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Review

Neuroprotective Potentials of Honey for Cerebral Small Vessel Disease

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Abstract

The nectar produced by bees in nature is known as honey and has been consumed for its nutritional and medicinal properties. There is growing evidence that honey and its compounds have anti-inflammatory, antioxidant and anti-microbial properties that are relevant to the maintenance of health and the prevention of illnesses, including cardiocerebrovascular disease. Cerebral small vessel disease (CSVD) is one of the major risk factors for diseases such as stroke, dementia, Alzheimer's disease, and Parkinson's disease. CSVD is prevalent with

aging and the presence of vascular risk factors. Its most common deleterious effect on the brain parenchyma is a neurological problem, causing a spectrum of subtle clinical manifestations such as neurocognitive dysfunction, emotional or behavioral disturbances, and gait dysfunction. Moreover, the pathological mechanisms and preventive strategies for CSVD remain elusive, which is reflected in the continued lack of effective therapeutic and preventive therapies. Given the growing literature on honey and its compounds as a superfood-based preventive measure, this narrative review highlights the neuroprotective potentials of honey and its compounds in relation to the current understanding of CSVD pathomechanism.

Keywords
Cerebral small vessel disease; cardio-cerebrovascular disease; honey; neuroprotective; aging

1. Introduction

Cerebral small vessel diseases (CSVD) are a significant precursor to 20% of all strokes, and 65% of ischemic stroke subtypes, and are the most common culprit of age-related cognitive decline and dementia and/or vascular dementia [1, 2]. However, although several trials and interventions have been reported to modify the course of CSVD, knowledge of their natural history (from onset and progression) remains limited [3]. The commonly accepted underlying pathomechanisms of CSVD include the interlinked roles of oxidative stress, neuroinflammation, and arteriolosclerosis. Risk factors for cardio-cerebrovascular diseases, such as aging, hypertension, type-2 diabetes mellitus, and cerebral amyloid angiopathy mediated by vascular deposition of β-amyloid, are frequently co-occurrence in CSVD manifestation. Moreover, CSVD has various and overlapping radiological manifestations, including white matter hyperintensities (WMHs) of presumed vascular origin or leukoaraiosis, lacunes (i.e., small subcortical infarcts and silent brain infarcts), enlarged perivascular spaces (ePVS), cerebral microbleeds (CMBs), and cortical microinfarcts [4, 5]. These CSVD manifestations are often covert in nature with aging and may progress rapidly without prior prevention strategies. As a result, these factors had contributed to CSVD being a major public health burden, with has been estimated that more than 20% of older adults (i.e., over 80 years of age) have more than one lacunes on brain imaging [3].

Given that CSVD may lead to various vascular-related brain injuries through multiple mechanisms and that these mechanisms are frequently synergistic or cumulative, an understanding of CSVD from molecular to cellular processes may be helpful for CSVD prevention and therapeutic strategies. On the other hand, an increasing number of pre-clinical and clinical data supported the medicinal values of honey. Honey has several biological activities such as anti-inflammation [6, 7], antioxidative stress [8], anti-hyperglycemic [8], and gastroprotection [9]. These properties are attributed to its rich content of vitamins, minerals, enzymes, and antioxidants (phenolic, flavonoids) that alleviate oxidative stress and neuroinflammation, protect against neurotoxin-induced neuronal injury, promote learning and memory, and improve cognitive function [10, 11]. Therefore, this narrative review attempts to describe the potential of honey in the neuroprotective effect of CSVD.

2. Cerebral Small Vessel Disease (CSVD)

CSVD is a common clinical and neuropathological process with several etiologies, centered on the cerebral microvasculature (or microcirculation). This network of small penetrating arteries (chiefly tributaries of the middle cerebral artery), arterioles, capillaries, and small veins (or venules), 50-400 mm in size, can supply deep into the grey and white matter of the subcortical regions of the brain [12, 13]. The silent or asymptomatic manifestation of CSVD with advancing age is the most important contributor to vascular Parkinsonism, dementia, Alzheimer's disease, and ischemic stroke. CSVD has been reported to be associated with nearly 45% of dementia, 20% of strokes, and over 70% of vascular dementia worldwide [1, 2].

2.1 Characteristics and Classification of CSVD

CSVD is mainly classified based on several pathogenetic mechanisms, of which the most well-known forms of CSVD are amyloidal CSVD (i.e., sporadic, and hereditary cerebral amyloid angiopathy), and non-amyloidal CSVD such as cardio-cerebrovascular risk factors-mediated small vessel disease including aging and arteriolosclerosis [2]. Other forms of CSVD include genetic or monogenic inherited CSVD distinctly different from cerebral amyloid angiopathy (e.g., Fabry's disease and cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy [CADASIL]), immune- and inflammation-mediated CSVD, venous collagenosis, and other CSVD (i.e., non-amyloid micro-vessel degeneration in Alzheimer's disease and post-radiation angiopathy) [14].

Moreover, over the past decades, the rapid advancement in neuroimaging technology has equipped the imaging-based identification, classification, and characterization of different manifestations of CSVD. Neuroimaging techniques, particularly brain magnetic resonance imaging (MRI) have been widely used and provide a significant role in the *in vivo* visualization of brain tissue (parenchyma) and cerebrovascular health, enabling identification, diagnosis, and prognosis of the multifaceted features of small vessel disease. Several well-characterized neuroimaging manifestations of CSVD include WMHs of the presumed vascular origin or radiologically known as leukoaraiosis, lacunes (i.e., small subcortical infarcts and silent brain infarcts), ePVS, cortical microinfarcts, and CMBs [4, 5] (Figure 1). Concerningly, CSVD can appear in a wide range of populations and the lesions can be silent (or occult), whereby the affected person may be asymptomatic. More importantly, a higher number of such silent lesions, single or multiple, is associated with a higher risk of mild cognitive impairment, dementia, Alzheimer's disease, vascular Parkinson's disease, and full-blown stroke [15-17].

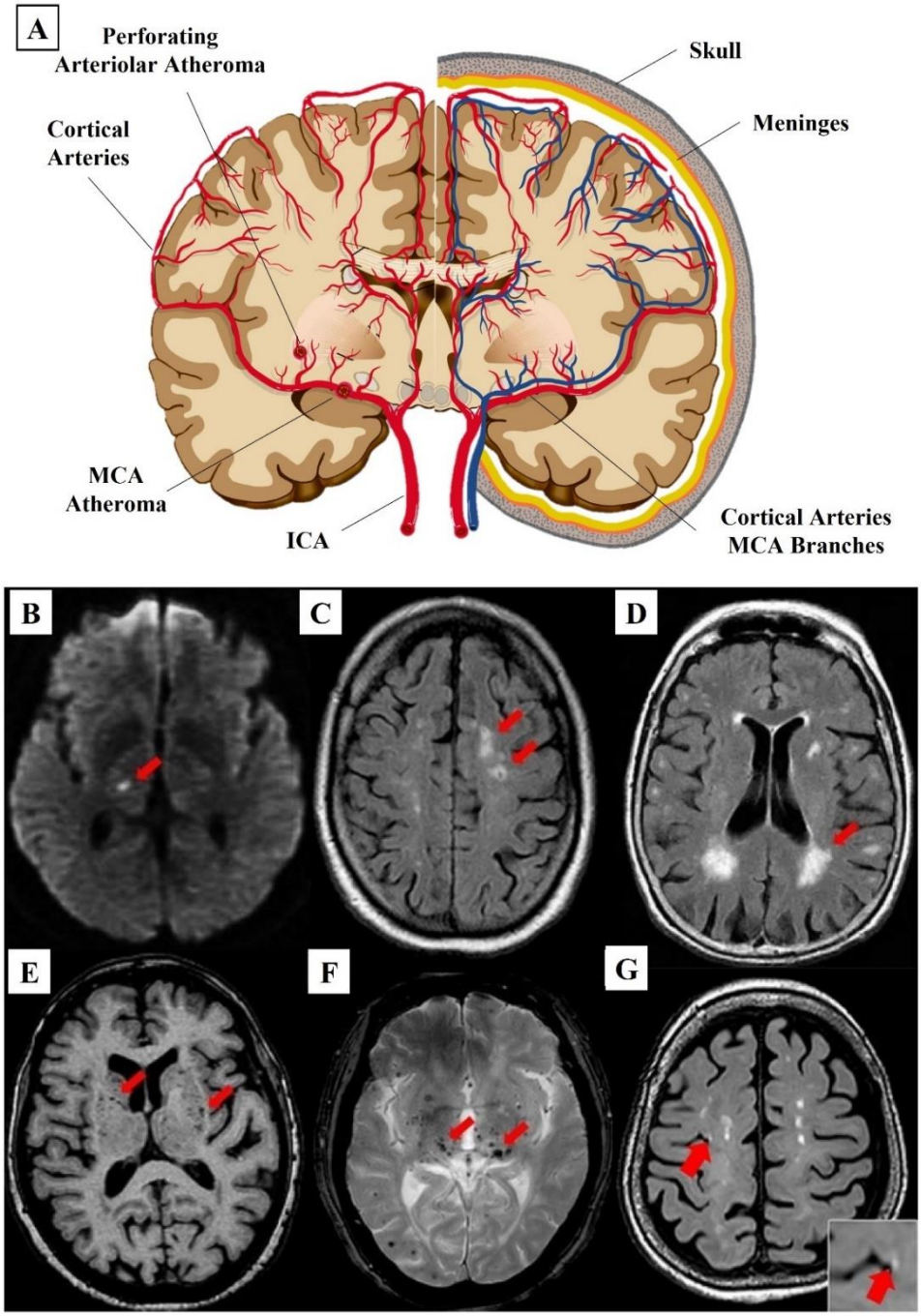

Figure 1 (A) Schematic representation of cerebral vasculature (penetrating arterial) supplies to the brain, vascular-pathological process (i.e., atheroma) of cerebral small vessel disease (CSVD), and neuroimaging manifestation and characterization of CSVD. **(B)** Diffusion-weighted imaging (DWI) showing recent small subcortical infarct (red arrow). **(C)** Fluid attenuated inverse recovery (FLAIR) image showing lacunar infracts (red arrow). **(D)** FLAIR showing white matter hyperintensities (WMHs) of presumed vascular origin (red arrow). **(E)** T1-weighted imaging showing enlarged perivascular spaces (ePVS) (red arrow). **(F)** T2*-gradient echo (GRE) showing cerebral microbleeds (CMBs) (red arrow). **(G)** T1-weighted (hypointense) of 3T MRI showing cortical microinfarcts (red arrow). ICA, internal carotid artery; MCA, middle cerebral arteries. Figures (B-F) were adapted from [18]; and Figure (G) was adapted from [19].

2.2 The Prevalence and Cognitive Burden of CSVD

Several neuroimaging manifestations of CSVD suggest that its prevalence varies across age groups and age stratification and thus its health burden affects both individuals with the disease and those in healthy conditions [20-22]. Multiple studies had reported that aging is an independent risk factor for CSVD [20, 21, 23], hence strengthening the fact that CSVD is prevalent with aging. Among several manifestations of CSVD, the prevalence of WMHs of presumed vascular origin was as high as 98% in patients with diseases, and 50% in healthy individuals, CMBs were found in 5% of disease individuals, and up to 35.7% of individuals aged 50 to 80-year-old, while lacunes or lacunar infarcts were found in 28% of patients and 8% of healthy individuals, whereby up to 17.3% of adults aged over 65 years affected [13, 20, 24, 25]. However, additional clarification is necessary due to the variation and distribution of neuroimaging manifestations of CSVD and its overall health burden across ages. Moreover, it has been hypothesized that all manifestations of CSVD are interconnected and frequently associated with detrimental effects on cognitive functions, which explains the variation of cognitive impairment [15, 16].

Additionally, ethnicity, race, and sex with adjusted age, also contribute to the variability of the neuroimaging findings. Several studies have shown that WMHs volume was higher in ethnic or racial minorities than non-Hispanic whites [26] and that women were more likely to have WMHs than men [27], but the exact mechanism of this gender difference is still unknown. Moreover, previous research revealed that stroke-free elderly Latinos and/or Hispanic are present with lacunar infarct in at least 16% of cases, primarily in the subcortical region (82.9%) [28] and in the perivascular spaces (48%) [29]. Another study on different ethnic groups revealed that the prevalence of WMHs in Europeans was comparable to that of South Asians, however, older South Asian populations with known cardio-cerebrovascular risk factor/s may have a higher risk for WMHs burden [30]. In addition, data from several Asian countries, including Korea, Hong Kong, and Singapore showed a higher CSVD burden in Asian older adults, which is associated with cognitive deterioration [31]. This was further supported by Taizhou Imaging Study, which found incidental WMHs (10.7%), ePVs (27.8%), CMBs (18.5%), and lacunes (26.7%) in elderly Chinese with known cardio-cerebrovascular risks [32]. As well as in the Malaysian population study, found WMHs (33%; mean age: 46.6 ± 12.2), and ePVS (48%; mean age 43.1 ± 12.2) among asymptomatic working-age adults [33]. In addition, most Japanese have mild to moderate ePVS, particularly in the basal ganglia and centrum semiovale [34].

The effect of CSVD on cognitive burden appears to be consistently influenced by the location of the lesion(s). For instance, in the presence of WMHs [21], lacunes (deep nuclear [78.2%] and posterior fossa [10.1%]) [35], and ePVS [34, 36], the impairment and/or reduced white matter integrity in the frontal lobe and its dysfunction are interrelated to diminished information transmission to other parts of the brain. On the other hand, the temporal lobe lesion is more closely connected with the results of lobar and deep CMBs [37]. Numerous research has shown that the higher WMHs burden is associated with worse general and domain-specific cognitive performance, particularly in executive function, processing speed, and working memory [1, 38]. Furthermore, the compelling data suggested that increased WMHs with reduced cognitive performance is comparable to a person with a high amyloid load, mild Parkinson's disease, and functional impairments [39]. Additionally, it has been noted that the presence of lacunar infarcts or lacunes of presumed vascular origin is associated with cognitive dysfunction in elderly and non-demented

individuals [21, 38]. On the other hand, in some cases, the existence of ePVS slows down the processing speed in individuals [33, 40], while in other cases it does not affect cognitive performance [36]. Last but not least, the presence of CMBs has been associated with a decrease in both global and domain-specific cognitive performance [41].

Taken together, more information is required to fully comprehend the impact of race and/or ethnicity on the various neuroimaging manifestations of CSVD, as well as on cognitive function overall.

2.3 Pathomechanism of CSVD and Roles of Oxidative Stress-Neuroinflammation

Two long-established clinicopathologic delineations of CSVD have drawn the greatest attention: (1) the occlusion of small cerebral penetrating arteries and (2) arteriosclerosis or lipohyalinosis (i.e., thickening and/or damage of the arteriolar wall) [42]. Nevertheless, it is now accepted that the majority of macrostructural changes observed from neuroimaging manifestations of CSVD are plausibly due to underlying meso-structural responses, such as obstruction of cerebral microcirculation flow [43]. In this case, the arteriolar narrowing and/or occlusion may result in a symptomatic ischemic event, as seen in small lacunar infarcts in the traditional CSVD spectrum, or simply occult.

At present, the precise underlying pathomechanisms of CSVD remain obscure, despite rapid new insights from physiologic, histopathologic, imaging, and epidemiologic studies. Nonetheless, the potential therapeutic insights on the recent pathomechanism of sporadic CSVD can be extrapolated from a number of systemic dysregulated molecular and cellular sequelae, including inflammation, oxidative stress, and microthrombosis, all of which may lead to cerebral microstructural changes (i.e., reduced cerebral blood flow and blood-brain barrier damage) prior to the clinical manifestations and/or imaging detection of CSVD.

There are increased research interests in the risk factors and causative mechanisms of arteriosclerosis and the role of oxidative stress in the formation of CSVD. Previous studies had successfully proven the interrelation between oxidative stress (i.e., a disturbance in the homeostasis between pro-oxidants and antioxidants species in favor of the former, which potentially results in cellular and molecular damages) [44], and nicotinamide adenine dinucleotide phosphate (NADPH) on the endothelium-dependent nitric oxide (NO) signaling [45, 46]. Moreover, oxidative stress and cellular inflammation can result from the heightened inflammatory response from endothelial cells (or endothelium) i.e., endothelial dysfunction. For instance, microthrombus on small vessel endothelium is susceptible to enzymatic and oxidative modifications by reactive oxygen species, such as hydrogen peroxide (H_2O_2), superoxide ($O_2^{\cdot-}$), and hydroxyl radical (·OH) and pro-inflammatory cells [47]. Additionally, reactive oxygen species have been reported to cause a disparity between antioxidants (i.e., endothelial cells-derived superoxide dismutase, and glutathione peroxidase) and pro-oxidants in age-related neurodegenerative diseases, in which the oxidative stress occurred due to overproduction of NADPH oxidases (Nox)-mediated pro-oxidants and altered activity of antioxidants enzymes [48].

Besides, the reactive nitrogen species also contribute to cerebral vascular oxidative stress, because both reactive oxygen species and reactive nitrogen species are mainly synthesized by mitochondria activity and specific pathways, including NO synthase (NOS) and oxidase enzymes such as NOS oxidase (Nox), uncoupled endothelial NOS (eNOS), cyclooxygenase, lipoxygenase,

xanthine oxidase, and myeloperoxidase. Contrary to eNOS dysfunction causing the superoxide release from endothelial cells, eNOS is crucial for endothelial NO production, therefore also playing a beneficial or protective role in the regulation of vascular tone [14]. Furthermore, reactive oxygen species elevate the inflammatory response affecting the parade of clots or thrombus, increasing pro-inflammatory cytokines such as interleukins (i.e., IL-6 and IL-8), tumor necrosis factor α (TNF-α), and monocyte chemoattractant protein-1, and causing endothelial dysfunction, as well as increasing the expression of vascular adhesion molecules (i.e., ICAM-1 and VCAM-1) [49].

Consequently, the increased reactive oxygen species and reactive nitrogen species have been correlated with oxidative stress-mediated cell proliferation and migration, apoptosis and necrosis, DNA damage, endothelial dysfunction, cellular autophagy, endoplasmic reticulum stress, and increased oxidized low-density lipoprotein levels [50]. Moreover, as a consequence of the overproduction of pro-inflammatory cytokines, the transcription factors such as nuclear factor-κB (NF-κB) and signal transduction cascades [51] are activated and further stimulating the release of cytokines and chemokines, hence exacerbating the inflammation [52]. Nevertheless, NO potentially inhibits the expression of NF-κB, indicating that NO is a beneficial anti-inflammatory molecule that may promote vasodilation and improve cerebral blood flow [47]. In addition, reactive oxygen species may affect the endothelial cells, including endothelial dysfunction through disrupting endothelial junction, gap formation, and alteration of phosphorylation of adhesion molecules [53], while the elevated cytokines influence inflammation by degradation of extracellular matrix followed by blood-brain barrier damage [54].

Therefore, the interplay of multiple cellular and structural components is anticipated to play an important role in the discovery and development of novel preventive strategies and therapies for CSVD. The damaged blood-brain barrier, endothelial dysfunction, and altered cerebral blood flow, due to increased oxidative stress and inflammation are arguably the key mediators of CSVD the genesis and progression. Establishing more precise pathomechanisms of CSVD will undoubtedly contribute to the development and testing of the potential pharmacotherapeutics targets, including pleiotropic compounds targeting neuroprotection, cerebral plasticity and/or compensatory mechanisms, and neurodegenerative-disease related molecular to cellular aberration.

3. Sources and Composition of Honey

Honey is a naturally occurring sweetener, primarily in the monosaccharides made by bees from nectar, secretions, or excreta of plant-sucking insects from living parts of plants [55]. Nectar is an aqueous solution of sugars that contains disaccharide sucrose, regurgitated by bees, and deposited into the cells which then undergo the ripening process to reduce the water content [56, 57]. An invertase enzyme produced by the bees' hypopharyngeal glands hydrolyses the disaccharide sucrose into the monosaccharides of glucose and fructose, thereby producing honey [58]. After that, honey is kept and sealed in beeswax combs or cerumen pots [59].

The main categories of bees are all honeybees (*Apis spp.*), stingless bees (*Melipona* and *Trigona spp.*), Nectarina wasps in South America, and many kinds of honey ants, including *Melophorus inflatus* in Australia [60]. The most widespread species of honeybees in the world are *Apis mellifera*, commonly found in Europe, Africa, and Asia. Meanwhile, stingless bees can be found in tropical and subtropical regions like Africa, South America, Australia, and East and South Asia [59, 61, 62]. In terms of hive structure, the honeybees produce honey called comb honey, which is constructed in

hexagonal combs with wax in the nests. While the stingless bees produce pot honey, which they store in horizontal pots made of cerumen, a mixture of propolis and wax for nesting [57].

There are two separate beekeeping terms of honeybees and stingless bees, known as Apiculture and Meliponiculture, respectively [56]. In addition to imported *Apis mellifera* species, there are other local *Apis* honeybee species in Malaysia like *Apis cerana*, *Apis dorsata*, *Apis koschevnikovi*, and *Apis florea*. Every species exhibits unique behaviors, for instance, the *Apis dorsata* builds single comb, open nests atop trees, which makes them prone to migrate. Whereas *Apis mellifera* and *Apis cerana* are typically raised in modern, movable wooden box hives for Apiculture [56]. The stingless bees, like the well-known *Apis mellifera*, live in stable colonies with a single queen, and worker bees collect pollen and nectar to feed larvae within the colony and similarly store honey in the hive for this purpose [63]. The most common stingless bees used in Meliponiculture are *Heterotrigona itama* and *Geniotrigona thoracia* [64]. Since log hives of *Heterotrigona itama* are easier to locate than those of *Geniotrigona thoracica,* therefore, in Malaysian forests, they are the most abundant species tamed by beekeepers [65]. Meliponiculture of stingless bees requires transferring the whole colonies from their log hive into wooden boxes with a hole in the middle and then set on top of tree trunks [57, 64].

3.1 Classification of Honey

Honey types differ according to their composition depending on their botanical and geographical origins, as well as the surrounding environmental conditions. In general, honey is classified according to the species of bee and source of floral nectar from which it was found, harvested, and processed [66, 67]. The nectar sources can be obtained from blossom or honeydew. Blossom honey is primarily collected by *Apis mellifera* bees from the plant nectar, alter by mixing with their specific substances, deposited, dehydrated, stored, and left in honeycombs to mature [60]. Honeydew honey, also referred to as forest honey, is 'honeydew' in plant saps collected by honeybees from the secretion of living plant parts or the excretion of plant-sucking insects. The plant-sucking insects (Hemiptera) pierce leaves or other plant covering parts, feed on the sap, and then excrete the excess droplets as honeydew, which are gathered by the bees [60, 67].

The blossom honey type is further classified into two subcategories: monofloral and multifloral. Most monofloral honey is obtained from a single botanical species that account for at least 45% of pollen grains. The most known monofloral honey is Manuka, which is predominantly made by honeybees in New Zealand and Southern Australia from the nectar of the Manuka honey bush (*Leptospermum scoparium*) [68, 69]. This manuka honey is known as the "gold standard" of honey as it has been thoroughly examined and classified in terms of its composition and phytochemical properties [68]. In Malaysia, monofloral honey or formally known as Gelam honey is made by *Apis dorsata* bees, which collect the plant nectar from *Melaleuca cajupati Powell* or locally known as the "Gelam tree" [70].

Multifloral honey, or polyfloral honey, is produced from the pollen grains of multiple botanical species and has no predominant plant pollen [71]. For instance, Tualang honey is a multifloral jungle honey made by *Apis dorsata* bees that build their hives in the branches of Tualang (*Kompassia excelsa*) trees. This tree locally known as Mengaris or Tualang tree is found mostly in the tropical rain forests of Kedah in the northeastern region of Peninsular Malaysia [68]. Similarly, stingless bees honey is likely to be a multifloral honey type. Stingless bee honey is commonly known by different

names, including Meliponine honey, pot-honey, sugarbag honey (in Australia), and Kelulut honey (in Malaysia). Kelulut honey is made by *Trigona spp.* which has a little sour taste and is more liquid than other types of honey.

3.2 Physicochemical Composition of Honey

Honey is a complex substance consisting of more than 200 compounds, including a mixture of macronutrients (80% carbohydrates), sugars (i.e., fructose, glucose, and small concentrations of disaccharide and trisaccharide), water (17%) as well as small volumes of other micronutrients (3%) such as proteins, enzymes (i.e., invertase, glucose oxidase, diastase), minerals (i.e., calcium, copper, iron, magnesium, manganese, phosphorus, potassium, sodium, and zinc), vitamins (i.e., pyridoxine, thiamine, niacin, riboflavin, ascorbic acid, and pantothenic acid), flavonoids, phenolic acids, organic acids, and other phytoconstituents [72-74]. The composition of honey depends mainly on the sources of nectar, but other factors, such as botanical and geographical origins, seasonality, processing, and storage conditions, also play a role [75, 76]. The quality of honey is different between species of bees, therefore several parameters including moisture content, reducing sugars (i.e., fructose and glucose) and non-reducing sugars (i.e., sucrose and maltose) contents, pH, free acidity, water activity, electrical conductivity, diastase activity, and 5-hydroxymethylfurfural content have been specified as indicators to commercialize honey (See Table 1) [65, 77, 78].

Table 1 Physiochemical compositions standards of honey and stingless bee honey in Malaysia

Physiochemical Composition	Honey	Stingless Bee Honey
Sugar (i.e., Fructose + Glucose)	≥60 g/100 g	≥40 g/100 g
Moisture	≤20 g/100 g	≤35 g/100 g
Sucrose	<5 g/100 g	<7.5 g/100 g
Ash content	<0.5 g/100 g	<1.0 g/100 g
Free Acids	<50 mg/kg	≤50 mg/kg
Hydroxymethylfurfural (HMF) content	<40 mg/kg	<30 mg/kg
Nitrogen content	5-200 mg/kg	107-816 mg/kg
Diastase number (DN)	≥8 DN	≥5 DN
Electrical conductivity (EC)	0.8 mS/cm	0.1 mS/cm
pH	3.2-4.5	3.2-6.6

g, gram; mg, milligram, cm; centimeter.

In addition, it has been reported the antioxidant activity of stingless bee honey is significantly higher than raw honeybee honey and even higher than that of processed honeybee honey [79]. Interestingly, the color intensity of honey was strongly correlated with the total antioxidant found in the honey, in which darker-colored honey (i.e., Manuka honey) has higher antioxidant levels compared to lighter-colored honey [77, 78].

The main element of honey is sugar. Honeybees or stingless bees obtained sugar from the nectar sucrose and converted it through enzymatic reactions, involving α- and β-glucosidase, the α- and β-amylase and β-fructosidase to form a variety of sugars, such as glucose and fructose. Most

monosaccharides are carbohydrates found in honey (65% to 80% of total soluble solids), with the remaining 10-15% being disaccharides, and trace amounts of other forms of sugars. Moreover, fructose (about 40%) and glucose (about 35%) are the most abundant monosaccharides in honey. The ratio of fructose to glucose is typically 1.2:1, but varies greatly depending on the source of the nectar from which the honey was extracted. Since glucose is less soluble in water than fructose, this ratio is significant for assessing the crystallization of the honey, [80].

The sugar profile of honey has been analyzed extensively and numerous sugars have been identified, including fructose, glucose, sucrose, rhamnose, trehalose, nigerobiose, isomaltose, maltose, maltotetraose, maltotriose, maltulose, melezitose, melibiose, nigerose, palatinose, raffinose, erlose and others [80, 81]. Generally, stingless bee honey contains a higher fructose content than glucose, and honeybee honey contains a higher glucose content than fructose. As a result, the fructose/glucose (F/G) ratio in stingless bee honey is greater than that of honeybee honey. The honey will crystallize slower in honey with an F/G ratio higher than 1.3. Most stingless bee honey has an F/G ratio above 1.0. Besides, sucrose was undetected in stingless bee honey, whereas honeybee honey showed a high sucrose content (3.9 g/100 g of honey) [65].

The second most abundant element in honey is water which is significant because it affects the shelf life of honey. The water content in honey depends on the storage, harvesting and climatic conditions. High water content can impair the physical properties of honey such as crystallization and viscosity. High-water content facilitates yeast proliferation, which causes a fermentation process during harvesting and storage, thus lowering the quality of honey [66, 84]. The water content in the stingless bee honey is higher (31-42%) compared to other *Apis sp.* honeybees (20%) [82, 83].

Honey contains approximately 0.1 to 0.5% proteins, which originate from the bees and the plant nectars [67, 85, 86]. Most proteins in honey exist in the form of enzymes, primarily invertase (i.e., saccharase), diastase (i.e., amylase), and glucose oxidase. In addition to this, the presence of catalase and acid phosphatase depends on the type of floral nectar source. Most recently, proteolytic enzymes have been identified in honey [67]. In addition to enzymes, honey contains 18 amino acids, with proline accounting for 50 to 85% of the total amino acid profile.

Trace elements of the vitamin B complex include thiamine (B1), riboflavin (B2), nicotinic acid (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B8 or H) and folic acid (B9) as well as vitamin C (i.e., ascorbic acid) and vitamin E are found in honey [60, 70, 80]. These vitamins are thought to originate from suspended pollen grains and are highly maintained because of the low pH of honey [80]. In addition, it has been noted that various minerals (i.e., calcium, iron, zinc, potassium, chromium, phosphorous, magnesium, and manganese) are present in unprocessed honey [60, 87].

The mineral content in honey was reported to range from 0.04% in light honey to 0.2% in dark honey [87]. Potassium is the most prevalent mineral, accounting for one-third of all mineral content in honey [87]. Other minerals, such as sodium, iron, copper, silicone, manganese, calcium, and magnesium are present in lesser amounts in honey. These vitamins and minerals perform key functions in biological systems by maintaining normal body physiological responses, inducing the overall metabolism, influencing the circulatory system and reproduction, and acting as catalysts in a variety of biochemical reactions [87].

Nonetheless, the crucial functional composition of honey is the polyphenols, consisting of phenolic acids and flavonoids. These polyphenols contribute significantly to the total antioxidant activity of honey and therefore can effectively exhibit beneficial effects on human health [60]. When

honeybees or stingless bees collect plant nectar, these bioactive compounds can be transferred from plants to honey [88]. Phenolic acids profile in honey includes benzoic, caffeic, chlorogenic, coumaric, ellagic, ferulic, gallic, 3-hydroxybenzoic, rosmarinic, syringic, and vanillic acids. Flavonoids in honey include apigenin, chrysin, galangin, hesperetin, kaempferol, luteolin, myricetin, pinocembrin, and quercetin [68, 89, 90]. Table 2 summarized the phenolic compounds in different types of honey [7, 68, 91].

Table 2 Phenolic Compounds in Four Different Types of Honey.

Phenolic Acids		
2-Hydroxycinnamic acid	$C_9H_8O_3$	TH, KH
2-Methoxybenzoic acid	$C_8H_8O_3$	MH
(4-Methoxyphenyl)-acetic acid	$C_9H_{10}O_3$	MH
3-Phenyllactic acid	$C_9H_{10}O_3$	MH
3,5-Dimethoxybenzoic acid	$C_9H_{10}O_4$	MH
4-Methoxybenzoic acid	$C_8H_8O_3$	MH, KH
Abscisic acid	$C_{15}H_{20}O_4$	MH
Caffeic acid	$C_9H_8O_4$	TH, KH, GH
Chlorogenic acid	$C_{16}H_{18}O_9$	GH
Cinnamic acid	$C_9H_8O_2$	TH, KH
Dihydrocaffeic acid	$C_9H_{10}O_4$	KH
Ellagic acid	$C_{14}H_6O_8$	GH
Ferulic acid	$C_{10}H_{10}O_4$	GH
Gallic acid	$C_7H_6O_5$	TH, MH, KH, GH
p-Coumaric acid	$C_9H_8O_3$	TH, KH, GH
Salicylic acid	$C_7H_6O_3$	MH
Syringic acid	$C_9H_{10}O_5$	TH, KH
Benzoic acid	$C_7H_6O_2$	TH, MH
Trans-cinnamic acid	$C_9H_8O_2$	TH
Flavonoids		
Apigenin	$C_{15}H_{10}O_5$	TH, MH, KH
Catechin	$C_{15}H_{14}O_6$	TH, KH
Chrysin	$C_{15}H_{10}O_4$	TH, MH, KH, GH
Galangin	$C_{15}H_{10}O_5$	MH
Hesperetin	$C_{16}H_{14}O_6$	GH
Isorhamnetin	$C_{16}H_{12}O_7$	MH
Kaempferol	$C_{15}H_{10}O_6$	TH, KH, MH, GH
Luteolin	$C_{15}H_{10}O_6$	TH, MH, GH
Myricetin	$C_{15}H_{10}O_8$	GH
Pinobanksin	$C_{15}H_{12}O_5$	MH
Pinocembrin	$C_{15}H_{12}O_4$	MH
Pinostrobin chalcone	$C_{16}H_{14}O_4$	MH
Quercetin	$C_{15}H_{10}O_7$	TH, MH, KH, GH
Hyacinthin	C_8H_8O	TH

Naringenin	$C_{15}H_{15}O_5$	TH
Desoxyanisoin	$C_{16}H_{16}O_3$	MH

Manuka Honey (MH); Tualang Honey (TH); Kelulut Honey (KH); Gelam Honey (GH) [7, 68, 91].

4. Health Benefits and Mechanistic Profiles of Honey

Apitherapy, which consists of the words Api (from Apis, which is "bee" in Latin) and therapy, describes the practices of using bee products, such as honey, pollen, royal jelly, propolis and bee venom as therapeutic agents [92]. Honey has been used by humans since ancient times, with various ancient civilizations, namely Egypt, Assyrians, Greeks, Rome, China, India, Christianity and Islam, having a millennia-old history of using honey as apitherapy. Honey was formerly used as a carbohydrate source and sweetener but due to its therapeutic potential, it was found as folk medicine.

For the last few decades, preclinical investigations have been conducted to explore the therapeutic capacity of honey. Antimicrobial, antiseptic, and wound healing activities of honey are well documented in many literatures, in addition, it has antioxidant, anti-inflammatory, immune-boosting and antitumor agents potential [93, 94]. Physical and chemical properties of honey such as low water content, high acidity, high permeability and the existence of hydrogen peroxide may be responsible for the bactericidal property of honey, while the components of honey, such as simple sugars, vitamins, minerals, enzymes, and antioxidants (i.e., phenolic and flavonoids) render its nutritional benefits.

Despite its growing popularity as an alternative medicine, honey has not yet become a mainstream therapeutic agent. The use of honey for other illnesses has not found a place in modern medicine, except for several licensed and medically-certified honey for professional wound care in Australia and Europe [95]. The clinical use of honey is hampered by the lack of clinical trials as well as the standardized use of alternative medicine methods [96]. Although the therapeutic potential of honey has been well documented in preclinical studies, for honey to become a mainstream therapeutic agent in modern medicine, it must be evaluated in clinical trials.

4.1 Honey as Anti-Oxidative Stress Agent

As described in the previous section, when reactive species are produced in excess, they will express deleterious effects on crucial cellular structures such as lipids, proteins, and nucleic acids [97, 98]. For example, an excess of $^{\bullet}OH$ and $OONO^-$ can cause lipid peroxidation which is harmful to cell membranes and lipoproteins resulting in the formation of malondialdehyde and conjugated diene compound, which is a cytotoxic and mutagenic compound [97]. It is important to note that although the mitochondria have an intrinsic scavenging capability, they do not effectively remove reactive species [99, 100]. Hence, the cells neutralize these detrimental effects by utilizing the antioxidant defense system in the form of endogenous enzymatic components (i.e., superoxide dismutase, catalase, and glutathione peroxidase), and non-enzymatic components (i.e., glutathione, vitamins C and E as well as other small molecules) [99, 101]. In addition, accumulating evidence shows that oxidative stress can be responsible, to varying degrees, for the onset and/or development of several human diseases such as cancer, diabetes mellitus, metabolic disorders, atherosclerosis, cardiovascular diseases, arthritis and neurodegenerative disorders as well as the aging process [102].

In addition to these mentioned endogenous antioxidants, there are several exogenous antioxidant molecules of animal or vegetal origin, that can be consumed through diet or nutritional supplementation [68, 89, 90]. Honey has been identified as a natural exogenous antioxidant due to its rich content of polyphenols [68, 89]. Although the antioxidant capacity of honey is predominantly contributed by its content of phenolic acids and flavonoids, other compositions such as enzymes, organic acids, ascorbic acid, carotenoid-like substances, Maillard reaction products, amino acids, and proteins also play a significant role in this capacity [77]. And the antioxidant characteristics of these polyphenols have been demonstrated by their effectiveness in scavenging free radicals and/or in chelating metal ions and affecting cellular enzymatic and non-enzymatic antioxidant systems [103].

The antioxidant capacity of honey can be measured using some *in vitro* chemical assays such as free radical scavenging using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, oxygen radical absorbance capacity (ORAC) assay and ferric reducing antioxidant power (FRAP) assay, 2,20-azinobis-(3-ethylbenzothiazoline-6-sulphonate) radical ($ABTS^{\bullet-}$) scavenging assay, cupric ions (Cu^{2+}) reducing power assay (Cuprac), FolinCiocalteu reducing capacity (FCR assay), peroxyl radical scavenging, superoxide anion radical (O_2^-) scavenging, H_2O_2 scavenging, hydroxyl radical ($^{\bullet}OH$) scavenging, singlet oxygen ($^1O_2$) quenching assay and nitric oxide radical ($NO^{\bullet}$) scavenging assay [104]. With those assays, various types of honey have been reported to possess high antioxidant properties which provide the basis for pre-clinical and clinical studies. It is noteworthy that the total antioxidant activity shown was significant regardless of the botanical species and geographical regions of honey.

Several *in vitro* studies have demonstrated the antioxidative effects of honey against oxidative stress induced by various insults or injuries. For instance, Manuka honey improved oxidative stress status in a dose-dependent manner by attenuating the levels of lipid peroxidation, protein carbonyl content and DNA damage, together with by increasing the activities of antioxidants enzymes (glutathione, glutathione peroxidase, glutathione reductase, glutathione S-transferase, superoxide dismutase, and catalase) in lipopolysaccharides-induced macrophages cells [105]. In another study, Manuka honey protected human diploid fibroblast against oxidative damage by increasing the expression of antioxidant enzymes via activation of the adenosine monophosphate protein kinase/nuclear factor erythroid 2-related factor 2 (Nrf2)/ARE signaling pathway [103]. While, in the study by Ahmad and colleagues, Gelam honey modulated the expression of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) at gene and protein levels in gamma-irradiated human diploid fibroblast, indicating its potential as a radioprotective agent [68].

A recent study reported that Kelulut honey displayed a cytoprotective mechanism by reducing DNA damage and apoptosis protein expression (Caspase-3) in gamma-irradiated zebrafish embryos [106]. Furthermore, Zhu and colleagues demonstrated that treatment with Chinese honey resulted in a significant reduction in hydroxyl radical-mediated DNA damage in mouse lymphocytes, indicating that honey effectively protected DNA from oxidative stress in mouse lymphocytes [107]. Similarly, Tualang honey exerted its anti-oxidative protection by improving the migration of human corneal epithelial progenitor cells and cellular resistance to hydrogen peroxide-induced oxidative stress [108]. Meanwhile, a study conducted by Ali et al. (2019) found that bee honey protected cultured cortical astrocytes from hydrogen peroxide-induced death, probably through its direct free radical scavenging activity [109].

Furthermore, the anti-oxidative effect of honey and the underlying mechanisms involved, have been examined in many *in vivo* studies. For instance, pre-treatment with 1 g/kg of Tualang honey significantly attenuated the kainic acid-induced increase in thiobarbituric acid reactive substances level and decrease in total antioxidant status level in the cerebellum and brainstem of male rats, which could protect rat brain from the neurotoxicant-induced damage [110]. Similar results were obtained by Ruslee et al. (2020), who reported that Tualang honey (200 mg/kg) significantly decreased the formation of oxidative stress in ovarian cadmium-exposed rats by normalizing the levels of lipid peroxidation product (i.e., malondialdehyde) and enzymatic antioxidant (i.e., catalase) and caused a significant improvement in morphological changes of ovarian follicles [111].

Additionally, the pre-treatment with Tualang honey (0.2 g/kg body weight) significantly increased the antioxidant activities and alleviated oxidative stress by enhancing levels of total antioxidant capacity, superoxide dismutase, catalase, and glutathione peroxidase, and concomitantly decreased the malondialdehyde levels in hypoxia-induced male rats [112]. Other than the rodent model, the antioxidant effects of honey have been studied in an adult *Drosophila melanogaster* model. Cruz and colleagues demonstrated that honey reversed reactive oxygen species production and enhanced the antioxidant enzymatic activities in hypoxia-induced oxidative stress in *Drosophila melanogaster* [113]. In another study, Sani and colleagues provided evidence that the combination of Gelam honey and ginger showed an enhanced antioxidative effect, compared to Gelam honey or ginger alone, as evidenced by significantly decreased enzymatic activities of superoxide dismutase and catalase, the level of malondialdehyde as well as increased levels of glutathione and glutathione/glutathione disulfide ratio in streptozocin-induced diabetic rats [114]. Moreover, in a recent study, Kelulut honey treatment (200 mg/kg/day and 400 mg/kg/day) was reported to decrease malondialdehyde and increase superoxide dismutase levels in the femur of glucocorticoid-induced osteoporosis rats [115].

4.2 Anti-Inflammatory Properties of Honey

Honey is considered to be a modulator of the inflammatory agents with a dual role: (1) anti-inflammatory activities by down-regulating inflammatory transcription factors, such as NF-κB and mitogen-activated protein kinase (MAPK), and/or thereby reducing the production of pro-inflammatory cytokines (i.e., IL-1β and IL-6), TNF-α, and/or (2) stimulating the production of inflammatory mediators, such as prostaglandins, cyclooxygenase, NO and inducible NO synthase (iNOS) [74, 116, 117]. These anti-inflammatory effects of honey are due to its high content of polyphenols.

A previous study reported that supplementation with diluted bee honey was associated with a decrease in pro-inflammatory prostaglandins including prostaglandin E2, thromboxane B2, and prostaglandin F2 alpha (PGF2α) in the plasma of healthy individuals [118]. The topical application of honey was also found to reduce exudate and edema extension in wounds, which are associated with the action of local inflammatory processes [11]. In addition, the intranasal spraying of honey improved the immunoglobin E (IgE)-mediated inflammation of allergic rhinitis as assessed by using the total sinonasal outcome test 22 (SNOT 22) score and each symptom score of nasal blockages, rhinorrhoea, and sneezing together with the measurement of total serum IgE level at the end of 6-weeks of treatment. This study suggested that honey acted as a protective mucous layer in reducing the attachment of allergens to the nasal mucosa [119]. Furthermore, a randomized clinical trial in

chronic smokers showed the opposite effects of Tualang honey (20 g/day daily) supplementation for 12 on plasma levels of TNF-α and C-reactive proteins in chronic smokers, suggesting the inconclusive effect of honey on inflammation. Hence, further clinical studies are needed for other inflammatory markers or other study populations [120].

Numerous *in vitro* and *in vivo* studies have demonstrated that honey displays a broad anti-inflammatory spectrum. For example, Manuka honey (3 mg/mL and 8 mg/mL) attenuated the lipopolysaccharides-induced cell injury in murine RAW 264.7 macrophages. Manuka honey has been reported to inhibit nitrite accumulation by 50% and TNF-α, IL-1β, IL-6 expression and iNOS activity by 60%, 80%, 50% and 65%, respectively [105]. Biluca and colleagues utilized a similar model, but they examined the anti-inflammatory effect of eight different stingless bee honey samples. The results showed that these stingless bee honey samples with concentrations of 1-100 μM significantly reduced NO and the pro-inflammatory cytokines such as TNF-α, IL-6, monocyte chemoattractant protein 1, IL-12p70, INF-γ and IL-10 levels, while two honey samples increased the levels of IL-10, an anti-inflammatory cytokine in inflammatory macrophages [121].

In carrageenan-induced acute paw oedema rats, Gelam honey was shown to decrease inflammatory mediators such as NO, prostaglandin E2, cyclooxygenase-2, TNF-α and IL-6 via attenuating the translocation of NF-κB to the nucleus and thus inhibiting the activation of the NF-κB pathway, which plays a key role for inflammation pathogenesis [122]. Consistent with this study, a pre-treatment of Gelam honey (20, 40, 60, and 80 μg/mL) also reduced the expression of phosphorylated c-Jun N terminal Kinase (JNK), an inhibitor of NF-κB kinase subunit beta (IKK-β), and insulin receptor substrate (IRS-1), which then significantly reduced the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β in oxidative stress-induced pancreatic hamster HIT-T15 cells [123]. Moreover, there was a significant increase in the phosphorylated Akt (i.e., the cellular homolog of murine thymoma virus akt8 oncogene), showing the protective effects of honey against inflammation and insulin resistance [123]. In another study, the results of Ranneh and colleagues showed that Kelulut honey (4.6 and 9.3 g/kg/day) protected rats from lipopolysaccharides-induced chronic subclinical systemic inflammation. It is noteworthy that the effect was related to the inhibition of inflammatory markers such as TNF-α, IL-1β and IL-6 through NF-κB, p38 MAPK, and Nrf2 signaling pathways [124].

Furthermore, Tualang honey (1.0 g/kg body weight) was found to reduce neuroinflammation in kainic acid-induced status epilepticus rats. It has been proposed that this neuroprotective effect of honey was mediated by reducing the elevation of TNF-α, IL-1β, glial fibrillary acidic protein, allograft inflammatory factor 1 and cyclooxygenase-2 as well as suppressing activation of caspase-3 activity in the rat cerebral cortex, cerebrum, and brainstem [125]. Taken together, all this evidence suggests that bee honey, regardless of its type and origin, exhibits great anti-inflammatory and immunomodulation properties which may be adopted in human studies and beneficial to human health. Table 3 summarized the list of pre-clinical and clinical studies on various diseases and the effects of interventions with different types of honey.

Table 3 Pre-clinical and clinical studies on various cardio-cerebrovascular diseases and beneficial effects of honey.

Disease/Experimental model	Model	Type of Honey	Human/Animal /Cells	Findings when intervened with honey	Ref
Kainic acid-induced status epilepticus	*In vivo*	Tualang	Male Sprague-Dawley rat	• Reduced pro-inflammatory factors such as TNF-α, IL-1β, Glial fibrillary acidic protein, Allograft inflammatory factor-1, and cyclooxygenase-2 levels in the brain • Attenuated the increment of caspase-3 in the cerebral cortex	[125]
Anxiety and reduced memory in metabolic disease-induced rats with high fructose diet	*In vivo*	Kelulut	Male Wistar rats	• Reduced anxiety, retain memory function • Normalize blood glucose • Reduced serum triglyceride and low-density lipoprotein levels	[126]
Head and neck cancer patients receiving radiotherapy	*In vivo*	Not stated	Head and neck cancer patients	• Improve the quality of life	[127]
Subarachnoid haemorrhage model constructed in rat femoral arteries	*In vivo*	Manuka	Female Wistar Albino rats	• Decrease vasospasm • Prevention of stenotic lumens and thickened vascular walls	[128]
Spatial memory	*In vivo*	Stingless bee honey	Female Swiss Albino mice	• Improve spatial working memory following Morris's water maze task • Upregulation of BDNF and ITPR1 genes	[129]
chronic cerebral hypoperfusion-induced neurodegeneration by permanent BCCA ligation	*In vivo*	Tualang	Male Sprague-Dawley rat	• Better spatial learning and memory performance in Morris's water maze task	[130]

Alzheimer's disease due to high acetylcholinesterase	*In vivo*	Acacia honey	Male Wistar Albino rats	• Reduced acetylcholinesterase activity in the serum	[131]
Isoproterenol-induced myocardial infarction	*In vivo*	Tualang	Male Wistar Albino rats	• Reduced serum cardiac marker enzyme activities (i.e., CK-MB, Aspartate transaminase, and Lactate Dehydrogenase) • Reduced serum total cholesterol and triglycerides levels, malondialdehyde, and antioxidative enzymes activities (i.e., glutathione peroxidase, glutathione reductase, glutathione S-transferase) in the heart • The reduced degree of infiltration of inflammatory cells into cardiac tissues, well-preserved cardiac muscle fiber morphology	[132]
Determination of biochemical parameters following daily consumption	*In vivo*	Acacia honey	Male Wistar Albino rats	• Improved body weight • Reduced creatinine, alanine transaminase, alkaline phosphatase, triglyceride, and very-low-density lipoprotein level	[133]
Aluminium chloride-induced neurotoxicity (Alzheimer's model)	*In vivo*	Thyme honey	Male Wistar rats	• Improved memory • Increased total antioxidant capacity in brains • Reduced malondialdehyde level • Preserves hippocampal neuronal density • Prevents neurons degradation, apoptosis, and necrosis	[134]
Lipopolysaccharide-induced inflammatory in macrophage cell lines; and *Ex vivo* batch gut model	*In vitro* and *ex vivo*	Sardinian honey, Eucalyptus honey, Red Gum honey, and White Gum honey	RAW 264.7 cells	• Suppresses the production of pro-inflammatory markers (i.e., NO, IL-1β and IL-6) in RAW 264.7 cells • Increase beneficial lactobacilli and reduced harmful Gram-negative enteric bacteria in microcosm tube	[135]

High-fat diet	*In vivo*	Acacia honey	Male Wistar rats	• Reduced body weight-gain • Reduced serum triacylglycerol, total cholesterol, low-density lipoprotein, very-low-density lipoprotein levels, Increased high-density lipoprotein • Improves cellular architecture of liver tissue	[136]
Obesity	*In vivo*	Propolis and honey trigona	Obese patients	• Reduced leptin level	[137]
Wound healing of uncontrolled type-2 diabetes mellitus	*In vivo*	Indonesian Randu honey	Type-2 diabetes mellitus	• Honey wound dressing fully closes the wound and the patient could walk with a stick	[138]
Alloxan-induced type-2 diabetes mellitus	*In vivo*	Omani Mountain honey	Male and Female mice	• Reduced blood glucose levels • Reduced wound size	[139]

BCCA, bilateral common carotid artery; BDNF, brain-derived neurotrophic factor; CK-MB, creatine kinase MB; IL-1β, Interleukin-1 beta; ITPR-1, Inositol 1,4,5-trisphosphate receptor type 1; TNF-α, tumor necrosis factor-alpha.

5. Potential of Honey as Preventive and Therapeutics Measures for CSVD

As aforementioned, CSVD represents a clinically significant precursor for major cardio-cerebrovascular diseases such as hypertension, thrombosis, atherosclerosis, myocardial infarction, cardiomyopathy, cardiac hypertrophy, cardiac failure, stroke, and cerebral ischemia, manifestations of which remain the leading causes of morbidity and mortality in the world today [140]. The diseases constitute a serious challenge to modern medicine since the pathological mechanism of CSVD is dynamic and remains unclear. Although great progress has been made over the past 20 years, to date, there are still no effective prevention and treatment strategies to reduce this epidemic of CSVD [141]. Therefore, it is critical to identify alternative and complementary strategies in the prevention and/or treatment of CSVD and cardio-cerebrovascular disease in general.

5.1 Pre-clinical Evidence on Anti-atherogenic Effects of Honey

Athero-, arterio-, and arteriolosclerosis are the major consequences of CSVD, and cardio-cerebrovascular disease and numerous studies have been attempted to explore the underlying mechanism for the antiatherogenic effects of honey in various atherosclerotic animal models. A high fructose diet was associated with an increased risk of cardiovascular diseases. In the study by Busserolles et al. (2002), France honey-fed rats had a significantly lower triglyceride level in comparison to fructose-fed rats. Honey also inhibited lipid peroxidation in the heart tissue of these honey-fed rats [142]. In contrast, plasma high-density lipoprotein-C was significantly increased in rats fed honey for a long period (52 weeks) compared to the sugar-free- and sucrose-fed rats [143].

It is widely known that with the obesity epidemic, type-2 diabetes mellitus has become very common which is a prime risk factor for CSVD and cardio-cerebrovascular diseases [144, 145]. In alloxan-induced type-2 diabetic rats, Nigerian honey administration (1 g/kg, 2 g/kg, 3 g/kg, daily for 21 days) was shown to significantly increase the plasma high-density lipoprotein-cholesterol levels while decreasing plasma triglyceride, very low-density lipoprotein cholesterol, and non-HDL cholesterol levels. Furthermore, the effect of Nigerian honey on lipid ratios such as low-density lipoprotein/high-density lipoprotein cholesterol, total cholesterol/high-density lipoprotein cholesterol and triglycerides/high-density lipoprotein cholesterol (a strong predictor of cardiovascular disease risk) in diabetic rats was evaluated. The results showed that honey supplemented (especially 1 g/kg/day and 2 g/kg/day) did not significantly reduce the atherogenic index (low-density lipoprotein/high-density lipoprotein cholesterol) while there was a significant reduction of coronary risk index (total cholesterol/high-density lipoprotein) and cardiovascular risk index (triglycerides/high-density lipoprotein) in diabetic rats [146]. The same research group also demonstrated the pre-treatment effect of Nigerian honey administration on the post-prandial lipid metabolism in high-fat diet rats. The results revealed a significant increase in the hepatic high-density lipoprotein-cholesterol, together with a marked reduction in the hepatic low-density lipoprotein-cholesterol in rats pre-treated with honey (1 g/kg) 60 minutes before high-fat diet feeding [147]. This effect seems to be partly attributed to the inhibition of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase, which plays a crucial role in the biosynthesis pathway of cholesterol [147].

These findings are consistent with Malaysian honey studies. The administration of Gelam and Acacia honey to high-fat diet-induced obese rats for 4 weeks promoted a significant decrease in plasma total cholesterol and triglyceride levels compared to the control group [148]. Similarly,

streptozotocin-induced diabetic rats treated with stingless bee honey (2 g/kg for 28 days) showed lower plasma total cholesterol, triglycerides and low-density lipoprotein-cholesterol levels and higher plasma high-density lipoprotein-cholesterol levels compared to non-diabetic rats [149]. In another study, serum total cholesterol and triglyceride levels were decreased in rats with isoproterenol-induced myocardial infarction after oral pre-administration of Tualang honey (4 g/kg) for 45 days compared to non-disease rats [132]. This finding implies that honey improves cardiac function by inhibiting oxidative stress, as determined by the content of thiobarbituric acid reactive substances and the activities of endogenous antioxidant enzymes in the rat myocardium.

Furthermore, Turkey-originated honey, mad honey contains the toxic compound grayanotoxin which can be poisonous to human and animal health [150-152]. In 2005, an *in vivo* study indicated that mad honey (50 mg/kg) showed a beneficial effect by decreasing the hepatic content of cholesterol, triglycerides and very-low-density lipoprotein in streptozotocin-induced diabetic rats [152]. However, Cakmak-Arslan and colleagues reported that a similar dose of mad honey administration resulted in a significant toxic effect on mouse cardiac muscle tissue lipids as analyzed by attenuated total reflection Fourier transform infrared spectroscopy [150]. Taken together, using the correct types of honey in the right amount/dosage may help attenuate the risk of CSVD-mediated athero-, arterio-, and/or arteriolosclerosis developing.

5.2 Clinical Studies on Anti-atherogenic and Cardio-Cerebral-Protective Effects of Honey

In a human clinical study, Al-Waili and colleagues investigated the cardioprotective effect of natural unprocessed honey consumption on a few cardiovascular risk indicators such as C-reactive proteins, homocysteine, and hyperlipidaemia in healthy, hypertriglyceridemia and type-2 diabetes mellitus subjects. This series of clinical experiments showed that after 15 days, honey consumption decreased the levels of the systemic risk factors for CSVD and cardio-cerebrovascular diseases, such as plasma glucose, insulin, C-reactive proteins, homocysteine, and lipid profile consisting of total cholesterol, triglycerides, low-density lipoprotein cholesterol, while increased the level of high-density lipoprotein cholesterol in the subjects. However, the effect of natural honey was more pronounced in subjects with abnormal parameters [153].

The findings were further supported by a randomized controlled trial study in 2008 in which Yaghoobi and colleagues demonstrated that daily consumption of 70 g of Iranian natural honey for one month caused a reduction in body weight and body fat, lowered fasting blood glucose and C-reactive proteins levels, and improved lipid profile among overweight individuals [154]. In another recent double-blinded randomized controlled trial study, 60 young healthy Iranian students were divided into an experimental group (orally given 70 g of natural honey in 250 ml water) and a control group (orally given 70 g of sucrose in 250 ml water). After 6 weeks, the result revealed that plasma levels of total cholesterol, triglycerides and low-density lipoprotein-cholesterol decreased and low-density lipoprotein-cholesterol increased in these honey-supplemented groups compared to the control group [155]. Moreover, it was noted that honey caused a significant reduction in fasting blood glucose but had no impact on the blood pressure of these students.

In contrast, healthy post-menopausal women supplemented with Tualang honey and its mixture with other bee products (95% honey, 4% bee bread, 1% royal jelly) for 12 months resulted in a significant decrease in diastolic blood pressure. It is noteworthy that Tualang honey showed a superior reduction effect in a magnitude comparable to its mixture [156]. Abdulrhman and

colleagues (2018) in their study of the effect of Yaman honey on the echocardiographic parameters of children with idiopathic dilated cardiomyopathy found that a period of 12 weeks of honey consumption significantly improved the ejection fraction and fractioning shortening outcomes in these pediatric patients with idiopathic dilated cardiomyopathy [157]. Therefore, the above evidence suggests that honey supplementations may help prevent the onset and progression of CSVD and cardio-cerebrovascular disease risk factors.

5.3 Pre-clinical Evidence on Anti-hypertensive Effects of Honey

Hypertension is a recognized risk factor for CSVD (i.e., arteriolo, arterio, and/or atherosclerosis) [158, 159]. The anti-hypertensive effects of honey have been demonstrated in a few animal models, mainly contributed by its antioxidant and anti-inflammatory activities. For instance, a Malaysian Tualang honey supplementation (1 g/kg/day) for 3 weeks reduced systolic blood pressure in streptozotocin-induced diabetic spontaneously hypertensive rats, but not in streptozotocin-induced diabetic Wistar-Kyoto rats [160]. To evaluate the possible mechanism of its hypotensive or anti-hypertensive effect, oral administration of Tualang honey (1 g/kg per day) to non-diabetic spontaneously hypertensive rats and Wistar-Kyoto rats [161] for 12 weeks revealed that systolic blood pressure and malondialdehyde level was reduced by attenuating oxidative damage in the kidney of spontaneously hypertensive rats.

Mechanistically, honey supplementation caused an insignificantly upregulate in Nrf2 mRNA expression, a reno-protective transcription factor together with a significant increase in activities of antioxidant enzymes such as glutathione-S-transferase and catalase as well as a reduction in lipid oxidative damage in the kidney, leading to ameliorated hypertension in this model [161]. Recent *in vivo* and *in vitro* analyses conducted by Devasvaran and colleagues showed that Tualang honey inhibited H_2O_2-induced vascular hyperpermeability in human umbilical vein endothelial cells and Balb/c mice. As emphasized by the authors, the mechanism of honey treatment may be due to the suppression of adherence junction protein redistribution via calcium and cyclic adenosine monophosphate [162].

In another study, pre-treatment with Egyptian natural wild honey at a dose of 5 g/kg for one hour significantly decreased venous blood pressure in adrenaline-induced cardiac injury and vasomotor dysfunction rats [163]. The positive effect is thought to be mediated via the vasodilator NO release through the influence of ascorbic acid found in this honey, thus leading to vasodilatation [163]. Besides modulating hypertension, a previous *in vitro* study showed the inhibitory effect of natural honey on platelet aggregation and blood coagulation [151]. Whereby, increased platelet aggregation and hypercoagulation have been proposed as an emerging molecular mechanism of CSVD [43, 114]. Interestingly, in a recent *in vivo* study, honey has been found to exhibit an anti-platelet effect by increasing bleeding time when a group of mice was given commercial honey for 12 days as compared to that aspirin [164]. These findings indicate the possible role of honey in hemostasis which could benefit cardio-cerebrovascular health in both healthy and diseased individuals through its capacity to control blood pressure and modulate hypertension.

5.4 Pre-clinical Studies of Honey on Myocardial and Cerebral Infarction

Coronary heart disease affects the heart due to the detrimental effects of acute myocardial infarction and ischemia-reperfusion injury [165]. *In vitro* and *in vivo* studies have been conducted

to understand the cardioprotective effects of honey in myocardial infarction. Isoproterenol is a synthetic catecholamine and β-adrenergic agonist that can produce severe oxidative damage to the myocardium when administered in large doses, leading to myocardial infarction [77]. In the isoproterenol-induced myocardial infarction rat model, oral pre-administration of Tualang honey (4 g/kg) for 45 days suppressed activities of cardiac troponin I and cardiac marker enzymes including creatine kinase-MB, lactate dehydrogenase, and aspartate transaminase. Furthermore, Tualang honey enhanced the histopathological result through the inhibition of lipid peroxidation and recovery of antioxidant enzyme activities in the myocardium of isoproterenol-induced myocardial infarction rats [132]. Likewise, Sundarban honey, native to Bangladesh, had the same beneficial effect on isoproterenol-induced myocardial infarction rats [166].

This finding supported a series of previous studies in *ex vivo* models of ischemic-reperfusion injury in isolated rat hearts. Whereby, it was reported that the administration of Iranian honey significantly decreased the extension of myocardial infarction areas and improved arrhythmias in comparison to the non-honey groups [167-171]. These cardioprotective effects of honey against myocardial infarction may be associated with its rich carbohydrate sources (i.e., fructose and glucose) and many micronutrient elements, including polyphenols and flavonoids, which act as antioxidants in honey composition [167].

Cerebral ischemia, often referred to as cerebral ischemic stroke or CSVD-induced cerebrovascular ischemia, the brain receives insufficient blood flow (i.e., reduced cerebral blood flow), and thus insufficient oxygen and glucose, resulting in loss of function and cell death. There are very limited studies investigating the neuroprotective effects of honey on cerebral ischemia, especially CSVD-related. Nonetheless, previous studies showed that honey prevented neuronal cell death in the hippocampal CA1 region of gerbils induced by transient cerebral ischemia [172]. However, it is very difficult to demonstrate the neuroprotective effects of honey, since this study only included honey as one of the six ingredients in Kyuang-OK-KO (KOK), a traditional oriental medicine used to improve blood circulation and age-related symptoms, including dementia and stroke [173]. Additionally, in a chronic cerebral hypoperfusion model induced by permanent bilateral common arteries ligation, Tualang honey significantly delayed neuronal cell damage and attenuated neuronal cell loss in the ischemic hippocampal CA1 region of rats. Interestingly, honey protected against ischemic-induced spatial learning and memory impairments [130, 174].

5.5 Related Studies of Honey on Stroke and its Subtype

To date, tissue plasminogen activator is the only Food and Drug Administration (FDA)-approved treatment for ischemic stroke, however, there are limited to no clinical data on this hyperacute treatment for CSVD. Though this treatment is most effective within a short therapeutic time window of 4.5 hours, there is a known risk of hemorrhagic transformation associated with cerebral ischemia-reperfusion injury [175]. It is well known that oxidative stress and inflammation play a crucial role in the pathophysiological mechanisms of CSVD and ischemic stroke [176]. Recently, there has been a growing interest in using natural products to treat ischemic stroke because of their various benefits, including antioxidative, anti-inflammatory and anti-apoptotic properties [177]. At the mechanistic level, honey and its polyphenols have been shown to activate transcription factors involved in antioxidant-responsive element pathways, such as Nrf2, thus promoting the expression of antioxidant enzymes including superoxide dismutase, catalase, glutathione peroxidase and heme

oxygenase-1 [103]. In the terms of inflammation, honey and its polyphenols have the potential to modulate NF-κB signaling pathway, thus suppressing the production of pro-inflammatory cytokines and mediators such as TNF-α, IL-1β and IL-6 as well as cyclooxygenase-2 and NO [124].

Notably, an *in vivo* study has shown a possible protective effect of honey on brain ischemic-induced injury [174]. In this study, permanent bilateral common arteries ligation (two vessels occlusion) was performed to induce chronic cerebral hypoperfusion in rats. The CA1 stratum pyramidal in the hippocampus of two vessels occlusion displayed the loose cellular arrangement with irregular, dark, shrunken cytoplasm with pyknotic nucleus (non-viable neurons), however, the supplementation of Tualang honey to these rats preserved the compact structure of CA1 stratum pyramidal and prevented neuronal cell loss with less pyknotic nuclei, which showed less neuronal cell damage in the hippocampus than the untreated group [174]. The hippocampus plays an important role in memory and learning and is extremely vulnerable to ischemia. Another study found that the two-vessel occlusion rats developed cognitive impairment, probably due to oxidative stress caused by chronic cerebral hypoperfusion [130]. While the supplementation with Tualang honey had improved spatial learning and memory performance as assessed by Morris's water maze task in the honey-treated two-vessel occlusion group [130]. This is an important observation as chronic cerebral hypoperfusion may contribute to the development of post-stroke dementia, though the underlying mechanism is still under active investigation [178].

Recent review perspectives revealed the potential supplementary therapy of Trigona honey for post-stroke survivors in preventing the progression of vascular cognitive impairment to dementia [179]. Mechanistically, the authors emphasized the possibility of an association between inflammatory biomarkers and CSVD manifestation (i.e., WMHs), which are involved in cognitive impairment and dementia [180, 181]. To the best of our knowledge, there is still no human intervention research or clinical trials involving honey in patients with CSVD and ischemic stroke. Since the data on the neuroprotective properties of honey are quite limited, special attention should be given to elucidating the precise role of honey in the preclinical models of CSVD and ischemic stroke. Therefore, in order to effectively conduct long-term, large-scale, and well-designed clinical trials, it will be important to further characterize honey molecular targets with potential activity in the onset and progression of CSVD and ischemic stroke.

5.6 Neuroprotective Potentials of Honey for CSVD

As described in the previous section, healthy and asymptomatic individuals with evidence of CSVD and without prior treatment may progressively develop severe cardio-cerebrovascular disease and lead to neurocognitive dysfunction i.e., memory loss and mild cognitive impairment. It has been proposed that honey may have potential moderating effects. For example, in one of the earliest randomized controlled trial studies on honey consumption, a total of 2290 cognitively intact subjects and 603 mildly cognitively impaired individuals aged 65 years and older were randomly assigned into two groups supplemented with one tablespoon of Middle East honey or placebo daily for 5 years. Of 489 subjects with dementia, only 20% were honey-supplemented, suggesting the neuroprotective effects of honey in preventing cognitive decline and development of dementia [182]. A similar result was found in a recent study, when the supplementation of one teaspoon of Astragalus honey with two capsules combined of sedge and saffron for 3 months influenced the

improvement of cognition and depression scores in patients with major neurocognitive disorder [183].

Despite that, these findings were consistent with *in vivo* studies done by Chepulis et al. (2009) [184] and Akanmu et al. (2011) [185]. The study of Chepulis et al. showed that, over a 12-month period, the middle-aged honey-fed (beech forest honeydew honey) rats had a better spatial memory with lesser anxiety compared to the sucrose or sugar-free diet-fed group [184]. While in the latter study by Akanmu and colleagues, the mice model was used to examine Nigerian honey and its neuropharmacological effects on (1) anxiolytic activities – through hole-board and elevated plus maze tests; (2) antidepressant effects - through forced swimming test; (3) spatial working memory – through Y-maze test and pentobarbital-induced hypnosis and assessment; (4) antinociceptive activity – through hot-plate and tail-flick tests; (5) anticonvulsant activity – through the use of picrotoxin seizure model. In this study, Nigerian honey appeared to improve spatial working memory, with anti-nociceptive, anti-convulsant, anti-depressant and anxiolytic effects [185], which are associated with the establishment of honey as a nootropic agent in improving memory and growth at earlier stages of human life. This also may become evidence that honey can prevent and protect the cerebral vasculature hence preventing the onset and/or progression of CSVD.

Tualang honey has now been extensively studied in pre-clinical and clinical research to evaluate its neuroprotective potential in Malaysia. In a randomized controlled trial study, Tualang honey was supplemented randomly to 102 healthy post-menopausal women for 16 weeks and was shown to improve immediate memory, but no such effect was observed in post-interference and delayed recall. Interestingly, this memory improvement was comparable to the group that received estrogen plus progestin therapy [186]. A recent study also concluded that estrogen-based post-menopausal hormone therapy is successful in relieving menopausal symptoms and reducing the chance of CSVD [187]. Furthermore, Tualang honey was found to significantly decrease the plasma level of lipid peroxidation marker (4-hydroxynonenal) and to boost the activities of plasma glutathione peroxidase and catalase in post-menopausal women supplemented with honey [188]. These findings were further confirmed by several *in vivo* studies, in stress-induced ovariectomized rats, where Tualang honey-fed rats showed neuronal proliferation in the hippocampal CA2, CA3 and dentate gyrus compared to the untreated group, demonstrating that Tualang honey improved both the short- and long-term memory [189]. Moreover, Tualang honey was shown to significantly decrease stress-induced anxiety-like behavior in ovariectomized rats, and in fact, their oxidative stress status was dramatically improved [190]. In a similar study, Tualang honey was found to exhibit anti-depressive-like effects in stress-induced ovariectomized rats, which was thought to be caused by the restoration of the hypothalamic-pituitary-adrenal axis and the increased concentration of brain-derived neurotrophic factor [189]. Hence, these studies advocate the supplementation of Tualang honey for its estrogen-like profile since its flavonoid content activates the estrogen receptor-mediated cell survival signaling pathways.

Of note, longitudinal data revealed that CSVD leads to stress and depressive symptoms via disruption of cerebral vasculature involved in emotion regulation in the elderly population [191]. In this case, Tualang honey also displayed an improved memory deterioration effect in aged-male rats exposed to noise stress, which may be associated with an increase in neuronal proliferation in the medial prefrontal cortex and hippocampus, possibly via reducing brain oxidative stress and/or elevating brain-derived neurotrophic factor concentration and cholinergic system [192, 193]. These

studies suggest that honey could be used as an alternative therapy for those suffering from memory loss due to oxidative stress exposure and/or aging.

Meanwhile, a similar observation was made in stress-induced memory deficit young-aged rats, where Tualang honey (200 mg/kg) supplementation was effective in attenuating depressive-like behavior and memory decline due to its antioxidant properties [194]. Furthermore, Tualang honey affected the spatial memory performance in healthy adult male rats by increasing hippocampal pyramidal neuronal cells [195]. Indeed, Azman and colleagues reported that the neuroprotective effects of Tualang honey were stronger in younger rats than in older rats, suggesting that the antioxidant defense mechanism is weakened with aging and therefore older rats may require a longer time or greater dose of honey supplementation [193]. A recent study demonstrated that Tualang honey supplementation to pregnant rats exposed to stress had improved the memory function of their offspring by increasing neurogenesis and decreasing malondialdehyde and N-methyl-D-aspartate receptor levels [196].

Furthermore, honey also protected neurons from excitotoxicity. A study on kainic acid-induced excitotoxicity in rats revealed that the neuronal loss was significantly reduced in the group pre-treated with Tualang honey, although it failed to avert kainic acid-induced seizures [110]. In addition, Tualang honey significantly reduced oxidative stress, neuroinflammation and apoptosis in numerous brain regions including the cerebral cortex, cerebellum, and brain stem in kainic acid-induced seizure rats [110, 125]. In another study, honey exhibited neuroprotective effects against the lead-induced cognitive deficit via boosting antioxidant activities, as shown by an increase in brain superoxide dismutase, glutathione S-transferease, and glutathione activities [197]. In addition, honey effectively reduced streptozotocin-induced neuronal apoptosis in the hippocampus of diabetic rats [198]. Thus, the antioxidant, anti-inflammatory and/or antiapoptotic activities of honey might protect the brain against excitotoxicity that may lead to neuronal loss and neurodegeneration.

Given its potential as a neuroprotective food supplementation, the capacity to inhibit acetylcholinesterase and butyrylcholinesterase activities has also been examined in the cell-free biochemical assay. According to Baranowska et al. (2020) [199], Polish buckwheat honey had the highest inhibitory capacity for acetylcholinesterase (39.51% inhibition), while Polish multi-floral honey had the highest inhibitory capacity for butyrylcholinesterase (39.8% inhibition). Because acetylcholinesterase is an important enzyme involved in the pathology of neurodegenerative diseases, the supplementation of honey is suggested to increase acetylcholine levels in the brain by inhibiting acetylcholinesterase. Subsequent investigations are required to confirm the activities of acetylcholinesterase and butyrylcholinesterase in all *in vitro*, *in vivo* and *ex vivo* models. Furthermore, Italian honey was reported to decrease the production of pro-inflammatory cytokines (TNF-α and IL-1β) in lipopolysaccharides-stimulated N13 microglial cells, implying the role of neuron-glial interaction in the pathology of neurodegenerative diseases, particularly neuroinflammation [200]. Collectively, honey and its compounds offer many potential bioactive therapeutic agents that can be extended for the prevention and/or treatment of CSVD by modulating its onset and progression in at-risk, targeted populations (see Figure 2).

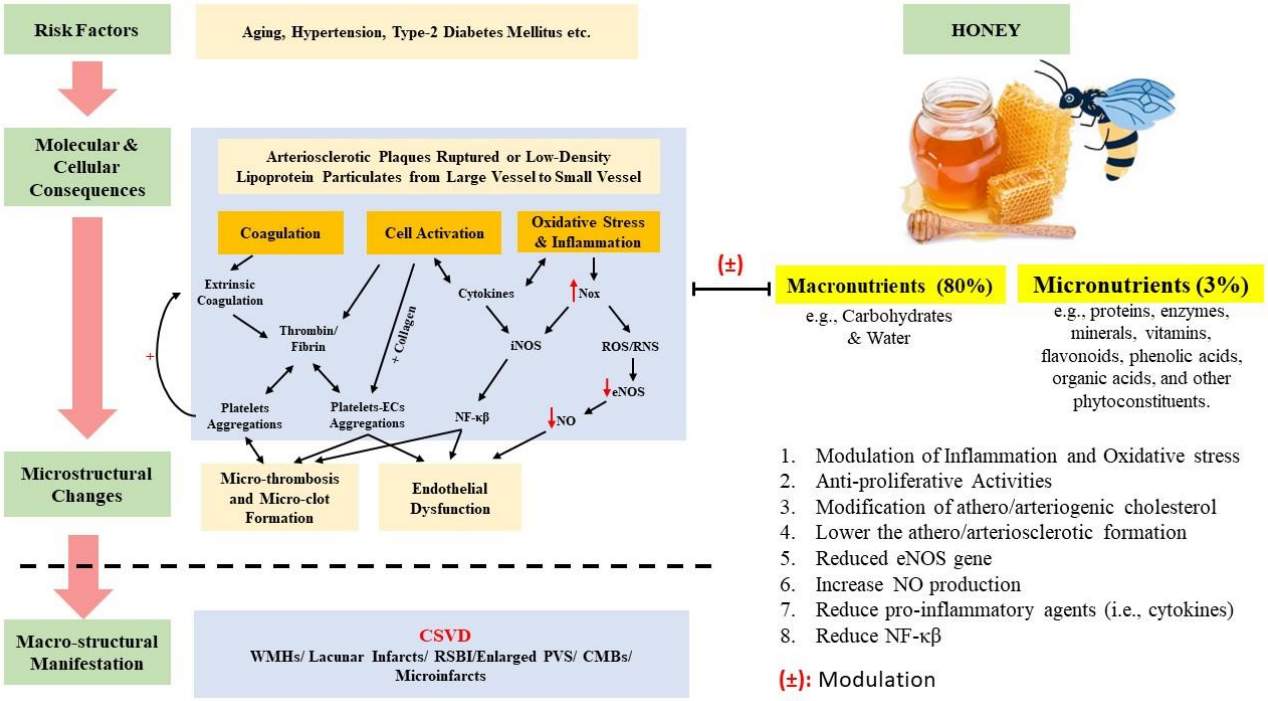

Figure 2 Neuroprotective potentials of honey for cerebral small vessel disease (CSVD). Honey and its compound may modulate the molecular and cellular consequences following cardio-cerebrovascular disease risks such as hypertension and type-2 diabetes mellitus. Micronutrients in honey, such as phenolic compounds, flavonoids and organic acids potentially modulate the inflammatory factors and oxidative stress mediators (i.e., ROS and RNS). ROS, reactive oxygen species; RNS, reactive nitrogen species; CMBs, cerebral microbleed; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; MMP, matrix NO, nitric oxide; NF-κB nuclear factor κB; RSBI, recent subcortical brain infarcts; PVS, perivascular spaces; WMHs, white matter hyperintensities.

6. Conclusion

In this review, we highlighted the neuroprotective potentials of honey as a complementary therapy and dietary supplementation, specifically for CSVD. These seemingly beneficial properties of honey provide an evidence-based basis for pharmacological drugs that mitigate oxidative stress, inhibit neuroinflammation, and attenuate apoptosis to influence the natural history of CSVD heterogeneous manifestations. A wealth of evidence from pre-clinical and human studies revealed that the honey products being tested vary widely, and that the dosage and duration required for most honey to produce health-related benefits are large. Despite inconsistent data, in the context of CVSD and considering the existing daily sugar intake recommendation, at least in adults, we advocate a routine daily intake of one to two tablespoons of unprocessed honey (12 to 24 g sugar; serving 3% of required daily energy) would be an optimal dose to consider, adjusted to gender and any pre-morbid conditions (such as obesity and diabetes mellitus). Further translational and clinical research can consider the putative mechanisms of action discussed here to demonstrate its possible beneficial effects as part of preventive and/or therapeutic strategies for CSVD and other cardio-cerebrovascular diseases. It is hoped that this approach could complement existing evidence-based

cardio-cerebrovascular disease care and contribute to halting the onset and progression of CSVD manifestation, a recognized aging-related pandemic.

Author Contributions

Muzaimi Mustapha, Hafizah Abdul Hamid and Che Mohd Nasril Che Mohd Nassir are responsible for the conceptualization, resources, and writing the original draft. All authors are responsible in review and editing the manuscript. All authors have read and agreed to the published version of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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