Trigona Honey as a Potential Supplementary Therapy to Halt the Progression of Post-Stroke Vascular Cognitive Impairment

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ABSTRACT

Background: **Vascular cognitive impairment (VCI) is a syndrome that includes all neurological disorders from mild cognitive impairment to dementia caused primarily by cerebrovascular disease. The prevalence of post-stroke VCI reported between 36 to 67 % of survivors.**

Objective: **This perspective review is to predict the potential effect of *Trigona* honey in halting the progression of VCI.**

Method: **Based on its rich content of phenolic compounds, Trigona honey could assist in regulation of oxidative stress, which attenuated free radical-mediated molecular destruction. This mechanism could prevent neuroinflammation and promote memory, learning, cognitive functions and protect against neurotoxin-induced neuronal injury. Besides, this antioxidant activity of *Trigona* honey could results in rapid decline in the levels of inflammatory biomarkers, and thus maintains healthier white matter microstructure in brain.**

Conclusion: **Therefore, the use of *Trigona* honey to enhance cognitive performance would be an interesting target for the future studies. The biochemical impact of *Trigona* honey makes it a potential complementary remedy to decrease the neuroinflammation and prevent the rapid progression of post-stroke VCI.**

KEY WORDS

***Trigona*, VCI, stroke, cognitive impairment**

INTRODUCTION

Vascular cognitive impairment (VCI) is defined as a syndrome that includes all neurological disorders from mild cognitive impairment to dementia caused by cerebral vascular disease that occurrs within three months after stroke onset. The prevalence of post-stroke VCI is reported between 36 to 67% of the stroke survivors[1-3)]. VCI is also thought to occur from stroke injury irrespective whether it involves vascular, neurodegenerative or mixed processes (e.g., large vessel occlusion and small vessel dysfunction); intracerebral hemorrhage and subarachnoid hemorrhage, and other factors (combined with Alzheimer's disease)[1,2,4,5)]. Other recognized risk factors of VCI include age, hypertension, hyperlipidemia, hyperuricemia, diabetes, cardiopathy, stroke, carotic plaque, smoking, and low educational level[1)]. Moreover, VCI is structurally related to the impairment within the cortico-striatal network, which involves in effort-reward calculation and warrants further research that can halt the progression from mild cognitive impairment to dementia[6)].

In VCI, scientists have reported the presence of multiple evolutionary trends in cognitive changes in chronic stroke patients and found an annual conversion of 8 to 13% to dementia within the first year after stroke[5)]. Neurological assessments done on chronic stroke patients demonstrated more than 60% of these patients exhibit cognitive impairment, accompanied with symptoms of depression[5)]. Finding of previous study suggested that the interaction between brain atrophy and white matter hyperintensities of infarcts could aggravate cognitive decline. There is evidence of the role of hippocampal mean diffusivity in the post-stroke cognitive state, beyond its volume and connectivity[2)].

Prevention strategies to delay the progression of cognitive impairment would reduce the number of dementia post-stroke cases. Although neuroprotective and neuro-recovery enhancement in rehabilitation are being studied in treating VCI, however it is difficult to establish a specific treatment to improve cognition in the pre-existing cognitively impaired patients[1,7)]. The strategies to prevent progression of mild cognitive impairment to dementia post-stroke by lowering blood pressure, and treating with statins, neuroprotective drugs and anti-inflammatory

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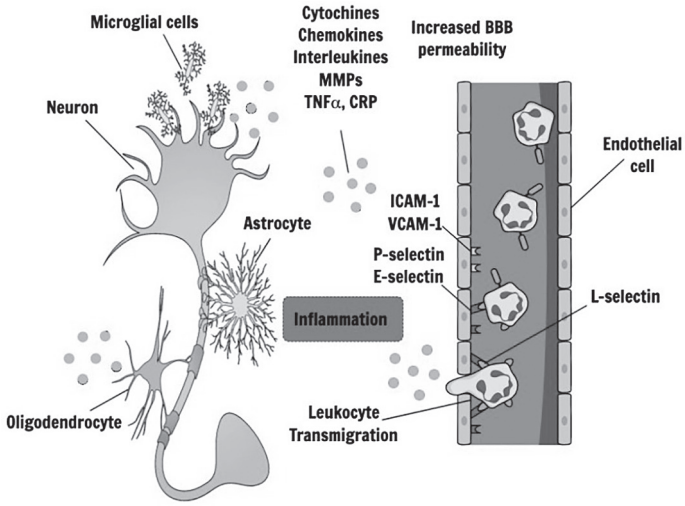

Figure 1: Endothelial dysfunction and cerebral inflammatory response in VCI result to enhance BBB permeability, neuron damage, transmigration of leukocyte to extravascular space and infiltration of inflammatory markers (Adapted from Cipollini *et al*, 2019[4]).

agents have all been studied with no evidence of efficacy whereas lifestyle interventions, physical activities and cognitive training are tested with missing large controlled trials[2]. However, aggressive treatment of vascular risk associated with the progression of vascular disease and risk of dementia such as anti-platelet therapy, antihypertensive drugs, statins, or anticoagulants may potentially reduce the risk of VCI[8].

Honey that is rich of antioxidants with well-known anti-inflammatory properties has a good potential to decline the progression of post-stroke cognitive impairment. The progression of post-stroke cognitive impairment or dementia can be delayed or prevented by introducing honey as supplementary therapy in early stage of stroke patient with mild cognitive impairment as evidenced in animal studies[7,9,10]. Honey is a natural food produced by both honeybees (*Apis* sp.) and stingless bees (*Meliponini* sp.) containing phenolic and flavonoid compounds that have antioxidant activity, hence beneficial for therapeutic, nutrition, cosmetic and industrial values[11,12]. According to Ayurveda perspective, honey offers lifespan prolongation, and enhances memory, intellect, concentration and physical strength. Honey is also shown to be a functional food with neuropharmacological activities such as anxiolytic, antinociceptive, anticonvulsant and anti-depression activities[13].

Trigona honey or also known as *Kelulut* honey in Malaysia, produced by *Trigona* species, is the most common type of stingless bees in Southeast Asia. Technically, stingless bees are capable to pollinate small-sized flower due to their small figure and they are easier to handle and extract honey from them as the name suggests. However, distribution of *Trigona* honey is still low despite its convenience management as the knowledge of this honey is limited. In Malaysia, development of Mustafa-Hive (Meliponiculture using split-able throne within air-jacketed palace for amplification-hive), a well structured, intensive bee hive have facilitates the research and development of *Trigona* honey[9]. The main components of *Trigona* honey includes sugars (fructose and glucose) with small amount of other compounds, such as organic acids, phenolic compounds (e.g., phenolic acids and flavonoids), proteins, amino acids (eg., phenylalanine, alanine, tryosine, valine, acetate and trigoneline), enzymes, vitamins and minerals[14]. Furthermore, the composition and therapeutic properties of *Trigona* honey is comparable to the common European bee honey from *Apis* sp. which is well known as therapeutic agents[15].

Honey has been used as a supplementary therapy in the management of chronic disease such as cancer, hypertension and diabetes in human[16]. Also, it has been shown to increase learning and memory performance in animal studies[17]. High antioxidant property of *Trigona* honey is observed to enhance the synaptic plasticity through synaptogenesis in mice[9]. Other findings reported that honey significantly reduced the number of degenerated neuronal cells and delayed the progression of cognitive impairment or dementia in animal[10]. Both short and long term supplementation with honey at a dose of 250 mg/kg of rats' body weight significantly increased the total brain protein and catalase activities which acts as defense mechanism against cell damage[18]. A randomized controlled trial done in both cognitively intact and mild cognitive impaired subjects (n = 1493) receiving one table spoon of honey daily showed only 95 subjects (6.3%) developed dementia compared to 394 subjects (28%) from placebo group (n = 1400), suggesting honey as a natural preventive therapy in cognitive decline and dementia[19]. Mechanistically, honey improves cognitive functions through its several properties such as nootropic, antioxidant and nutraceutical properties which may facilitates neurogenesis and provide mechanism against oxidative stress[20,21]. However, lack of evidences to support the association between honey and the progression of dementia limits this therapeutic potential of honey. So, there is a need to further determine the effectiveness of honey as a supplementary therapy for stroke patients with cognitive impairment in order to prevent the rapid development of dementia post stroke.

This review outlines the potential effect of *Trigona* honey as a supplementary therapy on inflammatory markers in prediction to halt the progression of post-stroke VCI. This is reviewed based on frontal cortical-basal ganglia-thalamic circuit model[22] to determine brain injury in cortico-basal ganglia which causes cognitive impairment and microvascular inflammation, a hypoperfusion model with dementia markers among stroke survivors. This review also covered the role of honey as one of the natural supplements and its antioxidants content as neuroprotective model worth to be explored for its potential in halting the progression of cognitive impairment and dementia.

PATHOPHYSIOLOGY OF INFLAMMATION RESULTED FROM VCI

Mild to moderate stroke patients with preexisting white matter lesion are prone to develop cognitive impairment regardless of their new ischemic lesions. Infarct in the brain at frontal cortical-basal ganglia-thalamic circuit affects cognitive domain. Cortical gray matter infarcts affect executive function, potentially because they predominantly encompassed the frontal lobe. Finding of previous study suggested that the interaction between brain atrophy and white matter hyperintensities of infarcts could aggravate cognitive decline. There is evidence of the role of hippocampal mean diffusivity in the post-stroke cognitive state, above and beyond its volume and connectivity[2,4].

There are evidences that chronic inflammation is involved in the pathogenesis of stroke and dementia[4]. Several studies have found that there are associations between inflammatory biomarkers and the progression of the disease[23,24]. The mechanism of vascular damage in brain is encouraged and maintained by cytokines, acute phase proteins, endothelial cell adhesive molecules and other immune-related proteins. The common biomarkers in VCI and dementia are interleukin-6 (IL-6), matrix metalloproteinases (MMPs), tumour necrosis factor alpha (TNFα), toll like receptor 4 (TLR4) and C-reactive protein (CRP). Microvascular inflammation is a hypoperfusion model with markers of chronic inflammation and endothelial activation, which lead to increase blood brain barrier (BBB) permeability and to infiltration of inflammatory factors (IL-6, MMPs, TNFα, TLR4 and CRP). Upon entry into the brain, these inflammatory factors would exacerbate the white matter damage that involves BBB disruption, hypoxia and hypoperfusion, oxidative stress, neuroinflammation and neurovascular unit injury[4]. The inflammatory process by these mediators is suggested to be involved in the early stages of Alzheimer disease, way before implicated into mild cognitive impairment (MCI)[25] (Figure 1).

In VCI, the goal of diagnostic biomarker development is to identify patients at early stage where treatment such as supplementation with *Trigona* honey may be effective in blocking the progression damage to the white matter. This review suggests that the consuming *Trigona* honey as supplementary therapy would halt the progression of cognitive impairment or dementia post-stroke through the measurement of inflammatory markers (IL-6, MMPs, TNFα, TLR4, CRP) level.

POTENTIAL NEUROPROTECTION MECHANISM BY HONEY AGAINST VCI

Honey contains various phenolic compounds such as kaempferol, chrysin, catechin, apigenin, quercetin and caffeic acids that have been identified as neuroprotective agents[26]. Neuroprotective effects of pheno-

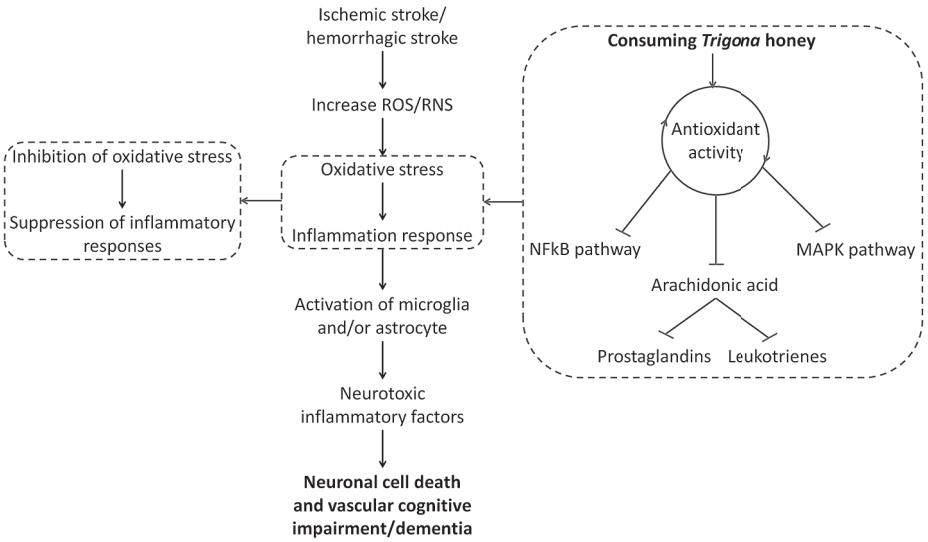

Figure 2: Potential mechanisms of action for *Trigona* honey as an antioxidant agent to halt the progression of vascular cognitive impairment to dementia.

lic compounds in honey may contribute in brain activities such as prevent neuro-inflammation, promote memory, learning and cognitive function and protect against neurotoxin-induced neuronal injury. As an antioxidant, honey provides a defense mechanism against oxidative stress and attenuates free radical-mediated molecular destruction[11,12]. Oxidative stress is a common manifestation of all type of biochemical insults to the structural and functional integrity of neural cells, such as aging, neuroinflammation and neurotoxins which further induces development of neurological diseases (Alzheimer disease and Parkinson's disease)[11,12,27]. Mechanistically, phenolic compounds in honey provide neuroprotection through the limitation of reactive oxygen species (ROS) generation, reinforcement of the cellular antioxidant defense system and attenuation of neuroinflammation and apoptosis[13]. Honey was reported to protect against chronic cerebral hypoperfusion such as in Alzheimer's disease and provide stimulatory effect on memory and learning process in preventing dementia[19]. In an animal study, honey is shown to enhance memory by increasing the proliferation of neurons in hippocampal region[12]. Apigenin content in honey acts as radical scavenger which protects neuron against oxygen-glucose deprivation/reperfusion-induced injury in cultured primary hippocampal neuron by improving sodium/potassium ATPase (Na +/K + - ATPase) activities. Apigenin is also shown to inhibit the kainic acid-induced excitotoxicity of hippocampal cells in a dose-dependent manner by quenching ROS and by inhibiting the depletion of reduced glutathione (GSH) level[28]. Meanwhile, caffeic acid that present in honey gives an effect as neuroprotective agent through the prevention of learning and memory deficits[29] and catechin acts as antioxidant that that delays memory impairment[30]. Another compound found in honey, quercetin is found to improve memory and hippocampal synaptic plasticity in memory impaired model caused by chronic lead exposure and reduced lipid peroxidation with increased GSH against colchicine-induced cognitive impairment *in vivo*[31,32].

Since these antioxidant compounds are abundantly available in *Trigona* honey as well with several other advantages (highly bioaccessible minerals, but with absence of heavy metals), studies have directed towards the potential of *Trigona* honey in neuroprotection[11,33]. A study in metabolic syndrome-induced animal shows a promising role of *Trigona* honey in attenuating neurodegenerative diseases through the improvement of memory and reduction of anxiety[34]. The neuroprotective effect of *Trigona* honey supplementation is modulated via brain derived neurotrophic factor and inositol tri-phosphate, which involved in synaptic function[35]. Overall, Figure 2 illustrates the potential mechanisms of action for *Trigona* honey that could cause neuroprotective effects in stroke patients. These mechanisms work mainly based on the high antioxidant activity of *Trigona* honey. This activity leads to inhibition of two key signaling pathways; the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinases (MAPK). This inhibition results in complicated cellular mechanisms such as suppression of inflammatory factors encoding genes, and thus inhibits the expression of those factors (e.g., TNF and IL-6). In addition, the antioxidant phenolic compounds from *Trigona* honey may reduce the release of arachidonic acids, which are released upon the oxidation of membrane phospholipids, and thus reduce also its metabolites such as leukotrienes and prostaglandins that considered as important inflammatory mediators[11].

FUTURE DIRECTIONS

In future, further study is suggested to investigate the association between inflammatory biomarkers (IL-6, MMPs, TNFα, TLR4, CRP) with the intervention using *Trigona* honey as a supplementary therapy in the early pathological process of VCI. Future studies can also predict the association between the role of antioxidant properties in *Trigona* honey and the white matter damage or hyperintensities, involving BBB disruption, hypoxia and hypoperfusion, oxidative stress, neuroinflammation and neurovascular damage. The prediction is based on the positive correlation between these markers with white matter hyperintensities in which increased BBB permeability is described to be involved in the cognitive impairment and dementia[4].

Future research should answer these questions; (1) Are there any changes in total cognitive scores at baseline and post supplementary therapy using *Trigona* honey group compared to placebo to halt the progression of post-stroke VCI? (2) Are there any changes in inflammatory markers (IL-6, MMPs, TNFα, TLR4, CRP) measured in pre and post supplementary therapy using *Trigona* honey group compared to placebo to halt the progression of post-stroke VCI? (3) Are there any changes in inflammatory markers (IL-6, MMPs, TNFα, TLR4, CRP) measured in pre and post supplementary therapy using *Trigona* honey group compared to placebo to predict the decline of VCI progression? (4) Are the increased levels of inflammatory markers (IL-6, MMPs, TNFα, TLR4, CRP) measured in supplementary therapy using *Trigona* honey group predict higher of the total cognitive score at certain duration post-stroke?

To determine the neuropsychological change post-stroke, the correct assessment tool done at baseline and post-intervention should be chosen to detect the progression of post-stroke VCI. The Mini-Mental State Examination (MMSE) or a Montreal Cognitive Assessment (MoCa) can be applied to identify specific cognitive deficit post-stroke that reveals executive functioning, attention, mental processing speed, visual perception, and construction ability are common elements in subacute and chronic patients[5,36].

CONCLUSION

This review may provide a new perspective for clinical studies to include the supplementary therapy with *Trigona* honey in mild stroke to prevent the progression of VCI to dementia among stroke survivors. The findings of these future studies could prove the fact of *Trigona* honey as

food, which is rich in phenolic compounds, will be a great potential as a supplementation therapy in stroke patients. Furthermore, understanding the association of *Trigona* honey with inflammatory markers used monitor the progression of VCI would further validates the potential of *Trigona* honey as supplementary treatment for post stroke survivors. Eventually, validations and commercialization of *Trigona* honey will further create spill over effect in terms of new job opportunities as well as promotion of stingless bee agricultural industry.

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