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Review

Harnessing role of sesamol and its nanoformulations against neurodegenerative diseases

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ABSTRACT

Sesamol is a lignan of sesame seeds and a natural phenolic molecule that has emerged as a useful medical agent. Sesamol is a non-toxic phytoconstituent, which exerts certain valuable effects in the management of cancer, diabetes, cardiovascular diseases, neurodegenerative diseases (NDs), etc. Sesamol is known to depict its neuroprotective role by various mechanisms, such as metabolic regulators, action on oxidative stress, neuroinflammation, etc. However, its poor oral bioavailability, rapid excretion (as conjugates), and susceptibility to gastric irritation/toxicity (particularly in rats' forestomach) may restrict its effectiveness. To overcome the associated limitations, novel drug delivery system-based formulations of sesamol are emerging and being researched extensively. These can conjugate with sesamol and enhance the bioavailability and solubility of free sesamol, along with delivery at the target site. In this review, we have summarized various research works highlighting the role of sesamol on various NDs, including Alzheimer's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Parkinson's disease. Moreover, the formulation strategies and neuroprotective role of sesamol-based nano-formulations have also been discussed.

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1. Introduction

Neurodegenerative diseases (NDs) are distinguished by the loss or degeneration of susceptible neuronal populations from various parts of the brain. Some of the most common NDs include Amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's disease (HD), and Alzheimer's disease (AD). The capacity to walk, speak, breathe, balance, or control one's heart rate is significantly challenged in people with NDs [1]. The commonly observed neurological signs include demyelination, neuronal damage, dendrites loss, abnormal misfolding and proteins, etc [2]. Although nerve degeneration is frequently inherited, it can sporadically be caused by conditions including alcoholism, smoking, lifestyle disorders, tumors, strokes, etc. In addition, the two main factors governing NDs are the formation of intra- or extracellular insoluble protein aggregates like β-amyloid (Aβ), α-synuclein, etc., and the loss of nerve cells from the appropriate brain areas [3]. Similar to the pathophysiology of neuronal degeneration, misfolded proteins, mitochondrial dysfunction, oxidative stress, as well as neuroinflammation are the factors that affect the pathogenesis of NDs. The extent to which NDs develop can be influenced by environmental variables such as diabetes, insufficient sleep, stress, poor eating habits, and environmental pollutants [4]. Effective therapies are crucial, but only if the root causes of each illness are well understood.

Sesamol is a phenolic chemical that is naturally isolated from the sesame (*Sesamum indicum*), family Pedaliaceae [5]. The "queen of oilseeds" is another name for it [6]. Sesame is characterized by an aromatic odor and a mellow taste [7]. It is valued for its medicinal values in both Indian and Chinese medicine systems [8]. It is primarily grown in Africa, Asia, South America, etc, with the chief cultivators in Tanzania, India, Ethiopia, Nigeria, etc. Sesamol is generally obtained from roasted sesame seeds and processed oil. In roasted seeds and processed oil, a higher amount of sesamol occur. One significant property of sesame oil is its inherent opposition to oxidative degradation or rancidity.

Chemically, sesamol is 3, 4-methylenedioxyphenol, the molecular formula being $C_7H_6O_3$ (molar mass: 138.12 g/mol). Sesamin and sesamolin are the two main lignans present in sesame oil, making more than 1.4% of the total content. While, the minor lignans are sesamol, samin and episesamin [9]. The derivatives of sesamol have been reported to possess significant potential for treating various diseases. Methylenedioxyphenyl ethers have demonstrated its excellent efficacy in the treatment of pyrethum synergists, while 2,2-disubstituted-5-hydroxy-1,3-benzodioxoles have exhibited promising responses in addressing oxidative stress [10]. Halogenated sesamol esters have been utilized effectively as insecticides, and 3-aryl-3-hydroxy-2-oxindole with a 1,2,3,-triazole moiety has shown promise in managing enantiomeric excess. Sesamin has displayed significant potential in treating various diseases due to its antioxidant and anti-inflammatory properties [11]. This indicated that sesamol can be an effective molecule to treat oxidative stress in brain. However, it is important to note that none of these derivatives have been yet explored for their potential in addressing neurodegenerative diseases. The molecular structure of sesamol and its derivatives are presented in Fig. 1 [12].

Sesamol is a water-soluble lignan. It can be taken orally because of its small size and low molecular weight. The log P value of sesamol is 1.3, accounting for its lipophilic and hydrophilic features [5]. The phenolic nature of sesamol allows it to form phenolic radicals rather than reactive oxygen species (ROS). These radicals either dimerize or rearrange themselves to form neutral and non-toxic components [13]. The several methods of extraction of phytoconstituents from sesame leaves are based on ultrasound-solvent assisted extraction [5], microwave-assisted

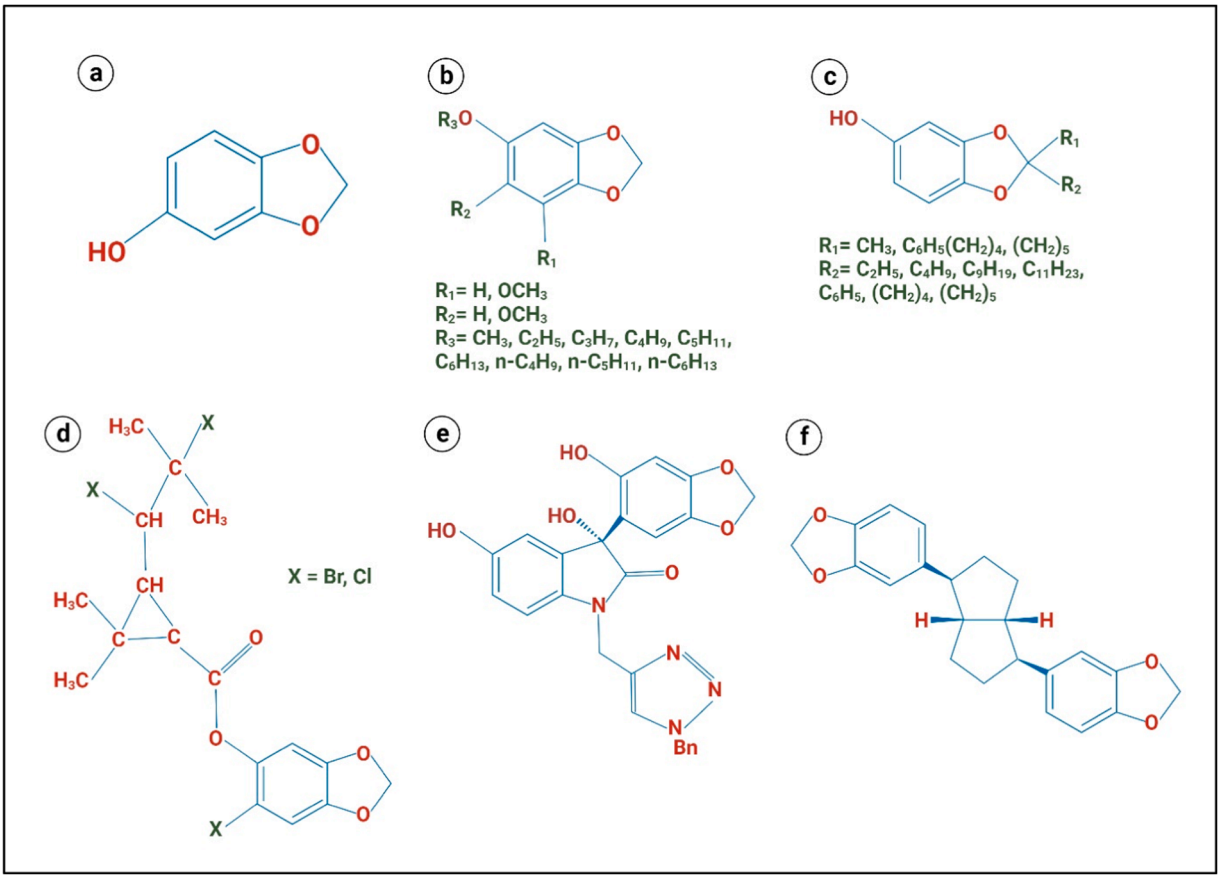

Fig. 1. Structure of the sesamol and its derivatives a. Sesamol, b. Methylenedioxyphenyl ethers, c. 2,2-disubstituted-5-hydroxy-1,3-benzodioxoles, d. Halogenated sesamol esters, e. 3-aryl-3-hydroxy-2-oxindole with 1,2,3,-triazole moiety f. Sesamin.

extraction [14], and various others.

It has grown in popularity as an adjuvant therapy for the detection, management, and prevention of a variety of diseases. It is commonly used to prevent numerous diseases and medical conditions as a result of several research. It possess various pharmacological effects such as anti-cancer, neuroprotective, cardioprotective, anti-inflammatory, hypolipidemic, radioprotective, anti-aging, anti-depressant, and anticonvulsant action [15]. Sesamol has been extensively studied for its potential as a medicinal agent, and there is strong proof that it operates as a metabolic regulator with advantages for the prevention of cancer, inflammation, hepatotoxicity, and free radicals [7,16]. It also activates caspase cascades and cell death in cancer cells through routes regulated by receptors and mitochondria [6].

In this review, we have focused on sesamol's potential against various NDs diseases. We have described relevant research and the need for their nano-formulations. Moreover, the nano-formulations have been described well.

2. NDs

AD is one of the most common types of NDs, described by Alois Alzheimer. Extracellular amyloid β (Aβ) buildup and intracellular neurofibrillary tangle (NFT) production are the two hallmarks of AD. More than 44 million people are diagnosed with AD worldwide [17]. In India, more than 4 million people are affected with AD till date [18].

Neuronal tau inclusions and deposits of Aβ, such as amyloid or senile plaques, in the parenchyma, both contribute to the mixed proteinopathy that characterizes the neuropathology of AD [19]. Additionally, amyloid angiopathy is commonly seen in AD patients. The early amyloid plaques are thought to be diffuse, non-compact amyloid deposits, sometimes known as "pre-amyloid" deposits since they do not stain well with normal amyloid dyes. Amyloid deposits, which frequently appear in the primary motor and visual cortices, can also have thick coarse, depending on the area of the brain [19]. Microglia, astroglia, and neuronal processes can all be seen in amyloid plaques (sometimes referred to as "dystrophic neurites"). Microglia are more common in areas with thick deposits [20,21].

Extrapyramidal motor abnormalities are a feature of Parkinson's disease (PD), and in this condition, dopaminergic neurons gradual degeneration is seen in the midbrain's substantia nigra pars compacta (SNPC). Over 10 million individuals worldwide suffered from PD till now. In the USA, there are around one million people with PD. The number might reach 1.2 million by the end of 2030. About $52 billion is spent annually on PD sufferers healthcare in the USA [22].

In PD, degeneration of dopaminergic neurons is commonly observed. According to research, healthy and dopamine-deficient individuals both have basal ganglia that work the same way. According to this theory, striatal dysfunction is mostly brought on by a dopamine shortage [23]. As a result, GABAergic striatal neurons provide less direct input to the substantia nigra pars reticulata (SNpr) and interior part of the globus pallidus (GPi), increased drive along the indirect route, especially through the external globus pallidus (GPe) and subthalamic nucleus (STN). Hence, this affects the activity of the brain stem motor neurons, such as those in the pedunculopontine nucleus and the thalamocortical motor system. The GPi and SNpr output structures of the basal ganglia are also impacted. Two signs of PD include a limited range of motion and trouble initiating movements [24]. This disruption is assumed to be the source of these symptoms. Although the idea successfully explains akinesia, it is more difficult to comprehend other significant PD characteristics like stiffness and tremor. Another feature of the idea that is disregarded is the fact that dopamine governs brain activity at cortical levels in addition to the striatum and other basal ganglia nuclei [25–27].

HD is a hereditary, autosomal-dominant disorder that affects the nervous system. The huntingtin (HTT) gene on the shorter arm of chromosome 4p16.3 is affected by HD, which is characterized by the increase of cytosine-adenine-guanine (CAG) trinucleotide repeats (36 replications or more). Globally, more than 5–8 cases of HD have been documented in every 0.1 million individuals until 2021. Multiple nations and ethnic groups throughout the world are currently diagnosing and reporting HD. American, Australian, and European countries have the highest rates of HD patients. In China, Japan, Finland and Africa, the prevalence of HD is less commonly documented. In the USA, 0.2 million individuals are at risk of getting HD, and there are around 0.03 million HD patients [28]. Symptoms typically start to appear between the ages of 30 and 50. Nearly 0.04–0.07 million of India's 1397 million individuals, or 3–5 per lakh, are estimated to have HD. Around 3–7 individuals per 10,000 people are said to have HD in Europe. According to reports, 46 HD cases per 0.1 million inhabitants are observed in South Africa. [29].

The pathophysiology of HD involves several elements, including oxidative stress, mitochondrial failure, genetic dysfunction, and neurodegeneration. The stress and inflammatory responses in the brain are brought on by the mutant huntingtin (mHtt) genes, which accelerate neuronal aging. Most of the genes have been found on chromosome 4p16.3, which contains neural cells, 3144 amino acids, and 67 exons. Studies have shown that the ribosomal RNA (rRNA) exons of normal human genes include 5–35 cytosine-adenine-guanine (CAG; coding for glutamine) triplet genes. Genetic mutation is the outcome of cellular translation being altered by the mHtt genetic code. The CAG repetition increases from 36 to 121 [30–32]. Depending on the patient's age at the time the illness first appeared, the amount of CAG repeats varied. The enhanced creation of ROS, mitochondrial dysregulation, neuronal inflammation, stress on the endoplasmic reticulum (ER), and synthesis of aberrant protein molecules are all linked to the mHtt gene [33]. The mitochondria need to maintain intracellular calcium homeostasis to stop the ER from producing free radicals, which in turn slows the apoptotic process. An early pathogenic HD expression has altered mitochondrial dysfunction [33]. The mHtt genes generate oxidative stress and malfunctioning of mitochondria via interaction with mitochondrial transporter II receptors [34–37]. Cerebrospinal fluid (CSF) experiences mitochondrial oxidation as a result of mitochondrial malfunction, which reduces the amount of glucose that can be used for metabolism. Mitochondrial failure raises lactate levels in the cerebral cortex and CSF [38,39]. It is currently unclear how oxidative stress functions in HD on a fundamental level. Enhanced lipid peroxidation, ROS, and genetic mutation may be the main causes of disease manifestation [40,41]. Moreover, several studies have demonstrated that oxidative damage, mitochondrial malfunction, and abnormal electron transport chain can also cause a rise in ROS [42]. Excitotoxicity, which can result in mitochondrial malfunction, a breakdown in the control of energy production, and metabolic inhibition, mainly occurs due to an increase in free radical concentration [43,44].

The uncommon NDs known as ALS, also known as Lou Gehrig's illness or Charcot disease, affects the motor neurons in the cerebral cortex, medulla oblongata, and spinal column of the brain. This is a very uncommon form of ND that affects the motor neurons in the brain's cerebral cortex, medulla oblongata, and spinal column. An individual is diagnosed with ALS every 90 min [45]. In the USA, 0.031 million individuals were still living with the illness in 2017 [46]. According to the Foundation for Research on Rare Diseases and Disorders, every 5th person per 0.1 million people in India is diagnosed with ALS. It occurs more frequently in adults over 50 [47].

The development of ALS is believed to be governed by complicated interplay at molecular and genetic levels. Due to malfunctioning of the excitatory amino acid transporter 2 (EAAT2) in the astrocytes, there is decreased glutamate absorption from the synaptic gap, which results in glutamate neuronal excitotoxicity. Glutamate induces excitotoxicity, which arises from the stimulation of Ca^{2+}- dependent enzymatic routes, which causes ND. Mutations occurring in the c9orf72, TDP-43, and fused in sarcoma (FUS) genes cause inadequate translation, disturbed ribonucleic acid (RNA) metabolism, and the formation of intracellular neuronal clumps. Superoxide dismutase-1 (SOD-1) gene mutations have

been associated with intracellular aggregates, increased oxidative stress, and decreased axonal transport in ALS. Furthermore, neurotoxic, and pro-inflammatory cytokines are produced by activated microglia [48, 49]. The pathophysiology of NDs is shown in Fig. 2.

3. Role of sesamol for the treatment of various NDs

3.1. AD

Several studies have been reported where sesamol shown significate role for the treatment of AD. Sesamol has shown antioxidant, anti-inflammatory and antiapoptotic effects by attenuating level of ROS, RNS, SOD, cytokines [50]. Those works are summarized in subsequent sections. Ren et al. (2020) reported that sesamol exhibited anti-oxidant effects for the treatment of AD in C57BL/6 J mice. AD was induced using the sugar D-galactose (at a dose of 300 mg/kg/day, intraperitoneally). By decreasing the levels of anti-oxidant enzymes, such as heme oxygenase (HO-1) and NADPH quinone oxidoreductase (NQO1), D-galactose harms the liver and exacerbates oxidative stress. Sesamol (100 mg/kg/day) exerted inhibitory effects on D-galactose and enhanced expression of HO-1, NQO1, chloramphenicol acetyltransferase (CAT), and glutathione (GSH). As revealed by biochemical estimation, elevation in CAT activity, and amount of GSH decreased in serum was noticed with sesamol. Moreover, the levels of inflammatory mediators as well as malondialdehyde (MDA) and myeloperoxidase (MPO) declined in sesamol-treated than D-galactose treated serum. In H_2O_2-induced SH-SY5Y cells, treatment with sesamol dramatically boosted the translocation of nuclear Nrf_2, raised the level of Nrf_2 in the nucleus, and boosted the expressions of the antioxidant enzymes in a dose-dependent way. Numerous behavioral tests, such as the Morris water test, the Y-maze test, and the locomotor activity test, have been evaluated. Eight weeks of D-galactose and sesamol treatment were given to the animals. In a Y-maze test, each mouse was put in the middle of the black Y-maze and given free rein for investigating the three arms for eight minutes, to assess basic memorizing skills and curiosity. The total number of platform crossings, the target quadrant swimming times, and the opposite, left, and right non-target quadrant swimming times were all kept track of using a visual tracking approach. The treatment with sesamol improved spontaneous alterations by 16.3% ($p < 0.01$), induced by oxidative stress. Researchers employed the Morris water maze test to evaluate the mice capacity for learning and remembering spatial connections. The system consists of a circular water tank with 100 cm diameter and 40 cm height. The clear platform was partially immersed in the water, just a centimeter below the surface. The mouse was allowed to take part in four training sessions each day for a total of four days. The mice time to emerge from the water was calculated for each experiment. Once the platform was removed for a probing test on the sixth day, the mice were permitted 60 s to swim at will. The following parameters were noted, i.e., swimming times in the target quadrant, the opposite, left, and right non-target quadrants, as well as the overall number of platform crossings. Sesamol decreased escape latency time period and distance than D-galactose on all four days. Additionally, the memory impairment was restored by sesamol [51].

Acetylcholine (ACh) levels drop in the occurrence of AD. The hyperactivity of Acetylcholinesterase (AChE) hydrolyzes ACh in various locations of the body. Thus, to provide symptomatic relief, AChE inhibitors are used. Topal (2019) evaluated the potential of sesamol to act against the AChE enzyme and it was found that the IC_{50} value of the AChE was 86.63 nM. The non-competitive inhibition by sesamol is facilitated by binding to the allosteric site of the enzyme and therefore, the ACh levels remain higher. Hence, it was concluded that sesamol is a potential agent for AD [52].

Mohamed and co-workers (2021) researched to reveal the improvement in $AlCl_3$-induced AD symptoms. For six weeks, the rats

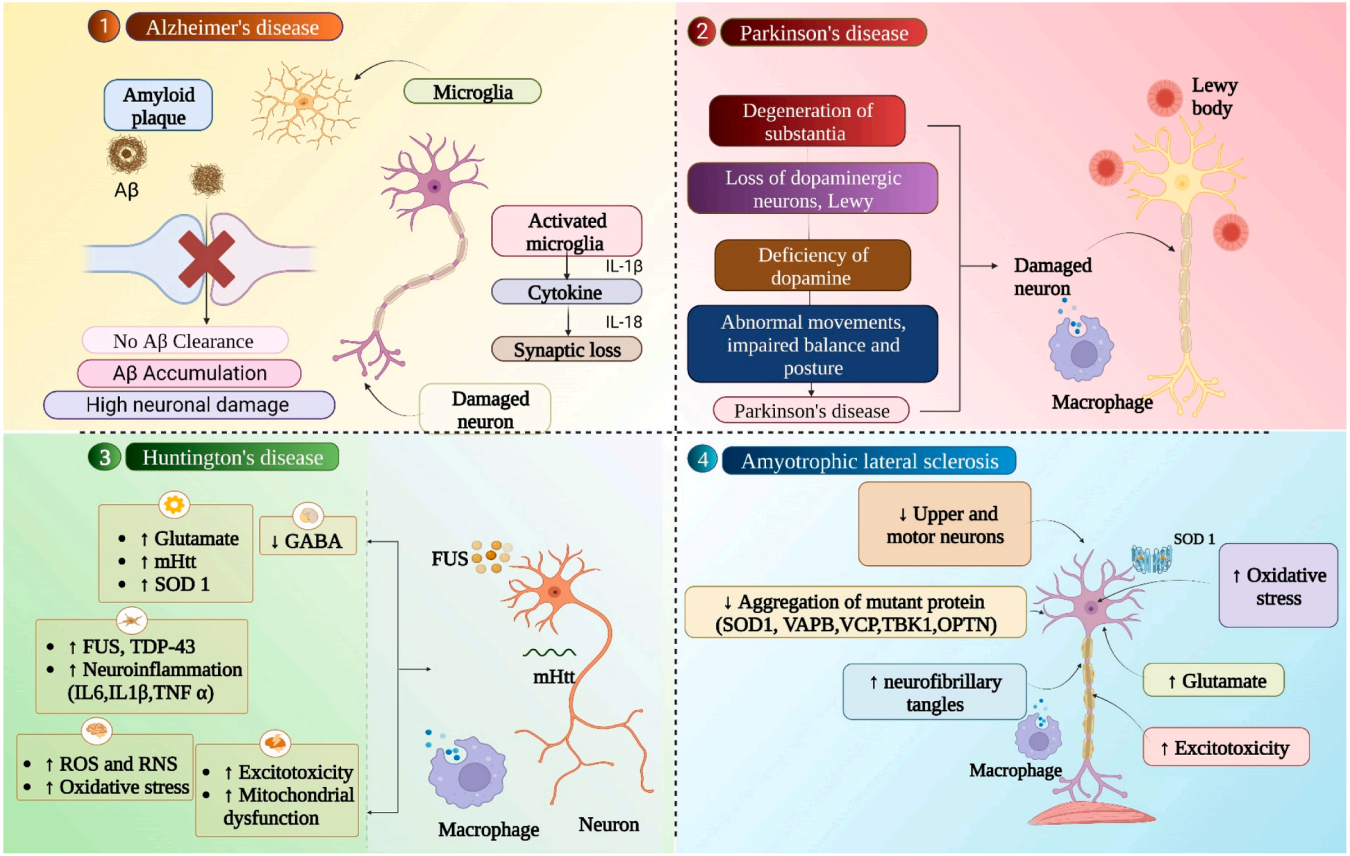

Fig. 2. Pathophysiology of NDs.

were treated with either $AlCl_3$ (100 mg/kg) via intraperitoneal injection or $AlCl_3$ and sesame oil (2 diverse doses). The behavioral studies (Open-field and Morris water maze tests) demonstrated improved memory. Additionally, the Aβ overexpression was restored by sesamol oil. Furthermore, the AD-inducing alterations in NF-κB/p38MAPK/BDNF/PPAR-γ signaling were restored to normal by the combined action of phytoconstituents of sesame oil. The modulation in oxidative stress and histopathological variations was achieved by the sesame oil [53].

Sesamol has been shown to have neuroprotective effects in the treatment of localized ischemia/reperfusion (I/R) damage, using a Sprague-Dawley rat brain, by Gao et al. (2017). The treatment with sesamol elevated the levels of antioxidants (e.g., SOD, GSH) and the expression of mRNA for proinflammatory cytokines was remarkably mitigated. The inhibition of apoptosis, oxidative damage, and inflammation were the actions displayed by the sesamol supplement [54].

The beneficiary role of sesame lignans. i.e., sesamol, sesamin, etc. in AD was studied by Keowkase et al. (2018). A transgenic worm *Caenorhabditis elegans (C. elegans)* model was used. The worm model is characterized by the occurrence of human Aβ fragments in the body wall muscle and progressive paralysis. The treatment with sesamin (100 μg/mL) extended the lifespan of the worm. Also, sesamolin (100 μg/mL) successfully delayed the paralysis by 1.83 h. The administration of sesamin reduced the Aβ oligomer band intensity, as demonstrated by western blotting. Modulation of chemotaxis behavior was exhibited by all sesame lignans. The antioxidant potential of sesamol was highest among other sesame lignans [55].

Katayama and coworkers (2016) studied age-related pathology of AD using a senescence-accelerated mouse prone 8 (SAMP8) model. Male SAMP8 (16 weeks old) were fed with freeze-dried sesaminol powder in the form of a standard chow diet. In in-vitro studies, sesaminol acted against Thioflavin T (ThT) fluorescence intensity (reduced to approx. 10%), as an indicator of Aβ aggregation, while the TEM analysis confirmed its action against the inhibition of Aβ fibril. The in-vivo studies were conducted on SAMP8 mice and oral administration of 0.05% w/w sesaminol was done for 16 weeks. Comparing the sesaminol-treated group to the control group, immuno-dot blotting showed that the production of Aβ oligomers was decreased. The reduced levels of 8-hydroxydeoxyguanosine (8-OHdG) in the serum of sesaminol-treated mice and the reduction in expression of genes for inflammatory cytokines (tumor necrosis factor (TNF-α), interleukin (IL-1β), and IL-6), using real-time polymerase chain reaction method, clarified its neuroprotective actions. Another accomplishment following sesaminol treatment was the raised amounts of ADAM10, a protein essential for the creation of a non-toxic amyloid precursor protein component [56].

In a study by Yun and team (2022), scopolamine was used to induce cholinergic disorders. C57BL/6 mice were pre-treated per-orally with sesamol (100 mg/kg/day) for a period of 30 days. Sesamol reversed cholinergic stress by inhibiting AChE action and enhanced choline acetyltransferase (ChAT) activity. Behavioral tests reported improvement in cognition and increased postsynaptic density in scopolamine-treated mice. Inflammation contributors and microglia were suppressed by sesamol treatment. The antioxidant enzymes amount was replenished and thus, oxidative stress was mitigated. Thus, sesamol was able to manage scopolamine-induced cholinergic dysfunction efficiently [50].

In AD, the ε4 allele of ApoE (apolipoprotein E) is a significant genetic risk factor for disease development. ApoE receptors can uptake the Aβ-ApoE complex. Yuan et al. (2019), conducted a study on wild-type and ApoE-deficient mice (C57BL/6), treated with a high-fat diet and sesamol in drinking water (0.05% w/v) for 10 weeks. Thioflavin S staining demonstrated reduced Aβ accumulation in sesamol-treated wild-type mice. The Aβ accumulation by sesamol was depicted in an ApoE-dependent fashion. Enhancement in cognition and anxiety issues were observed in wild-type mice. Moreover, also sesamol elevated ApoE, liver X receptor α (LXRα), and low-density lipoprotein receptor-related protein 1 (LRP1) expressions in high-fat diet-fed wild-type mice only and, not in ApoE-deficient mice. Thus, the study reported the ApoE-dependent neuroprotective actions of sesamol [57].

3.2. PD

The research work reported by Nija et al. (2020), successfully synthesized and described the ester prodrug, mefenamic acid-sesamol prodrug (MF-S), and the log P-value for MF-S was established to be 1.39. The structure of the MF-S prodrug as identified by fourier transform infrared spectroscopy (FTIR) was also supported by the spectrum analysis. The estimated *Madin-Darby canine kidney* (MDCK) permeability of the blood-brain barrier (BBB) by Qikprop's analysis revealed that the MF-S had higher permeability (3138.16) than the parent drug, which was 193.17. The drug and prodrug distribution may be evaluated using the in vivo bio-distribution method. 10 min after the prodrug MF-S injection, the (C_{brain} / C_{plasma}) ratios were found to be 0.491:0.013. The open field, water maze, and the marble burying test were used to track behavior related data. The second group, which received an oral injection of $AlCl_3$, significantly experienced neurotoxicity ($P < 0.001$), whereas the control group just received normal saline therapy. A notable decrease in escape latency was observed with the synthetic ester pro medications during the water maze test which, proved the neuroprotective effects of prodrugs. Conjugated ester prodrugs, which are organic antioxidants, were shown to have higher activity and were thus more successful in preventing the deterioration of nerve cells when the antioxidant qualities were examined. With the drug MF-S, a histopathological analysis of mouse brain revealed normal cortical cells free from any spongiform cells [58].

In a study by Park and team (2015), sesamin was also shown to suppress the mitogen-activated protein kinases (MAPKs) (ERK, p38MAPK, JNK1/2)-caspase-3 signaling axis, which halted the onset of 6-OHDA stimulated PD in mice. Most of these studies claimed that co-administration of folic acid synergistically enhanced sesamol's effects [59].

In research by Dogra et al. (2021)., the activities of the antioxidant enzymes were demonstrated to increase in sesame oil (SO)-treated groups up to a dose of 0.7% w/v coupled with a corresponding decrease in MDA (a marker of the significance of lipid peroxidation) levels, but starting at 0.9% w/v dose, the enzymatic actions reported 0% mortality. The levels of GSH and MDA were found to be within the prescribed limits, and it was demonstrated that the functions of antioxidant enzymes intensified with an elevation in the proportion of *Mucuna pruriens* (MP) extract and SO up to 2:3. Based on findings of mortality rate and biochemical investigations, it was shown that the 2:3 ratio of MP extract and SO was the suitable measure for treating the rotenone model of PD [60].

The effect of sesamol against the 6-OHDA induced PD rat model was evaluated by Baluchnejadmojarada and team (2017). Male Wistar rats received sesamol (10 or 20 kg/mg/day) treatment for a week before surgery. Afterwards, the striatum was lesioned. The treatment with sesamin (20 kg/mg/day) decreased the latency and total crossing time in the narrow beam test. Then, the oxidative stress markers were altered in the following ways: 35.3% reduction in MDA, 46.4% reduction in ROS, and 1.32 times elevation in SOD levels. The anti-apoptotic action depicted 32.8% reduction (at 20 mg/kg) in the activity of caspase-3. The western blotting analysis of α-synuclein protein indicated a 34.3% reduction in expression of the protein, upon treatment with 20 mg/kg sesamin. The prevention of damage to dopaminergic neurons was confirmed using tyrosine hydroxylase (TH) immunohistochemistry. With sesamol doses, i.e., 10 and 20 mg/kg, reduction in glial fibrillary acidic protein (GFAP) immunoreactivity was observed as 35.6% and 74.3%, respectively. It served as an indication that sesamol can attenuate astrogliosis, which is one of the major pathological hallmark observed in PD [61].

3.3. HD

Lowering the stress caused by enzymatic and non-enzymatic oxidants, aids in the reduction of lipid peroxidation [62]. Sesamol reportedly reduces nitric oxide production, which is considered to be its potent MOA to elicit protection against HD. Thus, it can be concluded that it boosts synaptic plasticity and neurotransmission while protecting the brain from memory loss brought on by 3-NP (3-nitropropionic acid), oxidative stress, and neuroinflammation in the neurons of the hippocampus [63–65].

Zeid et al. (2021) researched the action of sesamol on alumina nanoparticles (AlNPs, 100 mg/kg) induced neurotoxicity in Sprague-Dawley rats. For 28 days, AlNPs were given by gavage with or without sesamol (100 mg/kg). Reduction in AChE activity, improvement in 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in the brain, attenuation of AlNPs induced elevated expression of TNF-α, etc. were some of the prominent findings of the study. Sesamol was also shown to have anti-inflammatory, anti-apoptotic, and antioxidant properties [66].

For the treatment of HD, Kumar et al. (2021) explored the role and extent of the protective action of sesamol. (3-NP) (10 mg/kg, intraperitoneally for 14 days) was used to induce neurotoxicity in male Wistar rats. Sesamol (5,10, and 20 mg/kg) pre-treatment revealed improvement in behavioral parameters, oxidative damage, mitochondrial enzyme levels, etc. The restoration of mitochondrial enzymes in the brain by sesamol exaggerated its antioxidant potential. The levels of SOD and catalase enzymes returned to normal. The muscle grip strength improved in sesamol-treated (5,10 and 20 mg/kg, peroral) groups, as indicated by the rotarod test. The cellular viability was enhanced by treatment of sesamol at higher doses, i.e., 10 and 20 mg/kg [67].

3.4. ALS

According to the research of Wu et al. (2023), Cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) (the cGAS-STING) pathway also serves as a crucial route in the pathogenesis of NDs. It is stimulated by mitochondrial DNA (deoxyribonucleic acid) in ALS and, eventually, triggers microglia-mediated neuronal inflammation. Thus, utilizing cGAS-STING inhibitors, (like H151) the activity of the cGAS-STING pathway add providing symptomatic relief. It has been shown that manganese (Mn) acts as a cGAS activator and via enhancement of antineoplastic immune responses, improvement in immunotherapy is witnessed. It has been suggested that the cGAS-STING pathway in the microglia has been altered to explain the mechanism of neurotoxicity brought on by Mn exposure. In the current work, researchers investigated sesamol neuroprotective effects on neurotoxicity brought by Mn exposure to analyze the involvement of the cGAS-STING pathway. These studies found that sesamol successfully modulated the microglial cGAS-STING and NF-κB pathway, dropping Mn-induced neuroinflammation and improving cognitive damage in mice treated with Mn. This groundbreaking work illustrates how sesamol reduces neuroinflammation after Mn exposure and ameliorates cognitive diminishing by the microglial cGAS-STING/NF-κB route. Due to the bioavailability and tolerability of sesamol, it may be utilized as a preventative measure or therapy for a health condition brought on by Mn [68]. Various research works based on sesamol against NDs are tabulated in Table 1. The molecular mechanisms of sesamol for the treatment of NDs are presented in Fig. 3.

4. Need for NDDS based formulation

The benefits of organic drugs on neuroprotection have been demonstrated, but they also have a variety of drawbacks, such as limited bioavailability, insufficient BBB permeability, and poor water solubility. In various research, the bioavailability of sesamol has been reported as 35.5 ± 8.5%. Contrary to conventional medication administration methods, NDDS is believed to increase bioavailability, therapeutic effectiveness, stability, and permeability across BBB for herbal pharmaceuticals while decreasing their negative effects [74,75]. Because of their tiny particle size (approx. under 200 nm), herbal drug-incorporated nanoparticles are thought to decrease first-pass metabolism and increase bioavailability by passing through BBB endothelial cells via diffusion, transcytosis, etc [76]. Numerous studies have shown that plant extracts or their active components can improve pharmacokinetic characteristics like C_{max} and area under curve, enhancing their oral bioavailability [77]. Although sesamol exerts various beneficial effects, its therapeutic potential is hurdled by its pharmacokinetic properties. Despite its good water-soluble and lipophilic nature, its poor bioavailability and rapid elimination from the body pose limitations [78]. The novel drug-loaded nanocarriers assist in improving solubility, bioavailability, target-specific delivery, limited side effects due to dose reduction, sustained release of drugs, etc. Hence, they have been effective in treating several NDs, including PD and AD. It is important to note that much of the information on the creation of nanoparticles for the treatment of NDs originates from preclinical research and that there is currently a shortage of expertise in this area. Nonetheless, it is believed that NDDS may potentially be useful in treating NDs based on their track record. It is vital to research delivery methods that include extracts of the phytoconstituents to treat NDs and exert neuroprotective effects.

Table 1
Various research studies have depicted the action of Sesamol in NDs.

S. No.	NDs	Animal/Dose/ Study characteristics	Study Outcomes	Ref.
1.	AD	Human neuroblastoma cells (SH-SY5Y), 1 μM sesamol used	• Upregulated BCL-2 (an anti-apoptotic protein), downregulated BAX (a pro-apoptotic protein) • Boosted the expression of the SIRT1-SIRT3-FOXO3a pathway, demonstrating sesamol's anti-apoptotic properties	[69]
		APPswe/PS1dE9 transgenic mice with AD; Sesamol: (0.075%w/w)	• Exerted protective action for synaptic ultrastructure • Halted neuroinflammatory responses in the AD-induced mice brain • Repressed the hyperactivated microglia and attenuated the over-expressive TNF-α and IL-1	[70]
		CD-1 male mice, 12-month mice fed for 12 weeks on sesamol (0.1% w/w)	• Amended neuronal destruction and neuroinflammation due to aging • Decreased aggregation of $A\beta_{1-42}$ and release of lipopolysaccharide (LPS)	[71]
2.	PD	Male Wistar rats, sesamol dose: 30 mg/kg in saline via intraperitoneal administration	• Increased the levels of SOD, CAT, and GSH to enhance the antioxidant capacity of the brain tissues of PD-prone rats.	[72]
		Rotenone-induced PD model, orally administered sesamol (15 mg/kg)	• Improved the survival of dopaminergic neurons by raising parkin and DJ-1 (Parkinson Disease Protein) levels • Improved motor coordination as observed in the staircase test	[73]
3.	AD, PD, HD	Human neuroblastoma (SH-SY5Y), oxidative stress induced by H_2O_2, (400 μM) treatment:1 μM sesamol	• Reduced cell death and ROS formation, stimulated SIRT1-SIRT3-FOXO3a expression • Inhibited BAX) and improved BCL-2 expression	[69]

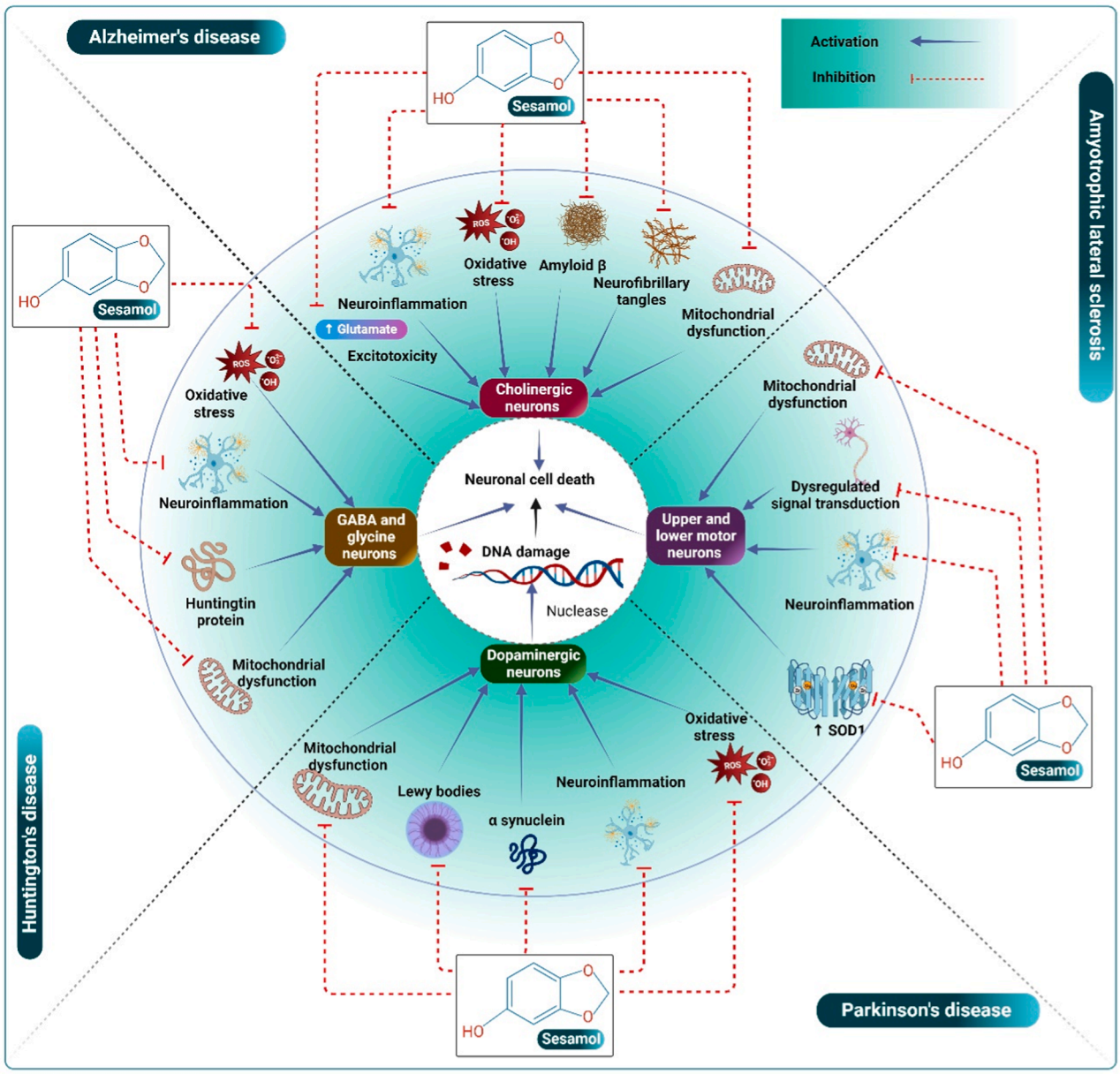

Fig. 3. Neuroprotective effects of sesamol.

4.1. *Mechanism utilized by nanocarriers to transverse BBB*

4.1.1. *Carrier-mediated transport*

Various transporter proteins are embedded in the cell membranes to facilitate the transport of endogenous substances, such as amino acids, glucose, etc. Facilitated diffusion and active diffusion are followed for the movement along and against the concentration gradient, respectively. The nanocarriers are formulated to mimic the endogenous substrates [79].

4.1.2. *Receptor-mediated transcytosis (RMT)*

Numerous receptors are present on the luminal side of endothelial cells, e.g., low-density lipoprotein, cholesterol, transferrin receptors, etc. The appropriate drugs conjugate with the ligand as vector and the drug as cargo and connect to the suitable carrier, i.e., nanocarrier via covalent linkage. Monoclonal antibodies (mAb), cell-penetrating peptides, etc. can be used as a ligand. Enhanced absorption and transport across the BBB have been reported [80].

4.1.3. *Adsorptive-mediated transcytosis (AMT)*

The cationic nanoparticles interact via electrostatic interactions with the negatively charged moieties on the luminal side of the endothelial membrane, and endocytosis follows. The endocytic vesicle exits the membrane via transcytosis and transports the nanocarriers across the BBB [81,82]. Various mechanism involved nanocarriers to transverse BBB are presented in Fig. 4.

5. Various NDDS-based formulations of sesamol against NDs

Various sesamol-loaded nanocarriers have been formulated for targeted drug delivery with improved efficiency. These may include nanostructured lipid carriers (NLCs), quantum dots, solid lipid nanocarriers (SLNs), nanosponges, micelles, etc. Various nanocarrier are shown in Fig. 5.

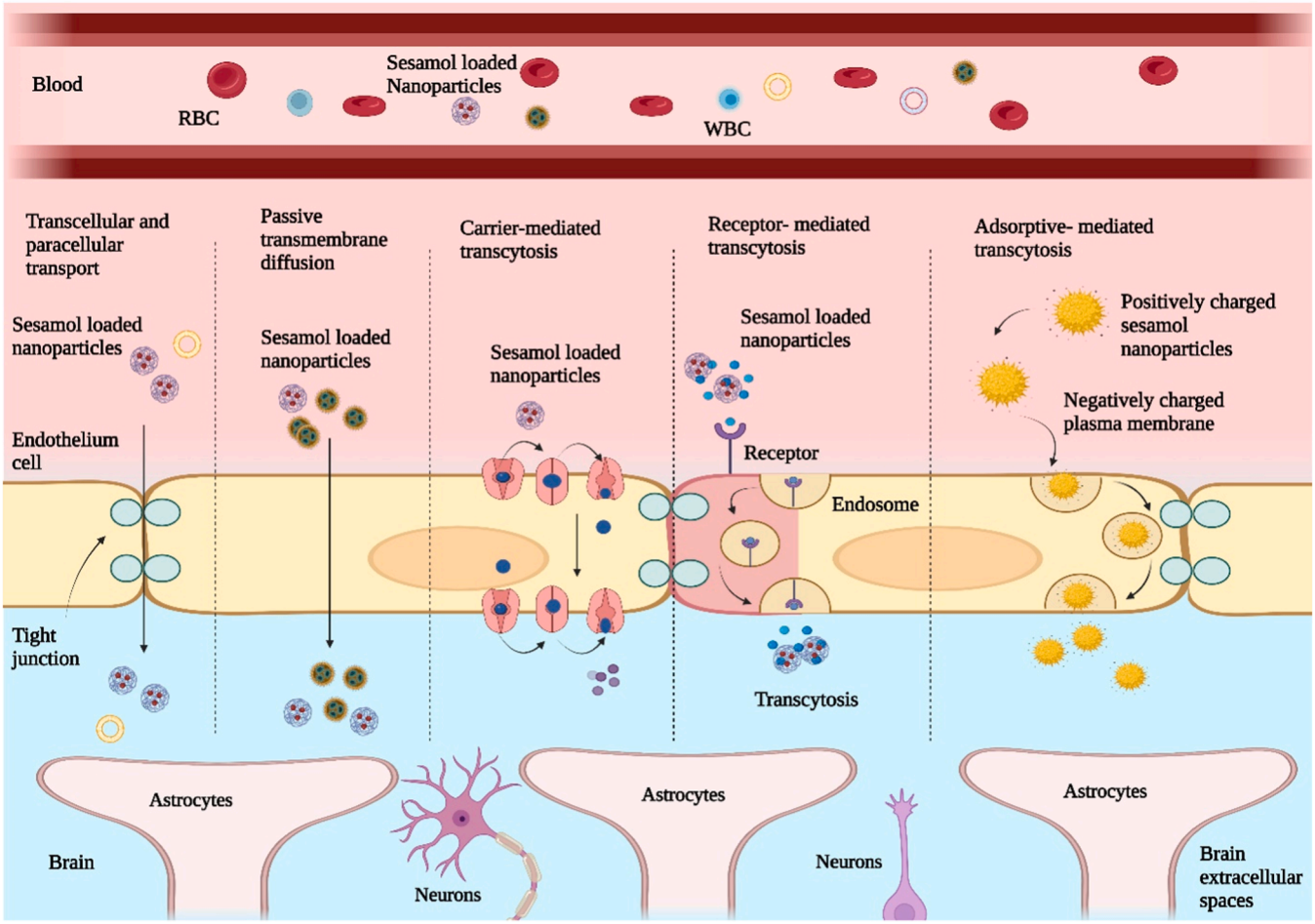

Fig. 4. Different mechanisms adopted by the nanocarriers to transverse BBB.

5.1. *Nanostructured lipid carriers*

NLCs are nanoparticles in the range of 10–1000 nm, prepared from solid and liquid lipids. These are the second generation of lipidic nanoparticles [83]. The components of NLCs are disseminated in an aqueous solution with a stable, cytotoxic-low, biocompatible surfactant. Owing to their smaller particle size NLCs highlight various advantages, with a few being listed as strong physical stability, improved drug entrapment, controlled drug release, enhanced permeability from gut membranes, easy formulation, etc [84]. NLCs can be manufactured by various techniques, including hot high-pressure homogenization (HHPH), cold HPH, emulsification-ultrasonication, solvent emulsification evaporation, film-ultrasonication, etc. Certain NLCs boost bioavailability by reducing first-pass metabolism, increasing drug penetration, minimizing drug degradation in the gastrointestinal tract (GIT), and quickly absorbing NLCs in the GIT. When placed into NLCs, it changes from its crystalline to an amorphous state, improving its solubility. For drugs that are susceptible to moisture, drug entrapment also protects lipid molecules from the outside environment. Moreover, it has been claimed that nanoparticles between 120 and 200 nm in size increase a drug's oral bioavailability by preventing the reticuloendothelial system from absorbing it [29,85,86]. Literature reported that the encapsulation of sesamol in NLCs improved its pharmacological activity as an antioxidant for the reduction of oxidative stress and exerts a neuroprotective effect. The improvement in the action against neurodegeneration was noticed as compared to the free drug.

Hassanzadeh and coworkers (2017) formulated sesamol-loaded NLCs by the HPH method. Using scanning electron microscopy, the drug release in a controlled manner from NLCs was established. Sesamol (present in two different concentrations, i.e., 80 and 100 μM) successfully attenuated cellular toxicity, and cell damage after 1 h oxygen-glucose deprivation (OGD), while sesamol-loaded NLCs (80 and 100 μM of sesamol) were operative at short-time exposure (1 h) as well as long-time exposure (8 h). Additionally, the activation of the PI3K pathway by sesamol-loaded NLCs may be helpful in NDs also [87].

5.2. *Solid lipid nanoparticles (SLNs)*

SLNs are regarded as the first generation of lipidic nanoparticles. These are safe, cheap, and lipid-based (solid, such as fatty acid, waxes, etc.) carrier systems [88]. Physiological emulsifiers and lipid molecules help to maintain the solid lipid matrix seen in SLNs. One technique for creating SLNs is called homogenization when drug particles are reduced in size due to high pressure and higher temperature brought on by mechanical and thermodynamic stress [89]. Many other techniques may be used to create SLNs, including HPH, high-speed stirring, ultrasonication, microemulsion, solvent emulsification evaporation, double emulsion, phase inversion temperature, membrane contactor, and solvent injection [83]. HPH may be used to create SLNs with diameters varying from 0 to 1000 nm. In addition to being biocompatible, SLNs are excellent nanocarriers for boosting hydrophobic compounds' solubility. By endocytosis, SLNs can readily pass through the endothelial cells of the BBB by bonding with a ligand (such as apolipoprotein E) linked to lipid-based nanoparticles, SLNs can increase their brain permeability. The lower drug loading capacity and ineffective entrapment efficacy of SLNs are among their drawbacks [89–91].

In a study by Misra et al. (2012), the sesamol SLN's activity was compared to rivastigmine. At different dosages, i.e., 4, 8, and 16 mg/kg,

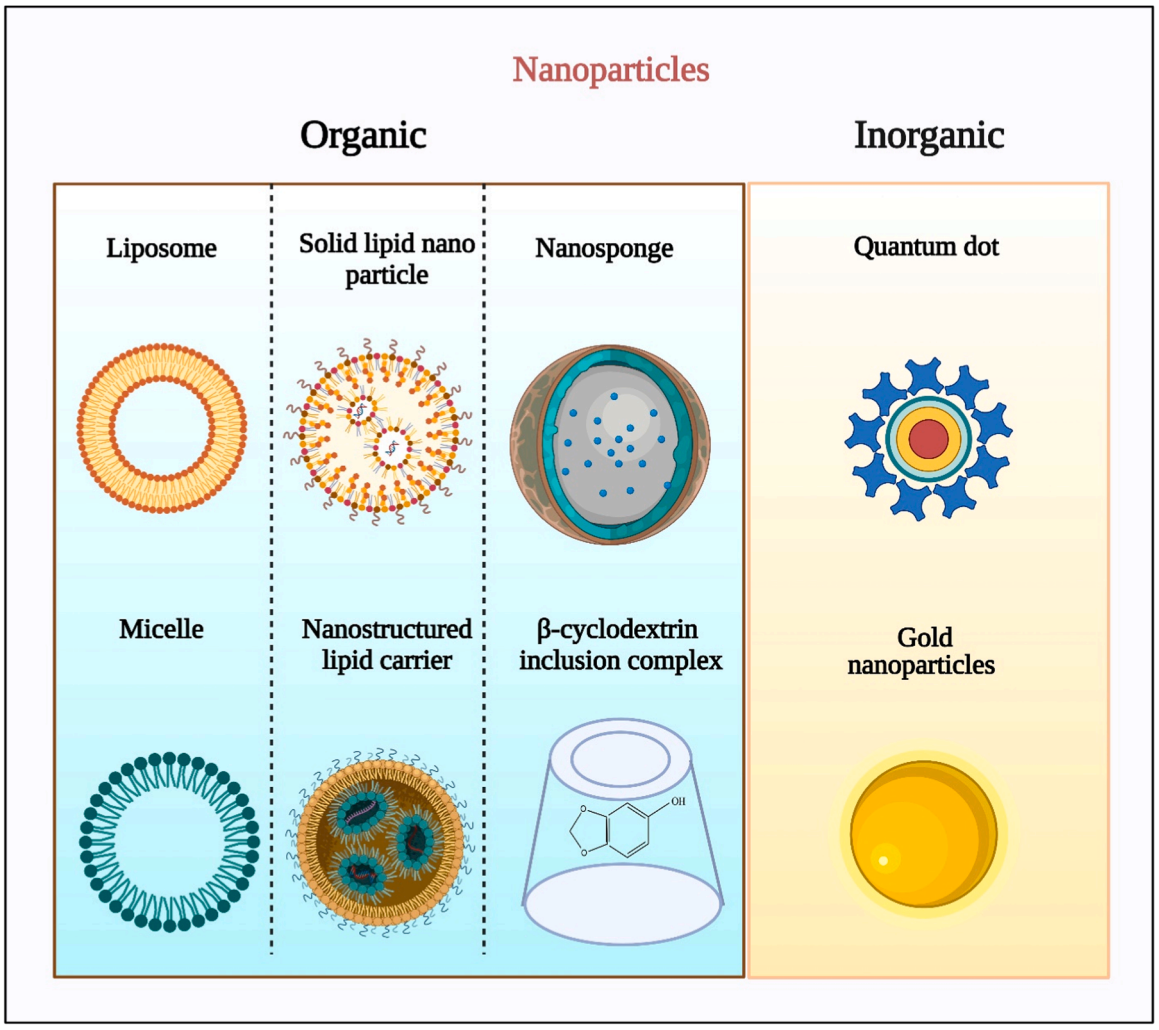

Fig. 5. Various organic and inorganic nanocarrier.

SLNs sesamol and plain sesamol significantly and dose-dependently decreased cognitive damage, AChE activity, oxidative-nitrergic stress, and inflammatory cytokines in intracerebroventricular streptozotocin (ICV STZ)-treated rats. At 16 mg/kg, it was demonstrated that sesamol SLNs were equally efficacious as rivastigmine at improving all behavioral and metabolic markers [92].

To compare the effectiveness of sesamol loaded in SLNs to the free medication, Nguyen et al. (2022) carried out the research. To treat glial cancer, sesamol was added to SLNs for nasal administration to the brain. SLNs (intranasal, IN) exhibited a greater C_{max}, brain (13.2-fold) and a briefer T_{max}, brain (10 min as opposed to 30 min) (intravenous, IV) as compared to free drug. The tests drug targeting efficiency (DTE%: 764), drug transport percentage (DTP%: 86.1), and B% (IN/IV: 590.4) demonstrated that the SLNs (IN) were more effective at targeting the brain than the free medicine (IV) [93].

Sesamol encounters limitations like low cellular uptake and less biocompatibility. To overcome the issues, SLNs were used to load sesamol. SLNs with sesamol loaded into them are investigated in a paradigm of cognitive decline brought on by ICV-STZ by Sachdeva and team (2015). Sesamol-loaded SLNs were formulated, with mean particle diameters between 122 and 200 nm and entrapment efficiencies ranging from 75.9% ± 2.91%. The Morris water maze and the elevated plus maze test were employed to assess the mental abilities of rats. The ICV-STZ mice experienced severe memory impairment. In addition to reducing oxidative stress and cytokine release, chronic therapy with sesamol-loaded SLNs dose-dependently improved cognitive impairments in ICV-STZ mice. A notably better decrease in the parameters related to oxidative stress served as evidence of the ability of SLNs to transport sesamol to the brain. Rats that had previously received streptozotocin (STZ) via ICV administration were given sesamol SLNs to elicit cognitive impairment. The research demonstrated much-increased efficacy than the group of rats given regular sesamol at a dosage of 16 mg/kg, nearly similar to the recommended dose of rivastigmine. The provision of sesamol SLN is an alternative for treating ICV-STZ induced neuronal disruption and memory impairment as a consequence of their behavioral and biochemical results [94,95].

With the progression of age, menopause in women is accompanied by a decline in the functionality of various organs of the body, including the CNS. In a study by Kakkar and co-workers (2011), it was established that the sesamol loaded in SLNs (S-SLNs) can be used as a therapeutic agent for ND patients in old age, including menopaused women. S-SLNs were found to have an average particle size of 122 nm and entrapment efficiency of 75.9 ± 2.91%, respectively. The SOD enzyme levels returned to normal using S-SLNs (4Sln & 8Sln doses), indicating its antioxidant action. The monitoring of anxiety and cognition in the OVX rat model of menopause concluded that the effective delivery of sesamol

took place using S-SLNs. 88% recovery in memory and a reduction in anxiety by 32.8% was achieved. The highlight of the study included the use of a co-surfactant, i.e., phosphatidylcholine (PC) for the preparation of S-SLNs for refining memory decline [96].

5.3. Micelles

These are spherical, amphiphilic nanostructures, composed of a hydrophobic core shielded by a hydrophilic periphery/corona. Their shell facilitates the enhanced duration of in-vivo circulation. Enhanced solubility, improved stability of the loaded drug, and controlled delivery of the drug are the advantages offered. While, the introduction of functional moieties on the periphery enhances its targeting ability, exploited in tumor penetration. The drug can be loaded in block copolymers via hydrophobic, electrostatic interaction, metal complexation, etc. The preparation of polymeric micelles can be achieved using dialysis, solvent evaporation, film dispersion method, etc. [97,98].

Wang et al. (2021) formulated stearic acid (SA)-CS nano micelles loaded with sesamol (SM). The solid product was obtained by centrifugation trailed by freeze-drying. Sesamol could be released continuously from nano micelles for 15 days while retaining stability in phosphate buffer solution (PBS), reaching over 100% after 50 h from the start of the in vitro release studies. The hybrid motoneuron-like cell line NSC-34 was used in the in vitro study. Before culturing with the materials, the cells were treated with LPS to investigate the protective properties of the nano micelles or free sesamol). Further in vitro experiments were conducted utilizing the cell line, i.e., 3-(4, 5-dimethylthiazol-2-yl)−2,5-diphenyl-tetrazolium bromide (MTT), lactate dehydrogenase, and intracellular ROS assay. The cellular studies were performed and highlighted the ability of SM@SA-CS in mitigation of oxidative stress, apoptotic and inflammatory signaling routes through the NF-κB pathway, as compared to free drug, on co-incubating with LPS for 24 h. Loaded nano micelles consistently produced the greatest outcomes, highlighting their potency as neuroprotective and antioxidant substances. Moreover, loaded nano micelles may control the levels and expression of genes linked to apoptosis and inflammation [99].

Sesamol was enclosed in phosphatidylcholine (PC) mixed micelles (PCS) by Yashaswini et al. in 2017. For the preparation, PC (1 part) and deoxycholate (DOC) (2 parts) were solubilized in chloroform and methanol solution (2:1 respectively). With gentle stirring, sesamol was usually added to the produced mixture. The prepared micelles particle size was discovered to be 3.0 ± 0.06 nm, and their entrapment effectiveness was reported to be 96.8%. Slower drug release was encountered from PCS. As a measure of antioxidant activity, inhibition of lipoxygenase (LOX) potential was evaluated. Fifty percent inhibition of LOX was achieved by sesamol-loaded PCS and free sesamol at concentrations 33.6 μM and 51.9 μM. respectively. Also, PCS attenuated ROS production by 74.8%. using caco-2 monolayer cells, it was evident that the PCS revealed 1.5 times and 1.23 times more cellular uptake at 5 h and 24 h cell lysate, respectively than the free sesamol [100].

5.4. Liposomes

These vesicular carriers are constituted by phospholipids or lipids that are comparable to those found in the physiological system. The body can handle them rather well and they don't produce any harmful breakdown products. Other vesicular systems include ethosomes, transferosomes, niosomes, etc. Conventional liposomes were initially described by Bangham as spherical, double-layered vesicular particles containing phospholipids and cholesterol. Due to their unique structural design, which incorporates hydrophilic medicines in the aqueous portion, while the lipophilic pharmaceuticals in the double-layered lipid assembly, they were able to encapsulate both hydrophilic and hydrophobic medications. Advantageously, this system's structure resembles the physiological system [101–104]. This system exhibits the potential to be utilized as a neuroprotective agent in the future. Research needs to be concentrated on the development of sesamol-loaded liposomes.

5.5. Quantum dots

The luminous semiconductor nanoparticles known as quantum dots consist of a core substance that is encased in a shell made from a different semiconductor material. The term "quantum dots" itself refers to the substance's optical and quantum confinement characteristics. Also termed as artificial atoms, these nanocarriers are resistant to degradation, thus, cellular activities can be traced for longer periods. They allow surface alterations, compatibility in in-vivo and in-vitro environments, longer circulation, etc. [105]. Top-down and bottom-up are the major methods for their synthesis [106].

Abdelhamid and the team (2019) aimed to improve the delivery of sesamol using quantum dots. Improvement in the activity of sesamol was observed by loading it onto cadmium sulfide (CdS) quantum dots (QDs) modified chitosan (CTS), leading to the formation of a stable complex, i.e., Sesamol-CdS@CTS. The adsorption post-loading approach was employed in this. Sesamol was continuously stirred, after adding into the CdS@CTS suspension for an hour at 400, 600, and 800 rpm at 20 °C, 40 °C, and 60 °C. The exploitation of the nanoparticles were done for the reduction in lipid peroxidation in cancerous cells. A similar kind of research can be extended to NDs. The nanoparticles formed had a particle size within the range of 3–5 nm, as confirmed by TEM. The values for zeta potential and polydispersity index of the formed complex were found to be + 9.3 ± 0.51 mV and 0.631 ± 0.178, respectively. The release of sesamol from the quantum dots followed a sustained release pattern. Also, the more effective activity of sesamol was witnessed. High drug loading efficiency (1.74 mg/mg; Sesamol/QDs) was evident from the study and can pave the way for its application in drug delivery [107].

5.6. β-cyclodextrin inclusion complex

Cyclodextrins (CD) are degradation products of starch, which are physically as well as chemically stable. In an aqueous environment, they form an inclusion complex (IC). The slight non-polar cavity entraps the water molecules via non-covalent bonding. The suitable drug molecules exchange themselves with water, and complexation occurs. Numerous derivatives of CD are available, such as α-, β-, γ-CD, methylated CD, hydroxypropyl CD, sulfobutyl CD, etc. β-CD offers advantages, such as cheap, ideal cavity dimensions, appropriate drug complexation, easily available, etc [6,108]. Via complex formation with CD, the solubility and bioavailability of poorly-aqueous soluble compounds can be improved [109].

Ma and team (2012) prepared an IC of sesamol and hydroxylpropyl-β-cyclodextrin (HP-β-CD), studied its physicochemical properties, and further investigated its free radical scavenging potential. For the preparation of IC, sesamol, and HP-β-CD were added to ethanol and agitated for 24 h for dissolution. After the ethanol was discarded, the remainder was filtered after dilution with water. The filtrate was lyophilized and collected after being refrigerated at 40 °C for 24 h. The outcome power consisted of IC of sesamol with HP-β-CD. Differential scanning calorimetry (DSC) revealed the occurrence of hydrogen-bond or van der Waals interactions for the complete dispersion of sesamol in HP-β-CD. Further, it was confirmed by X-ray diffraction analysis. It is possible that the high concentration of HP-β-CD is what caused the sesamol-loaded IC's antioxidant activity to be less potent than that of the free drug. However, a far greater amount of solubility enhancement was made [110].

5.7. Nanosponges

These are defined as minute, solid, and, three-dimensional (3D) porous assemblies with narrow cavities. The cavities can be loaded with suitable drugs. These are formed using polymer and cross-linking agents, whose concentrations can be varied to form nanosponges of varied sizes.

Depending on the functional groups, they can be targeted to specific sites. Various approaches for the synthesis of nanosponges are hot-melt, solvent condensation, micro-wave, or ultrasound-mediated preparation, etc. Their unique self-sterilizing potential can be attributed to minute pore size, which makes it difficult for bacterial invasion. They exhibit stability over a wide range of temperature and pH variations [111–113].

Gupta and team (2021) hypothesized the stability of sesamol-loaded cyclodextrin nano-sponges (CDNS) while maintaining their antioxidant and anti-tyrosinase action. The solvent evaporation technique was used to prepare sesamol-loaded CDNS (SES-CDNS). For this purpose, dimethylformamide (DMF) acted as an internal solvent. DSC demonstrated the successful integration of sesamol with CDNS, and remarkable encapsulation was confirmed using field-emission scanning electron microscopy. The encapsulation efficiency was found to be 90.66 $\pm$ 3.21%. Particle size and zeta potential of SES-CDNS were 189.46 $\pm$ 6.57 nm and 13.63 $\pm$ 0.6 mV, respectively. At 0 and 90 days, the antioxidant activity of SES-CDNS was assessed at various concentrations (i.e., 5, 10, 20, 50, and 100 μg/mL). The potential was retained in CDNS, with negligible loss after 90 days. FTIR results confirmed improved stability of sesamol after encapsulation in CDNS. Thus, with enhanced stability, the SES-CDNS were capable of exerting an antioxidant effect similar to the free drug, sesamol [114].

5.8. Gold nanoparticle

Gold nanoparticles provide an outstanding material for study due to the fact that they are one of the most stable, non-toxic, and easy to synthesize nanoparticles and exhibit various fascinating properties like assembly of various types and quantum size effect [115,116]. Gold nanoparticles exhibit the potential to be utilized as a neuroprotective agent in the future.

6. Conclusion

Sesamol has been evaluated for its neuroprotective effect by various research [66,117]. Numerous mechanisms have been proposed to treat NDs, including oxidative damage, neuroinflammation, inhibition of certain biochemical parameters, activation of protective mechanisms, etc [118]. The development of sesamol-incorporated nanoformulations has remarkably innovated the treatment approaches. Enhancement in sesamol solubility, and bioavailability with increased targeting efficiency are notable features. Sesamol's neuroprotective properties have been demonstrated in in-vitro and in-vivo investigations [92], however, there is still opportunity to open new avenues for more investigation using human participants. Few clinical studies have been carried out so far. Moreover, due to higher incidences of AD and PD, efforts have been done to investigate successful treatment approaches. While, for HD and ALS, more emphasis needs to be laid on the inspection of novel compounds and their associated role in these diseases. Nevertheless, the nanoformulations of sesamol have made its application wider against NDs. The proper understanding of NDs' pathology, formulation of economical and effective nanoformulations and their targeting at the correct site of action would definitely lead to successful treatment of NDs.

CRediT authorship contribution statement

Navneet Singh: Methodology, Data curation and Writing – original draft. **Sukriti Vishwas**; Methodology, Data curation and Writing – original draft. **Amandeep Kaur**; review & editing. **Harmanpreet Kaur**; review & editing. **Violina Kakoty**; review & editing, Methodology. **Rubiya Khursheed**; review & editing. **M.V.N.L. Chaitanya**; review & editing. **Molakpogu Ravindra Babu**; review & editing. **Ankit Awasthi**; review & editing. **Leander corrie**; review & editing. **Vancha Harish**; review & editing. **Palakurthi Yanadaiah**; revision, image creation. **Saurabh Gupta**; review & editing. **Amany A. Sayed**; review & editing. **Amr El-Sayed**; review & editing. **Iftikhar Ali**; review & editing. **Osama A. Kensara**; review & editing. **Nehmat Ghaboura**; review & editing. **Gaurav Gupta**; review & editing. **Ali M. Dou**; Software, revision & editing. **Mohammad Algahtani**; revision & editing. **Attalla F. El-kott**; revision & editing, Funding. **Kamal Dua**; Data curation and Writing – original draft. **Sachin Kumar Singh**; Conceptualization, Validation, Supervision and Writing – review & editing. **Mohamed M. Abdel-Daim**; Conceptualization, Validation, Supervision and Writing – review & editing, Funding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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