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Neuroprotective Potential of *Ocimum sanctum* Polyphenols: Mechanisms and Therapeutic Implications

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ABSTRACT

Neurodegenerative diseases are major global health concerns due to progressive neuronal deterioration. Natural compounds, particularly plant polyphenols, are being explored for their neuroprotective potential. *O. sanctum* (Holy Basil or Tulsi) polyphenols, which possess pharmacological activities, were emphasized in this review. *O. sanctum* contains flavonoids, phenolic acids, and tannins, which exhibit strong antioxidant activity through scavenging free radicals and boosting endogenous antioxidants. These compounds also demonstrate anti-inflammatory activities, modulate cytokine production, and increase synaptic plasticity. Their anti-apoptotic effects inhibit the degeneration of neuronal cells. Preclinical studies demonstrated potential neuroprotective effects of *O. sanctum* polyphenols in different NDD models, with a few clinical studies suggesting their safety and efficacy over conventional neuroprotective medicines. Elucidating these mechanisms could help the development of *O. sanctum* polyphenols as drugs to combat NDDs and improve patient outcomes.
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Keywords: Anti-inflammatory agents, Neurodegenerative diseases, Neuroprotection, *Ocimum sanctum*, Polyphenols

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INTRODUCTION

Neurodegenerative diseases are a group of disorders characterized by the progressive degeneration of neurons, leading to neuronal death. These diseases have become a global concern due to the absence of effective treatments. The most prevalent NDDs include AD, PD, HD, and ALS. These disorders are associated with various biological factors, such as aging, neuroinflammation, environmental influences, oxidative stress, protein misfolding and aggregation, as well as mitochondrial dysfunction[1]. Oxidative stress, in particular, is a hallmark of many chronic diseases, including NDDs, which arises from an imbalance between antioxidants and pro-oxidants, leading to an increased production of ROS. The generated ROS causes oxidative damage to proteins, DNA, and mitochondrial membranes, ultimately triggering apoptosis[2]. Given the role of oxidative stress in NDD pathogenesis, there is an urgent need for therapeutic approaches that can either elevate endogenous antioxidants or inhibit ROS generation to effectively combat these disorders.

Polyphenols derived from *O. sanctum*, including eugenol, rosmarinic acid, apigenin, and ursolic acid, have shown significant neuroprotection in various NDD models. In AD, *O. sanctum* polyphenols inhibit β-amyloid oligomerization and inhibit the activation of caspase-3 and -9 and hence neuronal apoptosis with preservation of cognitive function[3]. Rosmarinic acid

List of Abbreviations:
6-OHDA: 6-hydroxydopamine; **AD:** Alzheimer's disease; **ALS:** amyotrophic lateral sclerosis; **BDNF:** brain-derived neurotrophic factor; **COX-2:** cyclooxygenase-2; **HD:** Huntington's disease; **HPLC: High-performance liquid chromatography**; **IL:** interleukin; **LC-MS: liquid chromatography-mass spectrometry**; **MPTP:** 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine; **NDD:** neurodegenerative disease; **NF-κB:** nuclear factor-kappa B; **NGF:** nerve growth factor; **NMR:** nuclear magnetic resonance; ***O. sanctum:*** *Ocimum sanctum*; **OS:** oxidative stress; **PD:** Parkinson's disease; **ROS:** reactive oxygen species; **SOD:** superoxide dismutase; **TNF-α:** tumor necrosis factor-alpha

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and apigenin also enhance synaptic plasticity by upregulating BDNF, a molecule involved in the consolidation. In PD models, hydromethanolic extracts of *O. sanctum* mitigate MPTP-triggered oxidative and nitrosative stress by restoring glutathione levels and enhancing antioxidant enzyme activity like SOD and catalase[4]. These effects protect against dopaminergic neuronal loss in the substantia nigra. For HD and ALS, *O. sanctum* polyphenols have been shown to reduce glutamate-induced excitotoxicity and mitochondrial dysfunction, as evidenced by the improved neuronal density and motor coordination in preclinical models. Collectively, these findings underscore the disease-specific therapeutic relevance of *O. sanctum* polyphenols and support their integration into the targeted neuroprotective strategies.

The historical use of medicinal plants for neuroprotection underscores their potential in modern therapeutic strategies. Medicinal herbs, particularly their bioactive phytochemicals such as phenolics and flavonoids, are increasingly used for their broad spectrum of pharmacological properties, including neuroprotection in common NDDs[5]. The neuroprotective properties of polyphenols against the nervous system are primarily due to their potent antioxidant activities, which are able to resist oxidative damage caused by free radicals. Various studies have proven that polyphenols provide effective protection for the nervous system against NDDs by reversing oxidative stress and its undesirable effects[6].

O. sanctum, or Holy Basil or Tulsi, belonging to the Lamiaceae family, is the "queen of herbs" according to its wide spectrum of medicinal action. This sacred plant in India is a repository of natural antioxidants in the form of flavonoids and phenolics in the leaf, stem, and seed, possessing significant antioxidant properties (Table 1)[7]. *O. sanctum* has been utilized to avert lethal diseases such as diabetes mellitus, cancer, hypertension, respiratory diseases, and arthritis. It has antifertility, anticancer, antidiabetic, antifungal, antimicrobial, cardioprotective, analgesic, antispasmodic, and adaptogenic activities (Fig. 1)[8].

This review aimed to examine the mechanisms of action and the therapeutic significance of dietary polyphenols present in *O. sanctum* with neuroprotective activity against NDDs. By understanding the neuroprotective role of these bioactive polyphenols, their potential as therapeutic agents will be explored for mitigating the progression of NDDs and improving patient outcomes.

Bioactive polyphenols in *O. sanctum*

Types of polyphenols

O. sanctum is rich in a variety of polyphenolic compounds, all of which play a role in its impressive pharmacological benefits (Table 2). The structures of some important polyphenols are shown in Figure 2.

Flavonoids

These are a group of polyphenolic compounds with strong antioxidant activities. The primary flavonoids found in *O. sanctum* include orientin and vicenin, which have been shown to provide significant neuroprotective benefits[9].

Phenolic acids

Phenolic acids—such as rosmarinic acid, caffeic acid, and apigenin—are abundant in *O. sanctum*. These compounds are known for their antioxidant, anti-inflammatory, and neuroprotective properties. Rosmarinic acid, in particular, has been studied for its potential to protect neuronal cells from oxidative stress[10].

Tannins

Tannins are polyphenolic biomolecules that bind to proteins and other organic compounds, possessing antioxidant and anti-inflammatory properties. They contribute to the therapeutic effects of *O. sanctum* by modulating oxidative stress and inflammatory pathways[11].

Other significant polyphenols

O. sanctum contains other significant polyphenols such as eugenol, methyl eugenol, carvacrol, and circimaritin. Eugenol is particularly noteworthy for its antiviral, antibacterial, anti-inflammatory, and neuroprotective properties. It has been demonstrated to provide neuroprotection through various cellular and molecular pathways[12].

Extraction and characterization

To harness the neuroprotective polyphenols of *O. sanctum*, efficient extraction and characterization methods are crucial.

Table 1. A list of phytochemicals present in the leaves, stems, and seeds of Holy basil (*O. sanctum*

***O. sanctum* parts**	**Phytochemicals**
Leaf	Flavonoids, alkaloids, saponins, tannins, terpenoids, steroids, and phenols
Stem	Phenols, saponins, flavonoids, triterpenoids, and tannins
Seed	Fatty acids and sitosterol

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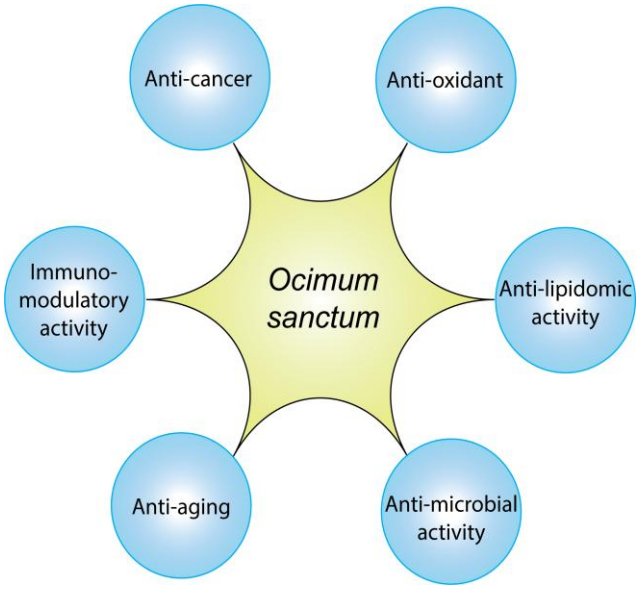

Fig. 1. Pharmacological actions of *O. sanctum.*

Methods of extraction

Solvent extraction

This conventional method uses solvents such as ethanol, methanol, and water to extract polyphenols from plant materials. It is widely used due to its simplicity and effectiveness[13].

Supercritical fluid extraction

This advanced method utilizes supercritical CO_2 to extract polyphenols, offering advantages such as lower extraction time and the absence of solvent residues in the final product[14].

Analytical techniques for polyphenol identification

High-performance liquid chromatography

HPLC is used for separating, identifying, and quantifying the polyphenols in *O. sanctum*. It provides high sensitivity and precision[14].

Liquid chromatography-mass spectrometry

The LC-MS technique combines the separation abilities of liquid chromatography with the analytical power of mass spectrometry, enabling a comprehensive characterization of polyphenols[15].

Nuclear magnetic resonance

NMR spectroscopy is used to elucidate the structure of polyphenolic compounds, providing detailed information about the molecular framework[15].

Quantitative analysis

Understanding the concentration of polyphenols in different parts of *O. sanctum* and how these concentrations vary due to the environmental factors is essential for optimizing their therapeutic use.

Concentrations of polyphenols in different parts of the plant

Leaves

The leaves of *O. sanctum* are the richest source of polyphenols, containing high concentrations of flavonoids, phenolic acids, and volatile oils like eugenol[16].

Stem

The stem of *O. sanctum* contains significant amounts of polyphenols, though typically at lower concentrations compared to the leaves.

Seeds

The seeds of *O. sanctum* consist of various polyphenols, though they are less studied compared to the leaves and stem.

Variations due to environmental factors

Soil quality, climate, and cultivation methods are some of the environmental aspects affecting the polyphenol level in *O. sanctum*. Research identified that plants with favorable growing conditions and enough light and water have higher polyphenols[9]. Changes in these environmental conditions can also cause variations in the composition and concentration of polyphenols in *O. sanctum*. Therefore, the composition of bioactive substances may differ, which has a direct effect on the pharmacological potency and therapeutic efficacy of the plant. Consequently, the plant extracts collected under different conditions may provide variable clinical effects, undermining reproducibility and reliability in therapy[17,18]. This variability is problematic to the standardization and quality control, which are essential in the formulation of consistent and effective herbal treatments.

Mechanisms of neuroprotection

O. sanctum contains different polyphenols that provide neuroprotection against NDDs. The antioxidant properties of these polyphenols neutralize ROS, have anti-inflammatory effects, and enhance synaptogenesis, as well as modulate programmed cell death of neurons (Fig. 2).

Antioxidant properties

The neuroprotective activity of bioactive polyphenols in *O. sanctum* is mainly attributed to their high antioxidant activity. These polyphenols possess excellent free radical scavenging activities that play a major role in the mitigation of oxidative stress—a key factor in NDDs[19]. Polyphenols such as eugenol,

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Table 2. Different bioactive components present in *O. sanctum*, their role, and their mechanism of action

Bioactive component	Role	Mechanism of action	Ref.
Eugenol	Antioxidant, anti-inflammatory, neuroprotective	Scavenges free radicals; inhibits COX-2 and NF-κB pathways; reduces oxidative stress and lipid peroxidation	[69]
Ursolic acid	Anti-inflammatory, anticancer, neuroprotective	Inhibits NF-κB signaling; induces apoptosis; reduces neuroinflammation; prevents neuronal death	[70]
Rosmarinic acid	Antioxidant, neuroprotective	Scavenges free radicals; inhibits lipid peroxidation and amyloid-β aggregation; protects neurons	[71]
Apigenin	Anti-inflammatory, anticancer, neuroprotective	Inhibits COX-2 expression; induces cell cycle arrest; reduces neuroinflammation and oxidative stress; modulates neurotransmitters	[72]
Luteolin	Anti-inflammatory, anticancer, neuroprotective	Inhibits NF-κB and AP-1 activation; reduces neuroinflammation and oxidative stress; modulates microglial activity	[73]
Ocimene	Antimicrobial, anti-inflammatory	Inhibits microbial growth; reduces inflammation	[74]
β-caryophyllene	Anti-inflammatory, analgesic	Binds CB2 receptors; inhibits pro-inflammatory cytokines	[75]
Caryophyllene oxide	Anti-inflammatory, anticancer	Inhibits NF-κB signaling; induces apoptosis	[76]
Linoleic acid	Anti-inflammatory, cardiovascular health	Modulates lipid metabolism; reduces inflammatory cytokines	[77]
Gallic acid	Antioxidant, antimicrobial	Scavenges free radicals; inhibits microbial growth	[64]
Orientin	Antioxidant, neuroprotective	Scavenges free radicals; protects neurons against oxidative stress	[78]
Vicenin-2	Antioxidant, neuroprotective	Scavenges free radicals; protects neurons from oxidative damage	[79]
Isorientin	Antioxidant, anti-inflammatory, neuroprotective	Scavenges free radicals; inhibits COX-2 and NF-κB; reduces neuroinflammation and oxidative stress	[80]
Methyl eugenol	Antimicrobial, antioxidant	Inhibits microbial growth; scavenges free radicals	[81]

apigenin, and rosmarinic acid in *O. sanctum*, scavenge ROS by donating electrons, thus preventing cellular injury[20,21]. Additionally, these bioactive compounds enhance the endogenous antioxidant defense system. Research has shown that *O. sanctum* polyphenols enhance the expression and activity of the key antioxidant enzymes, SOD and catalase. Increased expression of these enzymes plays an important part in detoxifying hydrogen peroxide and superoxide radicals, thereby protecting neuronal cells from oxidative stress[22]. Elevated levels of these antioxidants preserve the redox balance required for neuronal survival as well as neuronal function. Although *O. sanctum* polyphenols possess antioxidant and neuroprotective effects, yet can also become pro-oxidants under specific situations, such as high concentrations or in the presence of metal ions, resulting in potential oxidative stress[1,23]. For instance, eugenol has been shown to induce cytotoxicity through ROS at high concentrations[24]. These biphasic activities highlight the need for dose modulation and further investigation into their safety profiles.

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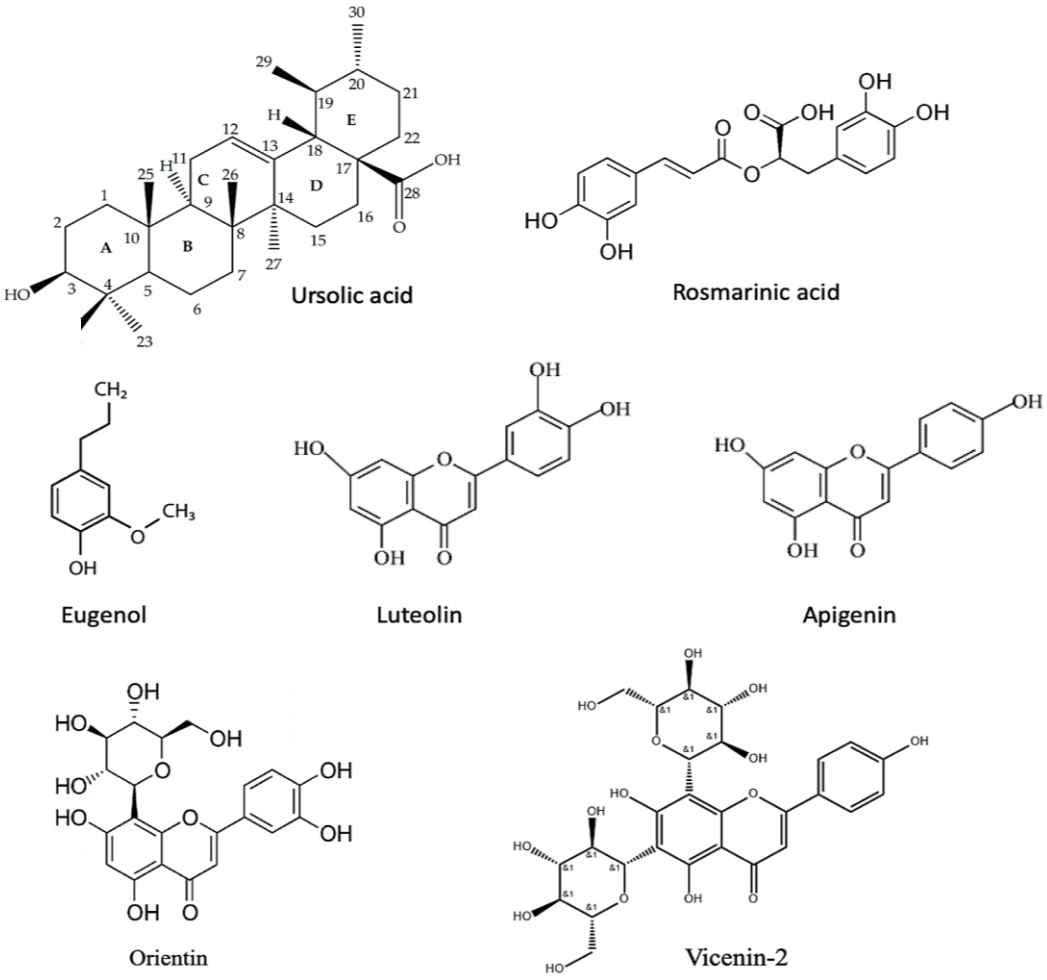

Fig. 2. Molecular structures of different neuroprotective components of *O. sanctum.*

Anti-inflammatory effects

Inflammation is a pathological hallmark of NDDs. Polyphenols found in *O. sanctum* exhibit strong anti-inflammatory effects, primarily by mediating inflammatory signaling pathways. For instance, eugenol and other polyphenols inhibit the activation of NF-κB, a key transcription factor that regulates the expression of various pro-inflammatory genes, including *COX-2*[25]. By suppressing NF-κB activity, these compounds reduce the production of pro-inflammatory mediators and enzymes, thus alleviating inflammation. Additionally, *O. sanctum* polyphenols influence cytokine regulation. They decrease the levels of pro-inflammatory cytokines, such as IL-1β and TNF-α, while increasing anti-inflammatory cytokines such as IL-10. This shift towards an anti-inflammatory cytokine profile contributes to the attenuation of neuro-inflammation, providing a conducive environment for neuronal repair and regeneration[26].

Neurogenesis and synaptic plasticity

Polyphenols in *O. sanctum* promote neurogenesis and enhance synaptic plasticity, which are vital for maintaining cognitive functions and neural network integrity. Neurogenesis, the process of generating new neurons, is stimulated by the activation of neurotrophic pathways, including BDNF and NGF pathways. Polyphenols such as rosmarinic acid and apigenin have been shown to upregulate BDNF and NGF, promoting the survival, differentiation, and maturation of new neurons[27]. In terms of synaptic plasticity, these compounds enhance synaptogenesis—the formation of new synapses—and increase dendritic spine density, which is crucial for synaptic transmission and plasticity. Improvements in synaptic structures support learning and memory functions, which are often impaired in NDDs[28]. Additionally, the presence of flavonoids like orientin and vicenin in *O. sanctum* further underscores its role in supporting neurogenesis and synaptic health[29].

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Anti-apoptotic activities

The anti-apoptotic properties of *O. sanctum* polyphenols are a significant mechanism contributing to their neuroprotective effects. Apoptosis, or programmed cell death, plays a crucial role in the progression of NDDs. Polyphenols inhibit apoptotic pathways by modulating the expression of apoptosis-related proteins. For instance, they prevent the apoptosis of neuronal cells by downregulating caspase-3 and -9 and inhibiting β-amyloid oligomerization[3]. Furthermore, these compounds provide mitochondrial protection, which is critical in preventing apoptosis. Mitochondrial dysfunction can lead to the release of cytochrome c and the activation of caspases, triggering the apoptotic cascade. Polyphenols help maintain mitochondrial integrity by preventing oxidative damage to mitochondrial membranes and ensuring efficient energy production[10]. This mitochondrial protection is vital for sustaining neuronal survival and function. Polyphenols from *O. sanctum*, such as eugenol, rosmarinic acid, and apigenin, may exert neuroprotective effects not only through antioxidant and anti-inflammatory actions but also by modulating key cellular and systemic processes implicated in NDDs[11].

Autophagy induction

Compounds such as rosmarinic acid and apigenin activate AMPK/SIRT1 and inhibit mTOR, promoting autophagy and mitophagy. This process facilitates the clearance of the aggregated proteins and damaged organelles, supporting neuronal health[30,31].

Mitochondrial biogenesis

Polyphenols enhance mitochondrial biogenesis by modulating key signaling pathways, including AMPK and SIRT1. This modulation leads to the activation of transcription factors such as PGC-1α, a key regulator of mitochondrial biogenesis. As a result, the expression of nuclear-encoded mitochondrial genes is upregulated, increasing mitochondrial DNA replication and promoting mitochondrial protein synthesis. This process results in an elevated mitochondrial content and improved respiratory capacity[32].

Mechanistic synergy in complex neurodegenerative environments

In NDDs, oxidative stress, inflammation, apoptosis, and impaired neurogenesis are interconnected processes. Oxidative stress activates NF-κB, which results in increased inflammation and neuronal death, while chronic inflammation suppresses neurotrophic factors such as BDNF[1,33,34]. Addressing how these pathways interact could provide a more comprehensive understanding of the therapeutic potential of *O. sanctum* in complex neurodegenerative conditions (Fig. 3)[35].

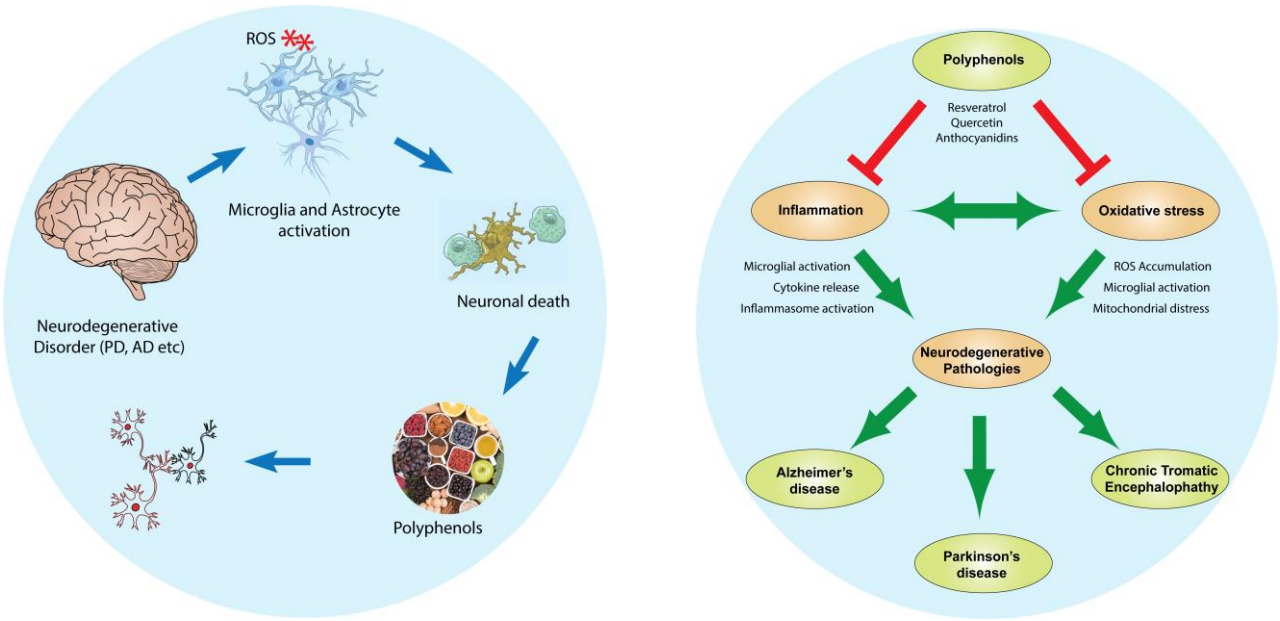

Fig. 3. Schematics representing the (A) polyphenols mitigate neurodegeneration by inhibiting ROS, glial activation, and neuronal death, thus slowing NDD progression in the first half; (B) polyphenols such as resveratrol, quercetin, and anthocyanidins present in the *O. sanctum* mitigate the progression of NDDs by modulating inflammation and oxidative stress pathways in the second half. Hence, polyphenols inhibit inflammation and oxidative stress, reducing key processes that drive NDDs like AD, PD, and chronic traumatic encephalopathy.

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Table 3. A comparative table summarizing effective doses, animal models, and biomarkers used in studies on *O. sanctum* and its polyphenols for neuroprotection

Study/ reference	Polyphenol/ extract	Effective dose (mg/kg; oral)	Animal model	Key biomarkers/ outcomes	Neuroprotective effects
[45]	Rosmarinic acid	50	6-OHDA-induced Parkinson's rat	SOD, MDA, TNF-α, motor coordination	Reduced oxidative stress and inflammation; improved motor function
[19]	Eugenol-rich extract	100	Transgenic Alzheimer's mice	Aβ plaque load, IL-1β, memory performance (Morris Water Maze)	Reduced amyloid pathology; improved cognition
[36]	Eugenol	10 µM (in vitro)	Cortical neuron cultures	ROS levels, NF-κB activity	Antioxidant and anti-inflammatory effects
[10]	Whole *O. sanctum* extract	200	Scopolamine-induced amnesia in rats	Acetylcholinesterase activity, SOD, and catalase	Enhanced cognition, reduced oxidative stress
[71]	Apigenin	20	LPS-induced neuroinflammation in mice	IL-6, TNF-α, microglial activation markers	Anti-inflammatory and neuroprotective effects

In vitro studies

In vitro studies have proven the neuroprotective action of *O. sanctum* bioactive polyphenols in cultured neuronal cells (Table 3). These studies simulated NDD neurotoxicity and demonstrated the pivotal role of eugenol, rosmarinic acid, and apigenin of *O. sanctum*-like compounds as protective molecules for cellular health. Eugenol, for instance, shows significant protection against hydrogen peroxide-induced oxidative stress in cortical neurons by neutralization of free radicals and enhanced activity of antioxidant enzymes[36]. Rosmarinic acid inhibits excitotoxicity induced by glutamate via the modulation of calcium influx and ROS production, thus preserving neuronal integrity[9]. Mechanistic insights from these studies highlight the role of these polyphenols in pathways such as Nrf2 activation by rosmarinic acid, leading to enhanced antioxidant defenses via *HO-1* expression[27]. Additionally, eugenol inhibits NF-κB, reducing the production of inflammatory cytokines [36].

Animal models

Animal models, particularly rodents, are a good model to investigate the neuroprotection of *O. sanctum* polyphenols in vivo against NDDs such as AD and PD. These models replicate the key pathological features of human disease, such as the use of transgenic mice expressing mutant forms of amyloid precursor protein to model AD and neurotoxins such as 6-OHDA or MPTP to model PD[28]. Behavioral studies have indicated the efficacy of *O. sanctum* extracts. For instance, eugenol treatment restores cognitive functions in AD models through improved performance in memory tasks[19]. Eugenol exhibited neuroprotective activity at low doses; however, at higher doses, toxicity increased. Eugenol has a narrow therapeutic window—oral dose of 10 mg/kg is generally safe, while 20–40 mg/kg doses can induce hepatic oxidative stress and histological liver damage in rats[37,38]. Additionally, eugenol may act as a pro-oxidant in glutathione-depleted states, exacerbating toxicity[39]. Despite its therapeutic promise, the lack of human dosing data and long-term safety evaluations limits clinical application. Therefore, standardized extract formulations and well-defined No Observed Adverse Effect Levels (NOAELs) are essential for safe use[40]. In PD models, the administration of rosmarinic acid improves motor coordination and diminishes tremors, validated through assessments such as the rotarod and pole test[9]. Biochemical analyses consistently revealed reductions in oxidative stress markers, lowered lipid peroxidation, and diminished inflammatory cytokine levels in the treated animals, supporting the antioxidative and anti-inflammatory underlying mechanisms of *O. sanctum* polyphenol neuroprotection.

Evidence from clinical studies

Clinical evidence has mentioned that current research has emphasized the hepatoprotective activity of terpenoids and polyphenols of *O. sanctum*[41]. A recent

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report has emphasized the chemotherapeutic relevance of eugenol, apigenin, and ferulic acid to regulate apoptosis and immune responses. However, their efficacy is hampered by poor bioavailability[42-44]. To address these challenges, innovative delivery approaches, including nanonization, have been proposed[45]. Altogether, these findings support the therapeutic potential of *O. cimum* phytochemicals, warranting further exploration through advanced molecular studies and clinical trials.

Traditional evidence

Tulsi (*O. sanctum*) has been revered in Ayurvedic and Siddha medicine. Its application includes the management of respiratory diseases (e.g., bronchitis and asthma), gastrointestinal diseases, stress disorders, and cutaneous infections/diseases. These applications are properly recorded in ethnobotanical as well as pharmacological literature[8]. The therapeutic activity of Tulsi is attributed to its intricate profile of polyphenolic bioactives, prominently rosmarinic acid and cirsilineol. These compounds exhibit potent antioxidant, anti-inflammatory, and antimicrobial properties. Antimicrobial activity of Tulsi encompasses bacteria, fungi, and viruses that are a part of dermal and systemic infections[46]. Ethnobotanical studies and clinical data are indicative of the adaptogenic activity of Tulsi, denoting that it helps the body manage physical and mental stress. Such activity has a mechanistic relationship with its activity in the neuroendocrine system, where it controls cortisol levels, supporting neurotransmitter balance and protecting against OS-driven cognitive decline[47].

Comparative analysis with other neuroprotective agents

Comparison with other natural compounds

The polyphenols found in *O. sanctum*, such as eugenol and rosmarinic acid, exhibit neuroprotective mechanisms that are similar to those found in other medicinal plants, such as turmeric and grapes. Curcumin, which is derived from turmeric (*Curcuma longa*), provides neuroprotection through its antioxidant, anti-inflammatory, and anti-amyloidogenic properties. However, its effectiveness is limited by poor bioavailability due to low water solubility and rapid metabolism[48,49].

Bioavailability challenges of O. sanctum polyphenols

Polyphenols such as eugenol, rosmarinic acid, and apigenin possess strong antioxidant and anti-inflammatory activities; however, their therapeutic activity is impaired by low solubility, rapid metabolism, poor intestinal absorption, and short systemic half-life. These limitations reduce their bioavailability and efficacy through oral administration[50].

Nanoformulation strategies for enhancing polyphenol delivery

As mentioned before, polyphenols such as eugenol, rosmarinic acid, and apigenin possess strong therapeutic activities but suffer from poor oral bioavailability due to the limited solubility, rapid metabolism, and low membrane permeability. Nanotechnology-based delivery systems offer effective solutions to these drawbacks. For instance, nanoparticles, liposomes, and nanoemulsions can encapsulate polyphenols, protecting them from enzymatic degradation and improving gastrointestinal absorption. Metal–phenolic networks and polyphenol–amino acid conjugates self-assemble into stable nanostructures with improved ROS scavenging and cell uptake. Site-specific transport is enabled by targeted delivery systems based on functionalized nanocarriers, which cause increasing local bioavailability and minimize systemic toxicity. These approaches significantly improve the pharmacokinetic profile and therapeutic efficacy of polyphenols[51-54].

Synergistic approaches to enhance the therapeutic efficacy of polyphenols

The therapeutic action of polyphenols can be significantly improved through strategic co-formulation with synergists, e.g., arginine, allowing nanoparticle formation and increasing biocompatibility, facilitating efficient cellular uptake. Phospholipid complexes and protein-based carriers further enhance membrane permeability and transport dynamics. Moreover, co-delivering polyphenols with adaptogens or antioxidants—such as *Cinnamomum zeylanicum*—may synergistically improve outcomes in stress-related, hepatic, and neurodegenerative disorders[55-57]. Resveratrol, a grape-derived polyphenol, has been found to activate the SIRT1 signaling pathway and enhance BDNF expression, allowing for neuronal survival and synaptic plasticity. However, it faces bioavailability challenges, often requiring higher doses to achieve therapeutic effects[58,59]. In contrast, the bioactive phytochemicals of *O. sanctum* possess superior antioxidant and anti-inflammatory effects, with potential for broader neuroprotective effect through their diverse exhibit superior bioavailability and synergistic effects, along with more selectively targeted activity compared to curcumin and resveratrol[60].

Comparison with synthetic neuroprotective agents

Polyphenols of *O. sanctum* possess significant advantages over conventional synthetic neuroprotective drugs, such as memantine and levodopa. Memantine, an antagonist of the NMDA receptor utilized to manage AD, reduces excitotoxicity but is linked to side effects, including dizziness, headache, and confusion[61].

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Levodopa, a dopamine precursor for PD, exhibits favorable effects on motor symptoms, but long-term treatment can result in complications such as dyskinesia and motor fluctuations[62]. In contrast, *O. sanctum* polyphenols provide a multi-targeted approach, combining antioxidant, anti-inflammatory, and neurogenic pathways, to combat multiple aspects of neurodegeneration simultaneously with fewer side effects[63]. However, the main limitation of these natural compounds is their lower bioavailability compared to synthetic drugs, which has led to ongoing research into advanced delivery systems to enhance their therapeutic potential.

Synergistic effects of O. sanctum with conventional neuroprotective drugs

A combination of polyphenols of *O. sanctum* (Tulsi) with traditional neuroprotective medication is a potential solution for increasing therapeutic effectiveness in NDDs. Eugenol, one of the predominant polyphenols of *O. sanctum*, obtained from the Tulsi plant, may be employed in conjunction with levodopa to enhance the motor function of PD patients as well as reduce oxidative stress and inflammation[64]. Although levodopa is the cornerstone treatment for PD, its long-term efficacy is hindered by oxidative stress and neuroinflammation that arise from dopamine metabolism[65]. Eugenol, known for its antioxidant and anti-inflammatory properties, enhances the therapeutic effects of levodopa[64]. It also suppresses NF-κB signaling and reduces the release of pro-inflammatory cytokines, which helps attenuate neuroinflammation linked to the levodopa-induced neurotoxicity[64,66]. Moreover, animal models have demonstrated that co-treatment of eugenol with levodopa induces greater behavioral recovery, reduced oxidative damage, greater glutathione content, and improved neuroprotection compared to levodopa alone. All these approaches enhance the motor effects of levodopa, reduce neurotoxic side effects, and improve overall functional benefit in PD models[64-67]. The efficacy of such combinations has been substantiated by evidence, since polyphenols are capable of enhancing the efficacy of synthetic drugs by modulating various cellular pathways in neurodegeneration. For instance, combining curcumin with memantine has demonstrated superior cognitive improvements compared to either agent alone in AD animal models[68]. This synergy, likely due to complementary mechanisms—such as antioxidant, anti-inflammatory, and neurogenic effects—suggests that the polyphenols in *O. sanctum* could similarly enhance the neuroprotective effects of other drugs, offering a multifaceted and side-effect-reducing therapeutic strategy.

CONCLUSION

This review highlights the significant neuroprotective potential of bioactive polyphenols present in *O. sanctum*, also known as Holy Basil or Tulsi. The major polyphenolic components like flavonoids, phenolic acids, tannins, and other important polyphenols possess potent antioxidant, anti-inflammatory, neurogenic, and anti-apoptotic activities. These mechanisms collectively account for the neuroprotective effects documented in many preclinical and clinical reports, efficiently scavenge free radicals, and strengthen endogenous antioxidant defenses through upregulation of enzymes such as SOD and catalase. These mechanisms suppress oxidative stress, a primary causative mechanism of neuronal damage in NDDs. The anti-inflammatory effects of these polyphenols are also crucial in their neuroprotection. They modulate inflammatory pathways by inhibiting NF-κB and COX-2 and cytokine release. Such an action causes a decrease in pro-inflammatory and an increase in anti-inflammatory cytokines. This biphasic activity is beneficial to manage neuroinflammation, a significant component of neurodegeneration. Furthermore, *O. sanctum* polyphenols activate the process of neurogenesis and enhance synaptic plasticity. They stimulate the factors, i.e., BDNF and NGF, involved in the growth and differentiation of new neurons and strengthening synaptic connections. Lastly, these polyphenols act anti-apoptotically by inhibiting apoptotic pathways and protecting mitochondrial integrity to inhibit programmed cell death and promote neuronal health. Taken together, the bioactive polyphenols present in *O. sanctum* are a therapeutic line for NDDs. Their polypharmacological neuroprotection mechanisms have the potential to revolutionize current treatment models, with more effective and integrative therapies. Continuing research and clinical exploration are needed to optimally develop their therapeutic possibilities and integrate them into standard clinical practice.

DECLARATIONS

Acknowledgments

No AI-assisted technologies were used in the preparation of this manuscript.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

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Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

NP: conceptualized the study conception and design, wrote the first draft of the manuscript, and critically revised the manuscript; SP: wrote the first draft of the manuscript; BP: conceptualized the study conception and design, wrote the first draft of the manuscript, and critically revised the manuscript.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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