

## ORIGINAL ARTICLE

# Potential Effects of Trigona Honey Supplementation and Associated Factors on the Progression of Mild Post-ischaemic Stroke Cognitive Impairment: An Exploratory Unicentral Randomised Controlled Trial

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## ABSTRACT

**Introduction:** Affecting up to 67% of stroke patients, PSCI is a complication that predicts poor quality of life, decreased independence, and substantial economic burden. PSCI remains a major post-stroke complication with limited therapeutic options. Based on current understanding of PSCI's pathogenesis, Trigona honey makes an attractive therapeutic option, as it can act on numerous neuropathological substrates implicated in PSCI's pathogenesis via the action of multiple polyphenols. **Materials and methods:** The study was conducted following a unicentral, randomised, concurrent active treatment controlled, superiority trial with two parallel groups model. The interventional group included participants who were administered supplemental honey in addition to standard treatment regimens, while those in the control group solely continued the standard therapeutic protocol. Two honey sachets were administered for daily oral consumption for three months, with a total daily dose of 20 g. Demographic and clinical characteristics questionnaire, MoCA, and NIHSS were used for data collection. Data collected was analysed using SPSS. **Results:** Difference in mean MoCA score gain between the two groups after three months was statistically significant ( $p < 0.05$ ), with the interventional group having greater gain by 3 points. No statistically significant relationship between demographic characteristics, clinical factors, stroke parameters, and the 3-month progression of PSCI was detected. The only exception was improved cognitive function in current smokers in the interventional group. **Conclusion:** Trigona honey supplements could be effective in halting progression of PSCI, and smoking can affect 3-month progression of PSCI. No association was detected between stroke severity, TOAST and OCSP classifications, and 3-month progression of PSCI.

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**Keywords:** Post-stroke cognitive impairment, Stingless bee honey, MoCA, NIHSS, Randomised controlled trial

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## INTRODUCTION

Strokes occur when cerebral blood supply is disturbed, either due to vessel blockage or rupture, leading to focal deficits in neurological function [1]. While the majority of the 15 million stroke cases recorded annually around the world are of ischaemic origin, both ischaemic and haemorrhagic incidents contribute to stroke's status as the global second-leading cause of mortality, and third-leading of combined death and disability [1,2].

Improvements in stroke survival rates have shifted

more focus to complications that are often secondary in attention to the more apparent physical debilities, such as post-stroke cognitive impairment (PSCI) [3]. PSCI can be defined as a novel impairment in cognitive faculties that is observed in the first 90 days post-stroke, with a minimum duration of six months, and cannot be attributed to another disease or condition. PSCI has been reported to affect up to 67% of stroke patients [1].

Diagnosing PSCI relies on the use of neuropsychological tests. However, there is a lack of consensus on the best neurophysiological approach to assess cognitive profiles post-stroke [4, 5]. The two most commonly employed screening tools of PSCI are the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), which are favoured for their broad scope of assessment and ease and swiftness

of administration [6]. Neuroimaging techniques have also been investigated as a diagnostic tool for PSCI [2], and several biomarkers are being studied as potential diagnostic targets [2, 4].

While PSCI can be caused by all subcategories of ischaemic and haemorrhagic strokes [4], the exact mechanism by which PSCI occurs remains to be elucidated. Several pathways and processes have been implicated in the pathogenesis of the disease, as illustrated in Fig.1 [1, 7].

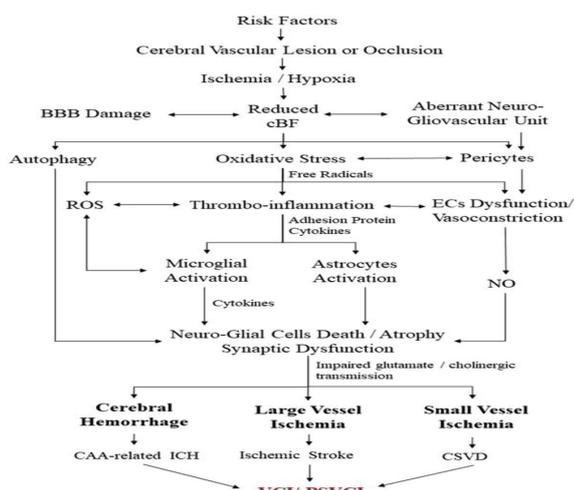


Fig. 1: Postulated pathophysiological cascade of PSCI.

Research also suggests that preclinical presence of Alzheimer’s disease (AD) predisposes stroke patients to a higher cognitive impairment and dementia risk. Indeed, multiple pathological elements have been detected in both disorders [4]. This mechanistic intersection of PSCI and AD could have inspired the use of AD therapies, such as cholinesterase inhibitors, in the treatment of PSCI [8], but they remain hindered by their inconsistent effect on global function and daily living activities [9]. Non-invasive methods, such as cognitive rehabilitation and repetitive administration of transcranial magnetic stimulation, have also been employed as potential therapies, but they are limited by various shortcomings [10].

Multiple strokes, number of infarcts, and lesion volume have also been correlated to a higher risk for dementia and exacerbated cognitive decline [4]. Vascular risk factors and several stroke characteristics, such as severity and pathophysiological subclassification, are additional parameters capable of influencing PSCI. [1, 7, 12-14]. Given this well-established correlation between strokes and progression of cognitive decline [4, 15], secondary prevention of strokes, in addition to the amelioration and proper management of associated risk factors- particularly modifiable ones- are key steps in the management of PSCI and prevention of dementia. [5, 9, 13]. As such, preventative measures and halting the progression of PSCI are a top area of interest and research [16]. This approach is further encouraged by the

difficulty of establishing tertiary therapeutic regimens in patients already suffering from cognitive impairment [1].

Preventative measures for ischaemic strokes, including preventative pharmacological interventions, could be useful [5, 8, 15]. Possible benefits of herbal supplements have also been investigated, with promising potential for the prevention and amelioration of PSCI [5]. This encourages the investigation of other compounds, such as honey, in the same capacity.

Since ancient times, honey has been appreciated for its therapeutic potential, now proven by modern laboratory techniques [17]. It has also been demonstrated that honey dietary supplements have numerous desirable neurological and neuroprotective effects, including anti-apoptotic, antioxidant, and anti-inflammatory effects [18]. Such benefits are attributed to the action of bioactive molecules, mainly phenolic acids and flavonoids, which belong to the polyphenols family [17]. These bioactive constituents can be found in varying percentages in different honey types [17].

Stingless Bee Honey (SBH) is the name given to the variety of honey that is produced by any of the more than 600 species of the Meliponinae taxonomical subfamily [19]. The most common genera of stingless bees in Southeast Asia is that of Trigona, with over 30 of its species found in Malaysia [11]. As such, SBH and Trigona honey are two of the terms that can be used interchangeably in reference to the same compound [1, 18, 19]. In comparison to honeybee honey, SBH offers a higher and more varied polyphenolic content, [19].

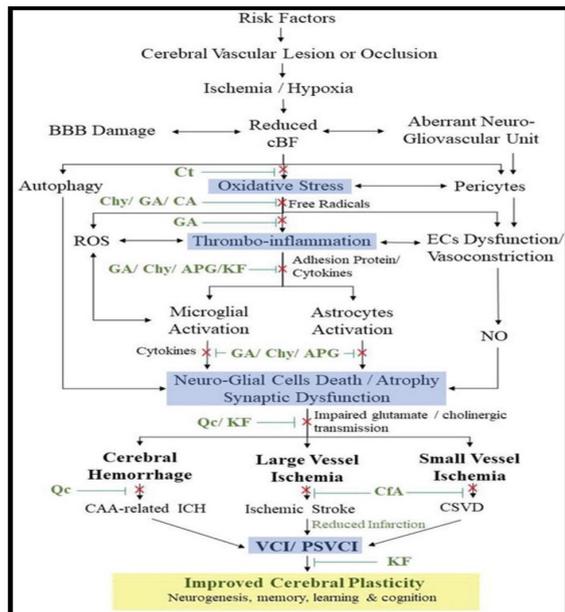
**Rationale and Study Significance**

The risk for cognitive impairment is reported to be heightened at least five to eight times following a stroke, and 20-30% of patients go on to develop dementia [2]. Furthermore, it has been demonstrated that PSCI is a frequent presence, even in patients who have successfully recovered clinically [20]. PSCI also forecasts a higher risk of dependency, compromised mental health, institutionalisation, death, and overall poor long-term outcomes [3]. PSCI was also linked to a triple increase in healthcare costs of stroke patients and a substantial burden on the caregivers, as well as poor life quality and restricted activity [8-10].

Despite the wider attention directed towards sequelae in the wake of improved stroke survival rates [3], PSCI remains one of the major post-stroke complications that still suffer from limited therapeutic options, with the currently available measures hindered by numerous deficiencies [10]. Thus, the absence of an effective therapy for PSCI necessitates further research.

Based on the current understanding of the major injury mechanisms involved in the pathogenesis of PSCI, honey makes an attractive therapeutic option

to halt the progression of the cognitive impairment, as it is hypothesised that honey can target multiple neuropathological substrates along the PSCI pathological cascade, as depicted in Fig.2 [1].



**Fig. 2: Postulated pathophysiological cascade of PSCI, with hypothesised mechanistic effects of specific polyphenols found in SBH, as well as the pathological substrates targeted, highlighted. Ct: Catechins, Chy: Chrysin, GA: Gallic Acid, CA: Cinnamic Acid, APG: Apigenin, KF: Kaempferol, Qc: Quercetin, CFA: Caffeic Acid**

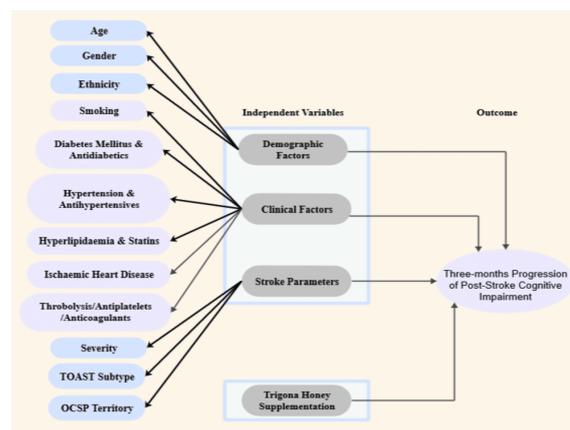
Since such benefits are due to the actions of the bioactive polyphenols, their higher concentrations and variety in *Trigona* honey makes this type of honey a strong candidate for potential therapy for PSCI [1, 11, 19]. Utilisation of SBH is further encouraged by its ease of access and cultivation, owing to the bees' stingless nature [19], which further encourages wider investigation of the honey's quality standard profile, bioactive constituents, and therapeutic potential, as well as its possible role in the context of PSCI [11, 19].

However, there is a distinct lack of studies on the potential of SBH in ischaemic brain injuries and associated cognitive decline in human subjects [18, 19] and thus a lack of knowledge on the potential benefits of honey in promoting functional recovery of cognitive function post-stroke or the halting of PSCI.

As such, this interventional study aimed to investigate the possible benefits of *Trigona* honey supplements in halting the progression of mild PSCI in acute ischaemic stroke patients admitted to Hospital Universiti Sains Malaysia (HUSM) by comparing MoCA scores prior to and following a three-month supplementation period. The study also investigated the correlation between the progression of PSCI and multiple demographic parameters, clinical factors, and stroke characteristics, due to their influence on the progression of cognitive impairment [12].

The study's focus on mild PSCI, as well as the specification of the intervention period as three months, was due to the evidence in literature to the benefits of early cognitive rehabilitative intervention on improving cognition post-stroke [21], as well as the difficulty of establishing tertiary therapeutic regimens in patients with cognitive impairment [11]. Moreover, it has also been demonstrated that the greatest improvement in cognitive function occur in the first 90-days post-stroke [22]. Recovery of neurological function after a stroke has also been shown to plateau after three months, and that there is a limited time window of heightened neuroplasticity following a cerebrovascular event [5].

This study exclusively recruited ischaemic stroke patients to allow for more accurate analysis, due to reports of variance in the cognitive domains affected by ischaemic and haemorrhagic PSCI [23]. Furthermore, focusing only on ischaemic patients allows the generalisation of the study's findings to 85% of stroke patients, compared to the 15% contributed by haemorrhagic strokes [24]. Findings from this study can help encourage the inclusion of *Trigona* honey in therapeutic approaches for PSCI, as well as research on a larger scale. Additionally, understanding the influence of different clinicodemographic and stroke parameters on the development of PSCI can be useful in the creation of prognostic models for PSCI with higher precision [13], and thus the development of more effective care and management protocols. Increased interest in SBH in countries with considerable stingless bee population, such as Malaysia, can also raise its commercial profile, thus promoting SBH related industries and employment opportunities [11]. Fig. 3 illustrates the conceptual framework of the study.



**Fig. 3: Conceptual framework of the study.**

## MATERIALS AND METHODS

### Study Design

This interventional study was designed as a unicentral, randomised, concurrent active treatment controlled, open-label superiority trial with two parallel groups. Randomisation of the participants into either the control or interventional group was implemented using

block randomisation with 1:1 allocation ratio. Fig. 4 summarises the flow of the study.

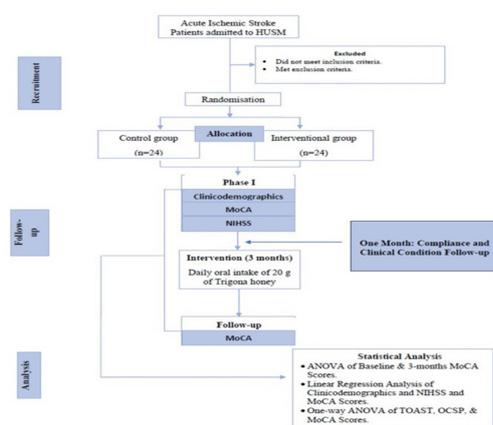


Fig. 4: Flowchart of the study.

### Study Location and Population

The study was conducted at the Neurology Ward and Specialist Clinic at HUSM. Ischaemic stroke patients admitted served as a source population for the target and reference populations of adult stroke patients in the state of Kelantan and adult individuals afflicted with stroke, respectively.

### Eligibility Criteria

#### 1. Inclusion Criteria

- Acute ischemic stroke patients admitted to HUSM between June 2021 and August 2022, within a maximum of 72 hours following the stroke incident.
- Aged between 20 and 70 years old.
- Mild cognitive impairment as assessed by the MoCA scores.

#### 2. Exclusion Criteria

- Refusal to provide consent, whether by the patient or their legal representative
- History of progressive cognitive impairment or dementia prior to the stroke incident.
- Presence of aphasia or dysarthria as indicated by NIHSS assessment.
- Presence of conditions impeding conduction of neuropsychological assessments.
- Diabetic with persistent hyperglycaemia (capillary blood glucose persistently > 10 mmol/L for 3 days following stroke onset).

### Sample Size

To meet all the study's objectives with sufficient analytic power, the target sample size was determined to be 70 participants, using G Power Software. However, only 48 participants were eligible.

### Instrumentation

1. Demographic Data and Clinical Characteristics Questionnaire/Proforma  
A multi-section questionnaire was used to collect

demographic information and clinical characteristics. Demographic data was recorded in part 1 of the questionnaire, which was offered in both Malay (Bahasa Malaysia) (BM) and English language. The data recorded included age, gender, ethnicity, marital status, educational level, occupation, socioeconomic status, smoking, alcohol intake, and medical history (hypertension, diabetes mellitus, hyperuricaemia, hyperlipidaemia, ischemic heart disease, and depression diagnosis) of the participant.

Part 2 of the proforma was used to record clinical information and depended on referral to the participants' medical records and neuroimaging scans. Information collected included the subject's diagnosis, the clinical subclassification of the stroke (as per the Oxfordshire Community Stroke Project (OCSP) classification system), and the location of brain lesions and size of the infarcts (as per CT/MRI scans). The aetiological stroke subclassification of the stroke (as per Trial of Org 101072 in Acute Stroke Treatment (TOAST) classification), onset of stroke prior to randomisation, as well as the results of laboratory investigations conducted, and treatment and medications administered upon patient admission were also collected.

#### 2. Montreal Cognitive Assessment (MoCA)

The validated version of the Montreal Cognitive Assessment (MoCA) in BM, as validated by Sahathevan *et al* [25], was used in this study to identify eligible patients (those with mild cognitive impairment) during the recruitment stage, and to assess the progression of PSCI during the follow-up stage. MoCA is a convenient tool for the screening of mild cognitive impairment. Utilising a total possible score of 30 and administration timeframe of 10 minutes, the one-page test allows the assessment of numerous cognitive domains [25, 26].

Compared to MMSE, MoCA was found to be a more sensitive scale when employed in the detection of early PSCI. [27].

#### 3. National Institutes of Health Stroke Scale (NIHSS)

The National Institutes of Health Stroke Scale (NIHSS) was used to clinically evaluate the severity of strokes during phase I. NIHSS is the gold-standard worldwide for the clinical evaluation of stroke severity and prediction of clinical outcomes [28]. On scales ranging from 0-4, NIHSS uses 15 items to assess possible deficits in 11 different domains. The total score is then tallied to identify stroke severity [29]. NIHSS has the advantages of simple and rapid administration, and its scores have been strongly correlated with long term post-stroke functional outcomes and early death [30, 31].

### Ethical Considerations: Informed Consent, Data Anonymity, Confidentiality, and Management

Informed voluntary consent was collected in writing from patients or their legal representative during a face-

to-face interview, where a member of the research team elaborated on the information provided in the consent form. Any questions and inquiries posted by the participants were answered, and they were assured that they are free to withdraw from the study at any point, and that their decision will not affect the standard of care they received.

All data collected, in accordance with the Malaysia Personal Data Protection Act 2010, is confidential. The data was anonymised by removing all identifiers (name, telephone number) and assigning a randomly generated alphanumeric code to each participant. The data was checked, cleaned, then stored in a secure database created using the Statistical Package for the Social Sciences (SPSS) software and was only available for access by members of the research team, the Ethical Review Board, and regulatory authorities.

### Study Procedure

#### 1. Participants Recruitment

Ischaemic stroke patients who were eligible for the study as per the inclusion and exclusion criteria were recruited using convenience sampling from multiple wards in HUSM.

### Data Collection

#### 1. Phase I

This phase took place during the acute inpatient recovery phase, 72 hours following stroke onset. Recruitment of patients in this phase can potentially offer improved outcomes, in accordance with evidence for the benefits of interventions in the first 72 hours [50]. A questionnaire was used to record demographic and clinical information. Scores from MoCA and NIHSS tests conducted upon patient admission were noted as baseline assessments of the severity of PSCI and stroke, respectively.

#### 2. Phase II

Following the interventional 3-month long phase, MoCA was readministered to assess the progression of PSCI.

### Intervention

Following baseline assessments, recruited subjects were equally randomised into either the control or interventional groups. Standard care and rehabilitation protocols were continued for both groups.

No placebo was administered to the control group, while participants in the interventional group were provided with Trigona honey sachets 3 days following stroke onset. Administration of honey supplements ceased after completion of the study. The sachets contained 10g of 100% SBH extracted from stingless bee species belonging to the *Meliponini* taxonomical tribe. The honey is marketed under the proprietary name Kelulo and is produced by the community bee farm Malaysia dan Honey Gold Enterprise (KT0336195). The

honey was processed by Halal dan MeSTI (*Makanan Selamat Tanggungjawab Industri*) and is authorized for consumption in Malaysia under the Halal certificate JAKIM.700-2/3/1 018-03/2017. Two honey sachets were administered to the participants for oral consumption for the duration of 12 weeks, one sachet in the morning and the other in the evening, with a total daily dose of 20g. This dose was chosen based on evidence in literature of its benefits, as it has been associated with improvements in immediate memory in schizophrenic patients [32]. The participants were free to consume the honey in any manner they wished.

One month following honey initiation, compliance of participants in the interventional group was assessed by counting the number of open honey sachets brought back by the participants during the follow-up. Clinical condition of patients in both groups was also evaluated after one month.

### Statistical Analysis

Statistical analysis was carried out using SPSS (v. 29.0.1.0). Firstly, descriptive statistical analysis was performed to obtain percentages (%) and frequencies (N) for categorical variables and means with standard deviation (SD) for continuous ones. Secondly, inferential statistical analyses were performed in accordance with the study's objectives. A significance level ( $\alpha$ ) of 0.05, power ( $\beta$ ) of 80%, and confidence level ( $1-\alpha$ ) of 0.95 (95%) were quoted for all tests. A  $p$  value below 0.05 ( $p < 0.05$ ) was considered statistically significant.

A 2x2 mixed-design Analysis of Variance (ANOVA) was conducted to evaluate the effect of Trigona honey supplementation on the 3-month progression of PSCI, as measured by the difference in MoCA scores after 3 months. Time (baseline and 3-month MoCA scores) was used as the within-subject factor, while group (control or interventional) was used as the between-subject factor.

The relationship between demographic characteristics, clinical factors, and the 3-month progression of PSCI was determined using a linear regression model. Demographic and clinical factors were first entered into individual simple linear regression models against difference in MoCA scores as a measure of PSCI progression. Factors that were found to be of significant association ( $p < 0.05$ ) were then entered into a multiple linear regression model.

Simple linear regression was chosen to determine the effect of stroke severity on the progression of PSCI by analysing the regression model between NIHSS and MoCA scores.

The effect of stroke pathophysiological subclassifications and vascular territories on the 3-month progression of PSCI was analysed using one-way ANOVA, where the difference in mean MoCA scores among the five

pathophysiological TOAST subclassifications and four OCSF vascular territories was compared.

**RESULTS**

**Demographic Characteristics**

Overall (N= 48), 32 (66.7%) of the participants were male, and 16 (33.3%) were female. Majority of the participants were of Malay ethnicity (n=47) (97.9%), and the mean age was 58.85 years (SD = 9.211). The youngest participant was 35 years old, while the oldest was 70.

Half of the participants were non-smokers (50%), but a significant portion were diabolic (62.5%) and hypertensive (95.8%). 17 (35.4%) participants suffered from Ischaemic heart disease. Hyperlipidaemia was a common condition among all participants (100%), as well as the use of antihypertensives (100%), statin (100%), antiplatelets (93.75%), and antidiabetics (66.7%).

Table I summarises the stroke parameters of the study population, including the severity of strokes and neurological deficits as measured by NIHSS scores, TOAST pathophysiological subclassifications, OCSF vascular territories, as well as the baseline MoCA scores as a measure of cognitive function. It could be seen that lacunar infarcts (LACI) (77.1% ) are the most common infarct vascular territory among the participants, and that small-vessel occlusion (SVO) (64.6%) is the most common TOAST subclassifications. The highest NIHSS score was 22, while the lowest was one (M = 4.27, SD = 3.595). The highest MoCA score recorded was 25, with the lowest being four (M = 19.25, SD = 4.853).

**Table I: Summary of stroke parameters and baseline cognitive function in the study population (N=48)**

Parameter	Frequency (n)	Percentage (%)	Mean (± SD)
<b>NIHSS Score Range</b>			4.27 (3.595)
1-4	36	75	
5-15	11	22.9	
21-25	1	2.1	
<b>TOAST Classification</b>			
Large-artery Atherosclerosis	9	18.8	
Cardioembolism	6	12.5	
Small-vessel Occlusion	31	64.6	
ODA	1	2.1	
UDA	1	2.1	
<b>OCSF Classification</b>			
PACI	5	10.4	
POCI	6	12.5	
LACI	37	77.1	

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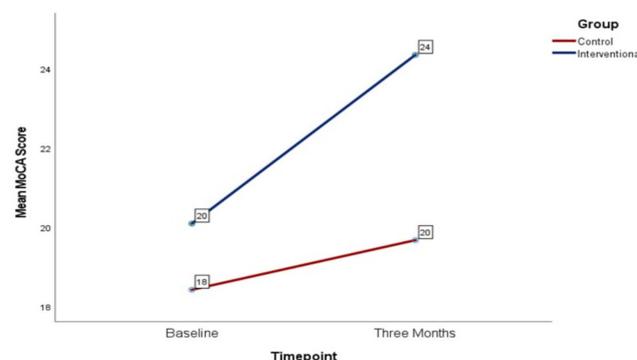
**Table I: Summary of stroke parameters and baseline cognitive function in the study population (N=48) (CONT.)**

Parameter	Frequency (n)	Percentage (%)	Mean (± SD)
<b>MoCA Score Range</b>			19.25 (4.853)
1-5	1	2.1	
6-10	2	4.2	
11-15	6	12.6	
16-20	17	35.5	
21-25	22	45.8	

NIHSS Minimum Score: 1, Maximum: 22, MoCA Minimum Score:4, Maximum: 25, NIHSS: National Institutes of Health Stroke Scale, TOAST Classification: Trial of ORG 10172 in Acute Stroke Treatment Classification, OCSF Classification: Oxfordshire Community Stroke Project Classification, ODA: Stroke of other determined aetiology, UDA: Stroke of undetermined aetiology, PACI: Partial anterior circulation infarcts, POCI: Posterior circulation infarcts, LACI: Lacunar infarcts, MoCA: Montreal Cognitive Assessment

**Mixed-design ANOVA**

The descriptive statistical output generated allowed the prediction of the existence of a difference between the two groups, as well as the nature of the difference; the mean MoCA score in the control group increased by 1.25 points, from 18.42 (SD = 5.12) to 19.67 (SD = 6.31), while that of the interventional group increased by 4.25 points, from 20.08 (SD = 4.53) to 24.33 (SD = 3.64). This is visually summarised in the profile plot depicted in Fig. 5, where it could be seen that the increase in the mean MoCA score over time of the interventional group was different from that of the control group. Furthermore, the plot allows the determining the nature of the interaction between time and group, where the non-parallel nature of the two lines forecast a significant interaction effect.



**Fig. 5: Profile plot depicting the difference in the means of MoCA scores between control and interventional groups over 3-month.**

The results of the univariate tests (Table II) indicated a significant effect for time, i.e., a statistically significant change in MoCA scores over time for all participants. They also indicated a significant interaction effect between time and group, meaning that a comparison between the change in MoCA scores over time in the control and interventional groups revealed a statistically significant difference. This is further supported by the results of the between-subjects test, which indicated a significant effect for group, indicating a statistically significant difference between MoCA values of the two

groups at 3 months i.e., a significant effect of different treatments.

**Table II: Results of ANOVA Within-Subject, Interaction, and Between-Subjects Effects**

	Wilk's $\Lambda$	df	F	Sig.	Partial Eta Squared
<b>Time</b>	0.636	1	26.379	<0.001	0.364
<b>Time* Group</b>	0.854	1	7.848	0.007	0.146
<b>Group</b>	-	1	5.597	0.022	0.108

According to the partial  $\eta^2$  values calculated, 0.364% of the variance in MoCA scores could be attributed to time, 0.146% to the interaction between time and group, and only 0.108% to the group.

### Linear Regression

A significant relationship ( $p = 0.01$ ,  $R^2 = 0.264$ ) was detected between smoking and the gain in MoCA scores in the interventional group. No significant relationship was detected between gain in MoCA scores and the other factors. Thus, no multiple linear regression was performed.

The results indicate that 0.264% of the variation in the progression of PSCI could be explained by smoking, and that smokers had a greater gain between baseline and 3-month MoCA scores by 0.514 points.

### Simple Linear Regression

NIHSS scores were entered into a linear regression model against the computed gains in MoCA scores of the entire population and the control and interventional groups. No linear relationship ( $p < 0.05$ ) was detected in any of the three models (Population:  $p = 0.574$ , Control:  $p = 0.544$ , Interventional:  $p = 0.350$ ).

### One-way ANOVA

Running a one-way ANOVA of the mean MoCA gains in the entire population and the control and interventional groups, with TOAST classification as the factor variable, revealed statistically significant difference between the different subclassifications in the population as a whole ( $p = 0.018$ ) and in the control group ( $p = 0.025$ ). *Post-hoc* Tukey test was thus performed after excluding subclassifications with less than 2 cases (strokes of other determined or undetermined aetiologies), but it detected no significant difference between any of the groups.

A one-way ANOVA of the mean MoCA gains in the entire population and the control and interventional groups, with OCSP classification as a factor variable, revealed no statistically significant difference between the different vascular territory classifications.

## DISCUSSION

The mixed-design ANOVA analysis generated multiple statistical outputs. Collectively, they demonstrated that

the gain in MoCA scores, and thus progression of PSCI, varied between the two groups, with the interventional group had a greater gain in MoCA scores over the duration of 3 months compared to the control group, allowing the conclusion that SBH played a role in halting the progression of PSCI, which was the expected outcome.

The main hypothesis of the study was that the polyphenols found in Trigona honey act on multiple neurological substrates along the PSCI pathogenic cascade. While the results support this hypothesis in the interventional group, there is a noted improvement in cognitive scores in the control group which cannot be attributed to intake of honey supplements. This could be due to either the standard of care the patients received, or due to the brain's endogenous reparative mechanisms and spontaneous recovery [7]. Such factors are important to investigate for better quantification of the honey supplements therapeutic effects.

Older age, particularly more than 60 years old, is one of the more consistently reported independent risk factors for PSCI and has even been linked to its exacerbation at 3 months following the stroke incident [5, 12, 14, 34].

With the majority (54.2%) of the participants in this study being older than 60 years old, detection of a significant relationship between cognitive outcome and age was expected. While it is important to take into consideration that several other studies similarly reported no significant association between age and cognitive decline [27], the lack of association between age and PSCI in this study could have been caused by the small sample size, which would have hidden associations of small effect sizes, such as impairment in executive functions in lacunar strokes [35]. Another possible explanation could be that age modifies cognitive decline in a domain-specific manner [36] and consideration of only the total score of the MoCA test could have been a source of bias. Another possibility is that hypertension could have exerted a neuroprotective effect against PSCI in older participants by improving cerebral blood perfusion [5].

Many of the demographic and clinical factors investigated in this study have been inconsistently reported in literature as predictors or risk factors related to PSCI [14]. This includes gender, whereby some studies report that females experience poorer cognitive outcomes following a stroke (37), while some other studies report no difference in post-stroke cognitive outcome between the two genders [34]. Sociodemographic and biological influences have also been highlighted as sources of potential bias when examining the association between gender and PSCI [37].

Ethno-racial variations in cognitive outcomes post-stroke, including the relationship between PSCI and vascular risk factors, have indeed been reported among

different populations [14]. However, in the current study, investigating the relationship between ethnicity and PSCI progression was not feasible due to the unequal representation of different ethno-racial groups among the study population (Only one participant of Chinese ethnicity in the control group and while all participants in the interventional group were of Malay ethnicity).

The association detected between current smokers and an improvement in cognitive function is contrary to evidence found in literature. Smoking is an established risk factor for cerebrovascular events [38], and has been associated with cognitive impairment, albeit inconsistently [4, 14, 39]. Furthermore, smoking has been reported as one of the factors contributing to dysfunction of cerebral microvasculature and damage to neurovascular unit [4], both of which are processes implicated in the pathogenesis of PSCI. Thus, it was expected that sustained smokers in the cohort would exhibit at least similar gains in MoCA scores to, if not less than, their non-smoking and ex-smoking counterparts.

The statistical findings could be explained by attributing the cognitive gain to smoking cessation, which could have been implemented as part of the stroke secondary prevention protocol recommended by the Malaysian Ministry of Health [40]. Numerous cognitive benefits have been ascribed to smoking cessation, including the restoration of normal hypercoagulability state within two months [38]. This is important to consider in the context of PSCI, as neuro-thrombo-inflammation is one of the processes found along PSCI pathogenic cascade [1]. Another possible explanation to the cognitive improvement observed among the smoking participants could be that they were mild smokers at the time of their stroke onset. In literature, mild smokers were found to be of better attention and alertness faculties compared to non-smokers, which could be attributed to the nicotine-mediated acetylcholine release [39]. This is also important to take into consideration, as disturbed cholinergic activity is yet another pathological neurological substrate of PSCI [1].

Exclusivity of significant cognitive gains among smokers to the interventional group compared to the control one could be explained by the unequal distribution of smoker participants among the two groups, with the greater proportion being part of the interventional group (9 smoking participants in the control group and 13 in the interventional group).

Although with some discrepancy, hypertension is another omnipresent PSCI predictor [4, 14, 27, 33]. No association between hypertension and PSCI was expected in the current study due to the administration of antihypertensive medication to all participants [33] and the unequal recruitment of non-hypertensive subjects (Two non-hypertensive participants in the interventional group and non in the control group).

Moreover, it has been reported that hypertension can exert a small modulatory effect on PSCI, [14] once again highlighting the need for a larger sample size to detect such effects. Interestingly, it is also possible that the statistical results reflect the neuroprotective action of antihypertensive medication, which include maintaining the integrity of the blood-brain barrier, maintaining mitochondrial and endothelial cells' function, and the attenuation of inflammation, all integral steps in PSCI pathogenesis [1, 5, 14].

Diabetes mellitus is another factor that can potentially affect the trajectory of PSCI [4, 5, 14, 27, 34]. While diabetes has been associated with poor cognitive outcomes even in non-stroke patients [14], and has been reported to increase the risk for post-stroke dementia by 1.5 fold [4], numerous other studies, including this one, detected no significant association between diabetes and the progression of PSCI. This could potentially be justified by the observation that the use of antidiabetic medication after a stroke was associated with long-term (12 months post-stroke) normal cognitive functions and a lower risk of PSCI exacerbation [12].

The administration of statin could have similarly affected the detection of a significant relationship between hyperlipidaemia and the progression of PSCI, with the drug having been linked to a lowered risk of cognitive impairment post-stroke [41]. Not only is dyslipidaemia an inconsistent predictor of cognitive decline, but it has been reported to be of opposing and conflicting effects in different populations which could be due to the different constituents assessed in each study [5, 27, 33, 34]. With statin administered to all the participants in the current study, no specific association between PSCI and hyperlipidaemia was expected, beyond its influence on silent infarcts and stroke recurrence which can exacerbate cognitive decline [33].

Ischaemic heart disease has been recognised as a predisposing factor to cerebrovascular damage, which is implicated in PSCI pathogenesis [1]. Furthermore, patients with coronary heart disease were found to be of poorer MoCA performance at 18 months [42]. Thus, a disparity in PSCI progression was expected between participants diagnosed with ischaemic heart disease and their counterparts. The lack of such an observation could potentially be attributed to the absence of matched-pairs design, meaning that the effects of other variables could not be eliminated during the analysis.

Furthermore, no significant influence of thrombolysis or antiplatelets and anticoagulants use on PSCI has been detected. The literature on the potential of anticoagulants and antiplatelets in ameliorating PSCI is promising but scarce, with inconsistent results in randomised controlled trials [43, 44]. Likewise, there is not much literature on the benefits of thrombolysis in regard to PSCI, but thrombolysis has been recognised

as an independent factor for a decreased dementia rate after first-ischaemic stroke events [45]. In the current study, no association was expected between thrombolysis and PSCI due to the majority (97.9%) of the participants not having undergone thrombolysis therapy. It is recommended that a matched-pair study in a larger cohort be carried out to better investigate any potential effects antiplatelets and anticoagulants might have on PSCI.

Results of the linear regression analysis revealed no association between stroke severity and the progression of PSCI. This is contrary to the study's hypothesis, which was based on the reported strong correlation between NIHSS scores and long-term functional outcomes [31].

However, by examining literature, evidence could be found of instances where NIHSS and MoCA outcomes do not correlate. It is postulated that this could reflect cognitive compensation due to the high cognitive reserve of the participants, which depends on the extent of education received [33, 46]. Such a buffering effect is supported by an observed strong interaction between NIHSS scores and cognitive reserves, as well as a better cognitive outcome post-stroke in patients with higher cognitive reserve in comparison to their counterparts [47]. Another possible theory is the NIHSS underestimation of the severity of strokes in the posterior circulation [30]. As such, it is important to consider a complete sociodemographic profile and neuroimaging findings, as well as a matched-pairs design, for a more reliable outcome.

Stroke localisation is an important factor to consider in the context of PSCI [7]. Ischaemic stroke patients with large-artery atherosclerosis (LAA) were associated with the greatest percentage of 3-month PSCI, followed by strokes of undetermined aetiologies (UDA), then cardioembolism (CE), strokes of other determined aetiology (ODA), and finally small-vessel occlusion (SVO) (48). Thus, a variation in the 3-month progression of PSCI was expected to be detected among the different subclassifications. While this was indicated by the one-way ANOVA, the subsequent *post-hoc* Tukey test failed to detect significant difference between the different groups. This could be attributed to the small overall sample size, as well as that of multiple subclassifications (Table I). This reduces the statistical power, rendering the test unable to detect significant differences during pair-wise comparisons, should they exist.

Literature on the effect of OCSP classification on cognitive impairment appears to be scarce, but anterior circulation strokes have been reported as an independent factor for dementia following a first-ischaemic stroke event [49]. Thus, variation in PSCI progress in different OCSP classifications was expected, but none was detected. This could similarly be attributed to a reduced statistical power as a result of the small overall sample size, as

well as that of multiple subclassifications (Table I).

#### • Limitations and Future Research Directions

As discussed, the study suffered from multiple limitations that need to be addressed in future research. These include:

- Small sample size
- Lack of homogeneous groups
- Lack of monitoring of clinical factors during the study
- Incomplete data collection, in addition to lack of complete sociodemographic profile and neuroimaging findings.
- Lack of matched-pairs design

Future research can also benefit from monitoring the participants' diets and physical activity, as well as the use of concurrent biochemical tests to confirm the therapeutic action of the polyphenols.

#### CONCLUSION

Trigona honey supplements could be effective in halting progression of PSCI, and being a smoker can also impact the 3-month progression of the cognitive impairment. However, with no statistically significant relationship detected, stroke severity, TOAST and OCSP classifications appear to have no effect on 3-month progression of PSCI. Various limitations could have impaired the detection of potential association between demographic and pathological factors and the progression of cognitive impairment.

Despite the limitations, conclusions from this study can be helpful in guiding hypotheses about the employment of Trigona honey in the therapy for PSCI, as well as the different factors and predictors influencing the trajectory of PSCI.

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