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Beneficial effects of propolis on human health and neurological diseases

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1.ABSTRACT

Propolis is a natural product, collected by honeybees *Apis mellifera,* from various plant sources. Propolis is extensively used in foods and beverages because it improves human health. It contains more than 300 natural compounds such as polyphenols, phenolic aldehydes, sequiterpene-quinones, coumarins, amino acids, steroids and inorganic compounds. Propolis exhibits a broad spectrum of biological and pharmacological properties such as antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, antitumor, anticancer, antiulcer, hepatoprotective, cardioprotective, and neuroprotective actions. The chemical composition and beneficial properties of propolis vary greatly depending on the phytogeographical areas, seasonal collection time, and botanical source. Polyphenols found in fruits and vegetables are beginning to receive increased attention due to their vital role in protecting neural cells from oxidative stress and neuroinflammation associated with normal aging and chronic age-related diseases. Propolis is one of the most abundant sources of polyphenols (mainly flavonoids and phenolic acids). This overview is an attempt to discuss the molecular mechanism underlying the potential beneficial effects of propolis on human health and neurological diseases.

2. INTRODUCTION

Propolis is a Greek word referring to a product that is involved in defending the city (1). This is exactly what propolis serves to the hive. Propolis is a natural resinous hive product that is manufactured by honeybees *(Apis mellifera* L.) from various plant sources. Honeybees collect natural balsamic resin actively, secreted by tree excudates mainly on leaf buds and barks, and mix it with beewax and glandular bee secretions (2). Honeybees use propolis as a sealing material during the construction of their hives and for shortening the hive entrance to prevent the entry of intruders (3). Propolis helps in maintaining the hive inside temperature ~ 35°C. Due to antimicrobial and anti-inflammatory activities, propolis protects hive inhabitants from the bacterial, fungal, and viral infections (3, 4), implicating its preventive role in the microbial diseases. Furthermore, propolis has been used by humans as a traditional folk medicine to maintain good health since ancient times, due to many beneficial properties (5). Due to a broad spectrum of activities, such as antioxidant, anti-inflammatory, immunomodulatory, antimicrobial, and antitumor effects among others, propolis has recently gained popularity as a natural product that may be potentially used as a therapeutic agent to improve health and prevent various human diseases (6-9). The chemical composition of propolis is very complex, and it basically

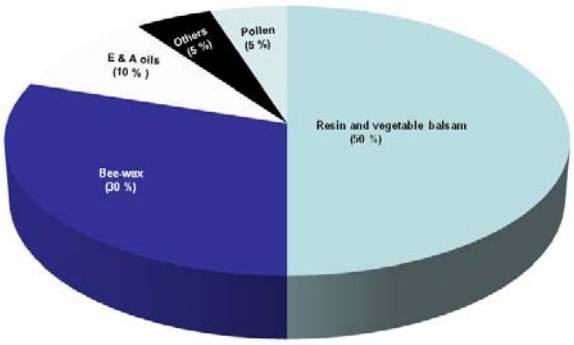


Figure 1. General composition of raw propolis. Polyphenolic fraction composed of flavonoids and related phenolic acids (Resin and vegetable balsam); essential and aromatic oils (E & A); waxes and fatty acids (Bee-wax); pollen protein and free amino acids (Pollen); substances like vitamins and minerals (Others).

depends on the plant source accessible to honeybees. Propolis contains pharmacologically active constituents such as polyphenols, terpenoids, steroids, and amino acids (1), therefore it possess a variety of biological and pharmacological activities. Different colors (yellow, green, brown, and red) and chemical variability of propolis depend on the sources of resin (botanical source) found in the particular area as well as age of preparation (10-12). A broad spectrum of biological properties of propolis, including anti-inflammatory, anti-oxidant, radical scavenging, and immunomodulatory actions, is related to its phenolic composition in flavonoids and phenolic acids (13).

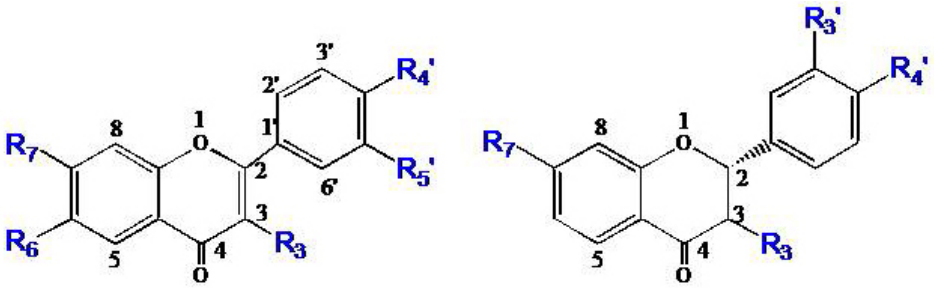
Neurological diseases include various neurotraumatic (such as ischemia and epilepsy) and neurodegenerative diseases (such as Parkinson disease, PD; Alzheimer disease, AD, and multiple sclerosis). Neurochemical mechanisms and causes of neurological diseases remain elusive. Neurological diseases are accompanied by an increase in oxidative stress, induction of inflammatory signaling, and slow immune responses in the brain tissue (14, 15). Recent studies have shown that caffeic acid phenethyl ester (CAPE), an active component of the propolis extract, provides protective effects on brain injury after focal permanent cerebral ischemia through its antioxidant action (16-17). CAPE protects neurons against glutamate-induced excitotoxicity by inhibiting phosphorylation of p38 and caspase-3 activation (18). It also prevents neurotoxic effects due to excessive inflammatory reaction in brain (19). Furthermore, pinocembrin (one of the flavonoids in propolis) reduces cerebral ischemia/reperfusion injury, possibly by exerting its anti-oxidative and anti-apoptotic activities (20). Propolis possesses potent antioxidant activity *in vitro* and *in vivo* (21, 22). Kainic acid (KA)-induced oxidative stresses and neuronal degeneration in rat can be significantly attenuated by the pretreatment with propolis (22). The effect of propolis against KA-induced neurotoxic oxidative damage is in part via adenosine A1 receptor modulation. These studies strongly support the view that propolis and its components have anti-inflammatory as well as anti-oxidant activities. It is proposed that propolis may be an effective candidate for the treatment of oxidative stress and neuroinflammation in neurological diseases. Present review discusses the chemical composition, biological properties, and possible molecular mechanism (s) of propolis with special emphasis on its therapeutic potential in treating neurological disorders.

3. CHEMICAL COMPOSITION OF PROPOLIS

The chemical composition of propolis is quite complex and varies with collection time (season), geographic origin, local flora, variety of trees and plant species used for collection. Strictly speaking, the chemical composition of propolis may vary from hive to hive, district to district, and from season to season. Among the types of substances usually found in raw propolis include approximately 50% resin (polyphenolic fraction composed of flavonoids and related phenolic acids), 30% bee-wax (waxes and fatty acids), 10% essential and aromatic oils (volatiles), 5% bee-pollen (pollen protein and free amino acids), and 5% other substances (organics and minerals) (Figure 1). Other substances of propolis include vitamins (vitamin B1, B2, B6, C, and E, nicotinic acid and folic acid), minerals (calcium, magnesium, iron, copper, zinc, manganese, nickel, cobalt, vanadium and strotium), sugars (fructofuranose, α-D, glucopyranose, β-glucopyranose), enzymes (adenosine triphosphatase, glucose 6-phosphatase, succinate dehydrogenase), aldehydes, ketones, alcohols, and steroids (11, 13, 23-26).

Propolis is one of the most abundant sources of polyphenols, and mainly contains flavonoides, phenolic acids, and their esters (1, 6, 27). The principal flavonoids in propolis are: (1) flavones, (2) flavonols, and (3) flavanones (Figure 2). Flavone is a class of flavonoids that is based on the backbone of 2-phenylchromen-4-one (IUPAC name: 2-phenyl-1-benzopyran-4-one). This class includes compounds such as chrysin, apigenin, luteolin, and rutin (Figure 2). Flavonol is a class of flavonoids that is based on the backbone of 3-hydroxy-2-phenylchromen-4-one. This class includes compounds such as galangin, quercetin, kaempferol and rhamnazin. This class is distinct from flavanol (e.g. catechin), another class of flavonoids not discussed here. The third class of flavonoids is called as flavanone, in which flavonoides are generally glycosylated by a disaccharide at position seven making flavanone glycosides. This class includes pinostrobin, pinocembrin, hesperitin, and pinobanksin. Most important flavonoids of propolis are apigenin, galangin, chrysin, quercetin, CAPE, luteolin, pinocembrin, pinobanksin, acacetin, and kaempferol (Figure 3). Propolis also contains other phenolics such as vanillin, *p*-coumaric acid, quinic acid, cinnamic alcohol, cinnamic acid derivatives, caffeic acid, ferulic acid, and isoferulic acid (Figure 4). Furthermore high levels of propolins, prenylated flavanone compounds designated as a, b, c, d, e and f, have been found in Taiwanes propolis (Figure 5), and the position of the geranyl or prenyl groups in the flavonoid skeleton is responsible for exerting their antioxidant activity (28).

Collectively, polyphenols are considered as main pharmacologically active molecules of propolis due to their



Flavone (H at R3)
Flavonol (OH at R3)

Flavanone

Flavonoids	R3	R6	R7	R4'	R5'	R3	R7	R3'	R4'
Flavones									
Chrysin	H	H	OH	H	H				
Apigenin	H	H	OH	OH	H				
Luteolin	H	H	OH	OH	H				
Rutin	H	H	OH	OH	OH				
Flavonols									
Galangin	OH	H	OH	H	H				
Quercetin	OH	H	OH	OH	OH				
Rhamnazin	OH	H	OCH_3	OH	H				
Kaempferol	OH	H	OH	OH	H				
Flavanones									
Pinostrobin						H	OCH_3	H	H
Pinocembrin						H	OH	H	H
Hesperitin						H	OH	OH	OCH_3
Pinobanksin						OH	OH	H	H

Figure 2. Structural backbone of the principal flavonoids such as flavones, flavonols, and flavanones.

proven ability to inhibit specific enzymes, to simulate some hormones and neurotransmitters, and to scavenge free radicals (29). The concentration of phenolic compounds and other active constituents may vary greatly due to differences in vegetation, phytogeographical areas and time of collection (30). Secondarily, differences in chemical composition of propolis may also depend upon the contamination in wax, variation in the extraction procedures, and to some degree on the sensitivity of the quantification methods. These variations may be responsible for their differing biological activities due to the presence/absence or concentration variability in constituents, and synergism or counteracting effect with other polyphenols, finally influencing body's physiological processes.

4. BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES OF PROPOLIS

Different combinations of substances in propolis samples have been demonstrated to be essential for its beneficial properties (27). Depending upon its chemical composition, propolis possesses a broad spectrum of biological and pharmacological activities (8, 13), including anti-oxidant, anti-inflammatory, immunomodulatory, antimicrobial, antitumor, anticancer, cardioprotective, neuroprotective, and many more (Figure 6). The anti-oxidant and anti-inflammatory capacities of propolis are mainly due to the flavonoids and phenolic compounds. The anti-oxidant activity of flavanoides present in propolis samples has been shown to scavenge free radicals (31).

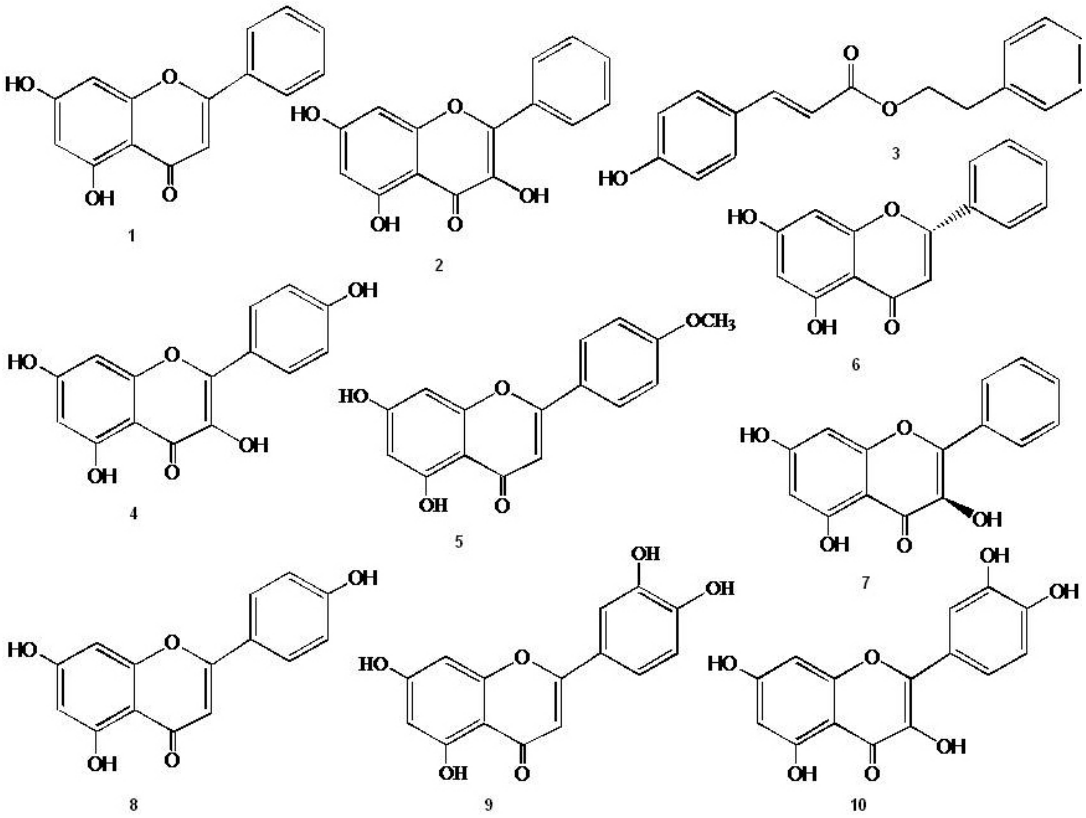


Figure 3. Chemical structures of major flavonoid constituents in propolis: (1) chrysin, (2) galangin, (3) CAPE, (4) kaempferol, (5) acacentin, (6) pinocembrin, (7) pinobaskin, (8) apigenin, (9) luteolin, and (10) quercetin.

Propolis samples possessing antioxidant activity also contain amino acids, phenolic acids, flavonoids, terpenes, propolins, steroids, aldehydes, and ketones (28, 32). Caffeic acid normally occurs as an ester with quinic acid, known as the chlorogenic acid, 5-caffeoylquinic acid. Chlorogenic acid and caffeic acid are antioxidants *in vitro*, and therefore they prevent oxidation of low-density lipoprotein, implicating their role in the prevention of various age-related diseases (33). The presence of chlorogenic acid can block oxidative damage of DNA by scavenging peroxynitrite, and reducing the release of myeloperoxidase during chronic infection and inflammation (34). Caffeoylquinic acid derivatives, artepillin C, and *p*-coumaric acid are partly responsible for neuroprotective effects of propolis (13, 35).

Propolis suppresses prostaglandin and leukotriene generation by inhibiting the expression and activities of cyclooxygenases (COX-1 and COX-2) and lipoxygenases (LOX), retarding the gene expression of inducible nitric oxide synthase (iNOS), blocking tumor necrosis factor-α (TNF-α)-mediated NF-κB activation, and reducing immune response in T cells (7, 36, 37). CAPE is a selective inhibitor of NF-κB activation, which may provide the molecular basis for its anti-inflammatory activity (13). Flavonoids need a 2–3 carbon double bond, a carbonyl group at carbon 4 of the C- ring, and two hydroxyl groups at carbons 5 and 7 of the A- ring (Figure 7) for anti-inflammatory activity (13, 38). Anti-oxidant activity of flavonoids is due to their ability to reduce free radical formation, scavenge free radicals, and chelate metal ions (39, 40). Flavonoids in propolis possess Fe^{2+} chelating properties (41). Flavonoids require a hydroxyl group at carbon 3 of the C- ring and two hydroxyl groups at carbons 3' and 4' of the B- ring (Figure 7) for their anti-oxidant activity (13, 42, 43). The good scavenging activity requires the presence of a catechol moiety on ring B along with 3-OH moiety in combination with a C2 C3 double bond in chelators (13). These structural requirements increase Fe^{2+} chelating and inhibit or decrease the rate of lipid peroxidation (41). Kumazawa *et al* (2007) have proved that the position of the geranyl or prenyl group in the flavonoid skeleton contributes to the anti-oxidant activity of Okinawan propolis (44). Furthermore, flavonoids found in propolis (both in the ethanol extract as well as in the water extract) have been shown to exhibit anti-oxidant activity (13).

Because of its multifactorial composition, and increasing number of *in vitro* studies emphasizing anti-inflammatory and anti-oxidant activities, propolis can be considered as a potential preventive or therapeutic agent to treat various human diseases, including neurological disorders. To understand the mechanism underlying the neuroprotective effect of flavonoids and their physiologically relevant metabolites in treating brain diseases, it is important to evaluate whether these

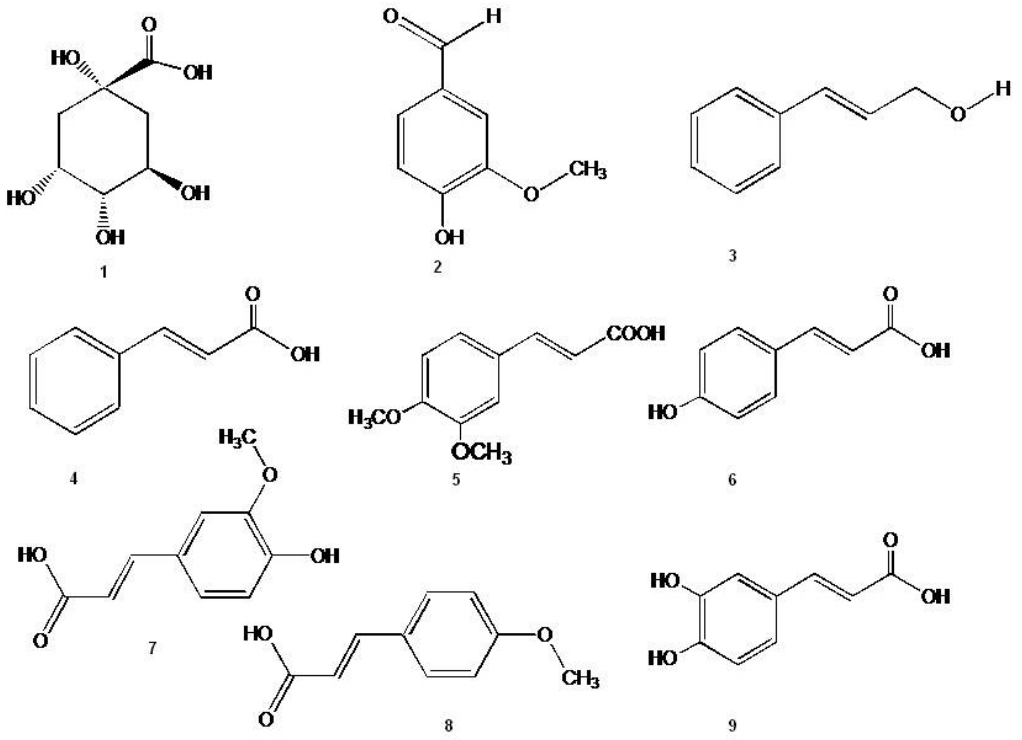


Figure 4. Major phenolic compounds (flavonoids and phenolic acid derivatives) in propolis: (1) quinic acid, (2) vanillin, (3) cinnamic alcohol, (4) cinnamic acid, (5) 3,4-dimethoxy cinnamic acid, (6) *p*-cumric acid, (7) ferulic acid, (8) isoferulic acid, and (9) caffeic acid.

constituents are able to enter into the brain endothelium and can cross the blood-brain barrier or not. To rule out whether observed activity is dependent on the concentration of one specific constituent or due to the potentiating effect of several, the bioavailability, biotransformation, and synergism of flavonoid constituents of propolis need to be investigated. Furthermore, the problem with potential medicinal use of propolis remains elusive because highly variable chemical composition of propolis will affect its biological activities, thereby influencing its therapeutic properties. Since the quality of propolis varies greatly, therefore, the exact quantification procedure for its quality control has to be standardized.

5. PROPOLIS USE IN THE MAINTAINENCE OF HUMAN HEALTH

Propolis has been used worldwide as a dietary supplement to maintain and improve human health. These days, it is also used in many medical formulas to treat infections, allergies, inflammatory diseases, asthma, diabetes, hypertension and many model systems of several human diseases (8, 13, 45). Propolis is also present in topical ointment, cream, lotion, mouth rinses and cosmetics, but whether the propolis concentration and constituents in these preparations closely resemble topical propolis products used in scientific research studies is not guaranteed (8). Although collective evidence shows reliable and relatively consistent scientific data regarding substantial health benefits of propolis, but effectiveness and safety of its doses need to be further established. Therefore, additional research and clinical trials with larger group of subjects, proper dose response, and different frequency of propolis administration are needed before a clear recommendation can be made about its role as a potential therapeutic agent (8).

6. PROPOLIS USE IN PREVENTION OF NEUROLOGICAL DISEASES

Neurological diseases show abnormalities in the nervous system (spinal cord, brain, and nerves), resulting in symptoms such as paralysis, muscle weakness, cognitive and motor decline, loss of memory, seizures, pain, altered levels of consciousness and confusion. Among patients of neurological disorders symptoms differ depending upon the part of the nervous system affected. Neurological diseases are accompanied with increased intensity of reactive oxygen species (ROS) generation, increased production of proinflammatory lipid mediators (eicosanoids and platelet activating factor), elevated secretion of proinflammatory cytokine (TNF-α, IL-1β) along with alterations in ion homeostasis, defective production of ATP, and alterations in cellular redox in brain (46, 47). In addition, mitochondrial dysfunction is another neurochemical change that may contribute to the degeneration of neurons in neurological diseases.

Propolis and its flavonoid constituents have been reported to exert neuroprotective properties in *in vitro* and

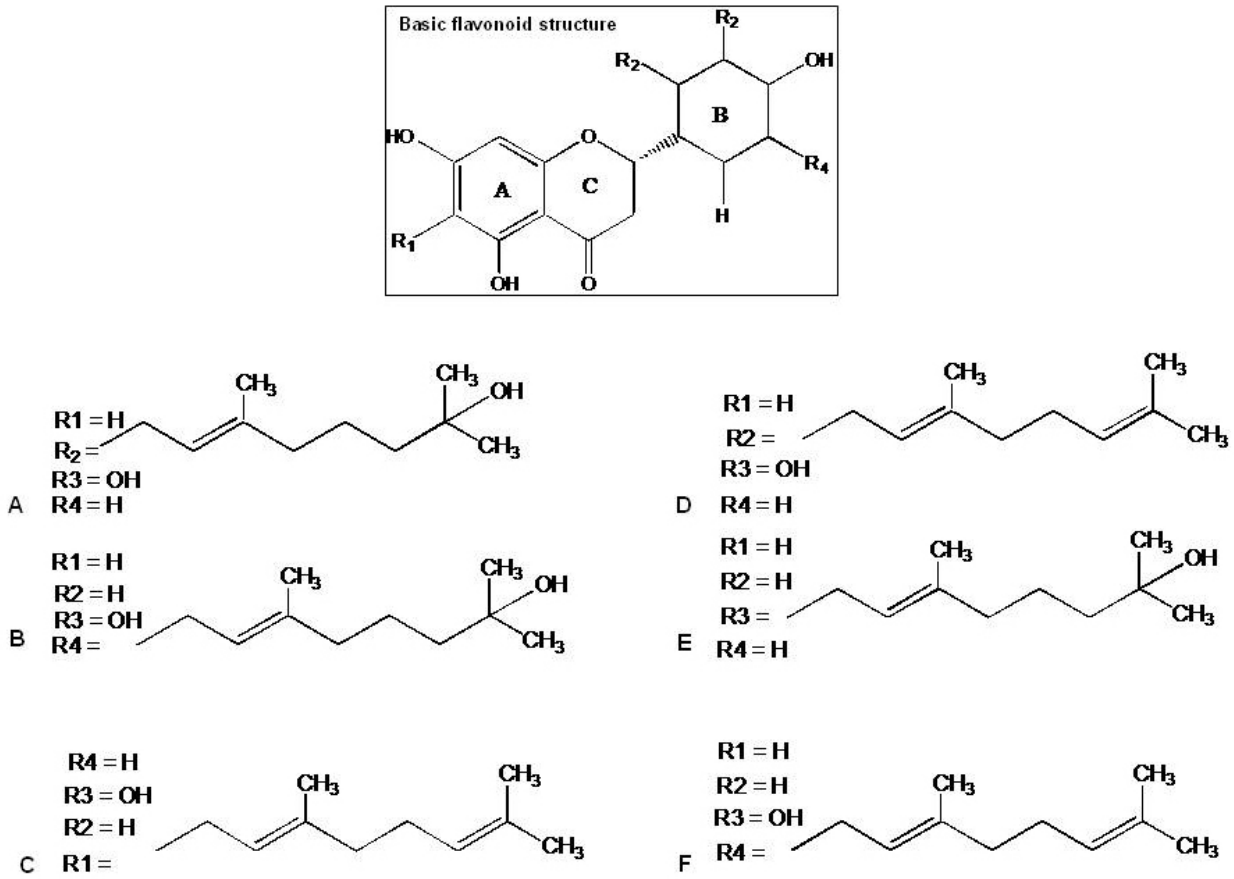


Figure 5. Chemical structures of propolins (prenylflavanone compounds) designarted as A, B, C, D, E and F. Propolins found in Taiwanese propolis exert strong antioxidant activity. Propolins A, B and E have hydrated geranyl side chains, whereas propolins C, D, and F have unhydrated geranyl side chains. Adapted from (27).

in vivo studies through their antioxidant, anti-inflammatory, and immunomodulatory actions (Table 1). In a rodent model system of PD, 6-hydroxydopamine (6-OHDA) induces neuronal death either via uncoupling mitochondrial oxidative phosphorylation resulting in energy deprivation or its ability to produce H_2O_2, $OH^{\cdot}$, and superoxide radicals. CAPE blocks 6-OHDA-induced toxicity, implicating its neuroprotective effect to dopaminergic neurons in the striatum (48). It protects from brain injury after focal permanent cerebral ischemia through its antioxidant actions in rat and rabbit brains (49, 50). Choi *et al* (2010) investigated a potential molecular mechanism underlying a CAPE-mediated protective effect against ischemia/reperfusion (51). According to this group, CAPE acts on the hypoxia-inducible factor (HIF) pathway as a potent inhibitor of HIF prolyl hydroxylase (51). CAPE's ablity to block glutamate-induced excitotoxicity in cerebellar granule neurons (CGNs) by inhibiting phosphorylation of p38 and caspase-3 activation further supports its neuroprotective action (18). In a middle cerebral artery occlusion-induced focal ischemia mice model, apigenin inhibits the production of nitric oxide (NO) and prostaglandin E_2 (PGE_2) in microglia by suppressing the expression of iNOS and COX-2 enzymes, thereby inhibiting neuronal cell death (52). The water-soluble derivatives (WSDP) of propolis prepared from fresh Chinese propolis, given by intragastric administration prior to the intraperitoneal injection of scopolamine, show significant mitigation of scopolamine-induced amnesia in mice (53). The WSDP inhibit acetylcholinesterase (AchE) activity in the hippocampus of scopolamine-treated mice, suggesting that propolis-mediated inhibition of AchE may be responsible for mitigating amnesia *in vivo.* Therefore, propolis or its flavonoids may be used as potential therapeutic agents for brain protection in neurological diseases.

Neuroinflammation mediated by microglia has been implicated in neurodegenerative diseases therefore suppression of microglial activation may contribute to neuronal cell survival. In lipopolysaccharide-stimulated microglia, chrysin has been shown to significantly inhibit the release of NO and proinflammatory cytokines such as TNF-α and interleukin-1β (IL-1β) (54). Chrysin not only inhibits the expression of iNOS and COX-2, but also blocks the activation of c-Jun N-terminal kinase (JNK) and NF-κB signaling, the processes closely associated with the induction and maintenance of neuroinflammation (54). CAPE has been reported to inhibit the cerebral inflammatory responses in a model of endotoxic insult

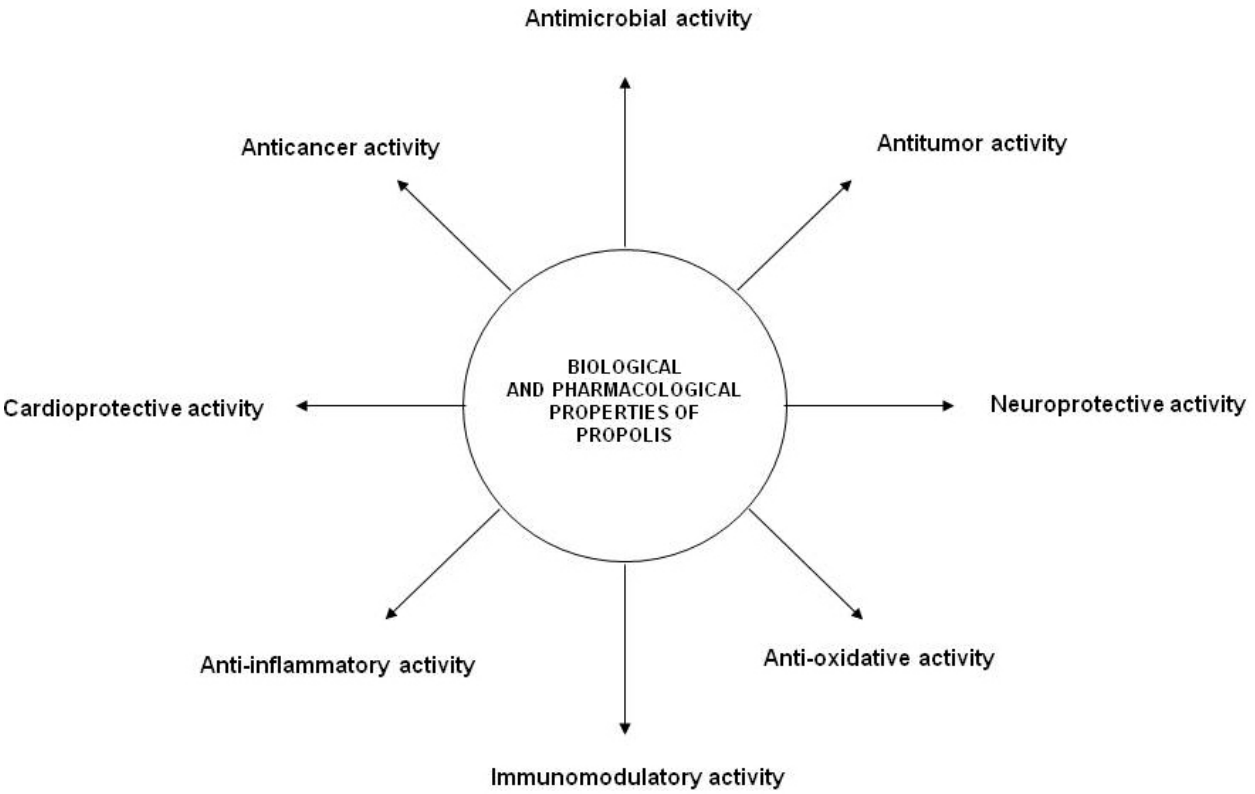


Figure 6. Biological and pharmacological properties of propolis.

(interferon-γ followed by lipopolysaccharide) on rat organotypic hippocampal slice cultures (55). Furthermore, beneficial effects of propolis during fluoride toxicity observed in rats are not only due to significant decrease in malondialdehyde level and increase in superoxide dismutase activity (SOD), but are also due to elevation in levels of reduced glutathione (GSH), indicating that propolis or its specific components have strong anti-oxidant activity *in vivo* (56). Pinocembrin has been reported to protect rat brain against oxidation and apoptosis induced by ischemia-reperfusion both *in vivo* and *in vitro* (57). However, kaempferol, but not quercetin or myricetin, protects SH-SY5Y cells and primary neurons from rotenone-mediated toxicity by reducing caspases cleavage, ROS levels, mitochondrial carbonyls, and apoptosis (58), suggesting that kaempferol-mediated antiapoptotic and antioxidant effects are due to the enhancement of mitochondrial turnover by autophagy. Thus kaempferol, an autophagic enhancer, may be used as a potential therapeutic agent for PD. Quercetin, another plant derived flavonoid of propolis, exerts a powerful antioxidant activity both *in vitro* and *in vivo*. In a recent study, nasal administration of quercetin liposomes show improvement in memory dysfunction and neurodegeneration in animal model of AD (59), suggesting a potential novel therapeutic strategy of using quercetin liposomes against AD. Luteolin belongs to the flavone subclass of flavonoids, and it possesses anti-oxidant and anti-inflammatory activities. Luteolin inhibits the lipopolysaccharide (LPS)-induced decrease in ^{3}Hdopamine uptake and loss of tyrosine hydroxylase-immunoreactive neurons in primary mesencephalic neuron-glia cultures (60). In addition, luteolin significantly inhibits LPS-induced activation of microglia and excessive production of TNF-α, NO, and superoxide anion ($O_2^{\cdot-}$) in mesencephalic neuron-glia cultures and microglia-enriched cultures, implicating that it may protect dopaminergic neurons from LPS-induced injury by suppressing microglia activation (60).

In addition to the abnormality in cytokine network and neurotransmitter homeostasis, abnormality in immune responses is also involved in the etiology of neurological disorders. Immunity in the CNS is markedly influenced by endogenous effectors (such as cytokines, interferons, and neurotransmitters) and cellular products (such as peptidoglycan, single-stranded RNA, lipopolysaccharide, double-stranded RNA, and immune complexes), and exogenous substances including infectious pathogens (bacterial or viral), drugs of abuse, and therapeutic compounds. Toll-like receptors (TLRs) belong to a larger group of proteins called pattern-recognition receptors, which are involved critically in the generation and regulation of the body's innate immune system (first line host defense system against foreign organisms), as well as initiation of subsequent adaptive immune responses (61-63). TLRs recognize invading microbes and activate signaling pathways that launch immune and inflammatory responses to destroy the invaders. Activation of TLRs occurs after the cognate ligand binds to the extracellular leucine-rich repeats portion of the receptor. Different TLRs

Table 1. Neuroprotective responses of propolis and its selected flavonoid constituents

Propolis and its constituents	Biological activity	Pharmacological response	Reference
Propolis	Anti-oxidative	Attenuates KA-induced seizures	(60)
WSDP	Anti-oxidative, anti-inflammatory	Mitigates scopolamine-induced learning and memory impairment	(53)
CAPE	Anti-oxidative	Neuroprotection against I/R injury (focal cerebral ischemia and permanent focal ischemia)	(49, 50, 51)
CAPE	Anti-oxidative	Blocks 6-OHDA-induced neurotoxicity	(48)
CAPE	Anti-oxidative	Protects CGNs against glutamate-induced neurotoxicity by inhibiting phosphorylation of p38 and caspase-3 activation	(18)
Apigenin	Anti-inflammatory	Inhibits NO and PGE_2 synthesis by suppressing the expression of iNOS and COX-2 in microglia	(52)
CAPE	Anti-inflammatory	Prevents inflammatory stress in organotypic hippocampal slice cultures	(55, 69)
Chrysin	Anti-inflammatory	Blocks NF-κB and JNK activations in microglia	(54)
Quercetin	Anti-inflammatory	Decreases iNOS gene expression by inhibiting IκB kinase, NF-κB and STAT1	(68)
Luteolin	Anti-inflammatory, anti-oxidative	Attenuates PS-induced dopaminergic neuronal loss by blocking NO generation in cultured rat microglia	(60)
Kaempferol	Anti-oxidative, anti-apoptotic	Protects from striatal glutamatergic response in rat brain slices by autophagy	(58)
Kaempferol	Anti-oxidative, anti-apoptotic	Protects from rotenone-induced acute toxicity in SH-SY5Y cells and primary neurons by autophagy	(58)
Quercetin	Anti-oxidative	Improves memory impairment by inhibiting the oxidative damage in hippocampus	(59)
Pinocembrin	Anti-oxidative	Protects brain against oxidation and apoptosis	(57)
Propolis	Immunomodulatory	Modulates innate immunity by upregulating the expression of TLRs and producing pro-inflammatory cytokines	(65)
Apigenin and Luteolin	Anti-inflammatory, immunomodulatory	CD40 immunomodulators and suppress TRIF-dependent signaling pathway of TLRs	(66,67)
CAPE, Chrysin	Anti-inflammatory, anti-oxidative, immunomodulatory	Specific inhibitor of activation of NF-κB	(13, 36, 37)

Abbreviations: I/R injury, Ischemia/reperfusion-induced injury; 6-OHDA, 6-Hydroxydopamine; CGNs, Cerebellar granule neurons; iNOS, Inducible nitric oxide synthase; COX-2, Cyclooxygenase-2; NO, Nitric oxide; PGE_2, Prostaglandin E_2; NF-κB, Nuclear transcription factor kappa B; JNK, c-Jun N-terminal kinase; Iκκ, IκB kinase; STAT1, a member of the signal transduction family of transcription factors; CD40, a cytokine receptor; TLRs, Toll-like receptors; TRIF, Toll/interleukin-1 receptor (TIR)-domain-containing adapter-inducing interferon-β; MyD88, Myeloid differentiation primary-response protein-88; CAPE, Caffeic acid phenethyl ester.

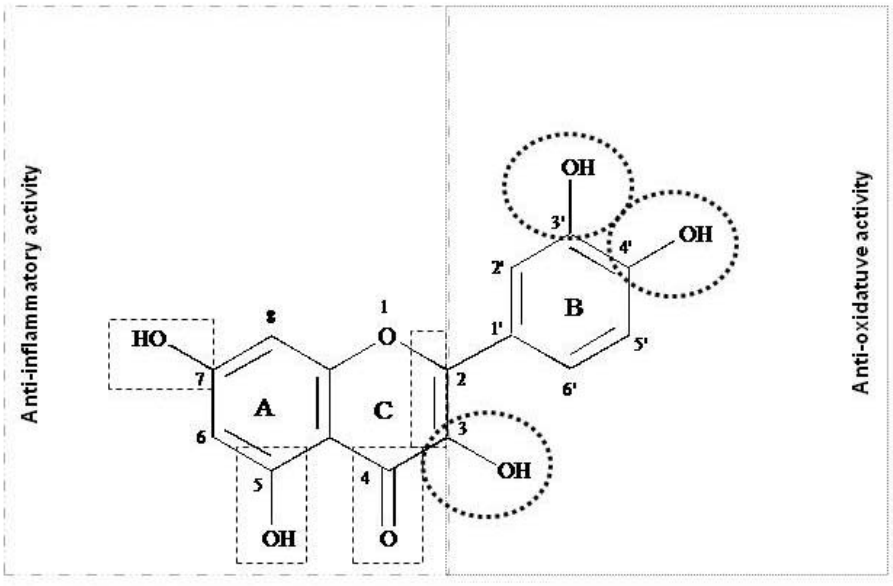


Figure 7. Requirements of flavonoids to exert anti-inflammatory and anti-oxidative activities. Anti-inflammatory activity requires a 2-3 carbon double bond, a 4-keto group on the C ring, and 5,7-dihroxyl groups on the A- ring. Anti-oxidant activity requires hydroxyl groups at the 3' and 4' of the B- ring, and 3 hydroxyl group at the C- ring, but none at the A- ring.

signal via combinations of various adaptor proteins such as myeloid differentiation factor 88 (MyD88) and Toll/interleukin receptor (TIR) domain containing adaptor inducing interferon-β (TRIF). These adaptor proteins activate other molecules within the cell and amplify the signal, leading to the upregulation of pro-inflammatory cytokine and interferon genes involved in the inflammatory response. Upon binding with their cognates, TLRs activate two major signaling pathways: (1) the core pathway utilized by most TLRs leads to the activation of NF-κB and MAPKs (p38 and c-Jun N-terminal Kinase, JNK), and (2) the activation of TLR3 and TLR4 results in the activation of both transcription factors NF-κB and interferon regulatory factor-3 (IRF3), allowing induction of additional set of genes such as interferon-β (IFN-β) and others (64). Although, TLRs system protects host from pathogens, but excessive activation of these receptors is hazardous to the host cell due to the overproduction of proinflammatory cytokines.

Dysregulation in TLRs-mediated immune responses can result in neural cell injury promoting neurological disorders, but modulation of TLRs signaling pathway by small molecules such as flavonoids may provide therapeutic potential against these diseases. Propolis has been shown to exert immunomodulatory action *in vivo* by upregulating TLRs expression and the production of pro-inflammatory cytokines in mice (65). Chronic activation of microglia, the resident immune cells of the brain, triggers and maintains an inflammatory response, ultimately leading to neuronal cell death in neurodegenerative diseases due to exposure of brain to neurotoxic molecules such as pro-inflammatory cytokines, complement proteins, proteinases, and ROS (66). CD40 signaling is critically involved in microglia-related immune responses in the brain. Apigenin and luteolin are known to exert anti-inflammatory and neuroprotective properties by modulating microglial activation via inhibition of STAT1-induced CD40 expression (66). Luteolin suppresses TRIF-dependent signaling pathway of TLRs, resulting in decreased expression of target genes (TNF-α, IL-6, IL-12, IL-27, IFNβ and CXCL9) and IL-27 in macrophages (67). It attenuates ligand-independent activation of IRF3 or NFκB induced by TLR4, TRIF or serine/threonine-protein kinase (TBK1). Luteolin-mediated inhibition of TBK1 activity and dimerization and phosphorylation of IRF3 reduces TBK1-dependent gene expression. Furthermore, structural analogs of luteolin (quercetin and chrysin) also inhibit TBK1 activity and its targeted gene expression (67), implicating the importance of anti-inflammatory flavonoids in the downregulation of TRIF-dependent signaling pathway. Quercetin blocks iNOS gene expression in mouse BV-2 microglia, not only by inhibiting an enzyme complex involved in propagating the cellular response to inflammation (IκB kinase), transcription factors NF-κB and STAT1, but also by inducing heme oxygenase-1 (68). CAPE inhibits TNFα-dependent NF-κB activation via direct inhibition of inhibitory protein-κB kinase (IKK), as well as through the activation of Nrf2 pathway (69). Based on collective evidence (Table 1), it can be suggested that certain flavonoid components of propolis may offer potential therapeutic role in treating or preventing many neurological diseases in humans.

7. MOLECULAR MECHANISM OF ACTION OF PROPOLIS

As speculated above that many therapeutic effects of propolis may be associated with its antioxidant, anti-inflammatory, and immunomodulatory activities (13). A hypothetical scheme for the molecular mechanism underlying the propolis-mediated protective effects in neurological disorders is shown in Figure 8. ROS (hydrogen peroxide, H_2O_2; hydroxyl ion, $OH\cdot$; and superoxide ion, O_2^{-}) are the intermediates in the reduction of molecular oxygen to water. ROS are inevitable by-products of many processes in aerobic cells, including electron transport chain in mitochondria, enzymic and non-enzymic oxidation of polyunsaturated fatty acids, iron-mediated peroxidation of unsaturated fatty acids, and activation of enzymes such as enzymes of mitochondrial electron transport chain, xanthine oxidase, COX-1, COX-2, LOX, NADPH oxidase, and NOS (15, 70). Low levels of ROS are needed for normal cellular functions in adult brain, but are not restricted to the regulation of neuronal excitability via redox-sensitive ion channels, synaptic plasticity, gene transcription, and for the activity of enzymes controlling protein phosphorylation. High levels of ROS and reactive nitrogen species (RNS) in neurotraumatic and neurodegenerative diseases cause ‘‘nitrosative and oxidative stress’’ by not only damaging DNA, lipids, proteins, and carbohydrates but also by generating high levels of variety of mediators such as 4-hydroxy-2-trans-nonenal, isoprostanes, isoketals, isofurans, 8-hydroxy-2’-deoxyguanosine (15, 46, 71).

NOS generates NO, which plays an important second messenger role in a wide range of physiological processes, including vasodilatation, immune response, and neurotransmission. NO can react with O_2^{-}, transition metals or with endogenous thiols and produces peroxynitrite ($ONOO^{-}$), nitrosyl–metal complexes, or S-nitroso-thiols, collectively called RNS (70). NO causes DNA damage as well as protein modifications such as nitrosylation and nitration. Protein nitration generally adds a nitro group on to one of the two carbons at position 3 of the aromatic ring of tyrosine residues to form nitrotyrosine. Peroxynitrite along with eicosanoids and platelet activating factor facilitate neuroinflammation (72). Neurons are highly susceptible to both ROS and RNS-mediated injury. ROS and RNS can also indirectly contribute to the brain damage by activating a number of cellular pathways resulting in the expression of stress-sensitive genes and proteins, causing oxidative stress-mediated injury. Moreover, oxidative stress also activates mechanisms that result in a glia-mediated inflammation, causing secondary neuronal damage (72, 15). Generation of higher levels of ROS, RNS, and other lipid mediators may lead to abnormal neural cell functions, early onset of neurotraumatic and neurodegenerative diseases, leading to neural cell injury.

In addition to oxidative stress, the pathogenesis of neurological diseases also involves inflammatory reactions, which not only isolate the injured cells from uninjured cells, but also destroy damaged cells, and repair the extracellular matrix. The main mediators of

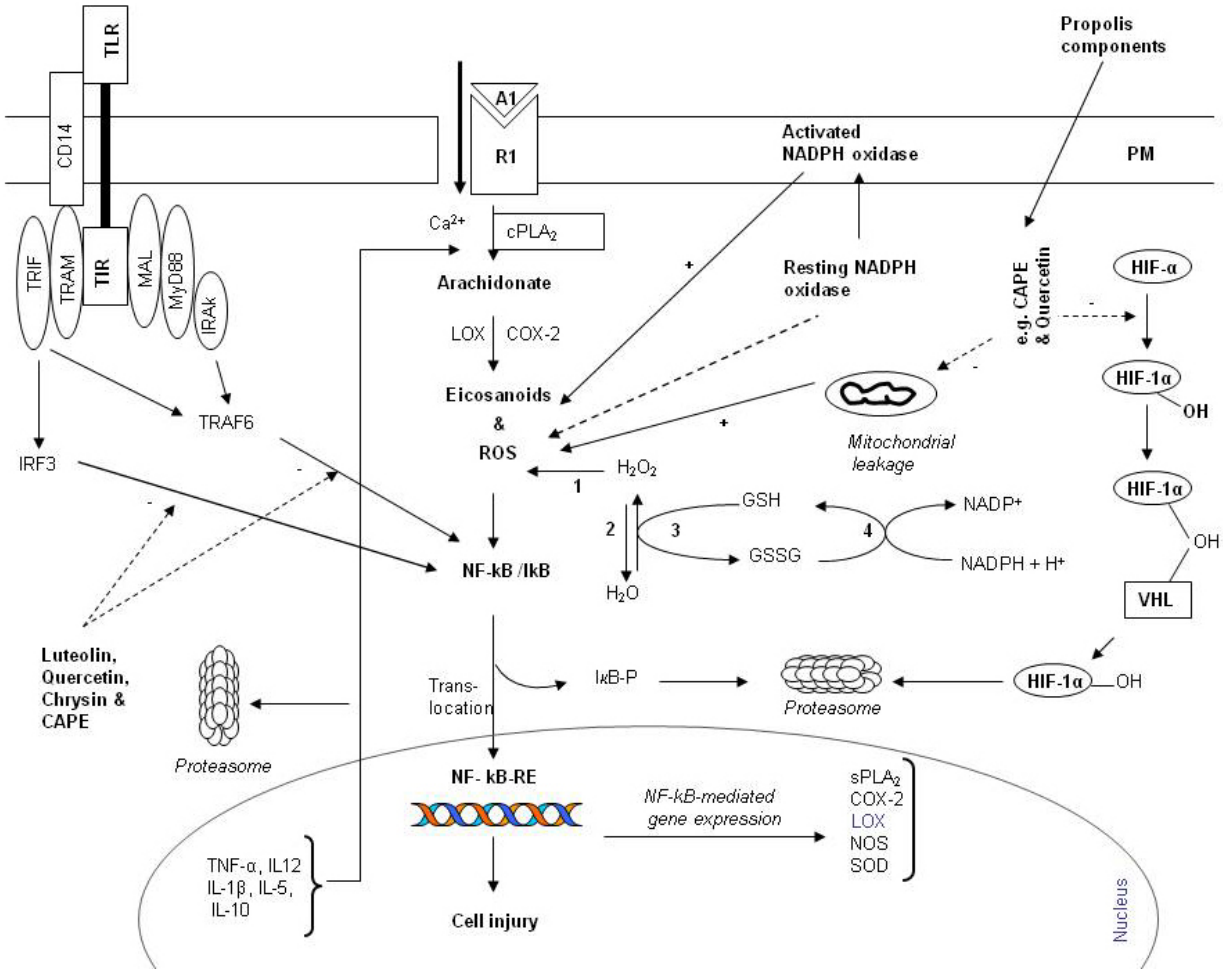


Figure 8. A hypothetical scheme showing generation of ROS, and neuroprotective effects of propolis against cell injury in neurological disorders. Enzymes: 1, Peroxidase; 2, Superoxide dismutase; 3, Catalase; 4, Glutathione reductase. Abbreviations: A1, Agonist; R1, receptor; $cPLA_2$, Cytosolic phospholipase A_2; ($sPLA_2$) secretory phospholipase A_2; COX-2, cyclooxygenase-2; LOX; lipoxygenase; SOD, superoxide dismutase; NOS, nitric oxide synthase; NO, nitric oxide; $OONO^-$, peroxynitrite; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1beta; GSH, reduced glutathione; GSSG, oxidized glutathione; H_2O_2, hydrogen peroxide; HIF-1α, hypoxia-inducible transcription factor 1 alpha; VHL, von Hippel-Lindau protein; TLRs, Toll-like receptors; TIR, Toll/interleukin (IL-1) receptor; CD14, protein encoded by *CD14* gene is a component of innate immune system; IFN, type 1 interferon genes; IRF3, interferon regulatory transcription factor; MYD88, Myeloid differentiation primary-response protein-88; IRAK, IL-1 receptor associated kinase; TRAF6, TNF receptor-associated factor 6; TRIF, TIR domain containg adaptor inducing IFNβ; TRAM, TRIF-related adaptor molecule; MAL, MYD88-adaptor like; NF-κB, Nuclear transcription factor kappa B; Nuclear factor kappa B response element (NF-κB-RE). Stimulation of NF-κB by ROS helps in its translocation to the nucleus where it not only facilitates the transcription of $sPLA_2$, COX-2, NOS, and SOD genes, but also upregulates expression of proinflammatory cytokines as well as IFN-β genes in the nucleus. Propolis also inhibits translocation of HIF-α to the nucleus.

inflammatory reaction are macrophages in visceral organs and microglia in brain tissue, respectively (72). In brain, the hallmark of neuroinflammation is the activation of microglial cells, whereas in visceral organs it is the activation of macrophages. It remains controversial whether macrophages or microglial cells have beneficial or detrimental functions in various pathological conditions. The chronic activation of macrophages may cause neuronal damage through the release of potentially cytotoxic molecules such as proinflammatory cytokines, eicosanoids, platelet activating factor, proteinases, and complement proteins (72, 73). Inflammation also generates the proinflammatory and neurotoxic factors through activation of microglial cells that initiate a rapid response, involving cell migration, proliferation, release of cytokines/chemokines trophic and/or toxic effects (72, 73). Cytokines/chemokines stimulate phospholipases A_2 (PLA_2), COX-1, and COX-2, resulting in the breakdown of membrane glycerophospholipids with the release of arachidonic acid (ARA) and docosahexaenoic acid (DHA). The oxidation of ARA produces pro-inflammatory lipid mediators (prostaglandins, leukotrienes, and thromboxanes) that lead to sustained chronic neuroinflammation, contributing to the pathogenesis of neurological disorders.

However, DHA and its lipid mediators (resolvins and neuroprotectins) inhibit the generation of pro-inflammatory mediators and thereby prevent neuroinflammation (15). The chemical nature of signals, which initiates the activation of microglial cell response to cell brain injury in neurological disorders remain unknown. However, it is suggested that the alterations in ion homeostasis, acid base balance, and generation of lipid mediators may play an important role in microglial cell activation, initiation, and maintenance of inflammatory responses (15, 72, 73).

A causal relationship between infection with Gram-positive bacteria, activation of the innate immune cells in the CNS, and subsequent neurodegeneration has been reported in neurological disorders (74). Emerging evidence indicates that as in peripheral organs innate immune system also takes place in the CNS (75, 76). As stated above, human neurons express the innate immune response receptors called TLRs in the CNS (76-78). TLRs recognize invading microorganisms such as bacteria and viruses, and activate signaling pathways that launch immune and inflammatory responses to destroy the microbial invasion of the CNS. Mammalian TLRs consist of an extracellular portion containing leucine-rich repeats, a transmembrane region and a cytoplasmic tail, called the Toll interleukin-1-Receptor (TIR) homology domain. Different TLRs serve as receptors for diverse ligands, including bacterial cell wall components, viral double-stranded RNA and small-molecule anti-viral or immunomodulatory compounds. TLRs expressed in microglia are likely to be involved with the first line of host-defense against microbial invasion. Other cells in the CNS (astrocytes, neurons, and oligodendrocytes) also express multiple functional TLRs that participate in tissue development, cellular migration, and differentiation; in limiting inflammation; and in mounting repair processes following trauma (76), suggesting other protective roles of TLRs in brain besides protection against microbial invasion. TLRs play roles in the cell development, cell-cell interaction, and the crosstalk between neurons and glial cells in the CNS (78). High levels of oxidative stress, neuroinflammation, and dysregulation of the immune system in the CNS may be directly linked with the etiology of neurological diseases (Figure 8) through turning on specific genes that induce cell death in a specific neuronal population in a particular region of the brain (70, 14, 15). Studies discussed about the use of propolis or its flavonoid constituents *in vitro* and *in vivo* model systems of neurological disorders (Table 1) support the potential therapeutic use of propolis or its flavonoid constituents (such as CAPE, quercetin luteolin, and apigenin) to treat neurological diseases due to its anti-oxidative, anti-inflammatory, and immunomodulatory (in some cases immunosuppressive and in others immunostimulatory) activities.

8. CONCLUSION

Propolis contains significant amount of polyphenols, mainly flavonoids and phenolic compounds, and exerts powerful antioxidant, anti-inflammatory, and immunomodulatory activites *in vitro* and *in vivo* model systems, appearing to be due to high concentration of flavonoid constituents. Flavonoids inhibit various enzymes, such as COX-1, COX-2, LOX, microsomal monooxygenase, glutathione S-transferase, mitochondrial succinoxidase and NADPH oxidase, which are involved in the generation of ROS and proinflammatory lipid mediators (79-82). Inhibition of ROS formation and inflammation by propolis and its components provide a potential molecular basis for the protective actions of propolis not only through the retardation of NF-κB activation, inhibition of eicosanoid synthesis, and reduction in expression of various inflammatory cytokines in the nucleus, but also through the inhibition of oxidative damage to proteins, lipids, DNA/RNA and carbohydrates, and influencing immune responses via modulating the expression and TLRs-mediated signaling. Therefore, there has been a considerable interest in the neuroprotective effects of propolis because of biological activities based on its flavonoids and rare side effects.

The pathogenesis of neurological diseases remains illusive, but there is increasing evidence that impairment of mitochondrial function, oxidative damage, and inflammation are contributing factors. The high morbidity, high socioeconomic costs and lack of specific treatments for neurological diseases such as stroke, AD and PD are key factors that define the need to develop protective strategy against these disorders by using natural neuronal protective agents such as propolis and its flavonoid compounds. Epidemiological studies have shown beneficial effects of flavonoids on arteriosclerosis-related pathology in general and neurodegeneration in particular. Flavonoids can protect the brain by their ability to modulate intracellular signals promoting cellular survival. In spite of beneficial activities of propolis, the most challenging problem is uncertainty of its correct dosage and safety. Since chemical composition of propolis varies greatly due to differences in time of collection, vegetation and geographic location, therefore biological activities of propolis gathered from different phytogeographical areas and time of collection will also vary greatly, making it a difficult task to define the right dosage. Furthermore, few individuals exhibit hypersensitivity to propolis. Despite of increasing number of *in vitro* and *in vivo* studies trying to unravel the mechanisms of action of propolis polyphenols, the research in this field is still incomplete. Questions about bioavailability, biotransformation, synergism with other dietary factors, mechanisms of the antioxidant activity, risks inherent to their possible pro-oxidant activities still remain unanswered. Although, the capacity of the majority of flavonoids of propolis to cross the blood-brain barrier and reach brain is still unknown, but it is a potential valuable candidate as a neuroprotective agent in neurological disorders. The degree to which propolis flavonoids can be absorbed has yet to be unanimously agreed upon.

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