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Effects of Six-Month Tualang Honey Supplementation on Physiological and Biochemical Profiles in Asymptomatic, Treatment-naïve HIV-infected Patients

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ABSTRACT

HIV-infected patients are at higher risk of developing metabolic abnormalities. Honey was reported to be beneficial in various metabolic diseases, yet its long-term effects in HIV patients remained unclear. This study aims to evaluate the safety of six-month Tualang honey supplementation in asymptomatic, treatment-naïve HIV-infected patients based on basic physiological and biochemical profiles. This is a randomised, controlled, open-labelled study. A total of 95 asymptomatic, treatment-naïve HIV-infected patients with CD4 counts between 250 to 600 cells/mm^3 were recruited in this study. Tualang honey supplementation at three different doses (20 g, 40 g and 60 g) were given daily for a total of six-month period. Control group was not supplemented with any honey. Body weight, body mass index (BMI), blood pressure (BP), serum glucose, lipid profiles, renal and liver function tests were measured at baseline, three-month and six-month follow-up. An increase in the mean total cholesterol (32% from baseline) was observed in control group at six-month follow up. The mean total cholesterol and other measured parameters were relatively maintained in Tualang honey-supplemented groups. A significant increase ($p = 0.003$) in the blood glucose was observed in group receiving 60 g honey at six-month follow-up but the level was still within normal range. In conclusion, at the doses and duration tested. Tualang honey supplementation is safe to be given and may potentially delay dyslipidaemia progression in treatment-naïve HIV-infected patients.

***Keywords*:** Tualang honey, HIV, Asymptomatic, Safety, Physiological profile, Biochemical profile.

Introduction

The human immunodeficiency virus (HIV) infection remains a major threat to global health which has claimed about 35 million lives so far.[1] As of 2018, about 37.9 million people living with HIV (PLHIV) with 1.7 million newly infected cases were reported globally.[2] In Malaysia, estimated PLHIV is 87, 122 with an average of 3400 new HIV infection cases per year were reported and remained relatively static between year 2010 and 2017. Among this, more than 70% of the new infection in 2017 occurs in people aged between 20 and 39 years old.[3]

Patients with HIV infection will slowly progress to develop acquired immune deficiency syndrome (AIDS) if they are left untreated. Although there is no drug that can cure the disease, antiretroviral therapy (ART) can be offered to slow down the disease progression and inhibit virus transmission.[2] However, in Malaysia, only approximately 54% of PLHIV were on ART coverage as of 2017.[3] Social stigma and discrimination, patient's willingness to initiate therapy as well as poor adherence to medication or follow-up clinic visits are among the hindering factors for low ART coverage and successful treatment plans.[4] In addition, poor adherence can be partly attributed to the short-term side effects of ART such as gastrointestinal disturbances or long-term side effects such as increased risk to develop metabolic syndromes and cardiovascular diseases.

Metabolic syndrome represents a cluster of risk factors including obesity, insulin resistance, impaired glucose metabolism, high blood pressure and dyslipidaemia which collectively contribute to increasing risk of cardiovascular disease and diabetes mellitus. HIV infection is also implicated in metabolic abnormalities independent of ART.[5] For instance, greater insulin resistance associated with coronary artery stenosis was reported in HIV-infected patients when compared to HIV-uninfected men.[6] Immunosuppression and active viral replication in HIV infection may also contribute to increased risk of hypertension.[7] Development of metabolic syndromes in HIV infection may be attributed to elevated oxidative stress and chronic inflammation which play important roles in the disease pathogenesis.[8]

Tualang honey is a wild, multifloral honey produced by *Apis dorsata.* This honey was named after the Tualang trees (*Koompassia excelsa*) found in the Malaysia rain forest where the giant bees build their hives. Tualang honey is rich in vitamins, minerals and phenolic compounds, some of which include gallic acid, caffeic acid, catechin, kaempferol, quercetin and others with antioxidant and anti-inflammatory properties.[9,10] Considering honey as a nutritious supplement, it may be useful in HIV patients who are prone to develop multinutrient deficiencies. The beneficial effects of Tualang honey have been reported in various disease models such as in postmenopausal women, oligospermic men, chronic obstructive pulmonary disease patients as well as in animal disease models.[11–15] Despite their beneficial effects in various disease models, the safety of long-term honey consumption particularly in vulnerable groups were relatively unknown. Therefore, this study aims to evaluate the safety of six-month Tualang honey supplementation based on basic physiological and biochemical profiles in asymptomatic, treatment-naïve HIV patients. This is important to ensure that honey is safe

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before long-term consumption can be recommended in chronic HIV infection.

Materials and Methods

Tualang honey

Tualang honey was supplied by Federal Agriculture and Marketing Authority (FAMA) Malaysia. The honey was gamma-irradiated at 20 Gy to ensure sterility and to prevent possible infection in immunocompromised patients. The honey was individually packed in a sachet of 20 g to ensure exact amount of honey was given to the subjects.

Subjects recruitment and study design

The G*Power software (version 3.0.10; Universitat Kiel, Germany) was used to calculate the sample size. Repeated measure ANOVA within-between interaction was used. The power of the study and effect size were set at 0.9 and 0.20, respectively. The total targeted sample size was 92 subjects after considering 20% dropout rate.

Asymptomatic HIV-positive subjects from the Pengkalan Chepa Prison, Kelantan, Malaysia who volunteered to participate were initially enrolled and screened for CD4 counts. Participants with CD4 counts between 250 to 600 cells/mm^3 and not on antiretroviral treatment (ART) were recruited in this study. Participants with any associated illness such as diabetes as well as chronic liver or renal diseases were excluded from this study. A written informed consent was obtained from all the participants.

The recruited subjects were block-randomized into four groups: three groups were given Tualang honey at 20 g, once daily (TH20; n = 26), twice daily (TH40; n = 24) or thrice daily (TH60; n = 22) for six months while the control group (CTRL; n = 23) was not given any honey throughout the study period. Tualang honey was consumed by the subjects followed by a glass of plain water an hour before their meal under the supervision of a prison officer to ensure compliance. All subjects (treatment and control groups) received same diet provided by the prison authority.

The physiological parameters such as body weight, body mass index (BMI) and blood pressure were recorded at baseline, three-month and six-month follow-up. During each follow-up, blood was collected in the morning (8-9 am) for measurement of serum glucose, lipid profile, renal function and liver function tests. Those who lost to follow-up were excluded from data analysis.

Ethical statement

Ethical clearance was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USMKK/PPP/JEPeM [198.3(1)]) in accordance to the guidelines outlined by Helsinki Declaration and was approved by the Malaysian Prison authority [JP/LTH/Rd/102/3 Klt.28 (91)].

Statistical analysis

Data entry was performed using a statistical software package for Windows (SPSS), version 22.0 (IBM Corporation, USA). The descriptive data were presented as mean [standard error of mean (SEM)]. Data were analysed using repeated measures ANOVA to assess if there were significant differences within-group (time effects) and between-groups (treatment effects). If within-group analysis showed significant differences ($p<0.05$), subsequent pairwise comparison with Bonferroni correction was performed. Meanwhile, if between-group analysis showed significant differences ($p<0.05$), post hoc multiple comparisons was used. The results were expressed in mean difference (95% confidence interval) [MD (95% CI)]. A two-sided p-value of less than 0.05 is considered statistically significant

Results and Discussion

A total of 95 subjects were recruited in this study. Majority were males (85.3%) and the subjects' age range from 21 to 58 years. The mean CD4 counts at baseline was 414.06 (98.20) cells/mm^3 and there were no significant differences between the groups. The descriptive statistics of all parameters measured were summarized in Table 1 (body weight, BMI, blood pressure, serum glucose and lipid profile) and Table 2 (renal and liver function tests). All the parameters were within normal range with exception to slightly higher total cholesterol (>5.2 mmol/L) in control group at six-month follow-up and generally lower HDL cholesterol (< 1 mmol/L) in all four groups.

The repeated measures ANOVA for within-group and between-groups analyses for all parameters were summarized in Table 3. For between-group analysis, no significant differences were observed, indicating honey supplementation at selected dose does not alter metabolic profiles of the subjects. For within-group analysis, significant differences in the serum glucose, low density lipoprotein (LDL) cholesterol, triglycerides (TG), blood urea, creatinine, albumin, globulin and gamma-glutamyl transferase (GGT) were observed, suggesting some changes occurred over time. However, subsequent pairwise comparison for LDL cholesterol, TG, creatinine, albumin and GGT showed no significant differences within the groups. Meanwhile, pairwise comparison for serum glucose, blood urea and serum globulin showed significant differences and the results were shown in Table 4. There was a significant increase in serum glucose at six-month follow-up when compared to baseline in TH60 group. Despite this observation, the mean level was still within normal range. For blood urea, significant reduction was observed in CTRL group at both three-month and six-month follow-up when compared to baseline. For serum globulin, a significant increased level at six-month follow-up was observed in the TH40 group when compared to baseline.

The use of honey as food and medicine was traced since ancient times and its consumption is widely considered safe in the general populations. However, the safety of long-term usage in HIV patients is relatively unknown. This study reports on the physiological and biochemical profiles of asymptomatic, treatment-naïve HIV patients following six-month Tualang honey supplementation.

Body weight loss and muscle wasting are important clinical comorbidities which may accelerate HIV disease progression and has been considered as a strong predictor for mortality in HIV patients.[16,17] In this study, no significant differences in the body weight and BMI at baseline, three-months and six-months follow-up were observed between control and honey-supplemented groups, similar to the findings reported by Woods *et al.* (2002)[18] and Alo *et al*. (2014)[19] In addition, a study in Botswana found that the BMI of HIV-infected adults not on ART remained stable throughout the 18 months follow-up period.[20] Hence, six-month follow-up in this study may not be enough to reflect the disease progression.

Another possible reason for the insignificant differences between control and honey-supplemented groups observed may be explained by relatively adequate and well-balanced diet from the prison. Nutritional requirement is generally increased during HIV disease progression and good nutrition is important to maintain as well as to delay the disease progression. World Health Organization (WHO) recommended that, regardless of HIV status, adequate nutrition through balanced healthy diet is essential for everyone to maintain health and survival.[21] Nevertheless, in asymptomatic HIV-infected adults, an increase in energy demands by 10% is recommended to maintain their body weight and physical activities. Therefore, additional calorie and nutrient intake from honey supplementation is believed to be beneficial to these patients. Furthermore, higher BMI was linked to significant reduced risk of AIDs-defining conditions such as opportunistic infections and cancers. In contrast, lower BMI (18-20 kg/m^2) was linked to significant HIV disease progression.[20] In this study, the BMI values for all groups were within optimal range (20-23 kg/m^2).

HIV patients have greater risk of mortality due to non-AIDS-related death which include cardiovascular diseases.[22] PLHIV or AIDS patients were frequently presented with abnormal lipid metabolism resulting from HIV infection.[23] For instance, low HDL cholesterol, hypertriglyceridemia and hypercholesterolemia are common among untreated HIV patients.[24] In this study, there were no significant changes in blood pressure and lipid profiles in both control and honey-supplemented groups after six-month follow-up. Similarly, Tualang

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honey supplementation up to one year did not significantly alter the lipid profile when compared to baseline were also previously reported in post-menopausal women.[25] However, it is worth mentioning that in the current study, increased mean total cholesterol level (approximately 32% from baseline) and consistently reduced HDL cholesterol level were observed in control group without honey supplementation at six-month follow-up. In contrast, total cholesterol and HDL cholesterol levels were relatively stable in honey supplemented groups in the study. These observations suggest that early dyslipidaemia may have occurred in HIV-infected patients and honey supplementation may confer some protective effects at least by slowing disease progression.

Other metabolic dysfunctions associated with HIV disease include insulin resistance, impaired glucose tolerance, body fat redistribution and abnormal lipid profile. [26,27] In this study, none of the subjects were diabetic since those with concomitant chronic diseases were excluded during subject recruitment. A significant increase in the mean blood glucose level following high dose (60 g) honey supplementation when compared to baseline was observed in this study. However, the levels were still within normal limit. Although statistically not significant, an overall increment in serum glucose level was also observed in control and groups supplemented with low (20 g) and intermediate (40 g) dosage of Tualang honey after six-month follow-up.

Table 1: Descriptive statistics for body weight, body mass index (BMI), blood pressure, serum glucose and lipid profiles.

Parameters	Time	Groups			
		CTRL (n = 23)	TH20 (n = 26)	TH40 (n = 24)	TH60 (n = 22)
Weight (kg)	Baseline	58.28 (1.49)	56.35 (1.53)	58.75 (1.69)	54.89 (1.46)
	3 months	58.79 (1.61)	56.56 (1.53)	58.33 (1.46)	55.71 (1.65)
	6 months	57.63 (2.01)	57.78 (1.65)	58.04 (1.49)	55.61 (1.82)
BMI	Baseline	22.71 (0.56)	21.47 (0.51)	22.22 (0.64)	20.80 (0.51)
	3 months	22.88 (0.56)	21.38 (0.54)	22.08 (0.59)	20.57 (1.05)
	6 months	22.48 (0.77)	21.80 (0.61)	21.71 (0.59)	20.91 (0.60)
SBP (mmHg)	Baseline	118.95 (3.43)	117.31 (2.53)	112.42 (2.21)	111.55 (2.75)
	3 months	117.24 (2.11)	118.04 (3.47)	112.50 (1.84)	114.27 (1.72)
	6 months	117.73 (2.51)	118.52 (2.88)	117.61 (2.04)	115.05 (1.78)
DBP (mmHg)	Baseline	75.59 (2.51)	71.50 (1.59)	70.92 (1.61)	70.59 (1.82)
	3 months	73.86 (2.37)	68.62 (1.86)	70.46 (1.68)	72.32 (1.49)
	6 months	73.32 (2.63)	71.24 (1.65)	72.78 (1.63)	69.64 (1.48)
Glucose	Baseline	4.56 (0.23)	4.59 (0.18)	4.47 (0.28)	4.41 (0.18)
(mmol/L)	3 months	4.83 (0.18)	4.62 (0.14)	4.22 (0.13)	4.61 (0.19)
	6 months	4.75 (0.19)	4.94 (0.18)	4.65 (0.25)	5.05 (0.20)
TC	Baseline	3.96 (0.27)	4.13 (0.17)	4.04 (0.24)	3.98 (0.14)
(mmol/L)	3 months	3.66 (0.19)	4.06 (0.17)	3.95 (0.17)	3.98 (0.15)
	6 months	5.23 (1.50)	4.22 (0.16)	4.02 (0.21)	3.97 (0.16)
HDL-C (mmol/L)	Baseline	0.92 (0.06)	1.00 (0.04)	0.92 (0.06)	0.92 (0.05)
	3 months	0.89 (0.04)	1.00 (0.04)	0.99 (0.09)	0.93 (0.06)
	6 months	0.86 (0.06)	0.99 (0.04)	0.89 (0.05)	0.91 (0.05)
LDL-C (mmol/L)	Baseline	2.22 (0.21)	2.37 (0.15)	2.48 (0.20)	2.33 (0.11)
	3 months	2.01 (0.16)	2.34 (0.13)	2.41 (0.15)	2.03 (0.12)
	6 months	2.22 (0.17)	2.57 (0.13)	2.45 (0.16)	2.39 (0.13)
TG (mmol/L)	Baseline	1.62 (0.15)	1.67 (0.13)	1.78 (0.19)	1.60 (0.15)
	3 months	1.59 (0.19)	1.54 (0.10)	1.56 (0.16)	1.64 (0.11)
	6 months	1.38 (0.14)	1.49 (0.12)	1.50 (0.14)	1.48 (0.12)

Data are presented as the mean (standard error of the mean) [Abbreviations: TH20 = Tualang honey (total 20 g daily), TH40 = Tualang honey (total 40 g daily), TH60 = Tualang honey (total 60g daily), CTRL = control, SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, TG = triglycerides]

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A higher incidence of glucose intolerance was reported in treatment-naïve HIV-infected patients when compared to HIV-negative patients.[28] Yaacob *et al.*[29] reported that honey supplementation (20g) causes glucose levels increment after four-months in post-menopausal women. Similarly, increased HbA1c levels were observed in diabetic patients receiving 8-week honey supplementation.[30,31] In contrast, reduction in HbA1c and blood glucose levels were also previously reported in both diabetic[32] and non-diabetic subjects[33] after honey consumption. The different effects of honey observed may be attributed to different types of honey used. Based on their floral origin, it is suggested that honey have different sugar compositions and hence, different glycaemic indices (GI).[34] For instance, raw Egyptian clover honey was reported to have a low GI value (0.61 ± 0.19),[35] while an intermediate GI values were reported in Malaysian honey (65 ± 7) and Australian honey (59 ± 5).[36] The relatively higher GI values of Malaysian honey together with low physical activity and a sedentary lifestyle may probably explained the higher blood sugar levels and increased weight observed in this study. Considering the reported different effects of honey,[29-33] close monitoring of glucose level is therefore recommended for long-term use of honey in HIV patients.

Table 2: Descriptive statistics for renal and liver function tests

Parameters	Time	Groups			
		CTRL (n = 23)	**TH20 (n = 26)**	**TH40 (n = 24)**	**TH60 (n = 22)**
Renal function					
Blood urea (mmol/L)	Baseline	4.49 (0.22)	3.85 (0.21)	3.67 (0.16)	4.10 (0.22)
	3 months	3.73 (0.21)	3.90 (0.15)	3.65 (0.14)	3.67 (0.15)
	6 months	3.64 (0.19)	3.75 (0.20)	3.61 (0.15)	3.73 (0.18)
Creatinine (mmol/L)	Baseline	76.10 (3.23)	75.65 (2.01)	75.92 (3.30)	75.59 (3.15)
	3 months	89.25 (14.47)	73.72 (1.94)	79.22 (3.33)	73.36 (2.74)
	6 months	73.11 (2.99)	73.50 (1.71)	75.68 (2.94)	71.92 (4.08)
Uric acid (µmol/L)	Baseline	381.30 (23.46)	381.88 (19.09)	351.83 (16.78)	369.50 (27.94)
	3 months	341.25 (14.67)	375.40 (14.48)	356.26 (17.09)	369.45 (26.65)
	6 months	382.37 (23.10)	376.88 (12.91)	345.05 (16.07)	367.05 (19.91)
Liver function					
Total Bilirubin (µmol/L)	Baseline	10.76 (1.10)	10.92 (0.98)	10.83 (1.03)	9.93 (0.85)
	3 months	9.89 (1.06)	11.28 (1.12)	10.17 (0.87)	9.37 (0.56)
	6 months	9.15 (0.80)	10.18 (1.16)	10.56 (0.88)	9.78 (1.00)
Albumin (g/L)	Baseline	40.10 (1.26)	40.92 (0.76)	41.50 (1.07)	39.41 (0.77)
	3 months	38.35 (0.84)	39.32 (0.63)	39.83 (0.79)	38.18 (0.71)
	6 months	37.79 (1.24)	38.96 (0.52)	38.41 (0.86)	38.23 (0.73)
Globulin (g/L)	Baseline	45.10 (1.71)	44.85 (1.17)	41.58 (1.46)	44.86 (1.43)
	3 months	44.40 (1.65)	45.12 (1.42)	43.00 (1.29)	45.14 (1.32)
	6 months	45.21 (1.07)	45.54 (1.18)	44.59 (1.63)	46.82 (1.44)
ALP (IU/L)	Baseline	91.10 (5.98)	82.54 (4.40)	84.96 (4.19)	78.86 (4.66)
	3 months	88.00 (6.01)	79.44 (3.90)	82.00 (3.76)	85.05 (5.04)
	6 months	85.84 (5.25)	83.38 (4.22)	82.27 (3.93)	83.09 (5.75)
AST (IU/L)	Baseline	40.00 (9.13)	29.35 (1.95)	33.83 (6.16)	32.09 (5.02)
	3 months	26.95 (2.43)	30.40 (2.17)	31.22 (3.84)	27.77 (3.02)
	6 months	28.63 (3.58)	33.08 (2.05)	45.64 (15.87)	31.32 (3.75)
ALT (IU/L)	Baseline	39.55 (10.06)	33.85 (4.88)	37.86 (10.25)	27.95 (5.13)
	3 months	23.85 (3.13)	30.80 (3.06)	35.91 (6.71)	23.82 (4.15)
	6 months	27.89 (6.05)	35.79 (4.14)	63.09 (32.26)	26.82 (3.48)
GGT (IU/L)	Baseline	41.60 (10.16)	44.50 (8.04)	43.58 (9.91)	35.00 (6.56)
	3 months	32.35 (6.20)	34.64 (5.56)	36.04 (7.49)	33.41 (5.47)
	6 months	31.05 (4.94)	47.46 (9.13)	41.59 (6.71)	37.73 (7.17)

Data are presented as the mean (standard error of the mean); [Abbreviations: TH20 = Tualang honey (total 20 g daily), TH40 = Tualang honey (total 40 g daily), TH60 = Tualang honey (total 60g daily), CTRL = control, ALP = alkaline phosphatase, AST = aspartate transaminase, ALT = alanine transaminase, GGT = gamma-glutamyl transpeptidase]

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Table 3: Summary of the repeated measures ANOVA for within-group (time-effect) and between-groups analysis for weight, BMI, blood pressure, lipid profiles, renal function and liver function tests.

Parameters	Within-group		Between-group	
	F-stat (df)	p-value	F-stat (df)	p-value
Weight (kg)	0.327 (2)	0.722	0.687 (3)	0.562
BMI	0.097 (2)	0.908	1.541 (3)	0.211
SBP (mmHg)	1.130 (2)	0.325	1.576 (3)	0.201
DBP (mmHg)	0.812 (2)	0.446	1.204 (3)	0.313
Serum glucose (mmol/L)	6.232 (2)	0.002*	0.696 (3)	0.557
Lipid profiles				
TC (mmol/L)	1.793 (2)	0.173	0.228 (3)	0.877
HDL-C (mmol/L)	1.441 (2)	0.240	1.613 (3)	0.193
LDL-C (mmol/L)	4.027 (2)	0.020#	0.566 (3)	0.639
TG (mmol/L)	6.088 (2)	0.003#	0.120 (3)	0.948
Renal function				
Blood urea (mmol/L)	8.595 (2)	<0.001*	0.642 (3)	0.590
Creatinine (mmol/L)	3.804 (2)	0.026#	0.936 (3)	0.427
Uric acid (µmol/L)	0.937 (2)	0.394	0.342 (3)	0.795
Liver function				
Bilirubin (µmol/L)	1.552 (2)	0.215	0.495 (3)	0.687
Albumin (g/L)	9.559 (2)	<0.001#	0.921 (3)	0.434
Globulin (g/L)	4.364 (2)	0.014*	0.907 (3)	0.442
ALP (U/L)	0.280 (2)	0.756	0.316 (3)	0.814
AST (U/L)	2.849 (2)	0.064	0.621 (3)	0.604
ALT (U/L)	3.052 (2)	0.053	1.321 (3)	0.273
GGT (U/L)	5.588 (2)	0.005#	0.268 (3)	0.848

Abbreviations: BMI: body mass index, BP: blood pressure, df: degree of freedom, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides, ALP = alkaline phosphatase, AST = aspartate transaminase, ALT = alanine transaminase, GGT = gamma-glutamyl transpeptidase, df = degree of freedom
*Pairwise comparison with Bonferroni correction indicate significant difference within group (refer Table 4).
#Pairwise comparison with Bonferroni correction indicate no significant differences within group.

Table 4: Pairwise comparison for within-group analysis of serum glucose, blood urea and globulin

Comparison	CTRL		TH20		TH40		TH60	
	MD (95% CI)	p-value	MD (95% CI)	p-value	MD (95% CI)	p-value	MD (95% CI)	p-value
Glucose								
Baseline-	0.30	0.894	-0.02	> 0.999	-0.25	> 0.999	0.20	0.883
3 months	(-0.43, 1.02)		(-0.51, 0.48)		(-1.13, 0.63)		(-0.28, 0.68)	
3 months-	-0.10	> 0.999	0.39	0.096	0.48	0.251	0.44	0.053
6 months	(-0.57, 0.38)		(-0.05, 0.83)		(-0.21, 1.16)		(0.00, 0.89)	
Baseline-	0.20	> 0.999	0.37	0.495	0.23	> 0.999	0.641	0.003*
6 months	(-0.37, 0.77)		(-0.30, 1.05)		(-0.45, 0.90)		(0.21, 1.07)	
Blood urea								
Baseline-	-0.76	0.014*	-0.05	> 0.999	-0.05	> 0.999	-0.42	0.104
3 months	(-1.38, -0.14)		(-0.60,0.50)		(-0.41, 0.40)		(-0.91,0.06)	
3 months-	-0.13	> 0.999	-0.13	> 0.999	-0.16	0.458	-0.06	> 0.999
6 months	(-0.65, 0.39)		(-0.62, 0.37)		(-0.43, 0.12)		(-0.40, 0.51)	
Baseline-	-0.89	0.005*	-0.17	> 0.999	-0.16	0.758	-0.37	0.142

6 months	(-1.52, -0.26)		(-0.73, 0.39)		(-0.52, 0.20)		(-0.82, 0.09)	
Globulin								
Baseline-	-0.47	> 0.999	0.52	> 0.999	0.71	> 0.999	0.27	> 0.999
3 months	(-4.71, 3.77)		(-1.67, 2.71)		(-1.89, 3.32)		(-2.87, 3.41)	
3 months-	-1.11	> 0.999	0.48	> 0.999	2.52	0.263	1.68	0.372
6 months	(-3.16, 5.37)		(-2.44, 3.39)		(-1.15,6.20)		(-1.05, 4.41)	
Baseline-	-0.63	> 0.999	1.00	> 0.999	3.24	0.010*	1.96	0.621
6 months	(-3.66, 4.92)		(-1.88,3.88)		(0.68, 5.79)		(-1.95, 5.86)	

Abbreviations: MD = mean difference, CI = confidence interval, TH20 = Tualang honey (total 20g daily), TH40 = Tualang honey (total 40 g daily), TH60 = Tualang honey (total 60g daily), CTRL = control
*p-values of less than 0.05 were considered significant

Other common causes of morbidity and mortality in HIV patients are impaired kidney and liver functions. For instance, the prevalence of chronic kidney disease (CKD) in HIV range from 2.4 % in Rwanda[37], 2 to 15.5% in the United States[38] and up to 23 % in a study conducted in Nigeria.[39] PLHIV also tend to develop abnormal liver functions and chronic liver diseases since they are associated with other co-morbidities. Among the common co-morbidities include abnormal lipid profiles, insulin resistance, hepatitis B or C co-infections, alcohol abuse as well as drug-induced hepatotoxicity.[40-42] Moreover, HIV itself can cause inflammation and eventually damage the liver. The liver damage may also occur in uncontrolled infection (such as cytomegalovirus, varicella zoster, herpes simplex and the Epstein–Barr virus) especially during immunosuppression.[43] PLHIV also reported to have higher incidence of non-alcoholic fatty liver diseases.[44]

In this study, all subjects showed normal renal and liver functions throughout the study period. Honey supplementation up to six months period did not cause any significant changes in renal and liver functions of HIV patients. Similarly, studies by Muhamad *et al.*[13] and Yaacob *et al.*[29] also showed no significant differences in both renal and liver functions in subjects supplemented with honey.[13,29] However, significant reduction in blood urea nitrogen was observed in control group at three-month and six-month follow-up. Although reduced blood urea nitrogen is clinically less common, it can occur in low protein diet and in advanced liver disease.[45] Considering all the subjects in this study received relatively well-balanced diet in the prison which rule out the diet factor, monitoring of liver function is therefore recommended for early detection of any deterioration in liver function.

Overall, most of the investigated parameters showed no significant changes after six-month follow-up even in the control group which did not receive honey supplementation. As a limitation, the duration of this study may be insufficient to reflect the metabolic changes at the later stage of HIV disease progression. However, it is worth mentioning that Tualang honey supplementation showed beneficial effects in the total cholesterol level which is an important risk factor for cardiovascular diseases. Therefore, a longer study duration is recommended to confirm the beneficial effects of Tualang honey.

Conclusion

In conclusion, at the doses and duration tested, Tualang honey supplementation is safe to be given and may potentially delay dyslipidaemia progression in treatment-naïve HIV-infected patients. However, precautions are needed for high dose honey supplementation as it may cause increased blood glucose levels as seen in this study. Longer study duration is recommended to understand the metabolic changes at later stages of the disease and to confirm the beneficial effects of Tualang honey.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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