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(REVIEW ARTICLE)

Propolis and propolis-derived constituents in experimental models relevant to alzheimer's disease: A narrative review of mechanisms and translational gaps

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Abstract

Background: Alzheimer's disease (AD) involves progressive cognitive decline associated with amyloid-β (Aβ) and tau pathology, oxidative stress, mitochondrial dysfunction, neuroinflammation, synaptic failure, and neuronal loss. Propolis contains geographically variable phenolic acids, flavonoids, and other potentially neuroprotective constituents.

Aim: This structured narrative review critically evaluates propolis extracts and derived constituents in AD-related and indirect neurodegeneration models, emphasizing mechanistic confidence and translational relevance.

Method: The review was developed from google scholar and semantic scholar database. Thirty-seven citation records in the source manuscript were audited; one conference record was confirmed as overlapping a later full article.

Result: Direct evidence was limited to APP-knock-in mice, Aβ-induced cellular and mouse models, and an Aβ-expressing Caenorhabditis elegans model. Selected Brazilian green propolis preparations and pinocembrin were associated with synaptic, cognitive, antioxidant, mitochondrial, inflammatory, and apoptotic outcomes in these systems. Most supporting studies, however, used indirect oxidative, ischemic, hypoxic, excitotoxic, or chemically induced impairment models. The evidence is predominantly preclinical, chemically heterogeneous, and incompletely reported, and no formal risk-of-bias assessment was performed.

Conclusion: Propolis-derived interventions provide mechanistic plausibility but cannot yet establish clinical efficacy or interchangeability among products. Standardized chemistry, brain-exposure data, rigorous age-appropriate AD models, safety studies, and controlled clinical trials are required.

Keywords: Alzheimer's disease; Propolis; amyloid-β; Pinocembrin; Neuroinflammation; Oxidative stress.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia. Its clinical course typically begins with impairment of episodic memory and other cognitive domains and advances to loss of independent function. The biological continuum develops over years and is defined by amyloid-β (Aβ) deposition and tau pathology, accompanied by synaptic dysfunction, maladaptive glial responses, and selective neuronal loss [1–3]. These processes are heterogeneous in timing and magnitude, and mixed vascular or other age-related brain pathologies frequently modify the clinical phenotype [2,3].

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AD pathogenesis extends beyond protein deposition. Oxidative stress, altered mitochondrial bioenergetics, impaired proteostasis, vascular dysfunction, and sustained neuroinflammation can interact with Aβ and tau to amplify neuronal injury [3–6]. Aβ engagement of receptors such as the receptor for advanced glycation end products (RAGE) can activate p38 mitogen-activated protein kinase, c-Jun N-terminal kinase, and nuclear factor-κB (NF-κB) signaling, while activated microglia and astrocytes can release mediators that further disrupt synaptic and neuronal function [6,7]. These pathways provide biologically plausible targets, but their coexistence does not imply that modulation of a single pathway will alter the human disease course.

Synaptic failure correlates more closely with cognitive impairment than plaque burden alone [8]. Brain-derived neurotrophic factor (BDNF) signaling, activity-regulated cytoskeleton-associated protein (Arc), calcium/calmodulin-dependent protein kinases II and IV (CaMKII and CaMKIV), cAMP response element-binding protein (CREB), AMPA-receptor trafficking, and long-term potentiation (LTP) contribute to activity-dependent plasticity and memory [9,10]. A credible neuroprotective hypothesis should therefore connect biochemical protection with synaptic or functional outcomes; antioxidant activity in a cell-free assay is insufficient evidence of disease modification.

Propolis is a resinous material produced when bees combine plant-derived resins with wax and secretions. It is a chemically variable natural product rather than a single pharmacological entity. Botanical source, bee species, geography, season, collection, storage, and extraction method influence its composition [11–13]. Brazilian green propolis is characteristically associated with Baccharis dracunculifolia and prenylated phenylpropanoids such as artepillin C; poplar-type, Chinese, and other temperate-zone propolis commonly contain flavonoids including pinocembrin, chrysin, galangin, and pinobanksin derivatives; and stingless-bee propolis may possess distinct phenolic and terpenoid profiles [11–13]. These broad chemical types are not interchangeable, and marker content must be demonstrated analytically rather than inferred from geographic naming alone.

Several propolis-associated compounds have shown neuroprotective activity in experimental systems. Pinocembrin has been examined in Aβ-related cellular and mouse models [14,15]; artepillin C in cellular stress, proteostasis, and neurotrophic systems [16,17]; chrysin in mitochondrial-apoptosis models [18]; a synthetic caffeic acid phenethyl ester (CAPE) derivative in oxidative and scopolamine paradigms [19]; and caffeoylquinic-acid derivatives in oxidative neuronal injury [20]. These studies support mechanistic hypotheses for defined molecules or preparations, but effects of an isolated constituent or synthetic derivative cannot be assigned automatically to whole propolis, and extract activity cannot be attributed to one constituent without comparative chemical and exposure data.

Translation is further constrained by model choice. Oxidative-stress, ischemia, hypoxia, excitotoxicity, scopolamine, and other chemically induced models isolate processes that may occur in AD, but they do not reproduce the chronic interaction among Aβ, tau, aging, glial dysfunction, vascular injury, and progressive synaptic loss in human disease [2,3]. Findings in such models provide mechanistic plausibility or support a preclinical hypothesis; they cannot establish efficacy for AD. Chemical heterogeneity, preventive treatment schedules, and pathway claims based only on correlated protein changes introduce additional uncertainty.

This structured narrative review critically synthesizes evidence for whole propolis preparations, fractions, isolated natural constituents, and synthetic or semisynthetic derivatives in experimental models relevant to AD. It distinguishes direct APP/Aβ models from AD-adjacent cognitive-impairment models and indirect neuronal-injury paradigms; evaluates oxidative, mitochondrial, inflammatory, apoptotic, proteostatic, and synaptic mechanisms; and identifies the chemical, pharmacokinetic, safety, and experimental requirements needed for credible translation.

2. Review methodology

2.1. Review design and research question

This work was conducted as a structured narrative review [21,22]. A narrative design was appropriate because the evidence comprised chemically heterogeneous preparations, isolated constituents, synthetic derivatives, and diverse direct and indirect models. The guiding question was: what neuroprotective mechanisms and functional outcomes have been reported for propolis-related interventions in experimental models relevant to AD, and how directly do those models support an AD-specific or translational inference?

2.2. Evidence identification

The attached manuscript identifies the primary evidence using google scholar and Semantic Scholar discovery. Semantic Scholar organizes scholarly records through a literature graph that supports relevance-based discovery [23].

The abstract's earlier statement that the evidence came from Google Scholar was not supported elsewhere in the attached material and was removed. Because the original Elicit export, platform log, or search record was not attached, the discovery source could not be independently confirmed beyond this internal description. The search date or period, complete query or Boolean string, language limits, duplicate-removal procedure, number of screeners, disagreement process, record-level exclusion log, and protocol registration were unavailable and were not reconstructed by assumption.

2.3. Data extraction and classification

The source report described abstract-based screening for records in which propolis, a propolis fraction, a defined propolis-associated constituent, or a synthetic derivative was evaluated in a neuronal, cognitive-impairment, or AD-relevant context. Eligible evidence addressed oxidative or neuronal injury, molecular mechanisms, experimental controls, or functional neurological outcomes. Human studies, if present, would have been eligible for translational evaluation; none meeting the review scope was identified. Records without a separable propolis-related intervention, non-neurological studies, citations that could not be matched to the stated content, and duplicate or overlapping reports were flagged rather than silently treated as independent evidence.

Thirty-seven citation records present in the source manuscript were audited against DOI, publisher, PubMed, Crossref, or other traceable bibliographic records. Data fields included publication type, model and species, injury or disease induction, intervention class, propolis origin and preparation, dose or concentration, treatment timing, comparator, biochemical and functional outcomes, proposed targets, and limitations. Evidence was classified as: (i) direct APP/Aβ models; (ii) AD-adjacent cognitive-impairment models; (iii) indirect oxidative, ischemic, hypoxic, excitotoxic, or toxicant models; (iv) in silico or biochemical evidence; or (v) incomplete, overlapping, or citation-content-mismatched records. Interventions were separately classified as whole extracts, fractions, isolated natural constituents, or synthetic/semisynthetic derivatives. After verification, 36 distinct records remained because one Cardoso conference abstract overlapped the later full journal article; the Xiao record remained incomplete and unverifiable.

Evidence was synthesized thematically rather than pooled statistically. Mechanistic confidence was judged descriptively as stronger when a finding was reproduced across models or supported by pathway inhibition, genetic manipulation, target-engagement evidence, rescue experiments, or convergent electrophysiological or behavioral outcomes. These labels are not formal GRADE ratings. AI-assisted discovery and extraction were treated as aids rather than verification: such tools may omit relevant studies, propagate metadata errors, misclassify records, or extract unsupported details, and comparative evaluations show that human verification remains necessary [24]. Full-text verification was limited by the materials available to the authors. No formal risk-of-bias tool was applied, so randomization, allocation concealment, blinding, attrition, selective reporting, and publication bias were not quantitatively assessed.

3. Chemical composition and pharmacological variability of propolis

Propolis samples represented in the evidence originated from Brazil, China, Portugal, Egypt, India, Algeria, and South American stingless-bee sources, while several studies did not report a geographic or botanical origin. This diversity is scientifically important. Brazilian green propolis is commonly associated with Baccharis dracunculifolia and artepillin C, but the concentration of this marker and the abundance of flavonoids can vary between products. Northeast Portuguese propolis was described as a phenolic-rich temperate-zone preparation containing pinocembrin, chrysin, and pinobanksin derivatives [25]. Chinese propolis and its constituents were examined in neuronal apoptosis systems, with chrysin emerging as an important active component in the reported comparison [18]. Indian and Algerian preparations were chemically profiled before network-pharmacology, docking, antioxidant, or cholinesterase analyses [26,27].

Extraction solvent changes both yield and composition. Water preferentially extracts relatively polar constituents, whereas ethanol or methanol can recover broader or different phenolic fractions. Brazilian green propolis ethanol extracts were more active than corresponding water extracts in an HT22 oxytosis/ferroptosis model [28]. Differently prepared extracts also produced distinct effects on mitochondrial function in ischemia-exposed brain cells [29]. These observations argue against reporting "propolis dose" without the mass of crude material, extraction ratio, solvent, dry-extract yield, marker concentrations, and final vehicle.

Preparation terminology also requires precision. A whole extract contains multiple known and unknown compounds. A flavonoid fraction is not equivalent to crude propolis. A "water-soluble derivative" may be chemically modified or formulated. An isolated constituent such as pinocembrin or artepillin C tests a defined molecule, whereas FA-97 is a

synthetic CAPE derivative and acetylated artepillin C is semisynthetic. Evidence from FA-97 provides proof of principle for a chemical scaffold but does not demonstrate that natural propolis provides an equivalent exposure [19].

Chemical standardization is fundamental to reproducibility. At minimum, future studies should report geographic location, plant source where known, bee species, collection season, extraction solvent and ratio, extraction yield, chromatographic fingerprint, quantitative marker compounds, contaminants, and batch-acceptance criteria. Without these data, divergent biological results may reflect chemical heterogeneity rather than genuine mechanistic inconsistency. The major propolis types, preparation methods, and interpretive limitations identified in the evidence base are summarized in Table 1.

Table 1 Propolis types and preparation-related variability

Propolis type	Preparation	Representative evidence	Key interpretive issue
Brazilian green	Ethanol, methanol, water, or unspecified formulated extract	[16,17,20,28–38]	Artepillin C-rich identity cannot be assumed without fingerprinting; solvent alters activity
Chinese/poplar-type	Whole extract and isolated constituents	[18,39]	Chrysin, pinocembrin, galangin, caffeic acid, and CAPE may contribute differently
Northeast Portuguese	Phenolic-enriched ethanolic extract	[25]	Record 37 likely overlaps with full publication [25]
Egyptian	Extract from locally obtained propolis	[40]	Botanical origin and reported dose require verification
Indian	Chemically profiled extract	[26]	Network/docking predictions require target-engagement and exposure confirmation
Algerian	Three regional ethanolic extracts	[27]	Regional chemical differences associated with different biochemical activities
Stingless-bee propolis	80% ethanolic extracts	[41]	Distinct bee species and chemistry; cannot be equated with *Apis mellifera* propolis
Unspecified origin	Extract, fraction, or product	[42–51]	Inadequate reproducibility and attribution

4. Overview of experimental evidence

4.1. Direct AD and Aβ-related models

The direct evidence base was small. In APP-KI mice, repeated Brazilian green propolis administration was associated with improved memory-related performance and hippocampal LTP at four months of age but not at 12 months, suggesting disease-stage or age dependence [31,32]. The accompanying cellular work indicated changes in intracellular calcium signaling. In the related memantine study, propolis enhanced memantine-associated rescue through a Kir6.2/CaMKII-linked mechanism, with single-dose and repeated-dose paradigms [37]. Because the intervention was combined with memantine, this study supports an adjunctive interaction rather than independent efficacy of propolis.

An $A\beta_{25-35}$ intracerebroventricular mouse model provided direct whole-extract evidence. Brazilian green propolis reduced AD-like cognitive impairment and was associated with altered glial and inflammatory markers [35]. This acute peptide model is useful for studying Aβ-associated toxicity but does not reproduce chronic plaque evolution, tau pathology, aging, or the genetic complexity of sporadic AD.

Pinocembrin was studied in both cellular and mouse Aβ models. In SH-SY5Y cells exposed to $A\beta_{25-35}$, pinocembrin reduced ROS accumulation, loss of viability, and apoptosis while increasing Nrf2 and heme oxygenase-1 (HO-1) [14]. Zinc protoporphyrin IX diminished the protection, providing evidence that HO-1 activity contributed causally. In mice receiving $A\beta_{25-35}$, oral pinocembrin at 20 or 40 mg/kg/day for eight days improved behavioral and neuropathological

outcomes [15]. Cellular experiments in the same study implicated mitochondrial preservation, apoptosis regulation, and attenuation of RAGE-associated signaling. The model and short treatment period nevertheless represent acute Aβ toxicity rather than established human AD.

Stingless-bee propolis extracts were evaluated in the amyloid-expressing C. elegans strain CL2006 [41]. The extracts delayed Aβ-associated paralysis and affected DAF-16 and SKN-1-linked stress-response pathways, homologous in part to mammalian FOXO and Nrf2 systems. This model offers rapid genetic and proteostasis experiments, but nematode longevity or paralysis cannot directly predict mammalian cognition or clinical benefit.

Ni et al. provided mixed evidence [30]. The main injury system was H_2O_2-exposed SH-SY5Y cells, but additional experiments examined whether propolis could counteract fibrillar Aβ- or interleukin-1β-associated impairment of BDNF-induced Arc expression. The study supports a mechanistic bridge between redox protection and synaptic-response pathways, not direct disease modification.

No study in the report directly examined tau aggregation, tau phosphorylation, tau spreading, or tau-mediated neurodegeneration. This absence is important because a compound that reduces oxidative stress or Aβ-associated toxicity cannot be assumed to influence tau biology. Direct APP/Aβ-related evidence and its model-specific limitations are summarized in Table 2.

Table 2 Studies directly investigating APP/Aβ-related models

Study	Intervention	Model and regimen	Principal findings	Major limitation	Certainty
Inagaki et al. [31]	Brazilian green propolis	Neuro-2A and APP-KI mice; repeated oral treatment reported as 300–1000 mg/kg/day for 8 weeks	Improved cognition and LTP at 4 but not 12 months; calcium signaling implicated	High dose; age-dependent failure; overlap with conference records	Moderate preclinical
Inagaki et al. [32]	Brazilian green propolis	APP-KI mice and Neuro-2A cells	Increased CaMKII/CaMKIV, CREB, BDNF, GluA1, and LTP	Conference abstract; likely precursor/overlap	Very low independent certainty
Wang et al. [14]	Pinocembrin	$A\beta_{25-35}$-exposed SH-SY5Y cells	Reduced ROS and apoptosis; increased Nrf2/HO-1; HO-1 inhibitor attenuated protection	Acute cell model; brain exposure not addressed	Moderate mechanistic
Liu et al. [15]	Pinocembrin	$A\beta_{25-35}$ ICV mice, 20 or 40 mg/kg/day orally for 8 days; complementary cell models	Improved cognition and neuropil integrity; reduced RAGE-associated signaling, mitochondrial dysfunction, and apoptosis	Acute peptide model; short treatment	Moderate preclinical
Arteman et al. [41]	Stingless-bee propolis EEP	Aβ-expressing C. elegans	Delayed paralysis; DAF-16/SKN-1 and stress-resistance effects	Nonmammalian model; extract-specific	Low translational
Ito et al. [35]	Brazilian green propolis	$A\beta_{25-35}$-induced cognitive impairment in mice	Improved memory-related outcomes and altered glial/inflammatory markers	Acute peptide model; chemical generalizability limited	Moderate preclinical

Moriguchi [52]	Propolis	APP-KI/synaptic-recovery research summary	Reported synaptic and cognitive recovery	Conference overview; overlapping evidence	Very low independent certainty
Moriguchi et al. [37]	Brazilian green propolis plus memantine	APP-KI mice and Kir6.2-related cellular/genetic models	Enhanced memantine-associated rescue, ATP, CaMKII/CaMKIV, and LTP	Combination study; not propolis monotherapy	Moderate adjunctive evidence

4.2. Other cognitive-impairment models

D-galactose is used to induce oxidative aging-like changes and cognitive impairment. A 2010 report described increased superoxide dismutase and glutathione peroxidase activities and reduced monoamine oxidase-B activity after a propolis flavonoid fraction [42]. Its citation and methodological details were incomplete; it should be treated as low-certainty evidence.

Scopolamine-induced amnesia was used to evaluate a water-soluble propolis derivative [39] and the synthetic CAPE derivative FA-97 [19]. These studies are relevant to cholinergic dysfunction and memory performance, but scopolamine models transient receptor blockade rather than progressive AD. A separate study combined propolis or other bee products with rivastigmine [51]. Unless propolis-specific treatment arms and interactions are clearly separable, the results cannot be assigned to propolis alone.

Hyperhomocysteinemia produced oxidative injury, protein aggregation, and cognitive dysfunction in cellular and mouse systems [36]. Brazilian propolis extract reduced ROS and cell death in vitro and was associated with less protein aggregation and cognitive impairment in mice. The findings support an indirect relationship among redox stress, proteostasis, and cognition, but the aggregated protein was not necessarily Aβ or tau.

An Indian propolis study integrated LC-MS/MS profiling, network pharmacology, molecular docking, cholinesterase assays, antioxidant assays, and PC12-cell experiments [26]. Targets included MAO-B, estrogen receptor-1, BACE1, acetylcholinesterase, CDK5, GSK3β, and cyclooxygenase-2. Computational association and enzyme inhibition generate hypotheses; they do not show that these targets are modulated in the brain after systemic administration.

4.3. Oxidative stress and neuronal injury models

Brazilian green propolis protected SH-SY5Y cells from H_2O_2-associated mitochondrial ROS, oxidative DNA damage, and loss of viability [30]. It also increased BDNF and Arc expression, linking stress resistance to neurotrophic signaling. Northeast Portuguese EEP reduced the H_2O_2-associated rise in ROS in primary cortical neurons, although it did not restore every measure of cellular reducing capacity [25]. This distinction illustrates why a favorable biomarker should not be summarized as complete neuronal protection.

Chinese propolis and chrysin inhibited staurosporine- or endoplasmic-reticulum-stress-associated neuronal death through effects on mitochondrial membrane potential, cytochrome-c release, and caspase activation [18]. Artepillin C and Brazilian green propolis were examined in other cellular stress systems [16,17,34]. The specificity of these effects varied: some studies used pathway inhibitors or measured neurotrophic proteins, whereas others relied on viability, ROS, or morphology.

HT22 cells subjected to glutathione depletion provided an oxytosis/ferroptosis-related model [28]. Ethanol extract was more protective than water extract, and selected flavonoids activated antioxidant-response-element activity. This study offers mechanistic evidence for preparation-dependent redox protection, but HT22 oxytosis is not equivalent to ferroptosis demonstrated in AD brain tissue.

4.4. Ischemia, hypoxia, excitotoxicity, and other indirect models

Brazilian green propolis reduced neuronal injury in PC12 cells exposed to H_2O_2 or serum deprivation and reduced infarct size in a permanent middle cerebral artery occlusion model [33]. Because administration occurred largely before ischemia, the study primarily tested preventive protection. Related investigations used OGD or retinal neuronal systems to examine gene-expression changes and caffeoylquinic-acid derivatives [20,38]. Pinocembrin also reduced oxidative and apoptotic injury after ischemia–reperfusion in vivo and reoxygenation in vitro [53]. These models are valuable for mitochondrial and oxidative mechanisms but are more directly relevant to cerebral ischemia than AD.

Hypoxia-induced microglial activation was associated with ROS generation, NF-κB activation, and release of interleukin-1β, tumor necrosis factor-α, and interleukin-6. Brazilian green propolis reduced these responses in cellular and mouse experiments reported in a conference abstract [46]. The limited publication format and incomplete methodological detail lower confidence.

Two reports from the same group used kainic acid at 15 mg/kg and propolis at 150 mg/kg in rats [43,47]. Outcomes included glutamine synthetase, nitric oxide, thiobarbituric-acid-reactive substances, total antioxidant status, tumor necrosis factor-α, nitric-oxide synthase, and caspase-3. The near-identical designs suggest that the publications may share an animal cohort and should not be counted as independent replication.

Other indirect models included sodium-nitrite-associated hippocampal injury [44], chronic stress [48], and aluminum-silicate cerebellar toxicity [40]. These studies reported favorable neuronal, apoptotic, biochemical, or ultrastructural outcomes, but preparation characterization and disease relevance were limited. Collectively, these indirect models provide mechanistic rather than direct AD evidence, as summarized in Table 3.

Table 3 Indirect neurodegeneration and neuronal-injury studies

Evidence group	Representative studies	Models	Main outcomes	Relevance and limitation
Oxidative neuronal injury	Ni et al. [30]; Cardoso et al. [25]; Jeong et al. [49]	H_2O_2-exposed SH-SY5Y or primary cortical neurons	Reduced ROS, oxidative DNA damage, caspase activity, or cell death	Mechanistically relevant but not AD-specific; one citation incomplete
Ischemia/OGD	Shimazawa et al. [33]; Liu et al. [53]; Nakajima et al. [38]; Balion et al. [29]	MCA occlusion, ischemia–reperfusion, OGD, primary brain cells	Reduced infarction/injury; mitochondrial and gene-expression effects	Stronger relevance to stroke; frequent pretreatment
Hypoxia/neuroinflammation	Jiang et al. [46]	Hypoxic microglia and mice	Reduced ROS, NF-κB, cytokines, and oxidative DNA damage	Conference abstract; incomplete methodological reporting
Excitotoxicity	Swamy et al. [43,47]	Kainic-acid-treated rats	Improved antioxidant status; reduced NO/NOS, TNF-α, and caspase-3	Likely overlapping animal cohort; propolis poorly characterized
Oxytosis/ferroptosis	Takashima et al. [28]	HT22 glutathione-depletion model	Ethanol extract more active than water; antioxidant-response effects	Cell model; not direct evidence of ferroptosis modulation in AD
ER stress/proteostasis	Hirata et al. [16]; Izuta et al. [18]	Protein aggregation, tunicamycin, or staurosporine	Reduced ER stress, aggregation, mitochondrial apoptosis	Constituent-specific and indirect
Toxicant/stress models	Kuswati et al. [44]; Omar et al. [40]; Nugroho et al. [48]	Sodium nitrite, aluminum silicate, chronic stress	Improved neuronal counts, Bax, ultrastructure, or related outcomes	Limited AD specificity and chemical characterization

Other cognitive models	Xiao [42]; Chen et al. [39]; Wan et al. [19]; Miyazaki et al. [36]; Dalal et al. [51]	D-galactose, scopolamine, hyperhomocysteinemia	Improved biochemical or memory-related outcomes	Model-specific; some incomplete or confounded records

4.5. In silico and network-pharmacology evidence

Network pharmacology and docking can prioritize compounds and targets in complex mixtures. Indian propolis and three Algerian propolis extracts were evaluated using combinations of chemical profiling, target prediction, docking, antioxidant tests, and cholinesterase inhibition [26,27]. These studies identified plausible interactions involving BACE1, acetylcholinesterase, butyrylcholinesterase, MAO-B, CDK5, GSK3β, and inflammatory targets. Docking scores are not evidence of target engagement in cells or animals. Enzyme inhibition in vitro is stronger than docking but still requires assessment of selectivity, metabolism, blood–brain barrier penetration, and achievable unbound brain concentration.

5. Molecular mechanisms of neuroprotection

5.1. Reduction of oxidative stress

Reduced ROS or oxidative-damage markers were among the most consistent findings across the evidence base. Brazilian green propolis reduced mitochondrial ROS and 8-oxo-2′-deoxyguanosine in H_2O_2-exposed SH-SY5Y cells [30]. Portuguese EEP attenuated ROS generation in primary cortical neurons [25]. Kainic-acid studies reported lower lipid-peroxidation-related measures and improved total antioxidant status [43,47]. In Aβ models, pinocembrin reduced ROS and mitochondrial oxidative stress [14,15].

Nevertheless, consistency of direction does not imply a common molecular mechanism. Extracts differed chemically, assays measured different oxidant species or downstream products, and pretreatment was common. Direct radical scavenging, induction of antioxidant enzymes, preservation of mitochondria, and reduced cell death can all lower ROS measurements. Many studies did not distinguish these alternatives.

5.2. Activation of Nrf2/HO-1 and endogenous antioxidant defenses

The clearest Nrf2/HO-1 evidence concerned pinocembrin. $A\beta_{25-35}$-exposed SH-SY5Y cells showed increased Nrf2 and HO-1 after pinocembrin, and the HO-1 inhibitor zinc protoporphyrin IX attenuated protection [14]. This inhibitor experiment supports pathway involvement beyond correlation, although off-target effects and incomplete inhibition remain possible.

FA-97 increased Nrf2-associated antioxidant proteins in oxidative neuronal and scopolamine paradigms [19]. Because FA-97 is synthetic, its effects cannot be presented as evidence that CAPE concentrations in natural propolis will produce the same response. In HT22 cells, kaempferide and kaempferol induced antioxidant-response-element activity [28]. The source report did not establish Nrf2 activation for every whole extract; broad statements that “propolis activates Nrf2” should therefore be avoided.

5.3. Preservation of mitochondrial function

Mitochondrial protection was supported by multiple model classes. Pinocembrin improved mitochondrial membrane potential and reduced mitochondrial oxidative stress in Aβ-related models [15]. Chinese propolis and chrysin reduced disruption of membrane potential and cytochrome-c release during apoptosis-inducing stress [18]. Extract-dependent effects on mitochondrial superoxide, respiration, or viability were reported in ischemia-exposed brain cells [29].

Mitochondrial readouts were often measured after injury and treatment, making it difficult to determine whether mitochondria were a primary target or preserved secondarily because overall injury was reduced. Stronger causal evidence would require temporally resolved bioenergetics, direct measurement of brain exposure, mitochondrial target engagement, and rescue or loss-of-function experiments.

5.4. Regulation of intrinsic and extrinsic apoptotic pathways

The intrinsic mitochondrial pathway was more consistently represented than extrinsic death-receptor pathways. Pinocembrin restored Bcl-2-related balance, reduced cytochrome-c-associated signaling, and decreased caspase-9 and caspase-3 activation in Aβ systems [15]. Chinese propolis and chrysin similarly affected mitochondrial apoptosis in SH-

SY5Y cells [18]. Portuguese EEP attenuated caspase-3 activity induced by H_2O_2 or staurosporine [25], while pinocembrin reduced caspase-3 activation, poly(ADP-ribose) polymerase degradation, and DNA fragmentation after ischemia–reperfusion [53].

Bax immunohistochemistry was reduced in the hippocampal CA1 region after propolis in sodium-nitrite-treated rats [44]. This finding is compatible with reduced apoptosis but is less mechanistically conclusive than functional pathway perturbation. Evidence for extrinsic apoptosis was sparse, and the manuscript should not imply balanced coverage of intrinsic and extrinsic pathways.

5.5. Suppression of neuroinflammation and NF-κB signaling

Hypoxia experiments indicated that Brazilian green propolis reduced ROS, NF-κB activation, and microglial inflammatory mediators [46]. Aβ studies reported changes in inflammatory or glial markers after Brazilian green propolis [35] and reduced downstream NF-κB-associated signaling after pinocembrin [15]. A rat study described decreased interleukin-1β expression in a model labelled as AD [45], but incomplete model and preparation details limit interpretation.

Inflammatory suppression may be secondary to reduced injury or ROS rather than a direct effect on microglial signaling. Cell-type-specific experiments, pathway reporters, NF-κB manipulation, and temporally ordered measurements are needed. Cytokine reduction alone does not demonstrate beneficial immune modulation, because glial responses may be protective or harmful depending on disease stage.

5.6. Modulation of Aβ toxicity, aggregation, and RAGE signaling

Pinocembrin reduced Aβ-associated toxicity without clear evidence that it decreased Aβ production [15]. Instead, the study supported reduced RAGE expression, attenuation of RAGE-associated p38/JNK signaling, preservation of mitochondrial function, and reduced apoptosis. This favors a model of resistance to Aβ-induced injury rather than removal of the initiating peptide.

Brazilian green propolis reversed fibrillar Aβ-associated suppression of BDNF-induced Arc expression in SH-SY5Y cells [30]. In APP-KI mice, propolis improved synaptic and cognitive outcomes in selected age groups [31,32,37]. None of these results demonstrates direct binding to Aβ, plaque clearance, or inhibition of human amyloid progression. Protein-aggregation findings with artepillin C or hyperhomocysteinemia models should also remain separate from Aβ-specific aggregation claims [16,36].

5.7. Regulation of ferroptosis, oxytosis, and protein homeostasis

Brazilian green propolis extracts and constituents protected HT22 cells against oxytosis/ferroptosis-like death [28]. The distinction between oxytosis and canonical ferroptosis is relevant: both involve glutathione depletion and lipid oxidative damage, but demonstration of ferroptosis ideally includes iron dependence, lipid-peroxidation measures, and rescue by validated ferroptosis inhibitors.

Artepillin C reduced endoplasmic-reticulum stress and protein aggregation in cellular models [16]. Stingless-bee propolis affected DAF-16/SKN-1-linked stress resistance and Aβ-associated paralysis in C. elegans [41]. Together these studies support potential regulation of stress responses and proteostasis, but cross-species differences and uncertain brain exposure prevent direct extrapolation.

5.8. Enhancement of BDNF, Arc, PI3K/Akt, CaMKII/CaMKIV, CREB, and synaptic plasticity

Brazilian green propolis increased BDNF and Arc expression in SH-SY5Y cells [30]. Wortmannin abolished propolis-associated Arc induction and the increase in BDNF was also PI3K-sensitive, providing mechanistic support for PI3K involvement. Because wortmannin affects PI3K signaling broadly, the precise upstream receptor remains uncertain.

In APP-KI mice, repeated propolis administration was associated with increased CaMKII and CaMKIV activation, CREB phosphorylation, BDNF production, GluA1 phosphorylation, and improved hippocampal LTP [31,32]. The memantine-combination study implicated Kir6.2 and ATP-dependent calcium signaling [37]. Genetic evidence from Kir6.2-deficient mice strengthened the proposed interaction, although it applied to the propolis–memantine combination.

Artepillin C and its acetylated derivative promoted neurite outgrowth in NGF-deprived PC12 cells [17]. Inhibitors of TrkA, PI3K/Akt, and MAPK/ERK were used, making this one of the more mechanistically interrogated constituent studies. Neurotrophic effects in PC12 cells, however, do not establish restoration of synapses in AD brain.

5.9. Effects on learning, memory, and behavioral outcomes

Improved behavioral outcomes were reported in APP-KI, $A\beta_{25-35}$, scopolamine, D-galactose, and hyperhomocysteinemia models [15,19,31,35–37,39,42,51]. Interpretation depends on treatment timing. Several experiments were preventive or began near the time of injury, whereas patients usually receive treatment after substantial pathology is established. Behavioral batteries, blinding, randomization, attrition, locomotor confounding, and sex-specific responses were not consistently available in the report.

The failure of repeated propolis to produce the same cognitive benefit in older APP-KI mice [31,32] is especially informative. It suggests that efficacy may decline with disease progression, age-related pharmacokinetic change, irreversible synaptic loss, or differences in pathway responsiveness. This negative or stage-dependent result should be emphasized rather than obscured. The model-specific integration of these mechanisms is summarized in Figure 1.

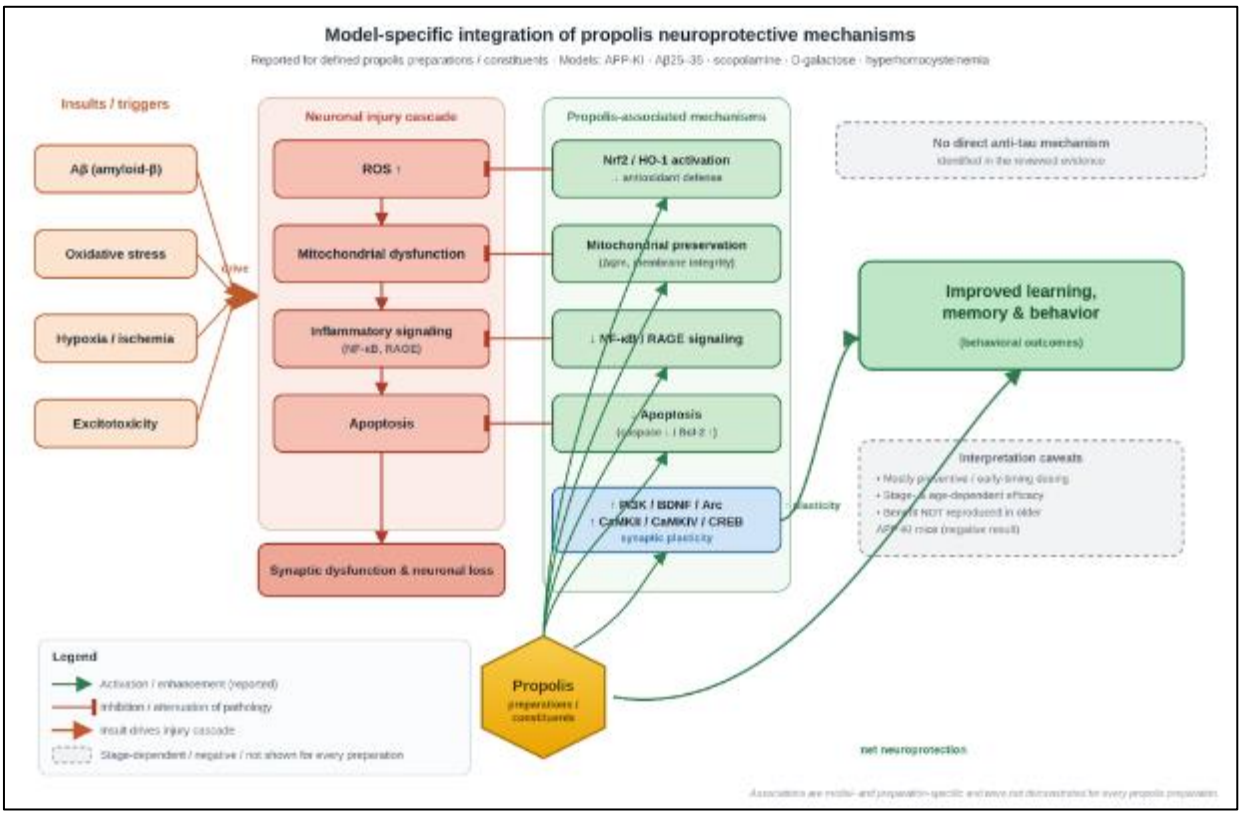

Figure 1 Model-specific integration of mechanisms reported for defined propolis preparations or constituents. Aβ, oxidative stress, hypoxia/ischemia, and excitotoxicity promote ROS, mitochondrial dysfunction, inflammatory signaling, and apoptosis. Selected interventions were associated with Nrf2/HO-1 activation, mitochondrial preservation, reduced NF-κB or RAGE-associated signaling, and enhanced PI3K/BDNF/Arc and CaMKII/CaMKIV/CREB signaling.

6. Bioactive constituents

6.1. Pinocembrin

Pinocembrin has the most direct constituent-level evidence. In $A\beta_{25-35}$-exposed SH-SY5Y cells, it reduced oxidative stress and apoptosis through an Nrf2/HO-1-associated mechanism [14]. In $A\beta_{25-35}$-treated mice and complementary cellular systems, it improved cognitive outcomes, preserved neuropil ultrastructure, reduced neuronal degeneration, inhibited RAGE-associated signaling, and regulated mitochondrial apoptosis [15]. It also protected against ischemia–reperfusion injury [53].

These findings support pinocembrin as a candidate neuroprotective molecule, but they do not demonstrate that all propolis products contain an effective dose. Oral bioavailability, metabolism, unbound brain concentration, and

exposure relative to active cellular concentrations must be established. Acute Aβ and ischemia models also do not reproduce chronic human AD.

6.2. Artepillin C

Artepillin C is a characteristic constituent of Brazilian green propolis. Studies implicated it in cellular stress resistance, inhibition of endoplasmic-reticulum stress and protein aggregation, and NGF-related neurite outgrowth [16,17,34]. Some experiments used inhibitors of TrkA, PI3K/Akt, or MAPK/ERK, supporting pathway involvement. An acetylated derivative showed related neurotrophic activity but should be identified as semisynthetic.

Artepillin C evidence was largely indirect. The report did not identify a direct artepillin C treatment study in APP transgenic or Aβ-injected mammals. Its contribution to the efficacy of whole Brazilian green propolis remains plausible but unproven without comparative depletion, reconstitution, or pharmacokinetic experiments.

6.3. CAPE and synthetic derivatives

CAPE was included among constituents evaluated in Chinese propolis experiments, but chrysin appeared more important in that particular mitochondrial-apoptosis model [18]. FA-97, a synthetic CAPE derivative, activated Nrf2/HO-1-related defenses and reduced oxidative neuronal apoptosis and scopolamine-associated cognitive impairment [19]. FA-97 should be used to illustrate medicinal-chemistry potential rather than presented as a naturally occurring propolis exposure.

6.4. Chrysin

Chrysin protected SH-SY5Y cells from staurosporine- and endoplasmic-reticulum-stress-associated death, with evidence involving mitochondrial membrane potential, cytochrome-c release, and caspases [18]. Chrysin was also identified in chemically profiled propolis samples used in biochemical assays [27]. Its clinical relevance depends on absorption, extensive metabolism, protein binding, and brain exposure. Concentrations effective in cultured cells may not be achievable as unbound concentrations after oral administration.

6.5. Caffeoylquinic-acid derivatives and other constituents

Water extract of Brazilian green propolis and caffeoylquinic-acid derivatives reduced neuronal injury through antioxidant actions [20]. Kaempferide and kaempferol contributed to antioxidant-response activity in HT22 cells [28]. Indian and Algerian profiling studies identified multiple flavonoids and phenolic acids with predicted or biochemical activity [26,27]. These multicomponent findings require isolation, concentration–response testing, selectivity assessment, and confirmation that the active constituent reaches the brain. Comparative constituent-level targets, evidence strength, and principal uncertainties are summarized in Table 4.

Table 4 Bioactive constituents, targets, and certainty

Constituent	Supported targets/pathways	Experimental evidence	Principal limitation	Certainty
Pinocembrin	Nrf2/HO-1; RAGE-associated p38/JNK/NF-κB; mitochondria; Bcl-2/cytochrome c/caspases	Aβ cell and mouse models; ischemia/reperfusion [14,15,53]	Human brain exposure and chronic AD efficacy unknown	Moderate preclinical
Artepillin C	ER stress/proteostasis; TrkA, PI3K/Akt, MAPK/ERK; neurite outgrowth	Cellular stress and NGF-deprived PC12 models [16,17,34]	Direct mammalian AD evidence absent	Low-to-moderate mechanistic
FA-97	Nrf2/HO-1-related defenses; oxidative apoptosis	Neuronal cells and scopolamine mice [19]	Synthetic CAPE derivative, not natural propolis exposure	Moderate proof-of-principle

Chrysin	Mitochondrial potential, cytochrome c, caspases	SH-SY5Y apoptosis/ER-stress models [18]	Bioavailability and brain concentration uncertain	Low-to-moderate mechanistic
Caffeoylquinic-acid derivatives	Antioxidant protection	Neuronal oxidative/ischemic-like models [20]	Limited direct AD evidence	Low
Kaempferol/kaempferide	Radical scavenging and antioxidant-response-element activity	HT22 oxytosis/ferroptosis model [28]	Cell-only evidence and uncertain exposure	Low
Acetylated artepillin C	NGF-related neurite signaling	PC12 neurite-outgrowth model [17]	Semisynthetic; no AD efficacy model	Low

7. Critical discussion

The evidence consistently suggests that propolis-related interventions can reduce experimental oxidative injury. This conclusion is supported across neuronal cell lines, primary neurons, ischemic models, excitotoxicity, acute Aβ exposure, APP-KI mice, and *C. elegans*. The direction of effect is therefore more consistent than the precise mechanism. Nrf2/HO-1, mitochondrial preservation, apoptosis regulation, inflammatory signaling, proteostasis, and synaptic pathways were not assessed in the same preparations or models.

Mechanistic confidence varies. HO-1 inhibition in the pinocembrin study, PI3K inhibition in the Brazilian green propolis BDNF/Arc study, receptor/pathway inhibitors in artepillin C experiments, and Kir6.2-deficient mice in the memantine-combination programme provide stronger evidence than simple correlations [14,17,30,37]. By contrast, reduced cytokines, Bax staining, ROS, or lipid peroxidation may reflect a downstream consequence of lower injury.

Chemical heterogeneity is the largest obstacle to interpretation. “Brazilian green propolis” is more informative than “propolis,” yet still does not define a reproducible intervention unless the botanical source, extraction yield, chromatographic fingerprint, and marker content are reported. Chinese, Portuguese, Egyptian, Indian, Algerian, and stingless-bee preparations should not be pooled as though chemically interchangeable. Solvent-dependent activity in ferroptosis and mitochondrial experiments reinforces this point [28,29].

Model heterogeneity is equally important. Direct APP/Aβ evidence exists, but much of the literature concerns ischemia, hypoxia, kainic acid, sodium nitrite, aluminum silicate, H_2O_2, staurosporine, or serum deprivation. These paradigms isolate processes relevant to AD but lack the chronic interaction of amyloid, tau, aging, vascular factors, glia, and synapses. Scopolamine studies demonstrate effects on transient cholinergic impairment, not slowing of neurodegeneration.

Dose–response relationships were inconsistently reported. Crude-extract doses cannot be compared with isolated-compound doses without marker quantification. Some reported APP-KI doses were high, while several cellular concentrations were affected by lost micro-unit symbols in the source report. Pharmacologically unrealistic concentrations may produce antioxidant effects that cannot occur in vivo. Future reports should compare total and unbound plasma and brain exposure with concentration–response data from relevant models.

Preventive and therapeutic administration must also be separated. Pretreatment before H_2O_2, ischemia, excitotoxicity, or Aβ exposure tests resilience to an impending insult. It does not show reversal after pathology is established. The lack of benefit in older APP-KI mice is consistent with a limited intervention window [31,32]. Studies should include both preventive and delayed-treatment arms, with pathology confirmed before treatment.

The available evidence cannot establish clinical effectiveness. No well-controlled human AD trial was identified. Safety cannot be assumed from natural origin: propolis can vary in allergens, contaminants, and pharmacologically active constituents. It may interact with antiplatelet, anticoagulant, metabolic, or other therapies, and allergy to propolis is clinically recognized. Product-specific toxicology and interaction studies are necessary.

published, while null findings may remain unavailable. Conference abstracts and incomplete citations further reduce certainty. The Elicit report's citation mismatch demonstrates why automated extraction must be checked against original papers. Overall, the evidence supports a research hypothesis and a set of candidate mechanisms—not a recommendation for treating AD with commercial propolis.

8. Conclusion

Experimental evidence supports a potential neuroprotective role for selected propolis preparations and propolis-derived constituents. The most directly relevant findings arise from APP-knock-in mice, Aβ-induced cellular and mouse models, and amyloid-expressing *C. elegans*. In these systems, Brazilian green propolis or pinocembrin was associated with reduced oxidative and mitochondrial injury, modulation of inflammatory and apoptotic signaling, preservation of synaptic pathways, and improved functional outcomes. Indirect ischemic, hypoxic, excitotoxic, ferroptotic, and chemically induced cognitive-impairment models provide additional mechanistic plausibility but should not be interpreted as direct demonstrations of efficacy in AD.

Substantial uncertainty remains. Propolis preparations are chemically heterogeneous, evidence for several pathways is compound- or model-specific, many experiments were preventive, and brain exposure was rarely connected to effective concentrations. No direct antitau evidence or well-controlled human efficacy trial was identified. Before clinical application, future research must use authenticated and marker-standardized products, establish pharmacokinetics and brain exposure, apply rigorous aged AD models with delayed treatment, evaluate safety and drug interactions, and conduct appropriately controlled clinical trials using clinically meaningful biomarkers and cognitive outcomes.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest for this manuscript

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