

NEUROPROTECTIVE PROPERTIES OF PROPOLIS: FROM CHEMICAL VARIABILITY TO THERAPEUTIC APPLICATION – A NARRATIVE REVIEW

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ABSTRACT

*Propolis, a resinous substance collected by bees (*Apis mellifera*) from plant exudates, has traditionally been recognized for its medicinal properties. The therapeutic effects are attributed to a rich chemical composition, dominated by polyphenols and flavonoids with antioxidative, anti-inflammatory and neuroprotective properties. This review synthesizes current scientific evidence regarding the neuroprotective potential of propolis, with a focus on the ecological and compositional factors that influence its bioactivity and chemical variability. Propolis production depends on bee behavior, botanical sources and environmental conditions, resulting in a considerable chemical variability among samples from different geographical regions. The key bioactive compounds include flavonoids such as chrysin, pinocembrin and galangin, but also the caffeic acid phenethyl ester (CAPE), contributing to neuroprotection through multiple mechanisms: antioxidative activity by the inhibition of lipid peroxidation and the Nrf2 pathway activation, anti-inflammatory effects by suppression of pro-inflammatory cytokines and inflammasomes and mitochondrial protection against ischemic lesions. Preclinical evidence supporting the potential of propolis in neurodegenerative diseases such as Alzheimer's, Parkinson's, and epilepsy is also discussed. Particular attention is given to Romanian propolis research, situating regional findings within this broader neuroprotective and standardization context. Despite this, the intrinsic chemical variability poses significant challenges for standardization and quality control, limiting broad clinical application. Sustainable apiculture practices highlight the necessity of robust standardization methods for the integration of propolis in modern therapeutic practices.*

KEY WORDS: *propolis, neuroprotection, standardization, neurodegenerative diseases, flavonoids.*

1. INTRODUCTION

Propolis, a resinous substance collected by bees from various plant exudates, has long been recognized for its diverse medicinal properties and has been used in traditional

medicine across cultures for centuries (Marcucci 1995; El-Seedi *et al.* 2020; Hossain *et al.* 2022). The therapeutic effects are attributed to a rich and diverse chemical composition, predominantly polyphenols and flavonoids, which collectively exhibit a range of biological activities, including antimicrobial, anti-inflammatory and anti-oxidative (Zullkiflee *et al.* 2022; Bhatti *et al.* 2024). The growing interest in natural products for medical use has propelled propolis in the spotlight as a promising agent for pharmaceutical development (Sarapa *et al.* 2025).

Despite the extensive traditional use and documented benefits, the specific chemical variability of propolis poses significant challenges for modern medical application (Hossain *et al.* 2022). Propolis composition is influenced by numerous factors, such as geographical origin, specific flora available to bees, seasonal changes and even genetic variability among bee colonies (Kasote *et al.* 2022; Wieczorek *et al.* 2022). This variability directly affects the pharmacological profile, making standardization and quality control difficult, compromising the reproducibility of therapeutic outcomes and hindering wide-scale clinical adoption (Bankova 2005; Galeotti *et al.* 2019; Kasote *et al.* 2022).

This review addresses a significant challenge by exploring the neuroprotective potential of propolis in the context of intrinsic chemical variability. While the neuroprotective effects of propolis, such as the ability to attenuate oxidative stress, inflammation and neurotoxicity are increasingly recognized (Balaha *et al.* 2021; Zuhendri *et al.* 2021; Scorza *et al.* 2024), a deeper understanding that encompasses diverse chemical profiles and their specific neurobiological properties is essential. This review aims to synthesize current scientific evidence on the neuroprotective mechanisms of propolis and its bioactive compounds, with emphasis on the ecological factors and the compositional heterogeneity that shapes these effects, highlighting the need for more robust standardized methods. The paper is structured as follows: firstly, there are presented the ecological and biological factors that govern the propolis production, followed by the chemical profile and relevant bioactive compounds. The following sections detail the neuroprotective mechanisms identified in the scientific literature, experimental and clinical evidence in selected neurodegenerative conditions and, lastly, the implications of standardization and of sustainable apiculture practices for therapeutic applications.

As this is a narrative rather than a systematic review, the literature was not identified through a pre-registered protocol or formal screening process. Sources were located mainly through Google Scholar and PubMed, using search terms such as propolis AND neuroprotection, propolis AND (flavonoid OR CAPE), and propolis AND

(Alzheimer OR Parkinson OR epilepsy) NOT dentistry, supplemented by manual checks of the reference lists of the retrieved articles. Preference was given to recent primary experimental and clinical studies, with reviews consulted for broader context; no formal quality appraisal or risk-of-bias assessment was carried out, consistent with the narrative scope of this work.

2. ZOOLOGY AND ECOLOGY OF PROPOLIS PRODUCTION

Propolis production is a complex biological process, closely dependent on bee behavior and environmental conditions. Honey-producing bees (*Apis mellifera*) constantly gather resinous exudates from various plant sources such as buds and flowers (Šuran *et al.* 2021). This resin is then mixed with beeswax, pollen, and certain bee-derived enzymes, yielding the final product, propolis (Šuran *et al.* 2021; Kasote *et al.* 2022).

Despite sharing the same raw materials, the chemical composition - and consequently the therapeutic properties - of propolis can vary considerably depending on plant origin and the geographical location of the hive (Huang *et al.* 2014; Kasote *et al.* 2022). Furthermore, bees exhibit selective foraging behaviors, showing preferences for certain plant species over others (Isidorov *et al.* 2016; Eroğlu *et al.* 2021). For example, in temperate regions of Europe, North America, and parts of Asia and New Zealand, the primary botanical source for propolis production is *Populus spp.*, yielding the characteristic poplar-type propolis (Isidorov *et al.* 2016; Dudoit *et al.* 2021; Caetano *et al.* 2023). In other regions and climates, such as Brazil, distinct propolis types exist: green, red or brown, each associated with a predominant plant source: *Baccharis dracunculifolia* for the green propolis or *Dalbergia spp.* for the red propolis types (Kumazawa *et al.* 2003; Dudoit *et al.* 2021; Caetano *et al.* 2023). This relationship between botanical source and chemical composition has been documented in studies comparing propolis from multiple regions, including Turkey and Spain (Çelemlı *et al.* 2019; Rendueles *et al.* 2023).

Beyond botanical sources, several other biological and ecological factors can significantly affect propolis quality. Geographical and climatic conditions affect the type and availability of local vegetation, influencing the chemical profile of propolis through marked variation in phenolic and flavonoid content (Shehata *et al.* 2020; Sarapa *et al.* 2025). The season of harvest also affects the availability of specific plant species, resulting in temporal variation in the phenolic and flavonoid composition of propolis (Fiordalisi *et al.* 2019). At the level of the producer itself, variation may arise between bee species and subspecies, as well as among genetically distinct populations, potentially

influencing both propolis composition and plant preferences (Huang *et al.* 2014; Herrera-López *et al.* 2023). Behaviorally, bees have been observed to maintain fidelity to a single resin source, demonstrating the ability to discriminate between closely related plant species (Eroğlu *et al.* 2021). External factors such as pollution and pesticides can compromise propolis quality through contamination, altering its chemical composition, reducing therapeutic benefit, and posing potential health risks depending on the nature of the contaminants (Bogdanov 2006; González-Martín *et al.* 2018). Some studies indicated that the propolis can accumulate lipophilic pollutants better than honey, highlighting its utility as a bioindicator of environmental pollution, while also underscoring potential risks associated with consumption (Simsek *et al.* 2021). Pesticides may originate from agricultural practices or from treatments applied within hives for parasite control (González-Martín *et al.* 2018; Blažková *et al.* 2022). The presence of toxic elements in propolis, such as heavy metals, is typically associated with anthropogenic pollution (Tosic *et al.* 2017; González-Martín *et al.* 2018).

This interplay between environmental conditions, the availability of specific resin-producing plants, and variability in bee collection preferences and processing results in the high chemical diversity characteristic of propolis (Huang *et al.* 2014; Kasote *et al.* 2022). This variability poses significant challenges for standardization and quality control, yet simultaneously highlights the broad potential for discovering diverse bioactive compounds with varied therapeutic applications (Kasote *et al.* 2022). Detailed chemical characterization can support geographic authentication and ensure consistent quality control of propolis.

3. CHEMICAL PROFILE AND BIOACTIVE COMPOUNDS

Propolis is a natural resinous substance known for its remarkably complex and diverse chemical composition. This complexity arises from the variety of plant resin sources utilized by bees, combined with bee-specific enzymatic processing. Since systematic compositional studies began, the number of identified compounds has grown steadily, surpassing 500 by 2012 and increasing by more than 300 additional compounds by 2018 (Šturm & Ulrih 2020; Kasote *et al.* 2022).

The primary constituents include resins, wax, essential oils, and pollen, alongside minor components such as vitamins, minerals, and enzymes (Kasote *et al.* 2022). Nevertheless, the biological activity of propolis is largely attributed to its secondary metabolites, including terpenes, aromatic acids, and esters (Stojanović *et al.* 2020; Kasote *et al.* 2022; Nefzi *et al.* 2023).

Polyphenols constitute the most abundant class of bioactive compounds in propolis and are predominantly responsible for its antioxidative and anti-inflammatory effects (Bazmandegan *et al.* 2020). Several neuroprotective effects of propolis are attributed to polyphenols, which neutralize free radicals and exert anti-inflammatory activity (Bazmandegan *et al.* 2020). Flavonoids represent a major and highly diverse subgroup of polyphenols in propolis, with well-documented neuroprotective properties (Nefzi *et al.* 2023). Key flavonoids identified include chrysin, pinocembrin, galangin, apigenin, quercetin, luteolin, catechin, tectochrysin, tinostrobin and acacetin (Bazmandegan *et al.* 2020; Stojanović *et al.* 2020; Amini *et al.* 2023; Nefzi *et al.* 2023). These flavonoids demonstrated neuroprotective activities through multiple mechanisms, detailed in the next section.

Certain phenolic acids and their esters - including caffeic, cinnamic, ferulic, benzoic, salicylic, and p-coumaric acids - have been documented for their beneficial effects on the nervous system (Nefzi *et al.* 2023; Stojanović *et al.* 2020). From these, the caffeic acid phenethyl ester (CAPE) is researched well enough and recognized for its spectrum of pharmacologic activities, including the neuroprotective activities (Tolba *et al.* 2013; Balaha *et al.* 2021).

To fully realize the therapeutic potential of propolis, robust extraction and standardized analytical methods are indispensable. The primary objective of extraction is to isolate bioactive compounds from the resinous matrix. The most commonly used approach is solvent extraction with ethanol, which effectively dissolves a broad range of bioactive compounds (Šuran *et al.* 2021). Alternative methods include aqueous extraction, supercritical extraction with CO₂ and ultrasound-assisted extraction (Šuran *et al.* 2021). Given the high compositional variability of propolis, standardization is crucial for ensuring consistency, predictable effects, and reliable therapeutic efficacy across products. This process typically involves the use of specific chemical markers - particularly key flavonoids - to ensure quality compliance across batches. Such standardization efforts aim to guarantee consistent pharmacological activity across batches, support appropriate dosing, and facilitate rigorous quality control (Kasote *et al.* 2022).

4. NEUROPROTECTIVE MECHANISM

Propolis exerts a multifaceted neuroprotective effect, encompassing the modulation of oxidative stress, inhibition of neuroinflammation, mitochondrial protection, and prevention of neuronal apoptosis. These mechanisms are interconnected and act

collectively to underpin the therapeutic potential of propolis in the context of neurodegenerative diseases.

4.1 ANTIOXIDATIVE MECHANISM

The brain is a particularly vulnerable organ to oxidative damage, owing to its high oxygen demand, elevated concentration of fatty acids, and relatively low endogenous antioxidant capacity (Alkis *et al.* 2015). Oxidative stress plays a critical role in ischemic cerebral injury and in neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Propolis exhibits antioxidant effects through multiple mechanisms. Animal studies have demonstrated that propolis extracts significantly inhibit lipid peroxidation in brain tissue and neutralize free radicals as assessed by the DPPH (2,2-diphenyl-1-picrylhydrazyl) assay, while also markedly reducing neurotoxicity induced by hydrogen peroxide exposure (Shimazawa *et al.* 2005).

In a mouse model of cerebral stroke, brown Iranian propolis restored the activity of key antioxidative enzymes - superoxide dismutase and glutathione peroxidase - and concurrently reduced lipid peroxidation and infarct volume (Bazmandegan *et al.* 2020).

At the molecular level, propolis activates the Nrf2 transcription factor, a master regulator of antioxidant gene expression, which, upon binding to the antioxidant response element (ARE), triggers transcription of a battery of cytoprotective enzymes (de Oliveira *et al.* 2017; Bhatti *et al.* 2024). Among the propolis-derived compounds acting on this pathway, CAPE has been specifically shown to activate Nrf2 signalling while concurrently suppressing the pro-inflammatory NF- κ B pathway, a dual mechanism considered central to its neuroprotective profile (Pérez *et al.* 2023).

At the cellular level, key flavonoids from propolis - including pinocembrin, galangin, and quercetin - contribute to neuroprotection through direct free radical scavenging (Ibrahim *et al.* 2023; Pluta *et al.* 2023). Galangin has also been shown to inhibit acetylcholinesterase activity, an important therapeutic target in neurodegenerative diseases (Kapare *et al.* 2022).

4.2 ANTI-INFLAMMATORY EFFECTS

Neuroinflammation represents a key pathophysiological mechanism in hypoxic-ischemic cerebral injury and in neurodegenerative diseases. Microglia, the resident immune cells of the brain, play a central role in the initiation and perpetuation of neuronal inflammatory response (Biswas 2023). Propolis acts as an anti-inflammatory agent through the inhibition and downregulation of specific inflammasomes and pro-inflammatory cytokines (Zulhendri *et al.* 2022). CAPE, a major bioactive constituent of propolis, is capable of inhibiting cytokine and chemokine production, T cell

proliferation, and lymphokine production, thereby attenuating the inflammatory response (Tolba *et al.* 2013).

CAPE further contributes to the anti-inflammatory profile of propolis and inhibits neuronal apoptosis through suppression of caspase-3 activation and the intrinsic apoptotic pathway (Tolba *et al.* 2013; Nugroho *et al.* 2017; Balaha *et al.* 2021; Ibrahim *et al.* 2023).

4.3 MITOCHONDRIAL PROTECTION

Mitochondria are both primary sources of reactive oxygen species and central mediators of ischemic injury in cerebral cells. Oxygen insufficiency triggers the overproduction of reactive oxygen species that impair mitochondrial integrity, ultimately compromising neuronal function and viability.

Balion *et al.* (2020) investigated the effect of propolis extracts on the viability, mitochondrial efficiency, and superoxide generation in ischemic conditions using primary cultures of rat cerebral glial neuronal cells, and found that the extracts significantly enhanced neuronal viability in ischemic cultures and reduced mitochondrial superoxide levels.

Pinocembrin enhances mitochondrial function and exerts anti-apoptotic effects by promoting neuronal stem cell differentiation and attenuating caspase activity (de Oliveira *et al.* 2017).

4.4 EXPERIMENTAL AND CLINICAL EVIDENCE OF PROPOLIS EFFECTS IN DIFFERENT NEURODEGENERATIVE DISEASES

Alzheimer's Disease

Propolis has demonstrated the potential to reduce amyloid fibrillation and attenuate the effects of amyloid accumulation, while also dose-dependently inhibiting acetylcholinesterase and butyrylcholinesterase activity (Zulhendri *et al.* 2021). Pretreatment with green Brazilian propolis for eight days significantly prevented cognitive impairment in an Alzheimer's mouse model (Ito *et al.* 2023). In human studies, propolis supplementation yielded positive effects on cognitive function, improving verbal memory, processing speed, complex attention, and focus (Asama *et al.* 2021). Furthermore, propolis demonstrated notable efficacy in inhibiting beta-amyloid aggregation and reducing neuroinflammation, both in animal models (Banaei *et al.* 2023) and human studies (Zhu *et al.* 2018).

Parkinson's Disease

In a rat model of induced Parkinson's disease, propolis treatment for 40 days attenuated neuronal loss and reduced the degeneration of striatal fibers (Gonçalves *et al.* 2020). Caffeic acid proved effective in reducing cerebral inflammatory markers and

protecting dopaminergic neurons in the substantia nigra in rotenone-induced Parkinson's rat models (Zaitone *et al.* 2019). Furthermore, a propolis polyphenol-based nanosheet formulation demonstrated neuroprotective effects in rotenone-induced Parkinson's rat models (Mamashli *et al.* 2023). Regarding human evidence, dedicated clinical trials for Parkinson's disease are still ongoing; however, analyses of clinical data such as Zulhendri *et al.* (2021) and Matias *et al.* (2025) confirm that propolis supplementation is safe and beneficial for improving antioxidative markers in Parkinson's patients - a finding relevant to managing the oxidative burden associated with this disease.

Epilepsy

Epilepsy involves neuronal hyperexcitability and secondary neuronal loss, processes in which oxidative stress and neuroinflammation play central roles — mechanisms that propolis targets through its bioactive constituents. Propolis has demonstrated the potential to reduce neuronal loss and improve the histopathological outcomes associated with epilepsy, through downregulation of inflammatory marker expression, maintenance of antioxidant status, and enhancement of motor and cognitive scores in animal models (Liu *et al.* 2012). Furthermore, propolis has shown promising neuroprotective and anticonvulsant properties in preclinical epilepsy models (Zulhendri *et al.* 2021). In animal models of pilocarpine-induced convulsions, propolis treatment produced favorable outcomes in reducing neuronal loss and improving hippocampal histopathology (Mannaa *et al.* 2011; Zulhendri *et al.* 2021). Specific constituents such as pinocembrin play an essential protective role against beta-amyloid-induced toxicity and mitochondrially mediated apoptosis - pathways relevant to seizure-induced neurodegeneration (Ibrahim *et al.* 2023; Liu *et al.* 2012).

5. ECOLOGICAL IMPORTANCE FOR MEDICINE

5.1. SUSTAINABLE APICULTURE AND PROPOLIS QUALITY

Sustainable apiculture practices are closely linked to the quality and medical-grade availability of propolis. The health and well-being of both hives and their surrounding environment directly affect the quality of propolis produced. Sustainable apiculture involves practices that minimize external stressors, including the avoidance of sites exposed to pesticides or environmental pollution. This is critical, as pollutants can become incorporated into propolis, reducing its medicinal properties and introducing potential health risks upon consumption (Bogdanov 2006; Blažková *et al.* 2022). By ensuring a clean and ecologically healthy environment, sustainable practices contribute to maintaining the purity and optimal chemical composition of propolis, thereby preserving its therapeutic properties (Bankova *et al.* 2023).

Sustainable apiculture also promotes biodiversity and ecosystem health, which in turn ensures a reliable and diverse supply of botanical sources for bees. This ecological stability can help mitigate variability challenges by providing consistent, high-quality raw materials, ultimately contributing to more uniform propolis (Contieri *et al.* 2022). Furthermore, sustainable harvesting strategies combined with the pooling of propolis from multiple hives or across different seasonal periods may help limit compositional variability (Peixoto *et al.* 2022). Such strategies can support standardization efforts by yielding a more balanced product with predictable biochemical profiles and consistent medicinal properties, helping to bridge the gap between natural variability and the demands of therapeutic application.

5.2. STANDARDIZATION AND REGIONAL PERSPECTIVES

A significant barrier to the clinical use of propolis is its chemical complexity combined with the absence of internationally harmonized standardization (Kasote *et al.* 2022; Salatino 2023; Pastor *et al.* 2025). Recent comprehensive appraisals of the wider propolis literature continue to echo this gap between its broad pharmacological potential and the absence of harmonized quality benchmarks (Balasubramaniam *et al.* 2025; Ballouk *et al.* 2025). Because bees collect resins from varied vegetal sources, propolis composition can differ not only between countries but even among hives within the same region, making the consistent reproduction of desired therapeutic effects challenging. Currently, bodies such as the International Honey Commission are working towards harmonizing analytical methods and establishing quality parameters, with the goal of establishing an ISO (ISO/TC 34/SC 19) global standard. This standard focuses on specific chemical markers - including total polyphenol content and key flavonoids such as pinocembrin and galangin - to ensure reproducible therapeutic outcomes (Pastor *et al.* 2025).

Standardization is particularly critical for neurodegenerative applications, where precise dosing of active compounds such as CAPE is required to achieve specific effects, such as dopaminergic neuroprotection (Matias *et al.* 2025). Standardized extracts have already been developed as models for pharmaceutical-grade products (such as the Brazilian extract EPP-AF or Eurasiatic s-HEP), designed to eliminate impurities and concentrate bioactive fractions (Matias *et al.* 2025; Salatino 2023). Recent research confirms that HPLC combined with mass spectrometry represents the most suitable technique for the rigorous chemical screening required for pharmaceutical-grade applications (Galeotti *et al.* 2019; Pastor *et al.* 2025).

In Romania, research on propolis has advanced from general characterization towards the identification of specific bioactive markers, and local samples -

predominantly of the poplar type - are distinguished by their elevated concentrations of phenolic and flavonoid acids, particularly pinocembrin, galangin, and chrysin (Niculae *et al.* 2015; Nichitoi *et al.* 2021). The high antioxidative capacity of propolis from Transylvania and Bihor (Heghedűş-Mîndru *et al.* 2024) can be directly associated with the inhibition of lipid peroxidation and the reduction of reactive oxygen species, central processes in neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Although a substantial portion of local research has focused on antimicrobial and antifungal properties, relevant neuroprotective mechanisms - including the inhibition of pro-inflammatory cytokines - have been identified for Romanian propolis (Albanese *et al.* 2025; Mărghițaș *et al.* 2013), providing a solid foundation for future research specifically directed at neuroprotective applications. This regional dataset can contribute meaningfully to broader standardization efforts by providing a well-characterized and predictable chemical profile representative of temperate European propolis.

6. CONCLUSION

Propolis, a remarkable natural product, demonstrates considerable therapeutic potential across a spectrum of biological activities, underpinned by its diverse and rich chemical composition. From its traditional medicinal uses to its growing recognition in contemporary research, propolis offers compelling benefits, particularly in the domain of neuroprotection. Its capacity to attenuate oxidative stress, exert anti-inflammatory effects, and protect against neurotoxicity points to promising potential as a complementary agent in addressing neurodegenerative conditions.

Despite these attributes, the intrinsic compositional variability of propolis remains a fundamental challenge for large-scale use and consistent clinical application. Factors such as geographical origin, specific botanical sources, and environmental contaminants substantially influence its composition, rendering standardization and quality control both complex and demanding. This variability directly compromises the reproducibility of pharmacological effects and calls for more rigorous and nuanced research into therapeutic application. Appropriate integration of propolis into contemporary medical practice depends on several key aspects: robust standardization, in-depth research correlating specific chemical profiles with neuroprotective and other therapeutic mechanisms, rigorous clinical validation, and, not least, the adoption of sustainable production practices. Propolis represents a highly promising natural therapeutic agent, especially given its neuroprotective capabilities, but realizing its full potential requires further well-designed studies. Priority research directions should include randomized clinical trials using standardized extracts, systematic correlation of

regional chemical profiles with specific therapeutic efficacy, and the development of targeted delivery formulations (such as propolis-based nanoparticles), an approach already shown to enable propolis to cross the blood-brain barrier in preclinical carrier systems. This review has certain limitations that should be acknowledged. As a narrative rather than a systematic review, the literature was not subjected to formal screening or quality appraisal, which may have introduced selection bias. The evidence base is also predominantly preclinical, drawn largely from animal and in vitro models; well-designed human trials, particularly for epilepsy, remain scarce. These limitations should be considered when interpreting the conclusions presented here. Propolis is not a panacea, but, when integrated into a rigorous and well-standardized therapeutic framework, it has the potential to become a valuable adjunct in the management of neurodegenerative conditions.

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