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Research Article

EVALUATING SESAME LIGNANS FROM SESAME SEEDS (*SESAMUM INDICUM* L.): UNVEILING ANTIDEPRESSANT AND COGNITIVE ENHANCEMENT POTENTIAL THROUGH *IN SILICO* MOLECULAR DOCKING AND *IN VITRO* STUDIES

ARUNA PRIYADHARSHINI M, PUNNAGAI KUMARAVELU*, BHUVANESWAR[1], ARAVINDKUMAR[4]

Department of Pharmacology, Tagore Medical College and Hospital, Chennai, Tamil Nadu, India.
***Corresponding author: Punnagai Kumaravelu; Email: punnagaiguna@gmail.com**

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ABSTRACT

Objective: Sesame lignans, sesamin and sesamolin, have shown promise due to their anti-inflammatory and antioxidant properties, but their precise neuropharmacological mechanisms and safety profiles remain inadequately explored. The study was purposed to Evaluating Sesame Lignans from Sesame Seeds (*Sesamum indicum* L.): Unveiling antidepressant and cognitive enhancement potential through *in silico* molecular docking and *in vitro* studies."

Method: This study employed an integrated *in silico* and *in vitro* approach. Molecular docking was performed to evaluate the binding affinity and interactions of sesamin and sesamolin with targets – amyloid-beta (Aβ), apolipoprotein E, and the norepinephrine transporter (NET). Pharmacokinetic and toxicity profiles were predicted using Swiss absorption, distribution, metabolism, and excretion, pkCSM, and ProTox-II. *In vitro* cytotoxicity was assessed in SH-SY5Y neuroblastoma cells using the MTT assay.

Result: Both lignans exhibited strong binding affinities for Aβ and NET, forming stable interactions via hydrogen bonds and hydrophobic contacts. They demonstrated favorable drug-likeness, high gastrointestinal absorption, and blood-brain barrier permeability. *In silico* predictions indicated a low toxicity risk, with no mutagenic or carcinogenic effects. Crucially, both compounds maintained high cell viability (>70%) in SH-SY5Y cells at concentrations up to 200 µg/mL, with half-maximal inhibitory concentration values of 386 µg/mL (sesamin) and 361 µg/mL (sesamolin), confirming their neuronal safety.

Conclusion: Sesamin and sesamolin demonstrate significant potential as multi-target neurotherapeutic agents. Their ability to modulate key pathological targets, combined with excellent pharmacokinetic properties and a high margin of neuronal safety, positions them as promising candidates for the treatment of cognitive disorders and depression, warranting further preclinical investigation.

Keywords: Sesamin, Sesamolin, Molecular docking, Neuroprotection, Amyloid-beta, Norepinephrine transporter, Cytotoxicity, SH-SY5Y cells, Absorption, distribution, metabolism, and excretion, Neurodegenerative diseases, Depression

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INTRODUCTION

Millions of people worldwide are affected by serious health conditions such as depression and cognitive disorders, including Alzheimer's disease. According to the World Health Organization, more than 280 million individuals suffer from depression, and the incidence of cognitive impairments is steadily increasing [1,2]. These illnesses worsen the quality of life for affected individuals and impose significant financial burdens on healthcare systems and society due to their challenging treatment and chronic nature. Selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors are two classes of pharmacological agents used frequently in the treatment of depression. SSRIs and MAO inhibitors work by increasing neurotransmitter levels, but they usually take 3–4 weeks to show noticeable effects. Moreover, they are ineffective in about 30–40% of cases and can cause side effects like drowsiness, weight gain, and sexual dysfunction [3]. Acetylcholinesterase inhibitors and behavior therapies for cognitive impairment mostly alleviate symptoms without addressing the fundamental causes of disorders such as amyloid-beta (Aβ) buildup or neuronal degeneration [4]. These issues underscore the need for novel therapeutic approaches that enhance efficacy, prolong action, and reduce adverse effects.

Natural chemicals derived from food sources have gained popularity as potential alternatives to conventional pharmaceuticals in recent years. This is due to their extensive array of biological activity and overall safety [5]. Sesame seeds (*Sesamum indicum* L.) represent a notable source of bioactive compounds [6]. They are esteemed not just for their culinary applications but also for their significance in traditional medicine. These seeds are rich in bioactive lignans, particularly sesamin and sesamolin, recognized for their capacity to combat inflammation and oxidative damage and regulate lipids. Research indicates that these lignans may benefit cardiovascular health, aid in cancer prevention, and maintain metabolic function. Significantly, recent data indicate that sesame lignans may safeguard the brain by mitigating oxidative stress, neuroinflammation, and neurotransmitter abnormalities. These are all significant elements in the progression of depression and cognitive deterioration. Sesamin has shown the capacity to reduce oxidative stress in neuronal cells,[7] whereas sesamolin has exhibited anti-inflammatory properties in several preclinical studies [7]. However, our understanding of the mechanisms by which these lignans function as antidepressants or cognitive enhancers remains limited, particularly regarding their interactions with critical targets such as Aβ, apolipoprotein E (ApoE), and the norepinephrine transporter (NET). Furthermore, further investigation is required to validate their therapeutic potential, since their safety profile in neuronal models, such as the SH-SY5Y human neuroblastoma cell line, remains undetermined.

Aim and objectives

The aim of the study was to explore the therapeutic potential of sesamin and sesamolin for depression and cognitive enhancement by integrating *in silico* molecular docking analysis with *in vitro* cytotoxicity evaluation.

Objectives

The objectives of the study are as follows:

- To perform molecular docking studies to predict the interactions of sesamin and sesamolin with target proteins implicated in depression and cognitive enhancement.
- To analyze drug-likeness and the toxicological profile of sesamin and sesamolin using the *in silico* molecular docking method.
- To evaluate the cytotoxicity of sesamin and sesamolin on the SH-SY5Y human neuroblastoma cell line using *in vitro* assays.

MATERIALS AND METHODS

Materials

The molecular structures of sesamin and sesamolin were obtained from the PUBCHEM database. The phytochemical was procured from Sigma-Aldrich, USA, with a stated purity of ≥98%, cell lines: SH-SY5Y cell lines (National Centre for Cell Science [NCCS], Pune); cell culture medium: Dulbecco's modified eagle medium (DMEM) + Ham's F-12- (Himedia), Fetal Bovine Serum (FBS) (#RM10432, Himedia), MTT reagent (5 mg/mL) (#4060Himedia).

Methods: Molecular docking

Target selection

In this study, key protein targets implicated in the pathophysiology of cognitive disorders were selected. These include Beta amyloid (PDB ID: 1AAP), ApoE (PDB ID: 6NCO), NET (PDB ID: 8Z1L), Beta amyloid (PDB ID: 1AAP), ApoE (PDB ID: 6NCO) and NET (PDB ID: 8Z1L) sequences were retrieved from the GenBank database (NCBI), followed by a BLAST analysis to identify homologous proteins. Sequences with the highest similarity scores were selected. Different conformers of the same protein were identified using the UniProt database, and homology models were generated using the SWISS-MODEL server. Structural validation of the modeled proteins was performed using quality assessment tools available in the Swiss Bioinformatics platform. Before docking, all water molecules and heteroatoms were removed. Polar hydrogens were added, and Kollman charges were assigned to each protein. Finally, the proteins were converted into PDBQT format using AutoDock Tools [8].

Ligand preparation

The three selected bioactive compounds, sesamin and sesamolin, were retrieved in SDF format from the PubChem database. The structures were converted to PDB format using Open Babel software. Hydrogen atoms were added to each ligand, and energy minimization was performed using the universal force field with the conjugate-gradient algorithm. The minimized structures were then converted into PDBQT format using AutoDock tools for further docking studies [8].

Docking study

Molecular docking was carried out using AutoDock Vina v1.2.0. The active sites of each protein were predicted using the PrankWeb server, which employs a phylogenetic algorithm to identify high-affinity binding pockets. The residues within the highest-ranked active site were selected, and their coordinates were used to define the docking grid. Docking simulations were conducted using the genetic algorithm with the local search method. Each docking run included 100 simulations using default docking parameters. Cluster analysis was performed on the generated structures using a root mean square deviation tolerance of 2.0 Å to assess conformational stability. The binding free energy and interaction profiles of each ligand-protein complex were evaluated. Molecular visualization and analysis of docking poses were carried out using Discovery Studio Visualize [9-11].

Toxicity prediction and pharmacokinetic analysis

The simplified molecular input line entry system (SMILES) notations for sesamin and sesamolin were generated using Swiss absorption, distribution, metabolism, and excretion (ADME) [12]. An online tool provided by the Swiss Institute of Bioinformatics. These SMILES structures were subjected to *in silico* toxicity screening using the pkCSM web server [13]. The following toxicity parameters were evaluated: AMES mutagenicity, acute oral toxicity, carcinogenicity, and rat acute toxicity (L_{D50}). In addition, organ-specific toxicities were predicted using the ProTox-II online platform to provide a comprehensive toxicity profile. This computational approach facilitates early-stage assessment of the pharmacokinetic and toxicological properties of the compounds [9].

Maintenance of cell lines and MTT assay

The SH-SY5Y human neuroblastoma cell line was procured from the NCCS, Pune, India. Cells were cultured in DMEM supplemented with 10% FBS and 1% antibiotic–antimycotic solution. Cultures were maintained at 37°C in a humidified incubator containing 5% CO_2 and 18–20% O_2. Cells were routinely sub-cultured every 3 days to maintain viability and ensure exponential growth. For the MTT assay, 200 µL of cell suspension was seeded into each well of a 96-well plate at a density of 20,000 cells/well. Cells were allowed to adhere and grow for 24 h at 37°C in a 5% CO_2 incubator. After the initial incubation, various concentrations of test agents (12.5, 25, 50, 100, and 200 µg/mL) were added to the wells, followed by a 48-h incubation under standard conditions. Post-treatment, the spent medium was removed carefully, and MTT reagent was added to each well to reach a final concentration of 0.5 mg/mL. The plate was covered with aluminum foil to protect it from light and incubated for an additional 3 h. After incubation, the MTT-containing medium was discarded, and 100 µL of solubilization solution (DMSO) was added to each well to dissolve the formazan crystals. Gentle shaking on a gyratory shaker facilitated complete dissolution; for denser cultures, careful pipetting was used as required. Absorbance was measured at 570 nm using a microplate reader [14,15].

Cell viability was calculated

Cell viability (%) = (Mean abs of treated cells/Mean abs of untreated cells) × 100. [Abs = Absorbance]

RESULTS

The current study investigated the neurotherapeutic potential of sesame lignans sesamin and sesamolin through *in silico* docking against cognitive and depression targets and *in vitro* cytotoxicity assessment using the SH-SY5Y neuroblastoma cell line. The binding energy data revealed that both sesamin and sesamolin exhibited a significant affinity for Aβ, ApoE, and the NET, with particularly strong interactions noted for Aβ and NET. These findings are of high relevance, given the established involvement of Aβ in the pathogenesis of Alzheimer's disease and the role of NET modulation in depressive disorders.

Docking study further illustrated the involvement of these lignans in multiple intermolecular interactions, including hydrogen bonding and hydrophobic contacts with active site residues of the selected proteins. Sesamin, for instance, formed hydrogen bonds with residues such as Ser293 and Phe338 in Aβ and Arg38 in ApoE, suggesting potential stabilization of protein conformations involved in pathological aggregation. Sesamolin displayed comparable interaction profiles, especially with NET and Aβ, reflecting a parallel pharmacodynamic potential. The drug likeness and pharmacokinetic profile of sesamin and sesamolin were evaluated using the online tool SwissADME. Both the sesamin and sesamolin did not violated any likeness rules (Lipinski, Ghose, Veber, Egan, and Muegge), suggesting both ligands are suitable for oral bioavailability. The bioavailability score of 0.55 for both sesamin and sesamolin further supports their potential as drug candidates, indicating oral absorption and systemic availability presented in Table 3.

In Table 5, the pharmacokinetic evaluation highlights key ADME parameters. Both compounds demonstrate high gastrointestinal (GI) absorption and the ability to cross the blood-brain barrier (BBB), making them promising for central nervous system (CNS)-targeted

Table 1: Intermolecular interactions and binding energy of proteins with sesamin

Targets	Binding energy kCal/mol	Hydrogen bonding interactions	Hydrophobic interactions
Beta amyloid	−9.2	Phe295 (2.1), Ser293 (2.5), Phe338 (2.2), Tyr337 (2.5), Tyr124 (1.6)	Trp86 (3.8), Trp286 (3.5), Phe297 (3.6), Phe338 (3.4), Tyr341 (3.3)
ApoE	−6.8	Glu27 (2.4), Leu30 (2.5), Trp34 (3.2), Asp35 (3.5), Arg38 (2.5), Asp153 (3.5), Gln156 (2.4)	Arg38 (4.7)
NET	−8.1	Arg30 (2.0), Ala246 (3.3), Asp401 (3.5), Glu402 (2.2), Phe405 (3.4), Thr409 (3.0), Trp467 (2.9), Val483 (3.4)	Trp409 (3.8), Lys398 (3.9)

Table 2: Intermolecular interactions of proteins with sesamin

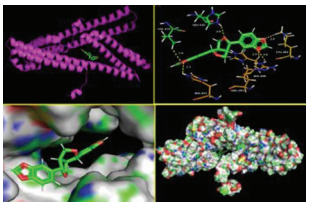
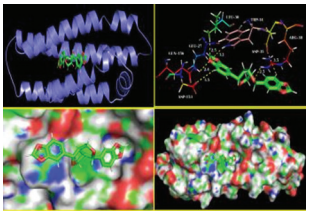
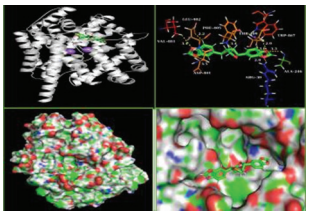
Targets	Intermolecular interactions	Hydrogen bonding interactions	Hydrophobic interactions
Beta amyloid (PDB ID: 1AAP)		Phe295 (2.1), Ser293 (2.5), Phe338 (2.2), Tyr337 (2.5), Tyr124 (1.6)	Trp86 (3.8), Trp286 (3.5), Phe297 (3.6), Phe338 (3.4), Tyr341 (3.3)
ApoE (PDB ID: 6NCO)		Glu27 (2.4), Leu30 (2.5), Trp34 (3.2), Asp35 (3.5), Arg38 (2.5), Asp153 (3.5), Gln156 (2.4)	Arg38 (4.7)
NET (PDB ID: 8Z1L)		Arg30 (2.0), Ala246 (3.3), Asp401 (3.5), Glu402 (2.2), Phe405 (3.4), Thr409 (3.0), Trp467 (2.9), Val483 (3.4)	Trp409 (3.8), Lys398 (3.9)

Table 3: Intermolecular interactions of proteins with sesamolin

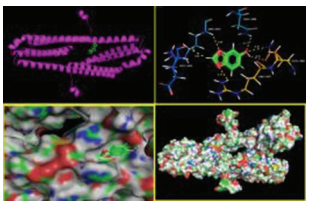
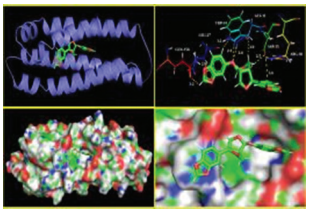
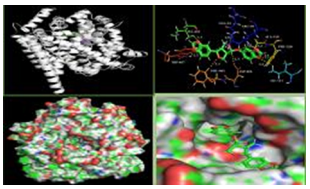
Targets	Intermolecular interactions	Hydrogen bonding interactions	Hydrophobic interactions
Beta amyloid (PDB ID: 1AAP)		Phe338 (2.7), Ser293 (2.3), His287 (3.0), Trp286 (2.8)	Trp286 (3.3), Tyr341 (3.6)
ApoE (PDB ID: 6NCO)		Glu27 (2.9), Gly31 (3.0), Trp34 (3.2), Asp35 (2.5), Arg38 (3.4), Gln156 (3.2)	Glu27 (3.8), Trp34 (3.8)
NET (PDB ID: 8Z1L)		Arg30 (2.9), Gln34 (2.8), Ile111 (3.2), Ile245 (3.3), Ala319 (3.6), Phe320 (3.2), Asp404 (2.5), Phe405 (3.3), Trp467 (2.5)	Ile245 (4.2), Ala319 (3.7), Trp467 (4.5), Tyr471 (3.7),

Table 4: Drug likeness of the selected ligands

Ligand	Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations	Bioavailability score
Sesamin	0	0	0	0	0	0.55
Sesamolin	0	0	0	0	0	0.55

Table 5: Pharmacokinetic properties of the selected ligands

Parameter	Sesamin	Sesamolin
GI absorption	High	High
blood brain barrier permeation	Yes	Yes
P-glycoprotein substrate	No	No
CYP1A2 inhibition	No	Yes
CYP2C19 inhibition	Yes	No
CYP2C9 inhibition	No	Yes
CYP2D6 inhibition	Yes	Yes
CYP3A4 inhibition	Yes	Yes
Log Kp (skin permeation)	−6.56 cm/s	6.44 cm/s
Total clearance	−0.056 log mL/min/kg	−0.056log mL/min/kg)

CYP: Cytochrome P450

Table 6: Estimated values of toxicity for the selected ligands

Ligand	Rat acute toxicity LD_{50} (mol/kg)	Oral rat chronic toxicity (lowest observed adverse effect level)
Sesamin	2.883	1.568
Sesamolin	2.761	1.554

therapies. In addition, none of them are P-glycoprotein substrates, increasing the therapeutic value. In cytochrome P450 (CYP) enzyme interactions, both compounds inhibit CYP2D6 and CYP3A4, which could potentially lead to drug–drug interactions if co-administered with other substrates of these enzymes. Sesamin also inhibits CYP2C19, whereas sesamolin inhibits CYP1A2 and CYP2C9, reflecting different metabolic pathways. Further, both chemical compounds were tested for the safety profile. The *in silico* acute and chronic organo toxicity were performed using online tools pkCSM and ProTox-3.0.

Sesamin and sesamolin exhibited relatively low acute and chronic toxicity profiles, suggesting a favorable safety margin for potential therapeutic applications. Rat acute toxicity (LD50) values for sesamin and sesamolin were predicted to be 2.883 mol/kg and 2.761 mol/kg, respectively, and oral rat chronic toxicity, expressed as lowest observed adverse effect level, was found to be 1.568 mol/kg and 1.554 mol/kg, respectively. These results support the potential use of sesamin and sesamolin as therapeutic agents, with a low risk of chronic toxicity at relevant doses. However, further *in vivo* studies and clinical validations are essential to confirm these findings.

The organ toxicity profile in Table 7 reveals notable differences between the two lignans. Sesamin is largely non-toxic across most of the parameters, except for nephrotoxicity and cardiotoxicity, where it is marked as active. In contrast, sesamolin exhibits hepatotoxicity, neurotoxicity, respiratory toxicity, and immunotoxicity, indicating broader potential for adverse effects. Importantly, both compounds are non-carcinogenic, non-mutagenic, and non-cytotoxic, supporting their safety for further development.

In vitro cytotoxicity assessments in the SH-SY5Y neuroblastoma cell line, both sesamin and sesamolin maintained cell viability above 70% up to a concentration of 200 µg/mL, with half-maximal inhibitory concentration values of approximately 386 µg/mL and 361 µg/mL, respectively. These results indicate a favorable safety margin for neuronal applications and suggest that both compounds can be employed at pharmacologically active concentrations without inducing cytotoxic effects in neuronal models.

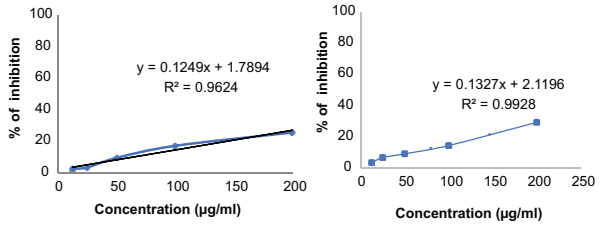
Table 7: Organo toxicity of the selected ligands

S. No	Organ toxicity	Sesamin	Sesamolin
1.	Hepatotoxicity	Inactive	Active
2.	Neurotoxicity	Inactive	Active
3.	Nephrotoxicity	Active	Inactive
4.	Respiratory toxicity	Inactive	Active
5.	Cardiotoxicity	Active	Inactive
6.	Carcinogenicity	Inactive	Inactive
7.	Immunotoxicity	Inactive	Active
8.	Mutagenicity	Inactive	Inactive
9.	Cytotoxicity	Inactive	Inactive

Table 8: Dose-dependent cytotoxic effect of sesamin on SH-SY5Y cells determined by MTT assay

S. No	Concentration of sample (µg/mL)	% cell viability	% inhibition
1.	Untreated	100	0
2.	12.5	97.572	2.428
3.	25	96.716	3.284
4.	50	90.693	9.307
5.	100	83.05	16.95
6.	200	74.622	25.378
	Half-maximal inhibitory concentration		385.9936 µg/mL

Table 9: Dose-dependent cytotoxic effect of sesamolin on SH-SY5Y cells determined by MTT assay



S. No	Concentration of sample (µg/mL)	% cell viability	% inhibition
1.	Untreated	100	0
2.	12.5	96.75	3.25
3.	25	93.49	6.5
4.	50	91.05	8.94
5.	100	85.77	14.23
6.	200	70.92	29.08
	Half-maximal inhibitory concentration		360.8168802

DISCUSSION

The collective data support the hypothesis that sesame lignans may exert neuroprotective and antidepressant effects through multi-target mechanisms. Their ability to bind Aβ may interfere with aggregation pathways central to Alzheimer's pathology, while NET interaction hints at mood-enhancing properties relevant to depressive symptoms. Additionally, their favorable ADME characteristics and predicted safety profiles further strengthen their promise as effective CNS-targeted therapeutic agents. Further,

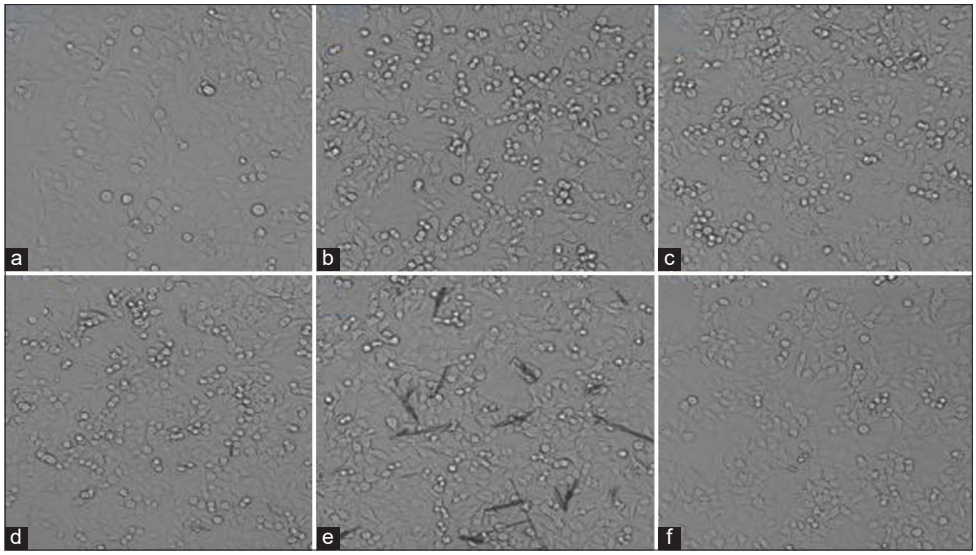


Fig. 1: Cytotoxicity of sesamin on SH-SY5Y cell line; (a) 12.5 µg /mL; (b) 25 µg /mL; (c) 50 µg /mL; (e) 200 µg/mL; (f) control

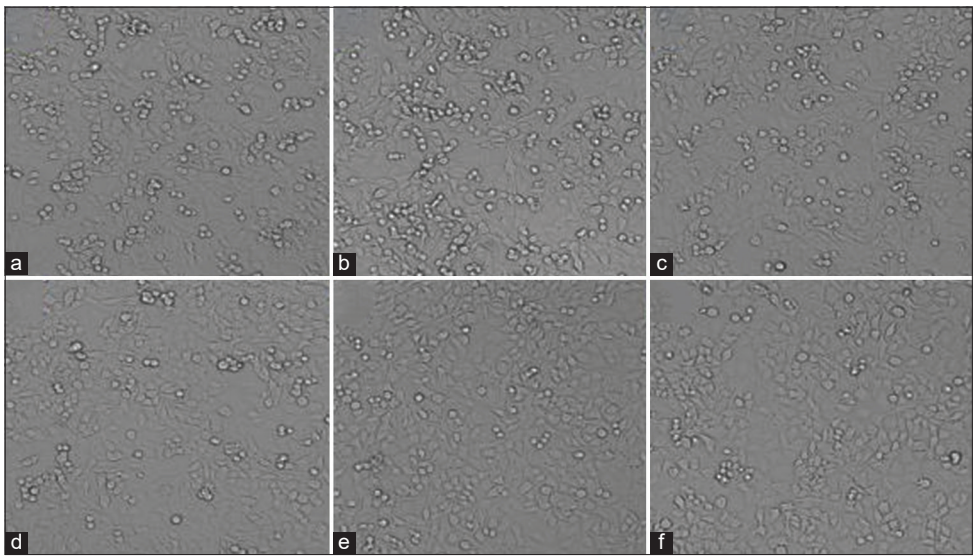


Fig. 2: Cytotoxicity effect of sesamolin on SH-SY5Y cell line; (a):12.5 µg/mL; (b)25 µg/mL; (c): 50 µg/mL; (d): 100 µg/mL; (e): 200 µg/mL; (f): control

Secoisolariciresinol diglucoside (SDG), primarily found in flaxseed (*Linum usitatissimum*), is one of the most extensively studied lignans for its antioxidant and neuroprotective effects. It has been demonstrated to reduce oxidative stress and improve cognitive function in experimental models of neurodegeneration [16]. However, the neuroprotection conferred by SDG primarily operates through indirect pathways, such as free radical scavenging and anti-inflammatory effects, rather than direct receptor or enzyme modulation [17]. In contrast, sesamin and sesamolin in the present study exhibit specific binding interactions with CNS targets, notably NET and Aβ, which are critical to the pathogenesis of depression and cognitive impairment. Furthermore, SDG's limited bioavailability restricts its clinical translation, while sesamin and sesamolin possess better lipophilicity and metabolic stability, suggesting improved CNS penetration and pharmacological efficacy.

Similarly, matairesinol, another plant-derived lignan structurally related to sesamin, has been reported to possess modest antioxidant and weak estrogenic activities, but lacks strong evidence for direct CNS engagement [18]. Unlike matairesinol, the sesame lignans evaluated in this study exhibit robust molecular interactions with CNS-related proteins and display high neuronal safety as shown by their non-toxic profile in SH-SY5Y cells. Although matairesinol may contribute indirectly to brain health through systemic anti-inflammatory pathways, sesamin and sesamolin offer more targeted mechanisms, reinforcing their potential as neurotherapeutic agents.

Arctigenin, a lignan from *Arctium lappa*, is recognized for its potent neuroprotective and anti-inflammatory activities. It has been shown to inhibit microglial activation, attenuate ischemic injury, and enhance memory performance in rodent models [19]. Mechanistically, it targets multiple CNS pathways, similar to the multi-target binding exhibited by sesamin and sesamolin in our docking analysis. However, arctigenin is known to inhibit mitochondrial respiration at higher concentrations, raising potential toxicity concerns [20]. In contrast, the current study provides quantitative cytotoxicity data that confirms the safety of sesamin and sesamolin at pharmacologically relevant doses, supporting a more favorable therapeutic window.

Another well-documented lignan is honokiol, a biphenolic compound from Magnolia officinalis. Honokiol exerts anxiolytic, antidepressant, and neuroprotective effect through mechanisms such as GABA-A

receptor modulation and inhibition of Aβ aggregation [21,22]. While honokiol's neuropharmacology aligns closely with that of sesame lignans in terms of anti-amyloid and antioxidant actions, it suffers from poor water solubility and limited CNS bioavailability, which can hinder its therapeutic applicability [23]. On the other hand, sesamin and sesamolin, due to their better lipid solubility and predicted BBB permeability, are more promising candidates for CNS drug development. Collectively, these comparisons emphasize the unique advantage of sesamin and sesamolin among lignans. They not only interact directly with neural targets implicated in both depression and neurodegeneration but also exhibit a high margin of safety in neuronal cells. These properties distinguish sesame lignans from other structurally related compounds and underscore their potential as multi-target neurotherapeutic agents with applications in mood and memory disorders.

The present study demonstrates that sesame-derived lignans, sesamin and sesamolin, possess promising neuropharmacological properties, exhibiting significant binding affinities toward key CNS targets implicated in depression and cognitive impairment, including Aβ, ApoE, and the NET. Their ability to form stable hydrogen bonding and hydrophobic interactions with these targets supports their potential role in modulating amyloid aggregation, enhancing neurotransmitter regulation, and promoting neuroprotection [24]. In addition, both compounds exhibited favorable pharmacokinetic profiles, including high GI absorption and ability to cross the BBB, which collectively enhance their suitability for CNS applications.

Furthermore, both compounds showed minimal cytotoxicity in SH-SY5Y neuronal cells, confirming their safety at therapeutically relevant concentrations. These findings highlight the therapeutic value of sesamin and sesamolin as multi-target agents with potential utility in the management of neurodegenerative and mood disorders. The dual demonstration of efficacy and neuronal safety positions these natural lignans as strong candidates for further preclinical validation and development into functional neurotherapeutic agents.

Limitations

The study's limitations include its reliance on predictive *in silico* and single-cell line *in vitro* data, which lack validation in functional assays or more complex *in vivo* models to confirm efficacy and safety.

CONCLUSION

This study provides compelling evidence for the significant potential of the sesame lignans, sesamin and sesamolin, in treating depression and enhancing cognitive function. Our integrated *in silico* and *in vitro* approach reveals that these compounds exhibit strong binding affinities for key targets – NET, Aβ, and ApoE. This multi-target mechanism suggests a capacity for dual therapeutic action. Crucially, their favorable predicted pharmacokinetic properties, such as high BBB permeability and GI absorption, position them as promising CNS-active agents. Collectively, these findings suggest that sesamin and sesamolin represent a unique class of natural compounds capable of simultaneously addressing cognitive decline and depressive disorders. The path forward is clear and critical: these findings must now be validated in advanced *in vivo* models of neurodegeneration and depression to confirm efficacy in a whole organism. Subsequent research should focus on elucidating the precise molecular pathways of their action, optimizing bioavailability, and establishing effective dosing regimens. Ultimately, this work paves the way for future clinical trials to translate these promising preclinical results into tangible human health benefits, potentially offering novel, naturally derived strategies to combat Alzheimer's disease, depression, and other CNS disorders.

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AUTHOR'S CONTRIBUTION

All authors have contributed to this work regarding experimental design, performing experiments, data completion, and progress of the manuscript.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

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