathways, and preserving the structural and functional integrity of skin tissues. Empirical evidence indicates that sesamol significantly reduces the incidence of UV-induced dermal lesions, ulcerations, and histopathological alterations, thereby preventing the progression of photoaging. Its antioxidative efficacy is attributed to the upregulation of endogenous defense enzymes and the inhibition of pro-oxidant and inflammatory mediators, highlighting its potential as a therapeutic agent in the prevention of UV-mediated dermal degeneration[33].

Anti-ulcer activity

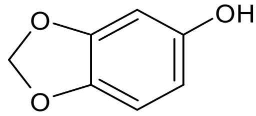
Previous investigations have explored the therapeutic potential of sesamol in a rat model of stress-induced gastric mucosal injury, specifically water immersion restraint stress (WIRS). Sesamol administration markedly attenuated WIRS-induced gastric hemorrhagic lesions and ulcer formation. The gastro protective effect of sesamol was associated with a significant suppression in the expression of key pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), within the gastric mucosa. Furthermore, sesamol inhibited the activation of nuclear factor-kappa B (NF-κB), a central transcriptional regulator of inflammation, in WIRS-exposed animals. Histopathological analysis also revealed elevated levels of CD68-positive macrophages and myeloperoxidase (MPO) activity in the gastric mucosal tissue of WIRS-treated rats, indicating enhanced inflammatory cell infiltration, which was effectively mitigated by sesamol treatment. These findings suggest that sesamol confers protection against stress-induced gastric mucosal injury primarily through its anti-inflammatory and antioxidative mechanisms[34]. Subsequent studies assessed the anti-ulcer efficacy of sesame (*Sesamum indicum*) seed extract in rat models of stress-induced peptic ulceration. Oral administration of the extract at both low and high doses significantly attenuated ulcerogenic parameters when compared to the positive control group. Specifically, a marked reduction was observed in gastric mucosal lesions, mucin content, gastric pH, gastric juice volume, and both total and free gastric acidity. Notably, animals treated with the higher dose of sesame extract exhibited physiological and biochemical parameters—such as gastric pH, mucosal protection (mucin content), gastric secretory volume, and acidity indices—comparable to those treated with standard anti-ulcer therapeutics. These findings suggest that sesame seed extract exerts dose-dependent gastro protective effects, likely mediated through modulation of gastric secretory function and mucosal defense mechanisms[35].

Anti-oxidant activity

Sesamol has been identified as a potent scavenger of a broad spectrum of reactive oxygen species (ROS), underscoring its potential as a candidate for therapeutic development in oxidative stress-associated pathologies. Its antioxidant efficacy was quantitatively assessed using cyclic voltammetry, which confirmed its robust electron-donating capacity indicative of high redox potential. Complementary biochemical assays further demonstrated that sesamol effectively inhibits lipid peroxidation, prevents hydroxyl radical-mediated deoxyribose degradation, and protects against oxidative DNA strand cleavage. These findings collectively support sesamol's role as a multifaceted antioxidant with significant potential in the prevention and management of ROS-induced cellular and molecular damage[36]. Sesamol also exhibits the ability to retard free radical chain reactions by effectively quenching reactive oxygen species (ROS). Its antioxidant mechanism involves redox-mediated electron or hydrogen atom transfer to neutralize radical species. During this redox transition, the unpaired electron is transferred to the sesamol molecule, resulting in the formation of a sesamol-derived radical intermediate. This intermediate is stabilized through extensive delocalization of the radical electron over the aromatic ring system via resonance, thereby minimizing its reactivity and preventing further propagation of oxidative damage. This resonance stabilization is a key factor underlying sesamol's pronounced radical-scavenging efficiency [37-38].

CHEMISTRY OF SESAMOL:

The chemical name of sesamol is 5-hydroxy-1,3-benzodioxole or 3,4-methylene-dioxyphenol. The molecular formula of sesamol is $C_7H_6O_3$, and it has a molar mass of 138.12g/mol.[39] The structure includes a phenol group and a methylenedioxy group attached to a benzene ring. Due to its bi-radical nature, molecular oxygen can easily accept electrons, thereby producing a series of partially reduced substances, collectively referred to as reactive oxygen species (ROS). Some of the radicals such as anions of superoxide ($O2^{-}$), peroxyl radicals (ROO), hydrogen peroxide, alkoxyl radicals (RO), and hydroxyl radicals (-OH). [40]



Sesamol (3,4-methylene-dioxyphenol)

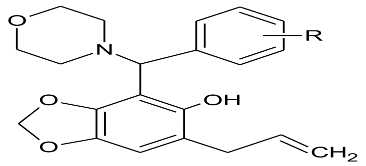
Sesamol combines phenolic and methylenedioxy moieties in its structure, and the antioxidant activity (AOA) of phenolic compounds of various origins is usually associated with the presence of OH moieties[41].

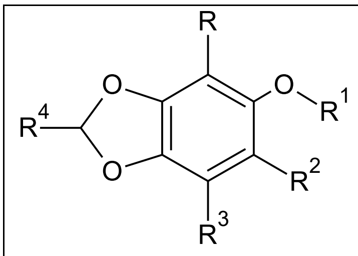
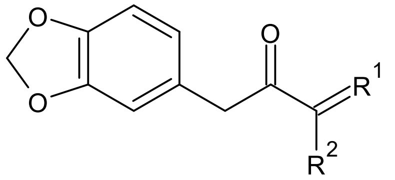
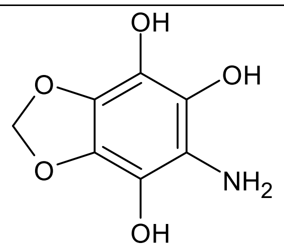
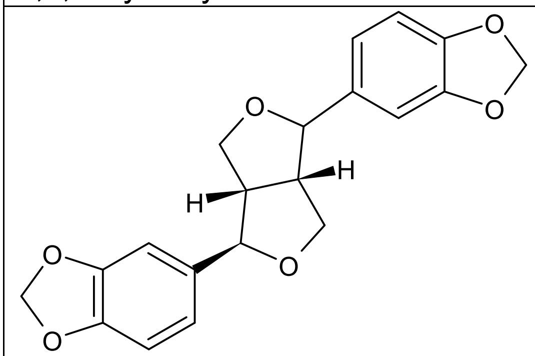
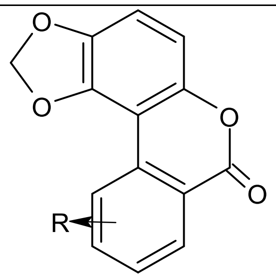
✓ **SYNTHETIC DERIVATIVES OF SESAMOL:**

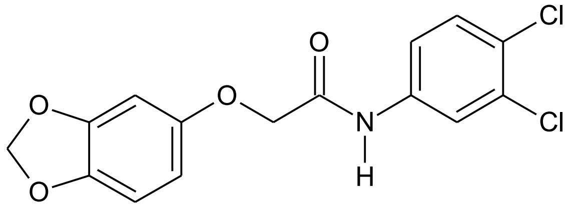
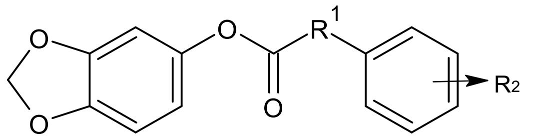
Aminomethyl derivatives of sesamol containing a tertiary amine moiety have been synthesized via the Mannich reaction using aqueous solution of formaldehyde and the secondary amines (dimethylamine, piperidine, morpholine, and thiomorpholine). The preparation of sesamol derivatives was achieved by the Betti base reaction between secondary amines, aromatic substituted aldehyde and sesamol. [42]

Alkylated modifications were found to generally increase the free radical scavenging activity of sesamol. The trimethylated and *t*-butylated analogs of sesamol showed the best theoretical results, exceeding the values for the classic antioxidants Trolox, BHT, and BHA. The introduction of alkyl groups led to the largest free radical stability and an increase of resonance structures when compared to sesamol. [43]

The benzo[d][1,3]dioxol-5-yl 5-(1,2-dithiolan-3-yl)pentanoate-15 has Phyto food source combination of lipoic acid and sesamol wherein the synergetic effect of individual bioactive compound is added to provide better efficacy in the combined food nutrient[44].

DERIVATIVES OF SESAMOL	OBSERVATION	CONCLUSION
 Mannich Bases (R), 4-(aminoalkyl)-6-allyl-sesamols	**Youg Guo et al., (2019):** Substituted benzaldehydes and piperidine/morpholine derivatives of 4-(aminoalkyl)-6-allyl-sesamol have shown antioxidant activity and exhibited with low cytotoxicity to normal cells[42].	• **Antioxidant activity,** • **Low cytotoxicity**

 Alkylated Sesamols	**Ivanete C. Palheta et al., (2020):** Alkyl substitutions at the ortho positions related to phenol moiety were found to be more effective than any other positions. The trimethylated derivative was more potent than Trolox. *t*-Butylated derivatives were stronger than all other alkylated derivatives[43]	• **Potent antioxidants**
 Benzo[D][1,3]dioxol- 5-yl methacrylate	**Jayaraj P et al 2022** Sesaminol is generated first from two molecule of E-Coniferyl alcohol. Sesaminol, a lignan found in sesame seeds, exhibits biological activity primarily through its antioxidant properties and ability to modulate cellular pathways. It acts as a potent free radical scavenger, protecting cells from oxidative damage. Additionally, sesaminol can influence antioxidant enzyme activity, reduce apoptosis, and impact the Nrf2-ARE pathway, contributing to its protective effects against various diseases[44]	• **Anti-oxidant property**
 1,2,4-Hydroxy-3-amino sesamol	**Laura M. Castro-González et al (2020):** 1,2,4-Hydroxy-3-amino sesamol is predicted to be better antioxidants than sesamol and Trolox. [45]	• **Plasminogen activator** • **Potent Antioxidant**
 Sesamin	**Chen Z, et.al 2023:** phenolic compounds as potential α-glucosidase inhibitors. B-ring's C-3′ hydroxylation shows the important role in the inhibitory activity of α-glucosidase, and flavonoids containing C-3′ hydroxyl group showed a stronger inhibitory effect. [46]	• **Antioxidant activity** • **Anti-inflammatory activity** • **Anti cancer activity**
 R: H,Cl sesamol derivative	**Shiyang Zhou et al,(2021) :** The antioxidant activity of these sesamol derivatives were tested, and the test results showed that these sesamol derivatives had a good antioxidant activity. [47]	• **Antioxidant activity**

 3,4-dichlorophenyl acetamide sesamol	**Sandeep Kumar et al, 2024:** The synthesized 3, 4-dichlorophenuy; A set of sesamol-derived acetamides was designed, synthesized, and evaluated against monoamine oxidases (MAO-A and MAO-B) and cholinesterases (AChE and BChE) for targeting neurodegenerative diseases. The 3,4-dichoro derivative was the most potent MAO-A inhibitor as compared to the reference inhibitors clorgyline (MAO-A) and selegyline (MAO B) and it showed antioxidant and iron-chelation properties. [48]	• **Antioxidant property** • **Iron-chelation property**
 Sesamol based Phenolic acid derivative	Yundong Xie **et al, 2021**: One of the phenolic acid derivatives of sesamol has reported hepatoprotective effect by inhibiting lipids accumulation in hepatic cells. The levels of PPAR-α receptor related to lipids metabolism in hepatic tissue were upregulated. It has also shown antioxidant and anti-inflammatory activity.	• **Hepatoprotective effect** • **Antioxidant** • **Anti-inflammatory activity** • **Hypolipidemic activity**

CONCLUSION

In the current review, most of the pharmacological effects (in vivo and in vitro) of sesamol and its derivatives are summarized as, hepatoprotective activity, anti-microbial, neuroprotective, cardio protective, anti-inflammatory, anticonvulsant, anti-anxiolytic, wound healing, cosmetic (skin whitening), anti-cancer, antioxidant, and other biological effects.

REFERENCES

1. Piyush Mehta, Atmaram Pawar, Kakasaheb Mahadik, C. Bothiraja, Emerging novel drug delivery strategies for bioactive flavonol fisetin in biomedicine, Biomedicine & Pharmacotherapy, Volume 106, 2018, Pages 1282-1291, ISSN 0753-3322, https://doi.org/10.1016/j.biopha.2018.07.079.
2. Abou-Gharbia, H.A.; Shehata, A.A.Y.; Shahidi, F. Effect of processing on oxidative stability and lipid classes of sesame oil. Food Res. Int., 2000, 33, 331-340. [http://dx.doi.org/10.1016/S0963-9969(00)00052-1]
3. Elleuch, M.; Besbes, S.; Roiseux, O.; Blecker, C.; Attia, H. Quality characteristics of sesame seeds and by-products. Food Chem., 2007, 103, 641-650. [http://dx.doi.org/10.1016/j.foodchem.2006.09.008]
4. Namiki, M. Nutraceutical functions of sesame: a review. Crit. Rev. Food Sci. Nutr., 2007, 47(7), 651-673. [http://dx.doi.org/10.1080/10408390600919114] [PMID: 17943496]
5. Chen, P.R.; Tsai, C.E.; Chang, H.; Liu, T.L.; Lee, C.C. Sesamol induces nitric oxide release from human umbilical vein endothelial cells. Lipids, 2005, 40(9), 955-961. [http://dx.doi.org/10.1007/s11745-005-1456-3] [PMID: 16329468]
6. Pathak, N.; Bhaduri, A.; Rai, A.K. Sesame: Bioactive Compounds and Health Benefits. In Bioactive Molecules in Food; Springer: Berlin/Heidelberg, Germany, 2019; pp. 181–200.
7. Chang, C.C., Lu, W.J., Ong, E.T., Chiang, C.W., Lin, S.C., Huang, S.Y., Sheu, J.R., 2011. A novel role of sesamol in inhibiting NF-κB-mediated signaling in platelet activation. J. Biomed. Sci. 18 (1), 93. https://doi.org/10.1186/1423-0127-18-93.
8. Mohamed, E.A.; Ahmed, H.I.; Zaky, H.S.; Badr, A.M. Sesame Oil Mitigates Memory Impairment, Oxidative Stress, and Neurodegeneration in a Rat Model of Alzheimer's Disease. A Pivotal Role of NF-KB/P38MAPK/BDNF/PPAR-γ Pathways. J. Ethnopharmacol. 2021, 267, 113468. [CrossRef]
9. Mohanty, C.; Das, M.; Sahoo, S.K. Emerging Role of Nanocarriers to Increase the Solubility and Bioavailability of Curcumin. Expert Opin. Drug Deliv. 2012, 9, 1347–1364. [CrossRef] [PubMed]
10. Yashaswini, P.S.; Kurrey, N.K.; Singh, S.A. Encapsulation of Sesamol in Phosphatidyl Choline Micelles: Enhanced Bioavailability and Anti-Inflammatory Activity. Food Chem. 2017, 228, 330–337. [CrossRef]
11. Di Costanzo, A.; Angelico, R. Formulation Strategies for Enhancing the Bioavailability of Silymarin: The State of the Art. Molecules 2019, 24, 2155. [CrossRef]
12. Salehi, B.; Azzini, E.; Zucca, P.; Maria Varoni, E.; Anil Kumar, N.V.; Dini, L.; Panzarini, E.; Rajkovic, J.; Valere Tsouh Fokou, P.; Peluso, I. Plant-Derived Bioactives and Oxidative Stress-Related Disorders: A Key Trend towards Healthy Aging and Longevity Promotion. Appl. Sci. **2020**, 10, 947.
13. Palheta, I.C.; Borges, R.S. Sesamol Is a Related Antioxidant to the Vitamin E. Chem. Data Collect. **2017**, 11, 77–83. [CrossRef]
14. Joshi, R.; Kumar, M.S.; Satyamoorthy, K.; Unnikrisnan, M.K.; Mukherjee, T. Free Radical Reactions and Antioxidant Activities of Sesamol: Pulse Radiolytic and Biochemical Studies. J. Agric. Food Chem. **2005**, 53, 2696–2703. [CrossRef] [PubMed]

15. Mahendra Kumar, C.; Singh, S.A. Bioactive Lignans from Sesame (Sesamum indicum L.): Evaluation of Their Antioxidant and Antibacterial Effects for Food Applications. J. Food Sci. Technol. **2015**, 52, 2934–2941. [CrossRef]
16. Geetha, T.; Singh, N.; Deol, P.K.; Kaur, I.P. Biopharmaceutical Profiling of Sesamol: Physiochemical Characterization, Gastrointestinal Permeability and Pharmacokinetic Evaluation. RSC Adv. **2015**, 5, 4083–4091.
17. Majdalawieh, A.F.; Mansour, Z.R. Sesamol, a Major Lignan in Sesame Seeds (Sesamum indicum): Anti-Cancer Properties and Mechanisms of Action. Eur. J. Pharmacol. **2019**, 855, 75–89.
18. Prakash, Om; Usmani, S; Gupta, A; Singh, R; Singh, N; Ved, A Bioactive Polyphenols as Promising Natural Medicinal Agents Against Cancer: The Emerging Trends and Prospective Goals. *Curr. Bioact. Compd.,* **2019**. [http://dx.doi.org/10.2174/1573407214666181030122046].
19. Anilakumar, K.R.; Pal, A.; Khanum, F.; Singh, A. Nutritional, Medicinal and Industrial Uses of Sesame (Sesamum indicum L.) Seeds - An Overview. *ACS Agric. Conspec. Sci.,* **2010**, *75*, 159-168.
20. Kapadia, G.J.; Azuine, M.A.; Tokuda, H.; Takasaki, M.; Mukainaka, T.; Konoshima, T.; Nishino, H. Chemopreventive effect of resveratrol, sesamol, sesame oil and sunflower oil in the Epstein- Barr virus early antigen activation assay and the mouse skin two-stage carcinogenesis. *Pharmacol. Res.,* **2002**, *45*(6), 499-505. [http://dx.doi.org/10.1006/phrs.2002.0992] [PMID: 12162952].
21. Iqbal, J.; Abbasi, B.A.; Mahmood, T.; Kanwal, S.; Ali, B.; Shah, S.A.; Khalil, A.T. Plant-Derived Anticancer Agents: A Green Anticancer Approach. Asian Pac. J. Trop. Biomed. **2017**, 7, 1129–1150. [CrossRef]
22. Pangeni, R.; Sahni, J.K.; Ali, J.; Sharma, S.; Baboota, S. Resveratrol: Review on Therapeutic Potential and Recent Advances in Drug Delivery. Expert Opin. Drug Deliv. **2014**, 11, 1285–1298. [CrossRef]
23. Prakash, Om; Usmani, S; Gupta, A; Singh, R; Singh, N; Ved, A Bioactive Polyphenols as Promising Natural Medicinal Agents Against Cancer: The Emerging Trends and Prospective Goals. *Curr. Bioact. Compd.,* **2019**.
24. Liu, Z.; Ren, B.; Wang, Y.; Zou, C.; Qiao, Q.; Diao, Z.; Mi, Y.; Zhu, D.; Liu, X. Sesamol Induces Human Hepatocellular Carcinoma Cells Apoptosis by Impairing Mitochondrial Function and Suppressing Autophagy. *Sci. Rep.,* **2017**, *7*, 45728.
25. Geetha, T.; Deol, P.K.; Kaur, I.P. Role of sesamol-loaded floating beads in gastric cancers: a pharmacokinetic and biochemical evidence. *J. Microencapsul.,* **2015**, *32*(5), 478-487.
26. Siriwarin, B.;Weerapreeyakul, N. Sesamol Induced Apoptotic Effect in Lung Adenocarcinoma Cells through Both Intrinsic and Extrinsic Pathways. Chem.-Biol. Interact. **2016**, 254, 109–116.
27. Geetha, T.; Kapila, M.; Prakash, O.; Deol, P.K.; Kakkar, V.; Kaur, I.P. Sesamol-loaded solid lipid nanoparticles for treatment of skin cancer. *J. Drug Target.,* **2014**, 1-11.
28. Pianjing, P.; Thiantanawat, A.; Rangkadilok, N.; Watcharasit, P.; Mahidol, C.; Satayavivad, J. Estrogenic activities of sesame lignans and their metabolites on human breast cancer cells. *J. Agric. Food Chem.,* **2011**, *59*(1), 212-221. [http://dx.doi.org/10.1021/jf102006w]
29. Xiong, J.; Sheng, J.; Wei, Y.; Sun, Z.; Xiao, X.; Zhang, L. Sesamol Augments Paclitaxel-Induced Apoptosis in Human Cervical Cancer Cell Lines. Nutr. Cancer **2022**, 74, 3692–3700. [CrossRef].
30. Ansari, M.A.; Fatima, Z.; Hameed, S. Mechanistic insights into the mode of action of anticandidal sesamol. *Microb. Pathog.,* **2016**, *98*, 140-148. [http://dx.doi.org/10.1016/j.micpath.2016.07.004] [PMID: 27392701].
31. Wu, X.L.; Liou, C.J.; Li, Z.Y.; Lai, X.Y.; Fang, L.W.; Huang, W.C. Sesamol suppresses the inflammatory response by inhibiting NF-κB/MAPK activation and upregulating AMP kinase signaling in RAW 264.7 macrophages. *Inflamm. Res.,* **2015**, *64*(8), 577-588. [http://dx.doi.org/10.1007/s00011-015-0836-7] [PMID: 26059394]
32. Yashaswini, P.S.; Kurrey, N.K.; Singh, S.A.; Singh, S.A. Encapsulation of sesamol in phosphatidyl choline micelles: Enhanced bioavailability and anti-inflammatory activity. *Food Chem.,* **2017**, *228*, 330-337.
33. Sharma, S.; Kaur, I.P. Development and evaluation of sesamol as an antiaging agent. *Int. J. Dermatol.,* **2006**, *45*(3), 200-208. [http://dx.doi.org/10.1111/j.1365-4632.2004.02537.x] [PMID: 16533216]
34. Hsu, D.-Z.; Chen, Y.-W.; Chu, P.-Y.; Periasamy, S.; Liu, M.-Y. Protective Effect of 3, 4-Methylenedioxyphenol (Sesamol) on Stress-Related Mucosal Disease in Rats. BioMed Res. Int. **2013**, 2013. [CrossRef] [PubMed]
35. Sori, R.K.; Balaji, O.; Adiga, S.; Thomas, H. Evaluation of the Antipeptic Ulcer Activity of the Seed Extract of Sesame (Sesamum indicum) in Stress Induced Peptic Ulcers in Rats. Int. J. Basic Clin. Pharmacol. **2018**, 7, 1131–1135. [CrossRef].
36. Joshi, R.; Kumar, M.S.; Satyamoorthy, K.; Unnikrisnan, M.K.; Mukherjee, T. Free radical reactions and antioxidant activities of sesamol: pulse radiolytic and biochemical studies. *J. Agric. Food Chem.,* **2005**, *53*(7), 2696-2703. [http://dx.doi.org/10.1021/jf0489769] [PMID: 15796613] [29]
37. Palheta, I.C.; Borges, R.S. Sesamol is a related antioxidant to the vitamin E. In: *CDC*; , **2017**; pp. 11-12-1-232.
38. Khamphio, M.; Barusrux, S.; Weerapreeyakul, N. Sesamol induces mitochondrial apoptosis pathway in HCT116 human colon cancer cells via pro-oxidant effect. *Life Sci.,* **2016**, *158*, 46-56. [http://dx.doi.org/10.1016/j.lfs.2016.06.017] [PMID: 27328416]
39. Kumar A, Bajaj P, Singh B, Paul K, Sharma P, Mehra S, Robin, Kaur P, Jasrotia S, Kumar P, Rajat. Sesamol as a potent anticancer compound: From chemistry to cellular interactions. Naunyn-Schmiedeberg's Archives of Pharmacology. 2024 Jul;397(7):4961-79.
40. Han P, An N, Yang L, Ren X, Lu S, Ji H, Wang Q, Dong J. Molecular dynamics simulation of the interactions between sesamol and myosin combined with spectroscopy and molecular docking studies. Food Hydrocolloids. 2022 Oct 1;131:107801.

41. Buravlev EV, Shevchenko OG, Suponitsky KY. Synthesis and Antioxidant Capacity of Some Derivatives of Sesamol at the C-6 Position. Chemistry & Biodiversity. 2021 Jun;18(6):e2100221.
42. Guo Y, Fan J, Qu L, Bao C, Zhang Q, Dai H, Yang R. Natural products as sources of new antioxidants: Synthesis and antioxidant evaluation of Mannich bases of novel sesamol derivatives. Industrial Crops and Products. **2019** Dec 1;141:111762.
43. C. Palheta I, R. Ferreira L, KL Vale J, PP Silva O, M. Herculano A, RHM Oliveira K, Neto AM, M. Campos J, BR Santos C, S. Borges R. Alkylated sesamol derivatives as potent antioxidants. Molecules. 2020 Jul 21;25(14):3300.
44. Jayaraj P, Narasimhulu CA, Rajagopalan S, Parthasarathy S, Desikan R. Sesamol: A powerful functional food ingredient from sesame oil for cardioprotection. Food & function. 2020;11(2):1198-210.
45. Castro-González LM, Alvarez-Idaboy JR, Galano A. Computationally designed sesamol derivatives proposed as potent antioxidants. ACS omega. 2020 Apr 13;5(16):9566-75.
46. Chen Z, Du S, Zhu K, Tian Z, Zhang J, Li F, Zhang S, Zhao S, Cui W, Yuan X, Chen K. Mn4+-activated double-perovskite-type Sr2LuNbO6 multifunctional phosphor for optical probing and lighting. ACS Applied Materials & Interfaces. 2023 May 30;15(23):28193-203.
47. Zhou S, Zou H, Huang G, Chen G. Preparations and antioxidant activities of sesamol and it's derivatives. Bioorganic & Medicinal Chemistry Letters. 2021 Jan 1; 31:127716.