Review Article
Pharmacological Properties to Pharmacological Insight of Sesamin in Breast Cancer Treatment: A Literature-Based Review Study

Md Sohel,1 Md. Nurul Islam,2 Md. Arju Hossain,3 Tayeba Sultana,3 Amit Dutta,3 Md. Sohanur Rahman4, Suraiya Aktar,5 Khairul Islam,1 and Abdullah Al Mamun1

1Department of Biochemistry and Molecular Biology, Mawlana Bhashani Science and Technology University, Santosh, Tangail 1902, Bangladesh
2Department of Pharmacy, Mawlana Bhashani Science and Technology University, Santosh, Tangail 1902, Bangladesh
3Department of Biotechnology and Genetic Engineering, Mawlana Bhashani Science and Technology University, Santosh, Tangail 1902, Bangladesh
4Department of Biochemistry and Molecular Biology, Trust University, Barishal, Ruiya, Nobogram Road, Barishal 8200, Bangladesh
5Department of Biochemistry and Molecular Biology, Rajshahi University, Bangladesh

Correspondence should be addressed to Abdullah Al Mamun; amamun42@gmail.com

Received 8 October 2021; Revised 20 January 2022; Accepted 26 January 2022; Published 17 February 2022

Academic Editor: Pranshu Sahgal

Copyright © 2022 Md Sohel et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The use of dietary phytochemical rather than conventional therapies to treat numerous cancers is now a well-known approach in medical science. Easily available and less toxic dietary phytochemicals present in plants should be introduced in the list of phytochemical-based treatment areas. Sesamin, a natural phytochemical, may be a promising chemopreventive agent aiming to manage breast cancer. In this study, we discussed the pharmacological properties of sesamin that determine its therapeutics opportunity to be used in breast cancer treatment and other diseases. Sesamin is available in medicinal plants, especially in Sesamum indicum, and is easily metabolized by the liver. To better understand the antibreast cancer consequence of sesamin, we postulate some putative pathways related to the antibreast cancer mechanism: (1) regulation of estrogen receptor (ER-α and ER-β) activities, (2) suppressing programmed death-ligand 1 (PD-L1) overexpression, (3) growth factor receptor inhibition, and (4) some tyrosine kinase pathways. Targeting these pathways, sesamin can modulate cell proliferation, cell cycle arrest, cell growth and viability, metastasis, angiogenesis, apoptosis, and oncogene inactivation in various in vitro and animal models. Although the actual tumor intrinsic signaling mechanism targeted by sesamin in cancer treatment is still unknown, this review summarized that this phytoestrogen suppressed NF-κB, STAT, MAPK, and PIK/AKT signaling pathways and activated some tumor suppressor protein in numerous breast cancer models. Cotreatment with γ-tocotrienol, conventional drugs, and several drug carriers systems increased the anticancer potentiality of sesamin. Furthermore, sesamin exhibited promising pharmacokinetics properties with less toxicity in the bodies. Overall, the shreds of evidence highlight that sesamin can be a potent candidate to design drugs against breast cancer. So, like other phytochemicals, sesamin can be consumed for better therapeutic advantages due to having the ability to target a plethora of molecular pathways until clinically trialed standard drugs are not available in pharma markets.

1. Introduction

Several diseases, from infectious to noninfectious, have become a burden globally. Cancer, especially breast cancer, is a noninfectious public health-related disease, considered the 2nd second most frequent cancer type after lung [1]. According to the literature review, conventional treatment modalities are surgery, radiation therapy, chemotherapeutics drugs, hormone therapy, targeted therapy, and immune therapy [2]. But these types of therapies are highly specific
and are not effective against all types of breast cancer. For example, chemotherapy is the only fruitful and effective therapy against estrogen nonresponsive cancer [3]. Furthermore, some breast cancer treatment strategies cause significant side effects that continue or appear months or after treatment has already ended [4]. Some chemotherapeutic drugs are becoming resistant to cancer cells [5]. So we should not be limited to these conventional therapies for breast cancer management. The use of natural-based phytochemicals should be given priority against both infectious [6] and noninfectious diseases [7, 8]. Hormone, i.e., estrogen, plays a significant role in breast cancer development [9] by stimulating breast cancer growth and promoting the normal and the neoplastic breast epithelium [10]. Phytochemicals can modulate estrogen receptors and several other growth factors. In this regard, phytoestrogen is the potent candidate due to its structural similarity with estrogen receptors [11, 12]. Phytoestrogens are reported to accelerate breast cancer cell growth at a lower concentration, but at higher concentrations, they may suppress cancer progression by controlling some regulatory point through ER-α, ER-β [13], and HER2 [14] and aromatase controlling [15].

Sesamin is a water-insoluble phytoestrogen, categorized into lignans, and recently received considerable attention from scientists that could be used to treat breast cancer. *Sesamum indicum* is a major source of sesamin, but other 30 medicinal plants in some specific genera contain minor amounts of sesamin [16]. Sesamin is widely used against inflammatory diseases [17], neurodegenerative disease [18], liver disease [19], diabetes, eye problem [20], cardiovascular disease [21], and lung disease [22]. Furthermore, the anticancer activities of sesamin have been documented against numerous human cancers in various in vitro and animal models [23]. However, therapeutic advantage of sesamin against breast cancer is limited. Therefore, we aimed to make an overview of sesamin and breast cancer, which will open a new door in the near future. The major advantages of using sesamin in breast cancer treatment are its availability in nature, structural chemistry, and formation of nanocarrier to increase bioavailability. Furthermore, sesamin possesses promising drug likeness properties, synergistic activities, less toxicity, and its metabolic intermediate. Metabolites of sesamin also possess anticancer activities against breast cancer [24, 25]. Dietary consumption of sesamin is attributed to anticancer activities by regulating cell death and viability by regulating cell cycle and proliferation, apoptosis-related signal transduction, angiogenesis and metastasis pathway, hypoxia regulation, and other unknown investigating the mechanism in in vitro and in vivo model systems.

This review summarizes about sesamin from sources, structure, metabolism, molecular pharmacology with anticancer mechanisms, and pharmacokinetics with a future prediction.

### 2. Overview of Sesamin Distribution

Sesamin is a type of lignan found in vascular plants [26]. Sesame species (*Sesamum indicum* L.) is one of the major sources of this sesamin [27], and Gomazou, a Japanese variety of sesame seeds, is reported to contain sesamin about 15 mg/1 gm dry weight of its seed [28]. The oil extracted from the sesame seed also contains sesamin that can be used for cooking and cosmetic preparation [29]. Followed by seed, leaves have a small amount (2.6 g g⁻¹ dry weight) of sesamin detected by Ultra Performance Liquid Chromatography-Fluorescence Detection (UPLC-FLD) [28]. Other than sesame seed, sesamin has been identified from stems and roots of several medicinal plants species, including *Piper* genus [30], *Magnolia coco*, *Bridelia retusa*, *Phyllarthron comorens*, *Zanthoxylum tetraspermum*, and *Stemona collinsae* [31–36]. Chinese wild ginger, paulownia, and gingko were also reported to contain sesamin. Sesamin was also detected as an endogenous secondary metabolite of a parasitic plant like *Cuscuta palaestina*. Some reported sources of sesamin are listed in Table 1.

#### 2.1. Chemistry.

Sesamin was first isolated in 1890 from the sesame seeds. It belongs to the benzodioxole family. The IUPAC name of this lignans is (15,3a R, 4 S,6a R)-1,4-bis (benzo[d][1,3]dioxol-5-yl)tetrahydro-1 H3-furo [3,4-c]fura, and the chemical formula of sesamin is *C*₂₀*H*₁₈*O*₆ [46]. It contains 26 heavy atom counts, 1 covalently bonded unit amount, and no formal charge [46]. The molecular weight of sesamin is 354.35 g/mol, but the exact mass is 354.36 [26, 47]. This chemical compound contains two fused dihydrofuran with two benzene rings replaced with a group of methylene dioxide (-O-CH₂-O-) at the 3 and 4 symmetrically attached to each of the carbon atoms near to the ether oxygen atoms [48]. Furthermore, this phytoestrogen does not contain any nonconjugated amine and carboxylic acid groups. Figure 1 portrays the chemical structure of sesamin.

#### 2.2. Metabolism.

Metabolism of sesamin appears to be species-specific. Liu summarized that sesamin was metabolized to other substances in the gut or liver [49]. The primary metabolic products of sesamin are enterodiol (ED) and enterolactone (EL), produced through fermentation with human fecal microbiota and colonic microflora [50]. Sesamin is successively metabolized in the liver by liver microsomes. Hydroxylated metabolites of sesamin were released in the bile in the liver [51], where cytochrome P450 is an essential enzyme in the liver [52]. According to the previous report, sesamin was converted into monocatechol metabolite (SC-1), and it was metabolized into glucuronide of SC-1 (SC-1-GlcUA) and methylated metabolites of SC-1 (SC-1m) by DP-glucuronosyltransferase and catechol O-methyl transferase, respectively, in the liver [53]. Recently, Sakaki added that CYP2C9 is the predominant enzyme for sesamin metabolism in the human liver [54]. Recently, in the case of microorganisms, i.e., *Sinomonas* spp. no. 22, enzyme SesA converts sesamin to their respective intermediate [55].

### 3. Sesamin with Nanoformulation to Increase the Bioavailability

Sesamin is fat-soluble or poorly water-soluble lignans (2.5 μg/ml), significantly limiting its dissolution rates and release efficiency [56]. Improving the absorption and
distribution of lipophilic components like sesamin can be possible by dissolving oil or various nanocarriers, i.e., a self-nanoemulsifying drug delivery system (SNEDD). Wang summarized that after self-emulsification of SNEDDS, droplet size was dispersed by sesamin at $66.4 \pm 31.4 \mu m$ with increased intestinal permeability, relative bioavailability, and absolute bioavailability by more than three-fold and 12.9-fold and 0.3% to 4.4%, respectively [57]. Iwamoto et al. stated that mixing with turmeric oil could increase the bioavailability of sesamin [58], where sesame extract with a turmeric oil mixture of sesame extract and turmeric oil (MST) was fed to Slc:ddY mice, and found that serum sesamin contents in the MST-treated group were 23-fold higher compared to the control group (administering sesamin extract alone). Sato et al. state that solid dispersion (SD) approach increased solubilizing effect of sesamin by using $\alpha$-glycosylated stevia (Stevia-G) carrier compounds [56]. They found that sesame-loaded SD with Stevia-G (sesamin/Stevia-G-SD) (20 mg sesamin) increased bioavailability around 30-fold higher with 190-fold dissolution than that of crystalline sesamin in Sprague-Dawley rats ($200 \pm 50$ g, 6–9 weeks). Furthermore, an experimental study by Ebrahim stated that formulation containing sesame oil (a significant source of sesamin) reduced the average droplet size of microemulsion samples with a range of 16.6 ± 0.1 -64.6 ± 0.2 nm with a polydispersity index (PDI) value of less than 0.5 [59]. So, the formulation procedure of sesamin has excellent potential for oral administration, enhancing its pharmacological application value.

4. Molecular Pharmacology of Sesamin in Breast Tissue

Sesamin is a type of phytoestrogen that belongs to lignans [60], associated with several pharmacological activities against breast cancer through regulating several receptors, like estrogen receptor-$\alpha$ (ER-$\alpha$), receptor-$\beta$ (ER-$\beta$), G protein-mediated signaling pathways, growth factor receptor, i.e., HER2 and EGFR, and some receptor tyrosine kinase (RTK). Estrogen receptor-$\alpha$ plays a significant role in estrogen-responsive breast cancer initiation and progression [61, 62]. Sesamin competitively bound with estrogen receptor in the form of antagonist and showed inhibitory activities on estrogen-mediated estrogen-responsive element (ERE) induction in T47D-KBluc cells at $10^{-9}$-$10^{-6}$ M [63]. There is huge of evidence that claims receptor tyrosine kinase (RTK): for instance, HER2 and EGFR [64], IGFIR [65], and hepatocyte growth factor receptor (HGFR) [66] are tumor initiators in breast tissue. So targeting these receptors is a novel strategy to treat breast cancer. Truan et al. summarized that sesamin suppressed the expression of HER2 and EGFR receptors and their activities in MCF-7 cancer cell lines and athymic mice [67]. It is found in some subtypes of metastatic breast cancer, particularly triple-negative breast cancer, the protein programmed death-ligand 1 (PD-L1) expressed highly, so targeting PD-L1in breast cancer is a potential complementary therapy in cancer patients [68]. Kongtawelert et al. summarized that sesamin (200 $\mu M$) suppressed PD-L1 expression through AKT, NF, and JAK/STAT signaling inhibition in MDA-MB 231 breast cancer

Table 1: Reported plant sources of sesamin.

| Name of the plant               | Plant parts used                  | Ref.  |
|---------------------------------|-----------------------------------|-------|
| *Sesamum indicum*               | Leaves and seed                   | [28]  |
| *Acanthopanax sessiliflorus*    | Fruit                             | [37]  |
| *Magnolia coco*                 | Stem                              | [32]  |
| *Zanthoxylum tetraspernum*      | Leaves                            | [33]  |
| *Zanthoxylum caudatum*          | Stem bark                         | [36]  |
| *Bridelia retusa*               | Stem bark                         | [36]  |
| *Zanthoxylum americanum*        | Fresh roots and stems             | [38]  |
| *Glossostemon bruguieri* (Desf.) | Roots                            | [39]  |
| *Piper longum*                  | Dried fruits                      | [40]  |
| *Asarum heterotropoides var. mandshuricum* | Roots                 | [41]  |
| *Fagara zanthoxyloides*         | Roots                            | [42]  |
| *Stemona collinsae*             | Roots                            | [34]  |
| *Cuscuta palaestina*            | Entire plant                      | [43]  |
| *Chrysanthemum cinerariaefolium*| Flower                           | [44]  |
| *Plindersia pubescens*          | Bark                             | [45]  |

**Figure 1:** Chemical structure of sesamin.
cell lines [69]. COX-2 enzyme mediates CYP-19 transcription and aromatase, which caused an increase in biosynthesis of estrogen and estrogen-responsive breast cancer [70]. However, information about sesamin-COX-2-related breast cancer treatment is rare, but sesamin could decrease COX-2 expression by inducing apoptosis and G1 phase arrest by targeting pAkt-P38 signaling in lung cancer [71]. However, the interaction of sesamin with the vascular endothelial growth factor receptor-2 (VEGFR-2) and insulin-like growth factor-1 (IGF-1R) signaling pathway in breast cancer cells is yet not established. Moreover, some of the sesamin metabolic intermediates have strong interaction with estrogen receptors and mediate anticancer activity. For instance, enterolignans, i.e., enterolactone and enterodiol, impede human estrogen receptor (ER) signaling in hormone-dependent breast cancer. These two enterolignans modulate ER-α and ER-β at the transcriptional level by regulating ER-α-targeted genetic elements by transactivation functions AF-1 and AF-2 [72]. The molecular pharmacology of sesamin in breast cancer is summarized in Figure 2.

5. Anticancer Effects of Sesamin and Their Metabolites

5.1. In Vitro Study of Sesamin. Sesamin has been shown to exhibit in vitro anticancer activities against various breast cancer cell lines. Kogntawerlt et al. conducted the antibreast cancer activities of sesamin and reported that sesamin (0-200 μM) inhibited cell proliferation with suppressing metastasis by the inactivation of oncosignaling pathways like PI3K/AKT, NF-κB, ERK, and JAK/STAT in MDA-MB 321 cell lines [69]. Furthermore, this phytochemical also arrested the G1 phase and downregulated PDL-1, MMP-9, and MMP-2 resulted in inhibition of cell migration at the same dose and cell line. Yokota et al. manifested the cell proliferation capability of sesamin in the breast cancer cell and found that sesamin inhibited cell proliferation through decreasing cyclin D1 gene expression that mediates cyclin D1 degradation with concomitant increasing retinoblastoma protein dephosphorylating, leading to expression of p15/p16 by sesamin at the dose of 1-100 μM [73]. In addition, sesamin (51.1 μM) inhibits cell proliferation through the mitochondrial-mediated pathway by downregulating Bcl-2 and cyclin D1 expression [74]. However, sesamin (25-100 μM) halted cancer progression by inhibiting the NF-κB, STAT3, JNK, ERK1/2, MAPK, and PI3K/AKT and activating tumor suppressor protein like p38 and p53 via downregulating tumor necrosis factor-alpha (TNF-α) [74, 75]. Sesamin (98.57 μM) decreased the cell viability and cytotoxic effect in MCF-7 breast cancer [76]. Similarly, sesamin (50 μM) declines cell viability with inducing apoptosis through the underlining mechanism of activating Bax, caspase 3, and tumor suppressor protein p53, leading to G1 phase cell cycle arrest [77]. Macrophage-induced proangiogenic activities were inhibited by sesamin (50-100 μM) in breast cancer cell line through the underlying mechanism of inhibiting major transcription factors including HIF-1α and NF-κB and signaling mechanism of ERK, JNK, and PI3K and metastasis factors including VEGF and MMP-9 in MCF-7 and MDA-MB 231 cancer cell [78]. Additionally, sesamin (50 μM) can decrease cell growth and cell viability by increasing apoptosis through the chain transfer pathway by upregulating p52 and progesterone receptor genes in T-47D breast cancer cells [63].

5.2. Anticancer Activity of Sesamin Metabolites (Enterolactone and Enterodiol). Sesamin is a plant compound, metabolized by the liver to produce some estrogenic metabolic intermediate. These metabolites link with estrogen receptors, but their mechanism of action, either estrogenic or antiestrogenic, is still unknown. Enterolactone and enterodiol are initial metabolites produced in a minor amount [50]. Liu et al. summarized that both metabolites have anti-breast cancer activities, but enterolactone attributes more potent anticancer activity with fewer side effects than enterodiol [79]. Enterolactone (25-75 μM) was found to downregulate MMP-2 and MMP-9 matrix enzyme expression with upregulating their inhibitors including TIMP-1 and TIMP-2. These are significant inhibitors of MMP-2 and MMP-9, resulting in the regulation of migration of breast cancer cells during metastasis in cell line MDA-MB 231 [24]. Furthermore, MDA-MB 231 cell growth inhibition of enterolactone was evident by accumulating cells at the S phase through the underlying mechanism of lowering cell cycle regulatory proteins cyclin A2, cyclin B1, and cyclin E1 genes expression without changing CDK4, CDK6, and cyclin D1 for G0/G1 phase regulation [80]. Enterolactone (10 ng/ml) also mediated the anticancer mechanism by interfering with TGF-β-induced EMT through blocking the ERK/NF-κB/snail, MAPK-p38, and a cluster of differentiation 44 (CD44) with upregulating the epithelial markers E-cadherin and occludin in similar cell lines [81]. Like enterolactone, enterodiol possesses anticancer activity by modulating cell migration and proliferation. Carreau et al. found that enterodiol suppressed MMP-2-9 and regulated MMP secretion in estrogen-responsive breast cancer cell MCF-7 [72]. However, the anticancer activity of other sesamin’s metabolites is still unknown. Summary of sesamin activities in breast cancer are listed in Table 2.

5.3. In Vivo and Clinical Trial Study. Sesamin has been widely tested in preclinical and clinical trials for several diseases, i.e., ischemic brain stroke [83], depression [84], Parkinson’s disease [85], osteoarthritis [86], diabetic retinopathy [20], and acute hepatic injury [87], but therapeutic activities of sesamin in in vivo breast cancer model are limited. Sesamin (1 g/kg, 8 wk the basal diet) supplementation in athymic mice reduced tumor size by around 23% compared to control through downregulating growth factor receptor including EGFR and HER2 and reducing pMAPK expression [67]. Furthermore, administration of DMBA for weeks in female Sprague-Dawley decreased the cumulative number of palpable mammary cancer by 36% in rats on a control diet. Again, sesamin reduced fatty acid in plasma and liver, and tumor phosphatidylcholine decreases the serum prostaglandin E2 in the sesamin group [88]. In a randomized, placebo-controlled, crossover study conducted by Wu et al., with 26 healthy postmenopausal women, they
found that sesamin (50 gm, five weeks) increased antioxidant status [89]. Although there is limited information on in vivo and clinical trials due to the lack of study, conducting more studies may reveal sesamin as the potential anticancer agent.

5.4. The Synergetic Activity of Sesamin in Breast Cancer Treatment. Synergy occurs when two or more substances work combined to produce a more considerable effect than the sum of their individual effects [75]. Information about the synergistic activity of sesamin in breast cancer treatments is scarce. Initially, Akl reported that sesamin (10-120 μM) with γ-tocotrienol synergistically inhibits growth-mediated EGF-dependent by decreasing phosphorylation of ErbB3 and ErbB4 receptor and mitogenic signaling, i.e., suppressed intracellular and phosphorylated oncogene c-Raf, MAPK/ERK kinase, extracellular signal-regulated kinase 1/2, phosphoinositide-dependent kinase-1, phosphoinositide-3-kinase, protein kinase B, p-NF-κB, JAK1, JAK 2, and STAT1 at a dose-dependent manner in mammary tumor cells [91]. Furthermore, one year later, they found that the antiproliferation actions of γ-tocotrienol synergize sesamin in neoplastic mouse (+SA) and estrogen-responsive and nonresponsive (MCF-7 and MDA-MB 231) breast cancer cell line. These synergistic activities are mediated by regulating cell cycle regulatory protein, i.e., activating retinoblastoma protein (p-RB, decreasing), cyclin D1, and its associated enzymes CDK2,
Table 2: Summary of the mechanisms of action of sesamin in in vitro breast cancer models.

| Sesamin/metabolites | Type of study       | Dose       | Molecular mechanism                      | Molecular target                                                                 | Ref   |
|---------------------|---------------------|------------|------------------------------------------|--------------------------------------------------------------------------------|-------|
| In vitro            | MDA-MB 232 and MCF-7| 0-200 μM   | Cell proliferation                       | PDL-1 (both mRNA and protein) expression                                       | [69]  |
| In vitro            | MCF-7               | 0-100 μM   | Migration                               | ↓P13K/akt,NF-xB, ERK, and JAK/stat signaling                                     |       |
| In vitro            | MDA-MB 232 and MCF-7| 51.1 μM    | Metastasis                              | ↓PDL-1 (both mRNA and protein) expression                                       |       |
| In vitro            | MDA-MB 232 and MCF-7| 98.57 μM   | Cell viability                          | ↑PUMA and Bax                                                                   |       |
| In vitro            | MDA-MB 232 and MCF-7| 25-100 μM  | Cell proliferation                       | ↑G1 cell cycle arrest                                                          |       |
| In vitro            | MDA-MB 232 and MCF-7| 50 μM      | Apoptosis                               | ↑G1 phase arrest, and CDK2                                                      |       |
| In vitro            | MDA-MB 232 and MCF-7| 50 μM      | Macrophage-induced proangiogenic activity| ↑G1 phase arrest, and CDK2                                                      |       |
| In vitro            | MDA-MB 232 and MCF-7| 50 μM      | Angiogenesis                            | ↑Macrophage-induced VEGF                                                        |       |
| In vitro            | (MCF-7)             | 50 μM      | Cell growth                             | ↑Macrophage-induced VEGF                                                        |       |
| In vitro            | +SA mammary epithelial cell and MCF-7 | 60-120 μM | Cell proliferation                       | ↑EGF-induced ErbB3                                                             |       |
| In vitro            | MDA-MB-231          | 25-75 μM   | Anticancer activity                     | ↑MMP-2 and MMP-9                                                                | [24]  |
| In vitro            | MDA-MB-231          | 10 ng/ml   | Anticancer mechanism                    | ↑MMP-2 and MMP-9                                                                |       |
| In vitro            | MCF-7               | 10 ng/ml   | Cell migration                           | ↑Anticancer mechanism                                                          |       |
| In vitro            | MCF-7               | 10 ng/ml   | Cell proliferation                       | ↑E-cadherin, occluding                                                         | [72]  |
| Enterolactone       | MCF-7               | 10 ng/ml   | Cell migration                           | ↑E-cadherin, occluding                                                         | [72]  |
| Enterodiol          | MCF-7               | 10 ng/ml   | Cell proliferation                       | ↑E-cadherin, occluding                                                         | [72]  |
CDK4, CDK6, and E2 transcription level 1, and upregulating tumor suppressor proteins p27 and p16 mediates the arrest cell cycle at the G1 phase [92]. As a result, to prevent or treat breast cancer, the synergistic growth inhibitory effects of γ-tocotrienol and sesamin treatment can be leveraged as a viable anticancer therapeutic strategy.

6. Toxicological Potential of Sesamin

Plant lignans, including sesamin, the most frequent lignans in sesame seed, are always beneficial to health [93]. Sesamin has many pharmacological advantages and can be used for hyperlipidemia, hypertension, and cancer treatment [75]. However, it has few toxicities toward normal cells [91]. Sesame seed oil decreases blood pressure, so sugar levels should be monitored while taking sesame seed oil [94]. Several studies show that sesamin might cause an allergic reaction in some people. Sesame oil can be used as a nasal spray, but it causes nasal dripping and blockage. People who already have low blood pressure and diabetes taking excessive sesame might lower blood sugar levels and drop blood pressure. Sesame also may interfere with blood sugar levels during or after surgery [95]. In microorganisms and animals, sesamin (155 μM) specifically inhibiting delta-5 desaturase decreased polyunsaturated fatty acid biosynthesis [96]. Sesamin is familiar with positively affecting HMG-CoA reductase [95] and lipid metabolism or fatty acid oxidation-related enzymes [96] by modulating their mRNA levels. Yasuda

| Table 3: Drug availability evaluation profile sesamin. |
|-----------------------------------------------|
| Category | Properties | Predictive remarks | Unit |
|----------|------------|-------------------|------|
| Drug-likeness | Lipinski | Yes | Yes/no |
| | Veber | Yes | Yes/no |
| | Muegge | Yes | Yes/no |
| | Ghose | Yes | Yes/no |
| | Egan | Yes | Yes/no |
| | Bioavailability score | 0.55 | N/A |
| Absorption | Water solubility | -4.223 | Log mol/l |
| | CaCO2 permeability | 1.399 | Log Papp (cm/s) |
| | Intestinal absorption(human) | 97.81 | % absorbed |
| Distribution | Skin permeability | -2.772 | Log Kp |
| | P-glycoprotein substrate | No | Yes/no |
| | P-glycoprotein I inhibitor | Yes | Yes/no |
| | P-glycoprotein II inhibitor | No | Yes/no |
| | VDss (human) | -0.17 | Log L/kg |
| | BBB permeability | -0.862 | Log BB |
| | CNS permeability | -2.939 | Log PS |
| Metabolism | CYP450 2C9 substrate | No | Yes/no |
| | CYP450 2D6 substrate | No | Yes/no |
| | CYP450 3A4 substrate | No | Yes/no |
| | CYP450 1A2 inhibitor | Yes | Yes/no |
| | CYP450 2C9 inhibitor | Yes | Yes/no |
| | CYP450 2D6 inhibitor | Yes | Yes/no |
| | CYP450 2C19 inhibitor | Yes | Yes/no |
| | CYP450 3A4 inhibitor | Yes | Yes/no |
| Excretion | Total clearance | -0.126 | Log ml/min/kg |
| Toxicity | Skin sensitization | No | Yes/no |
| | Hepatotoxicity | No | Yes/no |
| | Ames toxicity | Yes | Yes/no |
| | hERG I inhibitors | No | Yes/no |
| | hERG II inhibitors | No | Yes/no |
| | T. pyriformis toxicity | 0.34 | Log μg/l |
| Anticancer effect | P-GP inhibitor | Yes | Yes/no |
| | Aromatase | No | Yes/no |
| | ER binding | Yes | Yes/no |
et al. summarized that sesamin significantly inhibits CYP2C9, CYP21A2, and CYP23A4 in a dose-dependent manner [52], leading to drug toxicity, drug-drug interactions, and other adverse effects. Sesamin also inhibited the tocopherol [97] and arachidonic acid metabolism [97] by inhibiting CYP4F2. Therefore, beside the pharmacological advantages, it is important to consider the toxic effect of any naturally derived phytochemicals before use. However, more studies can help to reduce the toxicity or determine the effective safe dose of sesamin for the treatment of diseases.

7. Pharmacokinetics Prediction of Sesamin

In current drug discovery efforts, small molecule leads with appealing pharmacokinetic characteristics are typically sought out. So we liked to determine the pharmacokinetics properties of sesamin. ADME/Tox (absorption, distribution, metabolism, elimination, and toxicity) profile of sesamin was predicted using online accessible Swiss ADME [98] (drug-likeness properties), pkCSM (absorption, distribution, excretion, and toxicity) [99], and admet SAR [100] (metabolism) in in silico tools and listed in Table 3.

Our predicted result demonstrated that sesamin was within an acceptable range in all tested Lipinski, Ghose, Egan, Veber, and Muegge rules with a good bioavailability score (0.55), indicating sesamin maintained drug-likeness properties. Absorption is an essential property in drug discovery. Our predicted result showed that sesamin is highly soluble in water (-4.223), highly absorbed by the human intestine (97.81%), highly permeable to the skin, and Caco-2 with limited glycoprotein status. Distribution is followed by absorption, another principal descriptor for drug development, which depends on the aqueous solubility of compounds. Our in silico result revealed that sesamin could penetrate the central nervous system (CNS) and blood-brain barrier (BBB) with a poor steady-state volume of distribution (VSS). Human cytochrome P450 (CYP) isoforms are involved in drug metabolism in the liver, and its inhibition causes drug toxicity in the body. The predicted metabolic result reported that sesamin has poor metabolic status in both CYP isoform substrate and inhibition. Excretion property based on the total renal clearance parameter was predicted, where the sesamin’s total clearance (logCLtot) was -0.126 ml/min/kg. The toxicity profile of sesamin has been predicted based on eye corrosion, hepatotoxicity, AMES toxicity, and hERG potassium channel inhibition. The results outlined that sesamin showed toxicity only in the AMES test rather than eye corrosion, hepatotoxicity, hERG potassium channel inhibition, and T. pyriformis. P-glycoprotein (ATP-binding cassette (ABC) inhibition, aromatase, and estrogen receptor targeting of this protein) is a potent mechanism for any type of cancer treatment. Our analysis revealed that

![Figure 3: Overview of molecular targets influenced by sesamin in breast cancer. Studies have shown that sesamin can targets major molecular factors in breast cancer treatments. Downward directions (↓) represent downregulation, while upward directions (↑) represent upregulation.](attachment:figure3.png)
sesamin is a potent inhibitor of P-glycoprotein and can modulate estrogen receptors, but it does not inhibit aromatase enzymes.

To sum up, in our study, sesamin attributes some pharmacokinetics profiles (Table 3). So sesamin will facilitate the drug discovery process in computational chemistry, i.e., docking analysis, neural networking study, and pharmacophore-based virtual screening campaigns for the drug discovery community.

8. Limitation and Future Prospect of Sesamin in Breast Cancer Biology

The traditional treatment approaches used for breast cancer treatment are interrupted by many factors. Sesamin has a broad range of pharmacological properties that could be useful in therapeutics practices. Some of these properties contribute to sesamin as a potent anticancer agent. However, beside the pharmacological advantages, there is a major limitation to anticipate the real potentiality of sesamin against breast cancer treatment due to limited research on it. So, before delivering this phytochemical to the medicine cabinet as a natural therapeutic agent or medicament, it must first be approved by testing in vitro, in vivo, and clinical trial (stages I-IV). Long research is still needed to find out drug interaction, in vivo pharmacokinetic properties, accurate therapeutics dose, possible routes of administration, and established convenient nanoformulation of sesamin.

Furthermore, sesamin's structure-activity relationship (SAR) should be determined to predict biological activities. Acquisition of more information about synergistic activities of sesamin in combination with others phytochemicals and existing drugs can increase activities of drugs with reverse the anticancer resistance pattern by modifying those existing drugs. In addition, sesamin can be analyzed in computational chemistry studies, i.e., docking analysis, neural networking study, and pharmacophore-based virtual screening campaigns for the drug discovery community. Successful performance of all approaches will make sesamin an effective chemotherapeutic anticarcinogenic agent in treating various subtypes of breast cancer.

9. Conclusion

Along with other plant species, S. indicum, the oilseed crop has nutritional, medicinal, and industrial significance and assists as the main plant source for acquiring large amounts of sesamin. This phytochemical possesses a crucial functional group that attributes several biological functions. The evidence with sesamin highlighted in this review is insufficient, but we provided a comprehensive overview of the potential anticancer mechanism against breast pathobiology in in vitro and in vivo studies. The regulation of PI3K/AKT, JAK/STAT, and MAPK signaling pathways has been linked to sesamin's tumor-inhibitory activities, mediated by some typical receptor estrogen, HER2, and EGFR. Similar to sesamin, some of the sesamin metabolites possess anticancer activities in numerous cancerous cell lines. The prominent anticancer mechanisms of sesamin regulate transcription factors, apoptotic proteins, enzymes, receptors, growth factors, cell cycle regulatory protein and enzymes, and other numerous targets (Figure 3).

Moreover, sesamin has been found to attribute additive or synergistic activity with other phytochemicals such as γ-tocotrienol, a type of vitamin E. Little study has addressed the contradictory effect of sesamin. Pharmacokinetics parameters stated that sesamin satisfied all common properties that indicate good candidates for future drug development to treat cancer patients and other several other diseases. However, in the future, more experimental studies need to be conducted (in vitro, in vivo, and clinical studies) to assess sesamin’s efficacy on breast cancer and safety. Therefore, based on the review analysis (Figure 4), we hope that sesamin utilization in cancer biology can create an open door in the anticancer impact regarding breast cancer treatment as well as other diseases by using potential phytochemicals.
Conflicts of Interest
The authors declare that they have no conflicts of interest.

Acknowledgments
The authors thank the support from the Department of Pharmacy, East-West University, Dhaka, Bangladesh.

References
[1] H. Sung, J. Ferlay, R. L. Siegel et al., “Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries,” CA: A Cancer Journal for Clinicians, vol. 71, no. 3, pp. 209–249, 2021.
[2] M. I. Nounou, F. ElAmrawy, N. Ahmed, K. Abdelraouf, S. Goda, and H. Syed-Sha-Qhattal, “Breast cancer: conventional diagnosis and treatment modalities and recent patents and technologies,” Breast Cancer: Basic and Clinical Research, vol. 9, (Suppl 2), pp. 17–34, 2015.
[3] S. Mitra and R. Dash, “Natural products for the management and prevention of breast cancer,” Evidence-Based Complementary and Alternative Medicine, vol. 2018, Article ID 8324696, 23 pages, 2018.
[4] A. H. Partridge, H. J. Burstein, and E. P. Winer, “Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer,” JNCl Monographs, vol. 30, pp. 135–142, 2001.
[5] X. Wang, H. Zhang, and X. Chen, “Drug resistance and combating drug resistance in cancer,” Cancer Drug Resistance, vol. 2, no. 2, pp. 141–160, 2019.
[6] M. Sohel, M. Hossain, M. Hasan et al., “Management of mental health during COVID 19 pandemic: possible strategies,” Journal of Advanced Biotechnology and Experimental Therapeutics, vol. 4, no. 3, pp. 276–289, 2021.
[7] P. Paul, P. Biswas, D. Dey et al., “Exhaustive plant profile of ‘dimocarpus longan lour’ with significant phytomedicinal properties: a literature base-reviewed,” Processes, vol. 9, no. 10, p. 1803, 2021.
[8] M. Sohel, H. Sultana, T. Sultana et al., “Chemotherapeutic potential of hesperetin for cancer treatment, with mechanistic insights: a comprehensive review,” Helthyon, vol. 8, no. 1, article e08815, 2022.
[9] T. Saha, S. Makar, R. Swetha, G. G. J. M. Kuiper, J. G. Lemmen, B. Carlsson et al., “Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β,” Endocrinology, vol. 139, no. 10, pp. 4252–4263, 1998.
[10] J. Russo and I. H. Russo, “The role of estrogen in the initiation of breast cancer,” The Journal of Steroid Biochemistry and Molecular Biology, vol. 102, no. 1–5, pp. 89–96, 2006.
[11] G. G. J. M. Kuiper, J. G. Lemmen, B. Carlsson et al., “Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β,” Endocrinology, vol. 139, no. 10, pp. 4252–4263, 1998.
[12] M. Sohel, P. Biswas, M. Al Amin et al., “Genistein mediated molecular pharmacology, cell-specific anti-breast cancer mechanism with synergetic effect and in silico safety measurement,” 2021.
[13] I. Bilal, A. Chowdhury, J. Davidson, and S. Whitehead, “Phytoestrogens and prevention of breast cancer: the contentious debate,” World Journal of Clinical Oncology, vol. 5, no. 4, pp. 705–712, 2014.
[14] H. S. Seo, H. S. Choi, H. S. Choi et al., “Phytoestrogens induce apoptosis via extrinsic pathway, inhibiting nuclear factor-kappaB signaling in HER2-overexpressing breast cancer cells,” Anticancer Research, vol. 31, no. 10, pp. 3301–3313, 2011.
[15] E. D. Lephart, “Modulation of aromatase by phytoestrogens,” Enzyme Research, vol. 2015, Article ID 594656, 2015.
[16] A. A. Dar and N. Arumugam, “Lignans of sesame: purification methods, biological activities and biosynthesis - a review,” Bioorganic Chemistry, vol. 50, pp. 1–10, 2013.
[17] S. Udomruk, C. Kaewmool, P. Pothacharoen, T. Phitak, and P. Kongtawelert, “Sesamin suppresses LPS-induced microglial activation via regulation of TLR4 expression,” Journal of Functional Foods, vol. 49, pp. 32–43, 2018.
[18] M. Fukunaga, M. Ohnishi, A. Shirasuchi et al., “Sesamin increases heme oxygenase-1 protein in RAW 264.7 macrophages through inhibiting its ubiquitination process,” European Journal of Pharmacology, vol. 741, pp. 214–221, 2014.
[19] T. Yoshikawa, T. Ide, H. Shimano et al., “Cross-talk between peroxisome proliferator-activated receptor (PPAR) α and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. I. PPARs suppress sterol regulatory element binding protein-1c promoter through inhibition of LXR signaling,” Molecular Endocrinology, vol. 17, no. 7, pp. 1240–1254, 2003.
[20] S. Ahmad, N. ElSherbiny, M. S. Jamal et al., “Anti-inflammatory role of sesamin in STZ induced mice model of diabetic retinopathy,” Journal of Neuroimmunology, vol. 295-296, pp. 47–53, 2016.
[21] W. J. Lee, H. C. Ou, C. M. Wu et al., “Sesamin mitigates inflammation and oxidative stress in endothelial cells exposed to oxidized low-density lipoprotein,” Journal of Agricultural and Food Chemistry, vol. 57, no. 23, pp. 11406–11417, 2009.
[22] P. S. Yashaswini, B. Sadashivaiyah, T. R. Ramaprasad, and S. A. Singh, “In vivo modulation of LPS induced leukotrienes generation and oxidative stress by sesame lignans,” The Journal of Nutritional Biochemistry, vol. 41, pp. 151–157, 2017.
[23] A. F. Majdalawieh, M. Massri, and G. K. Nasrallah, “A comprehensive review on the anti-cancer properties and mechanisms of action of sesamin, a lignan in sesame seeds (Sesamum indicum),” European Journal of Pharmacology, vol. 815, pp. 512–521, 2017.
[24] A. V. Mali, A. A. Joshi, M. V. Hegde, and S. S. Kadam, “Enterolactone suppresses proliferation, migration and metastasis of MDA-MB-231 breast cancer cells through inhibition of uPA induced plasmin activation and MMPs-mediated ECM remodeling,” Asian Pacific Journal of Cancer Prevention: APJCP, vol. 18, no. 4, pp. 905–915, 2017.
[25] G. Flower, H. Fritz, L. G. Balneaves et al., “Flax and breast cancer,” Integrative Cancer Therapies, vol. 13, no. 3, pp. 181–192, 2014.
[26] E. Ono, M. Nakai, Y. Fukui et al., “Formation of two methylenedioxy bridges by a Sesamum CYP81Q protein yielding a furofuran lignan, (+)-sesamin,” Proceedings of the National Academy of Sciences of the United States of America, vol. 103, no. 26, pp. 10116–10121, 2006.
L. Jayasinghe, B. M. M. Kumarihamy, K. H. R. N. Jayarathna, Y. Ju, C. C. Still, J. N. Sacalis, J. Li, and C. T. Ho, “T. Pacher, C. Seger, D. Engelmeier, S. Vajrodaya, O. Hofer, V. S. Parmar, S. C. Jain, K. S. Bisht et al., N. Rangkadilok, N. Pholphana, C. Mahidol et al., A. S. M. T. Haque, J. N. Moon, P. S. Saravana, A. Tilahun, and F. Chaaib, E. F. Queiroz, K. Ndjoko, D. Diallo, and K. Hostettmann, “Antifungal and antioxidant compounds from the root bark of Fagara zanthoxyloides,” *Planta Medica*, vol. 69, no. 4, pp. 316–320, 2003.

S. Abu-Lafi, S. Makhama, I. Rayan et al., “Sesamin from Cuscuta palaeatina natural plant extracts: directions for prospective applications,” *PLoS One*, vol. 13, no. 4, article e0195707, 2018.

R. W. Doskotch and F. S. El-Feraly, “Isolation and characterization of (+)-sesamin and β-cyclopyrethrosin from pyrethrum flowers,” *Canadian Journal of Chemistry*, vol. 47, no. 7, pp. 1139–1142, 1969.

A. F. Hollis, R. H. Prager, E. Ritchie, and W. C. Taylor, “The chemical constituents of Australian flindersia species. XIV. The constituents of flindersia pubescens bail. And f. Schottiana f. Muell,” *Australian Journal of Chemistry*, vol. 14, no. 1, pp. 100–105, 1961.

Sesamin [C20H18O6- PubChem, 2005, https://pubchem.ncbi.nlm.nih.gov/compound/72307.

A. F. Majdalawieh, S. Dalibalta, and S. M. Yousef, “Effects of sesamin on fatty acid and cholesterol metabolism, macrophage cholesterol homeostasis and serum lipid profile: a comprehensive review,” *European Journal of Pharmacology*, vol. 885, article 173417, 2020.

A. Kamal-Eldin, A. Moazzami, and S. Washi, “Sesame seed Lignans: potent physiological modulators and possible ingredients in functional foods & nutraceuticals,” *Recent Patents on Food, Nutrition & Agriculture*, vol. 3, no. 1, pp. 17–29, 2011.

Z. Liu, N. M. Saarinlen, and L. U. Thompson, “Sesamin is one of the major precursors of mammalian lignans in sesame seed (Sesamum indicum) as observed in vitro and in rats,” *The Journal of Nutrition*, vol. 136, no. 4, pp. 906–912, 2006.

J. L. Peñalvo, S. M. Heinenon, A. M. Aura, and H. Adlercreutz, “Dietary sesamin is converted to enterolactone in humans,” *The Journal of Nutrition*, vol. 135, no. 5, pp. 1056–1062, 2005.

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

K. Yasuda, S. Ikushiro, M. Kamakura, M. Ohta, and T. Sakaki, “Metabolism of sesamin by cytochrome P450 in human liver microsomes,” *Drug Metabolism and Disposition*, vol. 38, no. 12, pp. 2117–2123, 2010.

K. Yasuda, S. Ikushiro, M. Kamakura, E. Munetsuna, M. Ohta, and T. Sakaki, “Sequential metabolism of sesamin by cytochrome P450 and UDP-glucuronosyltransferase in human liver,” *Drug Metabolism and Disposition*, vol. 39, no. 9, pp. 1538–1545, 2011.

T. Sakaki, K. Yasuda, M. Nishikawa, and S. Ikushiro, “Metabolism of sesamin and drug-sesamin interaction,” *Yakugaku Zasshi: Journal of the Pharmaceutical Society of Japan*, vol. 138, no. 3, pp. 357–363, 2018.

T. Kumanono, E. Fujiki, Y. Hashimoto, and M. Kobayashi, “Discovery of a sesamin-metabolizing microorganism and a new enzyme,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 113, no. 32, pp. 9087–9092, 2016.

H. Sato, A. Aoki, A. Tabata et al., “Development of sesamin-loaded solid dispersion with α-glycosylated stevia for improving physicochemical and nutraceutical properties,” *Journal of Functional Foods*, vol. 35, pp. 325–331, 2017.
[57] C. Y. Wang, C. C. Yen, M. C. Hsu, and Y. T. Wu, “Self-nanoemulsiﬁng drug delivery systems for enhancing solubility, permeability, and bioavailability of sesamin,” *Molecules*, vol. 25, no. 14, p. 3119, 2020.

[58] K. Iwamoto, S. Matsumura, Y. Yoshioka et al., “Using turmeric oil as a solvent improves the distribution of sesamin-sesamolin in the serum and brain of mice,” *Lipids*, vol. 54, no. 5, pp. 311–320, 2019.

[59] M. Ebrahimi, F. Dehghani, N. Farhadian, M. Karimi, and S. Golmohammadzadeh, “Investigating the anti-apoptotic effect of sesame oil and honey in a novel nanostructure form for treatment of heart failure,” *Nanomedicine Journal*, vol. 4, no. 4, pp. 245–253, 2017.

[60] A. K. Tanwar, N. Dhiman, A. Kumar, and V. Jaitak, “Engagement of phytoestrogens in breast cancer suppression: structural classiﬁcation and mechanistic approach,” *European Journal of Medicinal Chemistry*, vol. 213, article 110307, 2021.

[61] S. Ali and R. C. Coombes, “Estrogen receptor alpha in human breast cancer: occurrence and signiﬁcance,” *Journal of Mammary Gland Biology and Neoplasia*, vol. 5, no. 3, pp. 271–281, 2000.

[62] S. Arnesen, Z. Blanchard, M. M. Williams et al., “S. Estrogen receptor alpha in human breast cancer cells cause gene expression changes through constant activity and secondary effects,” *Cancer Research*, vol. 81, no. 3, pp. 539–551, 2021.

[63] P. Jain, A. Thiantanawat, N. Rangkadirak, P. Watcharasit, C. Mahidol, and J. Satayavivad, “Estrogenic activities of sesame lignans and their metabolites on human breast cancer cells,” *Journal of Agricultural and Food Chemistry*, vol. 59, no. 1, pp. 212–221, 2011.

[64] J. L. Hsu and M. C. Hung, “The role of HER2, EGFR, and other receptor tyrosine kinases in breast cancer,” *Cancer Metastasis Reviews*, vol. 35, no. 4, pp. 575–588, 2016.

[65] S. M. Saldana, H. H. Lee, F. J. Lowery et al., “Inhibition of type I insulin-like growth factor receptor signaling attenuates the development of breast cancer brain metastasis,” *PLoS One*, vol. 8, no. 9, article e75406, 2013.

[66] Y. J. Kim, J. S. Choi, J. Seo et al., “MET is a potential target for use in combination therapy with EGFR inhibition in triple-negative/basal-like breast cancer,” *International Journal of Cancer*, vol. 134, no. 10, pp. 2424–2436, 2014.

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

[68] G. Planes-Laine, R. Rochigneux, F. Bertucci et al., “PD-1/PD-L1 targeting in breast cancer: the ﬁrst clinical evidences are emerging: a literature review,” *Cancers*, vol. 11, no. 7, 2019.

[69] P. Kongtavewlert, B. Wudthiwi, T. H. Shwe, P. Pothacharoen, and T. Phitak, “Inhibition of programmed death ligand 1 (PD-L1) expression in breast cancer cells by sesamin,” *International Immunopharmacology*, vol. 86, article 106759, 2020.

[70] R. E. Harris, B. C. Casto, and Z. M. Harris, “Cyclooxygenase-2 and the inﬂammogenesis of breast cancer,” *World Journal of Clinical Oncology*, vol. 5, no. 4, pp. 677–692, 2014.

[71] Q. Fang, Y. Zhu, Q. Wang, M. Song, G. Gao, and Z. Zhou, “Suppression of cyclooxygenase 2 increases chemosensitivity to sesamin through the Akt-PIK signaling pathway in lung cancer cells,” *International Journal of Molecular Medicine*, vol. 43, no. 1, pp. 507–516, 2019.

[72] C. Carreau, G. Flouriot, C. Bennetau-Pelissere, and M. Potier, “Enteroﬁodiol and enterolactone, two major diet-derived polyphenol metabolites have different impact on ERα transcriptional activation in human breast cancer cells,” *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 110, no. 1–2, pp. 176–185, 2008.

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

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

[75] M. Saeed, H. Khalid, Y. Sugimoto, and T. Effert, “The lignan, (+)-sesamin reveals cytotoxicity toward cancer cells: pharmacogenomic determination of genes associated with sensitivity or resistance,” *Phytomedicine*, vol. 21, no. 5, pp. 689–696, 2014.

[76] E. Kim, H. J. Kim, H. N. Oh et al., “Cytotoxic constituents from the roots of asarum sieboldii in human breast cancer cells,” *Natural Product Sciences*, vol. 25, no. 1, pp. 72–75, 2019.

[77] A. C. Xiao, C. W. Hou, Y. H. Kao, and K. C. Jeng, “Effect of sesamin on apoptosis and cell cycle arrest in human breast cancer MCF-7 cells,” *Asian Paciﬁc Journal of Cancer Prevention*, vol. 16, no. 9, pp. 3779–3783, 2015.

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

[79] H. Liu, J. Liu, S. Wang et al., “Enterolactone has stronger effects than enteroﬁodiol on ovarian cancer,” *Journal of Ovarian Research*, vol. 10, no. 1, pp. 1–9, 2017.

[80] X. Y. Xiong, X. J. Hu, Y. Li, and C. M. Liu, “Inhibitory effects of enterolactone on growth and metastasis in human breast cancer,” *Nutrition and Cancer*, vol. 67, no. 8, pp. 1326–1334, 2015.

[81] A. V. Mali, A. A. Joshi, M. V. Hegde, and S. S. Kadam, “Enterolactone modulates the ERK/NF-κB/Snail signaling pathway in triple-negative breast cancer cell line MDA-MB-231 to revert the TGF-β-induced epithelial-mesenchymal transition,” *Cancer Biology & Medicine*, vol. 15, no. 2, pp. 137–156, 2018.

[82] S. Mehmood, D. A. Saeed, M. Rizwan et al., “Impact of different amendments on biochemical responses of sesame (Sesamum indicum L.) plants grown in lead-cadmium contaminated soil,” *Plant Physiology and Biochemistry*, vol. 132, pp. 345–355, 2018.

[83] S. Ahmad, N. M. Elsherbiny, R. Haque et al., “Sesamin attenuates neurotoxicity in mouse model of ischemic brain stroke,” *Neurotoxicology*, vol. 45, pp. 100–110, 2014.

[84] Y. Zhao, Q. Wang, M. Jia et al., “(+)-Sesamin attenuates chronic unpredictable mild stress-induced depressive-like behaviors and memory deﬁcits via suppression of neuroinﬂammation,” *The Journal of Nutritional Biochemistry*, vol. 64, pp. 61–71, 2019.
[85] T. Baluchnejadmojarad, M. Mansouri, J. Ghalami, Z. Mokhtari, and M. Roghani, "Sesamin imparts neuroprotection against intrastriatal 6-hydroxodopamine toxicity by inhibition of astroglial activation, apoptosis, and oxidative stress," *Biomedicine & Pharmacotherapy*, vol. 88, pp. 754–761, 2017.

[86] T. Phitak, P. Pothacharoen, J. Settakorn, W. Poompimol, B. Caterson, and P. Kongtawelert, "Chondroprotective and anti-inflammatory effects of sesamin," *Phytochemistry*, vol. 80, pp. 77–88, 2012.

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

[88] N. Hirose, F. Doi, T. Ueki et al., "Suppressive effect of sesamin against 7,12-dimethylbenz[a]-anthracene induced rat mammary carcinogenesis," *Anticancer Research*, vol. 12, no. 4, pp. 1259–1265, 1992.

[89] W. H. Wu, Y. P. Kang, N. H. Wang, H. J. Jou, and T. A. Wang, "Sesame ingestion affects sex hormones, antioxidant status, and blood lipids in postmenopausal women," *The Journal of Nutrition*, vol. 136, no. 5, pp. 1270–1275, 2006.

[90] R. Pezzani, B. Salehi, S. Vitalini et al., "Synergistic effects of plant derivatives and conventional chemotherapeutic agents: an update on the cancer perspective," *Medicina*, vol. 55, no. 4, p. 110, 2019.

[91] M. R. Akl, N. M. Ayoub, and P. W. Sylvester, "Mechanisms mediating the synergistic anticancer effects of combined γ-tocotrienol and sesamin treatment," *Planta Medica*, vol. 78, no. 16, pp. 1731–1739, 2012.

[92] M. R. Akl, N. M. Ayoub, B. S. Abuasal, A. Kaddoumi, and P. W. Sylvester, "Sesamin synergistically potentiates the anticancer effects of γ-tocotrienol in mammary cancer cell lines," *Fitoterapia*, vol. 84, no. 1, pp. 347–359, 2013.

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

[94] P. Bigoniya, R. Nishad, and C. S. Singh, "Preventive effect of sesame seed cake on hyperglycemia and obesity against high fructose-diet induced type 2 diabetes in rats," *Food Chemistry*, vol. 133, no. 4, pp. 1355–1361, 2012.

[95] WebMD, Sesame: Uses, Side Effects, Dose, Health Benefits, Precautions & Warnings, WebMD, 2022, https://www.emedicinehealth.com/sesame/vitamins-supplements.htm?fbclid=IwAR2TUw8-Anuxy.cfMzbY8m2MOUFS_57_RS69wFdJc7AizJQcnOgA4mbBR_E.

[96] S. Shimizu, K. Akimoto, Y. Shinmen, H. Kawashima, M. Sugano, and H. Yamada, "Sesamin is a potent and specific inhibitor of Δ5 desaturase in polyunsaturated fatty acid biosynthesis," *Lipids*, vol. 26, no. 7, pp. 512–516, 1991.

[97] T. J. Sontag, *Enzymatic regulation of vitamin E status: identification and characterization of the novel tocopherol-omega-hydroxylase pathway of vitamin E catabolism [Ph.D thesis]*, Cornell University, New York, 2005.

[98] A. Daina, O. Michielin, and V. Zoete, "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," *Scientific Reports*, vol. 7, no. 1, pp. 1–13, 2017.

[99] D. E. V. Pires, T. L. Blundell, and D. B. Ascher, "pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures," *Journal of Medicinal Chemistry*, vol. 58, no. 9, pp. 4066–4072, 2015.

[100] F. Cheng, W. Li, Y. Zhou et al., "AdmetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties," *Journal of Chemical Information and Modeling*, vol. 52, no. 11, pp. 3099–3105, 2012.