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Review Article

A Review on Impact of *Syzygium aromaticum, Nigella sativa,* and *Mesua ferrea* on Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD), characterised by cognitive impairment and memory loss, is primarily caused by the deterioration of the central nervous system, which is a vital component of the human body. Amyloid-beta plaque buildup in the brain and cognitive impairment are two hallmarks of AD, a progressive neurodegenerative disease. AD involves neuroinflammation that contributes to its progression, signifying the important need for neuroprotection to reduce brain damage and improve patient outcomes. sEH has gained attention as a potential therapeutic target due to its role in modulating neuroinflammation and promoting neuroprotection. There are significant therapeutic gaps as a result of numerous researchers' inability to develop medications with neuroprotective properties that target AD, highlighting the continuing challenges in the effective treatment of this severe illness. Inhibition of sEH activity by medicinal plants such as *Mesua ferrea* (Ceylon ironwood), *Nigella sativa* (black seed), and *Syzygium aromaticum* (clove) could have neuroprotective effects. These plants neuroprotective effects, their role as sEH inhibitors. As well as the impact of sEH in the development of AD is emphasized in this review.

Keywords: Alzheimer's disease, *Mesua ferrea*, Neuronal disorders, *Syzygium aromaticum*, *Nigella sativa*, Soluble epoxide hydrolase, Neurodegeneration.

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INTRODUCTION

During the 19th and 20th centuries, drug composition and pharmacy evolved significantly, with medicinal plants playing an important role in this transformation (Amin *et al.*, 2020). These advancements from medicinal plants help in treating various diseases. So, the plants suitable for medicinal purposes perform a pharmacological action. The growth of knowledge to cure diseases continued at an accelerating pace, and the number of new plant-derived drugs increased likewise (Kumar *et al.*, 2016). More than 85-90% of the world's population depends on the traditional medicine system for combating various diseases. Nowadays, about 70,000 medicinal plants have been used for new drug discovery in Asian medicinal applications (Nasim *et al.*, 2022). Drug discovery is a challenging scientific task to find robust and viable leads, which is nothing but the process flow from a screening of natural products to a new isolate that requires expertise and experience. However, in addition to their chemical structure diversity and their biodiversity, the development of new technologies has revolutionised the screening of natural products in discovering new drugs (Perveen and Al-Taweel, 2019). The screening of natural products in discovering new drugs involves traditional medicinal plants, such as *German chamomile, Digitalis lanata, Echinacea purpurea, Zingiber officinale, Syzygium aromaticum, Nigella sativa, Mesua ferrea*, etc., which have long been utilised for treating various ailments, including inflammation, cardiovascular conditions, respiratory diseases, and neurological disorders (Shekhar *et al.*, 2018). Particularly, the neuroprotective effects of *Syzygium aromaticum* (clove), *Nigella sativa* (black cumin), and *Mesua ferrea* (Nagkesara in Hindi and Ceylon ironwood in English) have been emphasized on their neuroprotective potential. Research is being done on these medicinal plants as alternative or complementary therapies for neurodegenerative disorders. Also, these traditional medicinal plants provide a promising avenue in addressing neurological disorders, which were the sixth leading cause of death globally in 2016 (Abdel-Razik, 2019). The sales and production of medicines derived from medicinal plants have gained thrust, and their systematic and economic significance in the healthcare sector is rising (Bordoloi *et al.*, 2024). Despite extensive research efforts, recent drug developments targeting AD have largely failed to

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produce effective disease-modifying treatments due to substantial presymptomatic neuronal damage caused by Amyloid β (Aβ) peptide accumulation and tau protein abnormalities (Tatulian, 2022). This situation has resulted in therapeutic gaps, including disconnected healthcare systems, a lack of comprehensive services for patients with dementia and their careers, and inconsistency in the perceived effectiveness of treatments. Traditional medicinal herbs like *Curcuma longa, Withania somnifera, Bacopa monnieri, Panax ginseng, Camellia sinensis, Rosmarinus officinalis, Syzygium aromaticum, Nigella sativa*, and *Mesua ferrea* have revealed encouraging results in filling these therapeutic gaps due to their diverse bioactive compounds. For illustration, *Syzygium* species blocks AChE and enhances antioxidant enzymes through activating the insulin signalling system (Rawa *et al.*, 2022). Also, *Nigella sativa* has been found to alleviate memory impairment, anxiety, depression, and other neurodegenerative symptoms. Similarly, *Mesua ferrea* has antioxidant, anti-inflammatory, and neuroprotective effects, making it a potential therapeutic agent for Central Nervous System (CNS) disorders. Some of the benefits of *Syzygium aromaticum, Nigella sativa,* and *Mesua ferrea* targeting sEH and its neuroprotective effects are explained in Figure 1.

Widely acknowledged as a characteristic of AD, neuroinflammation plays a key role in disease progression. It has been demonstrated that neuroinflammation can be successfully prevented by the inhibition of the soluble Epoxide Hydrolase (sEH) enzyme *(Jarne-Ferrer et al.*, 2022). Significantly, several neuroprotective processes linked to AD, including endoplasmic reticulum stress, oxidative stress, and inflammation, are associated with the inhibition (Ferré *et al.*, 2023). According to Iyer *et al.*, (2022) sEH is a crucial enzyme that breaks down the bioactive Epoxy Fatty Acids (EFAs) in the arachidonic acid signalling pathway and transforms them into vicinal diols. *Syzygium aromaticum, Nigella sativa*, and *Mesua ferrea* may serve as potential sEH inhibitors, putatively reducing AD pathology. Key molecules such as eugenyl acetate, -caryophyllene, kaempferol, eugenitin, -humulene, and -copaene, from *Syzygium aromaticum*; thymoquinone, myristic acid, palmitoleic acid, linoleic acid, linolenic acid, and -sitosterol, in *Nigella sativa*; and mesuaferrone-A, mesuaferrone-B, mesuol, mesuferrol, mesuagin, and ferraxanthone from *Mesua ferrea*, respectively, offer a novel therapeutic strategy. The general flow of the literature review is explained in Figure 2.

LITERATURE REVIEW

CNS diseases, particularly AD, represent a major global health challenge due to their progressive nature and the lack of effective treatment strategies. The symptoms of Alzheimer's develop gradually over many years and eventually become more severe. The pathogenesis of AD is multifactorial, with key mechanisms including oxidative stress, neuroinflammation, amyloid-beta plaque deposition, and neurovascular dysfunction. Soluble Epoxide Hydrolase (sEH), an enzyme that modulates bioactive lipid mediators, has been implicated in the progression of AD through its role in worsening inflammation and altering cerebral blood flow. Recent studies have identified sEH as a potential therapeutic target for neuroprotection in AD and other CNS disorders (the importance of sEH is depicted in Table 1). This review explores the neuroprotective potential of natural compounds found in *Syzygium aromaticum, Nigella sativa, and Mesua ferrea,* three plants long valued in traditional medicine. *Syzygium aromaticum* is widely known for its pain-relieving, antioxidant, and antimicrobial properties. *Nigella sativa* offers benefits ranging from immune support to antifungal and cholesterol-lowering effects. Meanwhile, *Mesua ferrea*, though less common, has been traditionally used for its anti-inflammatory, antiseptic, and immune-boosting qualities. Together, their rich blend of bioactive compounds may offer promising avenues for supporting brain health. A new therapeutic approach, referred to as sEH, has been developed.

When initiating the review, the 1st step involves examining the neurodegeneration pathways in AD to understand the underlying mechanisms of neuronal damage and cognitive decline. The 2nd step focuses on the role of sEH in AD, highlighting its contribution to neuroinflammation and disease progression. Next, the neuroprotective properties or effects of the stated medicinal plants, *Syzygium aromaticum, Nigella sativa*, and *Mesua ferrea*, are analysed, demonstrating their potential in combating neurodegenerative processes. Finally, the potential of these medicinal plants as sEH inhibitors is explored, presenting them as promising therapeutic agents for inhibiting sEH activity. This offers protection against neurodegeneration in AD. By following these steps, the discussion provides detailed information on how the stated medicinal plants can contribute to the development of effective treatments for AD through their neuroprotective and sEH-inhibitory effects, ultimately aiming to mitigate the impact of this debilitating condition on cognitive health. Overall, this review contributes to the growing body of evidence supporting the exploration of plant-based compounds as different interventions in handling AD and other neurodegenerative disorders.

NEURODEGENERATION PATHWAYS IN AD

As mentioned, the initial step in the literature review is to explore the neurodegeneration pathways in AD. In neurodegeneration, some proteins in the brain do not function correctly, and this causes the formation of clumps in different parts of the brain (Guo *et al.*, 2021). The neurodegenerative disorder in AD is responsible for up to 70% of dementia cases. This disease is characterised by the presence of aggregates of pathologically misfolded proteins, including the extracellular senile plaques built mainly of Amyloid β (Aβ) (Czubowicz *et al.*, 2019a). Some of the neurodegeneration pathways in Alzheimer's disease, such as antioxidant action, oxidative stress, and stress-related conditions

(Franzoni *et al.*, 2021, *Olufunmilayo et al.*, 2023). Oxidative stress plays a key role in Alzheimer's disease, with mitochondrial dysfunction driving ROS accumulation that damages lipids, proteins, and DNA, especially in the ageing brain with limited antioxidant defences. (Mecocci *et al.*, 2018), apoptosis in neuronal cells, mitochondrial dysfunction, microglial hyperactivity and inflammation, the role of cholesterol in neurodegeneration, tau hyperphosphorylation and amyloid-beta deposition, and ER stress and blood-brain barrier dysfunction are explained below in Table 2.

Haan *et al.*, (2018) explained this study examined post-mortem retinal tissue from Alzheimer's Disease (AD) patients and controls, revealing increased diffuse Phosphorylated Tau (pTau) in the inner and outer plexiform layers of AD retinas, especially in peripheral regions. No typical Aβ plaques were observed, and APP/Aβ staining did not differentiate AD from controls. The findings suggest that retinal pTau, rather than Aβ, holds greater potential as a biomarker for *in vivo* AD detection.

Preis *et al.*, (2024) explained the assessment of BBB dysfunction and its association with cognitive impairment, neuroinflammation, and Alzheimer's pathology. The cross-sectional study was conducted to investigate BBB (Blood Brain Barrier) dysfunction in participants using DCE-MRI (Dynamic Contrast-Enhanced Magnetic Resonance Imaging) and sPDGFRβ levels in cerebrospinal fluid. From the analysis, it was found that the soluble Platelet-Derived Growth Factor Receptor beta

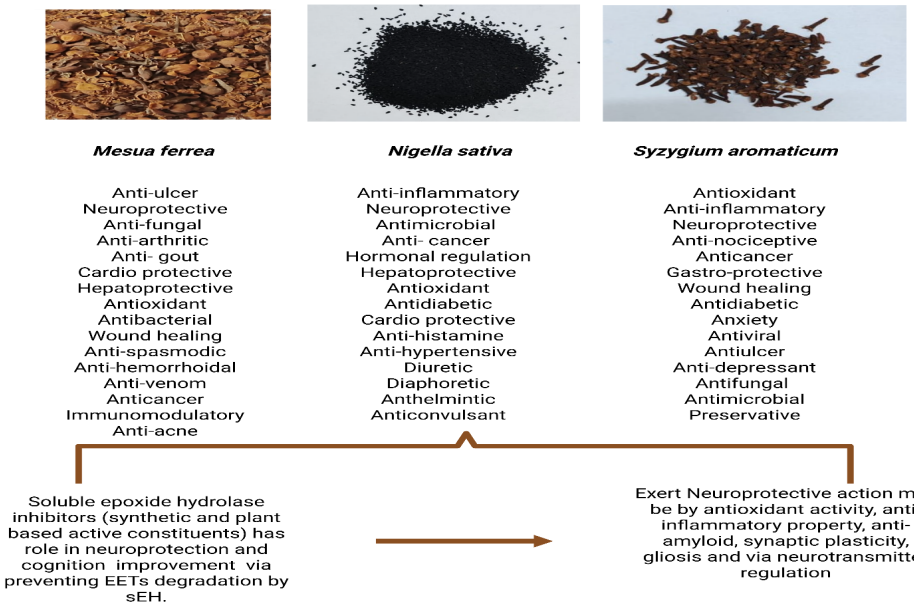

Figure 1: Therapeutic Potential of *Mesua ferrea*, *Nigella sativa* and *Syzygium aromaticum* through sEH inhibition.

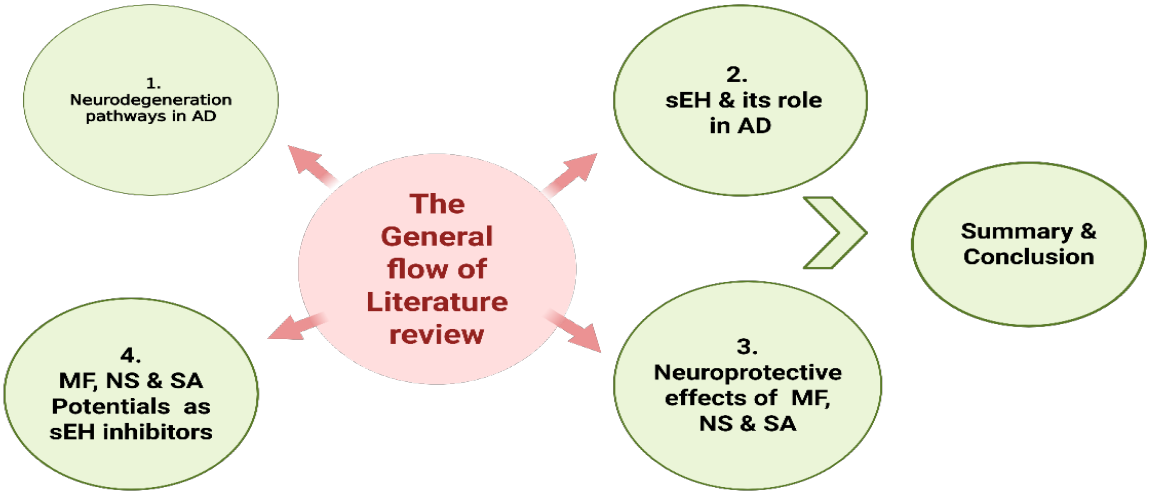

Figure 2: Subheadings of the literature review.

Table 1: The importance of soluble epoxide hydrolase.

Authors	Importance of sEH	Outcome
(Codony *et al.*, 2022)	sEH plays a key role in AD neuroinflammation by sEH inhibition retains anti-inflammatory lipid mediators (EETs).	sEH confirmed multitarget therapy couples sEH inhibition with AChE inhibition synergistic benefits in treating AD, the dual sEH/AChE inhibitor recovered memory, decreased neuroinflammation.
(Griñán-Ferré *et al.*, 2020)	sEH were upregulated in AD patients brains.	The study provides strong pharmacologciacl validation that targeting she in the brains may be effective treatment strategy which addressing inflammatory component.AS-2586114, TPPU, UB-EV-52 structurally different sEH inhibitors led to improvements in cognition by blocking She.
(Griñán-Ferré *et al.*, 2024b)	sEH contributes to inflammatory stress by conversion of astrocytes into neurotoxic reactive form.	UB-SCG-51, sEH inhibitor, showed protective effects, reduced neuroinflammation, and tau hyperphosphorylation in the AD mouse model (5XFAD). Improved cognitive deficits.
(Borkowski *et al.*, 2021)	sEH converts anti-inflammatory epoxy fatty acids into proinflammatory diols, which contribute to systemic and brain inflammation.	This study demonstrates sEH dysregulation as a hallmark of inflammation in AD and also identifies cognitive resilience biomarkers and AD progression.
(Sun *et al.*, 2021)	sEH expression was significantly increased in the hippocampus in AD mouse model. Its activity also affected several pathways like GSK3B-mediated NF-kB, Nrf2.	TPPU (sEH inhibitor) administration alleviated memory deficits and spatial learning in Ab-INDUCED ad MICE. She INHIBITON RESULTED IN PROINFLAMMATORY AND pro-apoptotic signaling pathways.
(Lee *et al.*, 2019)	In APP/PS1 transgenic mice, AD model She LEVELA INCREASED NOTABLY IN THE MOUSE BRAIN, especially in the hippocampus, this denotes a contributory role of She IN AD.	Genetic deletion of she in APP/PS1 mice showed enhanced performance in behavioral tests like nesting, spatial learning, and memory as decreased amyloid beta plaque deposition in the cortex and hippocampus
(Liang *et al.*, 2019)	In AD she level elvated in turn led to metablosin of EETs which has anti-inflammatory property, led to neuroinflammation.	TPPU in the AD mice model decreased cognitive impairment and memory loss evidenced by behavioral assessment.
(Ghosh *et al.*, 2020)	sEH metabolizes anti-inflammatory epoxy fatty acids into less active diols. Thereby exacerbating neuroinflammation and neuronal damage.	TPPU treatment correlates an increase in EpFA concentrations in the brains of 5xFAD mice, demonstrating brain penetration and target engagement of this small molecule. These findings support further investigation of TPPU as a probable therapeutic agent for the handling of AD.

(sPDGFRβ) showed significant positive associations with soluble Aβ levels. Due to the study design, sPDGFRβ and the biomarkers of neuroinflammation could not be analysed.

sEH AND ITS ROLE IN AD

After exploring the neurodegeneration pathways, it is essential to explain the sHE and its role in AD. Clinical therapeutic effects of sEH inhibition have shown many disorders associated with peripheral inflammation (Ferré *et al.*, 2020; Lee *et al.*, 2019). It plays a key role in the pathophysiology of inflammatory and neurodegenerative illnesses and is expressed in different types of brain cells (Codony *et al.*, 2022). Through the (Kelch-like ECH-associated protein 1 (Keap1)-Nuclear factor erythroid 2-related factor 2 (Nrf2) Keap1-Nrf2 cascade, inhibition of sEH may reduce Aβ-induced oxidative stress and stop the development of Aβ plaque and Tau protein hyperphosphorylation (Sun *et al.*, 2021).

Ferré *et al.*, (2024) described the molecular mechanism that drove neuroprotection after sEH inhibition and their perceptions for AD therapeutics. The Ct (Cycle threshold) method was used in this study to conduct the test on UB-SCG-51 (a selective sEH inhibitor) in the neuroblastoma cell line. As per the analysis, the combination of treatments resulted in an increase in C3 gene expression after T/I/C (Transcriptional/Inflammatory/Cellular) compared with the sEH group in cultures. The treatments and therapies led to limited effects in terms of clinical benefit.

Table 2: Neurodegeneration pathways in AD.

Authors' Name	Purposes	Neurodegeneration pathways in AD	Outcomes	Limitations
(Youssef *et al.*, 2018)	To identify extreme beta-amyloid oligomers and oxidative damage by analyzing endogenous antioxidant activity and expression profiles in matched human AD patients.	Antioxidant Action and Oxidative Stress.	As per the analysis, the immune blotting showed increased AT8 tau-positive bands (between 45-79 kDa) in the AD-STG.	The AD-STG showed that there was limited ability to decompose accumulating H_2O_2 enzymatically.
(Dhapola *et al.*, 2022)	Oxidative phosphorylation was the major generator of Reactive Oxygen Species (ROS), leading to mitochondrial damage. So, the main purpose of this study was to reduce the ROS by using antioxidants like MitoQ, Curcumin, and Vitamin E.	Mitochondrial Dysfunction.	The result showed that the heterozygous mutations in the TFAM gene resulted in around 40% decrease in mtDNA copy number.	The reduction of Ca^{2+} store might lead to the deposition of Ca^{2+} in the mitochondrial matrix.
(Roca-Agujetas *et al.*, 2021)	To investigate how changes in neuronal cholesterol affect the autophagic clearance of mitochondria in AD.	Role of Cholesterol in neurodegeneration.	In cholesterol-enriched SH-SY5Y cells, a high intracellular cholesterol level was attained in mitochondrial PINK1.	The role of SQSTM1 was limited to mitochondrial clustering.
(Czubowicz *et al.*, 2019b)	To assess the potential of two flavonoids kaempferol-3-O-rhamnoside and quercetin-3-O-rhamnoside isolated from *M. ferrea* flowers.	Flavonoids act as multi-target neuroprotective agents in the AD neurodegeneration pathway such as inhibiting AChE, reducing oxidative stress, Preventing Aβ aggregation Promoting neuronal survival.	Both the compounds bind effectively to AChE on key regions of (at both CAS and PAS) regions of Aβ1-42, inhibiting its aggregation.	The study focuses only on two compounds from *Mesua ferrea* flowers, limiting wider applicability or comparison with other known AD-related flavonoids.
(Preis *et al.*, 2024b)	This study explored how Blood-Brain Barrier (BBB) dysfunction relates to Alzheimer's disease, using (DCE-MRI) and biomarkers (sPDGFRβ in CSF), to assess links with amyloid, tau, neuroinflammation, cognitive decline, and disease progression.	BBB disruption may contribute to neurodegeneration through toxic proteins impaired clearance, and vascular dysregulation, induction of inflammatory responses.	BBB dysfunction was found in AD dementia, while sPDGFRβ correlated with age, neuroinflammation, and soluble Aβ, but not with amyloid plaques.	Cross sectional study, sample size, limited assessment of BBB, heterogeneity mechanism of biomarker (sPDGFRβ).
(Den Haan *et al.*, 2018b)	The purpose was to identify the AD neuropathological biomarkers in post-mortem retinas of AD patients. Goal is to investigate non-invasive biomarkers foe early detection of AD.	Tauopathy, possibly led to neuronal death and visual dysfunction hence the presence of pTau in the retina, indicating variations in how AD manifests neurodegeneration in ocular tissue.	Study identified the presence of diffuse phosphorylated tau (pTau) in the inner and outer plexiform layers of the retina od AD patient compared to control. But an absence of amyloid plaques.	Small samples, qualitative methods.

Borkowski *et al.*, (2021) explained the association of plasma and CSF cytochrome P450, sEH, and ethanolamide metabolism with AD. The targeted quantitative mass spectrometry method was used to measure the lipid mediators. From the analysis of results, the operator characteristic curves attained 0.82 to 0.92 ranges for cerebrospinal fluid and plasma metabolites. The small number of subjects in the prediction model created a potential overfitting in attaining the result.

Liang *et al.*, (2019) introduced TPPU (1-Trifluoromethoxyphenyl-3-(1-Propionylpiperidin-4-yl) urea) as a selective and effective dual inhibitor of sEH and p38 kinase that mediates in Alzheimer's signalling in human nerve cells. The targeting neuroinflammation strategy was conducted to keep neurons alive for AD therapy. According to the findings, TPPU exhibited a synergistic effect on several AD signalling pathways, and it was a strong and selective dual inhibitor of sEH and p38β kinase. The extensive pharmacological studies on inflammatory disorders targeting sEH were still limited.

Ghosh *et al.*, (2020) conducted an experiment based on the reduction of sEH inhibitor neuroinflammation in a mouse model of AD. The cytometry-based Concurrent Brain cell type Acquisition (CoBrA) method was used to simultaneously isolate astrocytes, microglia, and vascular endothelial cells. Combining AD and APP/Aβ mouse brain samples using heightened sEH expression resulted in reduced EpFA in 5xFAD mice. However, the efficacy was limited due to the rapid hydrolysis of sEH.

NEUROPROTECTIVE PROPERTIES OR EFFECTS OF STATED MEDICINAL PLANTS

This section completely explains the neuroprotective properties and impacts of the mentioned medicinal plants. Eugenol is a medicinal value-rich compound present in the buds and leaves of the *Syzygium aromaticum*. Eugenol acts as a neuroprotective against toxicity, ischemia, and amyloid-β peptide. It also restrains the conduction of activity potential in sciatic nerves and enhances neuronal and vascular intricacies in exploratory diabetes. The active compounds in many ayurvedic drugs constitute compounds like eugenol, which is used for neuroprotective roles and neurodegenerative diseases (Giridharan, 2016). Neuroprotection properties refer to the mechanisms and strategies employed to defend the Central Nervous System (CNS) against injury due to both acute (e.g., trauma or stroke) and chronic neurodegenerative disorders. The neuroprotective role of *Syzygium aromaticum* increases antioxidant activity, decreases oxidative stress, and normalises the AChE and GABA levels (Aboubakr, 2019). Some of the neuroprotective effects of *Syzygium aromaticum, Nigella sativa*, and *Mesua ferrea* are explained in Table 3.

Yadav *et al.*, (2022) explained the neuroprotective role of *Syzygium aromaticum* on SIRT1 (sirtuin family of proteins) and oxidative balance in AD. In differentiated SHSY-5Y (human neuroblastoma cell line) cell line, the antioxidative potential of *Syzygium aromaticum* was examined in relation to Aβ-induced neurotoxicity. *Syzygium aromaticum* increased the proportion of antioxidant enzymes and was able to scavenge ROS. *Syzygium aromaticum* downregulated the amount of γ-secretase and activated and increased SIRT1 levels.

Sudha *et al.*, (2024) described the evaluation of the neuroprotective effect of *Nigella sativa* Linn. Seed using the Zebrafish Model for AD. Scopolamine-induced T-maze, escape, site preference, and bite tests were among the experiments, which provided compelling evidence that conserved regulatory systems-controlled zebrafish behaviour. The behaviour test results showed that *Nigella sativa* improved memory and learning, which were adversely impacted by scopolamine therapy. Notably, a comprehensive histoarchitecture investigation showed that kaempferol 3-(2-Galloyl-Alpha-L-Arabinopyranoside) had no negative effects. This suggested that it could be a promising treatment option for such a multifactorial AD.

Chahar *et al.*, (2012) demonstrated mesuol's immune response through increasing antibody titres and paw volume in cyclophosphamide-induced immunosuppressed rats, which were sensitised with sheep red blood cells, indicating dose-dependent immune function restoration. It also has an impact on bone marrow supporting function and immune health by effectively reversing myelosuppression caused by cyclophosphamide.

Chaithanya K *et al.*, (2018) explained that *Mesua ferrea*, a traditional medicinal plant, showed strong anti-inflammatory effects both in cell culture (*in vitro* test using RAW 264 macrophage cells) and animal studies (*in vivo* tests using carrageenan-induced paw edema in Wistar rats). Especially, its ethyl acetate bark extract demonstrated significantly reduced inflammation, highlighting its therapeutic potential for inflammation-related conditions.

POTENTIAL OF *SYZYGIUM AROMATICUM, NIGELLA SATIVA*, AND *MESUA FERREA* AS sEH INHIBITORS

Finally, the three plants exhibit potential as sEH inhibitors, which are explained in detail to understand how the stated plants become useful in treating AD. Plants, such as *Syzygium aromaticum,* provide the potential to act as sEH inhibitors. Several studies have shown that *Syzygium aromaticum* is the richest source of phenolic compounds (i.e., eugenol, tannins, gallic acid, and so on), and extracts have strong antioxidant activities (Atif *et al.*, 2024). Also, the components of *Nigella sativa* are known for their intense immune-regulatory properties (Elaemary *et al.*, 2020). Karri *et al.*, (Karri *et al.*, 2018) explained the *in vitro* antioxidant activities of bioactive flavonoid mesuaferrin from stem bark ethyl acetate extract of *Mesua ferrea* L. The standard methods were used to evaluate the *in vitro* antioxidant potential of mesuaferrin-A by using ABTS and NBT riboflavin photoreduction. The results

Table 3: Neuroprotective properties or potential effects of *Syzygium aromaticum, nigella sativa*, and *Mesua ferrea*.

Authors Names	Objectives	Medicinal Plant species	Outcomes	Limitations
(Butt *et al.*, 2018)	To examine neuroprotective effects of the ethanolic extract of *Nigella sativa L.* seeds on Pb-induced oxidative stress in the developing brain.	*Nigella sativa*	The extract enhances the expression of neuroprotective genes such as Superoxide Dismutase (SOD1) and peroxiredoxin (Prdx6), which are crucial for combating oxidative damage.	Further characterization of *Nigella sativa* L. compounds is needed.
(Sharma *et al.*, 2023)	To study the neuroprotective mechanism of *Syzygium aromaticum* extract and major bioactive compounds induced oxidative stress in human neuroblastoma SH-SY5Y cell lines.	*Syzygium aromaticum*	*Syzygium aromaticum* (Clove) extracts have neuroprotective capacity through the reduction of ROS, recovering mitochondrial membrane potential, rising GSH, and lowering lipid peroxidation in SH-SY5Y cells subjected to H_2O_2-induced oxidative stress. Besides exhibiting anti-acetylcholinesterase activity, anti-glycation activity, and inhibition of Aβ oligomerization/ fibrilization, multitarget neuroprotective strategy of Clove renders it an ideal drug candidate for AD.	Emphasize the necessity of additional*in vivo* research, thorough mechanistic studies, optimization of doses, and standardization to confirm and translate the neuroprotective potential of clove extracts into clinical practice.
(Islam *et al., 2015)*	To investigate the effects of *N. sativa* seed extracts of different germination phases on the CNS Anxiolytic and locomotor activity of extracts was evaluated in stressed and unstressed animal models.	*Nigella sativa*	The*N. sativa* extracts of varying germination stages showed anxiolytic activities under unstressed and stressed states, with 5th-day germination having the best activity, also showing significantly decreased locomotor activity under unstressed and stressed states, with the 5^{th}-day germination stage extract having the most pronounced effect.	Touching stress and physiological stress caused reduced mobility and violent behavior, finding achieved by rats cannot necessarily be applied to human beings because there are differences between species when it comes to physiology and CNS response. Lack of long-term assessment.
(Elibol *et al.*, 2019)	To investigate the effects of thymoquinone on neuroinflammation and neuroprotection in an $Aβ_{(1-42)}$ infused rat AD model.	*Nigella sativa*	From the findings, it was established that DCX protein levels increased as a consequence of the TQ therapy compared to the control group. MAP2 and PARP protein levels were lower in both $Aβ_{(1-42)}$ and $Aβ_{(1-42)}$ +TQ groups than in the sham control group.	Limitations indicate that future studies with extended treatment durations, increased sample sizes, heterogeneous models, and mechanistic studies are needed to comprehend TQ's therapeutic potential in AD fully.
(Plekratoke, Boonyarat, *et al.*, 2023)	To identify the effects of *Mesua ferrea* Linn flower (MFE) extract on the pathogenic cascade of AD using *in vitro* and cell culture models.	*Mesua ferrea* Linn	It was discovered that the MFE extract possessed numerous mechanisms of action against AD pathogenesis, which included antioxidant, anti-acetylcholinesterase, and anti-Aβ aggregation activities and neuroprotection.	Potential side effects and toxicity of the extract were not fully known and require thorough investigation.
(Plekratoke, Waiwut, *et al.*, 2023)	To isolate the two flavonoids from *M. ferrea* L. flowers against AD pathogenesis.	*Mesua ferrea* Linn flower	The neuroprotection study revealed Kaempferol-3-O-rhamnoside and quercetin-3-O-rhamnoside, two flavonoids derived from *Mesua ferrea* L. flowers, were investigated for their anti-Alzheimer's potential human neuroblastoma (SH-SY5Y) cell death induced by H_2O_2. Overall, the results show that both flavonoids exert multiple mechanisms relevant to AD pathogenesis.	The multiple targets linked to AD were still limited.

showed that the mesuaferrin-A (25, 50, and 100 µg/mL) had significant ABTS and superoxide free radical inhibiting activity. The inhibiting activity depended on light-induced superoxide generation by riboflavin, thereby causing a corresponding reduction of NBT.

Sundar *et al.*, (2023) explained the Pharmaconostic evaluation and *in vitro* evaluation of the antioxidant activity of *Mesua ferrea* Linn. The main focus of this research work was to perform a detailed Pharmacognostic study on antioxidant activities. As per the analysis, the total phenolic content of alcoholic, hydroalcoholic, and water extracts was found to be 16.95mg GAE/g, 27.16 mg GAE/g, and 14.61 mg GAE/g, respectively. The data based on the antioxidant activity was limited in this study.

Therefore, these medicinal plants have great potential to act as a superior sEH inhibitor, and they are also used as a major treatment drug for several diseases. Most importantly, inhibiting sEH stabilises endogenous EpFAs that have demonstrated beneficial effects in regulating inflammation in neurological diseases. This review mainly focuses on AD, which is one of the most common neurodegenerative disorders characterised by dementia. Thus, the inhibition of sEH based on these medicinal plants regulates inflammation in Central Nervous System (CNS) diseases.

CONCLUSION

This review overviews "sEH inhibitors and neuroprotective effects of *Syzygium aromaticum, Nigella sativa, and Mesua ferrea* in AD". AD is a brain disorder and a neurodegenerative disease that usually starts slowly and progressively worsens, causing 60-70% of cases of dementia. Several researches on this treatment did not give effective results in developing a drug. The therapeutic gap had given progressive changes in AD-affected patients. So, to overcome these challenges, the stated medicinal plants acted as the best therapeutic agent and sEH inhibitor for neurological-based disorders. Inhibiting sEH stabilised endogenous EpFAs, which provided beneficial effects in regulating inflammation caused by neurological diseases. Although it had advantages, limitations also occurred. When utilising the sEH inhibitors and the neuroprotective effects of the sEH inhibitors, the most frequent adverse effects were headaches and contact dermatitis. Therefore, this review gave an explanation based on the natural compounds found in *Syzygium aromaticum, Nigella sativa*, and *Mesua ferrea*, which acted as a good server for the potential of sEH inhibitors and provided a treatment related to AD. Future studies will be carried out by the researchers to develop a drug to eradicate AD.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CNS: Central Nervous System; **AD:** Alzheimer's disease; **sEH:** Soluble epoxide Hydrolase; **Aβ:** Amyloid β; **EETs:** Epoxyeicosatrienoic Acids; **EFAs:** Epoxy Fatty Acids.

SUMMARY

AD is a brain disease that causes a progressive decline in memory, thinking, learning, and organising skills. In this disease, the inhibition of sEH reduces oxidative stress and inflammation. Also, sEH Stabilises the level of EETs and alleviates AD through the GSK3β signalling pathway. sEH is predominantly expressed in astrocytes, and its concentrations are elevated in postmortem brain tissue from AD patients and in the 5xFAD β-amyloid. More research on the growth of drugs against AD has largely failed to produce effective treatment due to tau protein abnormalities. Neuroinflammation is intimately linked to the oxidative stress associated with AD, controlling the interactions between the immune system and the nervous system. However, several antioxidant therapies and nonsteroidal anti-inflammatory drugs have failed in clinical trials. So, therapeutic breaks occur in the health care systems. Inhibitors of sEH block this degradation and stabilize EET levels. To overcome this problem, this review gives a comprehensive explanation based on the AD treatment. The neuroprotective effects of the stated medicinal plants are examined through their bioactive compounds, which are known to possess antioxidant and anti-inflammatory properties. The study suggests that these herbal extracts may mitigate cognitive decline and neuronal damage in AD models. Overall, the information provided in this review supports the exploration of sEH inhibitors and these herbal remedies as promising strategies for developing effective treatments for AD. Therefore, the present review focuses on the role of sEH in the metabolism of Epoxyeicosatrienoic acids (EETs), which have neuroprotective effects. Inhibiting sEH may increase EET levels, potentially reducing Neuroinflammation and oxidative stress linked with AD.

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