ORIGINAL ARTICLE

Tualang Honey Ameliorates The Cholesterol Diet-Induced Non-Alcoholic Steatohepatitis in an Animal Model

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ABSTRACT

INTRODUCTION: Non-alcoholic steatohepatitis (NASH) is the progressive form of non-alcoholic fatty liver disease (NAFLD) with potential progression to cirrhosis. Currently, no definitive treatment is available. This study evaluated the protective effects of Tualang honey (TH), which possesses antioxidant and anti-inflammatory properties, against a high cholesterol diet-induced NASH in an animal model. **MATERIALS AND METHODS:** Thirty-six male Sprague–Dawley rats were fed a 1% cholesterol diet (CD) for 14 weeks, followed by a 12% CD for 6 weeks to induce mild to moderate NASH. At week 20, rats were randomised into groups that continued the CD, with three groups receiving TH at doses of 0.2, 1.2, or 2.4g/kg/day for 4 weeks. Liver function tests, fasting insulin, HOMA-IR, and lipid profiles were assessed. After 24 weeks, livers of the rats were harvested for histological evaluation. Data were analysed using one-way ANOVA with Duncan's and Tukey's post hoc tests; $p < 0.05$ was considered significant. **RESULTS:** TH significantly reduced serum ALT (77.25±16.32 to 50.25 ± 10.56 U/L; p=0.025) and AST (193.25±43.95 to 106.75 ± 24.46 U/L; p<0.01). The 1.2 g/kg/day group showed marked improvement in insulin resistance, with reductions in fasting insulin (4.61 ± 1.38 to 0.18 ± 0.18 mIU/L) and HOMA-IR (1.14 ± 0.38 to 0.03 ± 0.03; both p=0.001). LDL-c decreased while HDL-c increased significantly. Histological analysis of the liver demonstrated improved NAFLD activity scores across treated groups. **CONCLUSION:** Tualang honey improved liver function, insulin resistance, dyslipidaemia, and hepatic histology in a mild–moderate NASH rat model.

Keywords
High Cholesterol Diet, NASH, Tualang Honey

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver condition that arises without evident infection or substantial alcohol consumption. It's progressive form called non-alcoholic steatohepatitis (NASH), is defined by hepatic fat accumulation accompanied by inflammation in the periportal and lobular regions.[1] The development of the disease is multifactorial and strongly associated with obesity, type 2 diabetes mellitus, and insulin resistance.[2,3] NASH may advance to cirrhosis, which can subsequently result in complications including hepatocellular carcinoma and liver failure.[4,5,6]

Animal models are crucial for understanding the pathogenesis and progression of diseases, as well as for developing therapeutic strategies.[7] The methionine-choline deficiency (MCD) diet rapidly induces liver injury, with significant inflammation and fibrosis appearing within two to four weeks. It has a significant impact on the expression of genes related to fibrogenesis, oxidative stress, and inflammation pathways. Despite its effectiveness in mimicking the histological aspects of NASH, the MCD model lacks key features of metabolic dysfunction commonly observed in humans, including obesity and insulin resistance. In comparison, the high-fat

diet (HFD) mouse model better represents the metabolic disturbances linked to NAFLD, such as obesity, insulin resistance, and dyslipidaemia. Nevertheless, the development of liver fibrosis in this model occurs more gradually, usually taking 24 weeks or longer, and the disease is generally less pronounced. Additionally, the HFD influences the expression of genes and proteins related to lipid metabolism, inflammation, and oxidative stress, though the pattern differs from that seen with the MCD diet.[8]

Our pilot study demonstrated that administering a 1% high-cholesterol diet (HCD) for 14 weeks, followed by a 12% HCD for an additional 6 weeks, successfully induced mild NASH in the rat model. This was evidenced by elevated serum alanine aminotransferase levels, increased homeostatic model assessment of insulin resistance (HOMA-IR), and an altered lipid profile.[9]

Tualang honey (TH), a multifloral wild honey produced by the rock bee (*Apis dorsata*), is well known in Malaysia for its diverse medicinal benefits, including antimicrobial, antioxidant, anti-inflammatory, and wound-healing properties.[10] Harvested from hives built high on the giant *Koompassia excelsa*, also known as the "*Tualang* tree," found in the rainforests of Kedah, Malaysia, it has long been used in traditional therapies. The collection of TH is carried out by licensed bee hunters under the supervision of the Malaysian Federal Agricultural Marketing Authority (FAMA). Rich in antioxidant and anti-inflammatory properties, TH shows potential in supporting the management of NASH.[10]

This study aims to evaluate the effects of Tualang honey at varying concentrations in our established NASH animal model.[9]

MATERIALS AND METHODS

Animals

A total of thirty-six male Sprague-Dawley rats (6–8 weeks old, weighing 200–250 g) were obtained from A-Sapphire Enterprise, Seri Kembangan, Selangor, for this study. The rats were housed in pairs under controlled conditions of 60 ± 5% relative humidity and 20 ± 2ºC, with a 12-hour light/dark cycle. Prior to the experiment, all animals were given free access to water and standard rat pellets for two weeks to allow acclimatisation to the new environment.

Cholesterol diet

Analytical-grade cholesterol powder (Nacalai-Tesque, Kyoto, Japan) was incorporated into powdered commercial rat pellets to prepare the experimental diets. For the 1% cholesterol diet (CD) mixture, 1 kg of powdered rat pellets was blended with 10 g of cholesterol and 0.2 g of cholic acid. For the 12% CD mixture, 1 kg of powdered pellets was combined with 120 g of cholesterol and 2 g of cholic acid. To minimize oxidative modification of cholesterol, all diet preparations were freshly prepared daily.

Tualang honey

Tualang honey (TH) (AgroMas, Malaysia) was obtained from the FAMA, Kedah, Malaysia. Its nutritional composition and specifications are summarized in Table I. TH was given once daily to the experimental groups by oral gavage, with the dosage adjusted according to each body weight of the rats. The selected doses (0.2, 1.2, and 2.4 g/kg/day) were based on average local human consumption and converted to rat-equivalent doses using the Km factor.[11] On average, a healthy adult human weighing 60 kg consumes about one teaspoon of honey per day, equivalent to approximately 12 g. This corresponds to 0.2 g of honey per kilogram of body weight (0.2 g/kg). The equivalent rat dose was then calculated using the Km factor as shown below:

Table I: Nutritional composition and specifications of Tualang honey

Parameter, Unit	Result	Standard (Food Reg 1985,Reg. 130)
Reducing Sugar, g/100g:		>60.0
-Fructose	38.0	
-Glucose	36.9	
Sucrose, g/100g	Not detected (<0.01)	<10.0
Ash, g/100g	0.02	<1.0
Moisture, g/100g	23.1	<20.0

Experimental design

Twenty-four male Sprague-Dawley rats were initially fed a 1% cholesterol diet (CD) mixture for 14 weeks. From week 14 onward, all rats received a 12% CD mixture for an additional 6 weeks to establish a mild-to-moderate NASH model. At week 20, once NASH was confirmed

histologically, the rats were randomly allocated into four groups. All groups continued on the CD, while three groups additionally received TH supplementation at doses of 0.2, 1.2, and 2.4 g/kg body weight per day, respectively, for a duration of 4 weeks.

Biochemical study

After 24 weeks, all rats were fasted overnight, weighed, and fully anesthetised with diethyl ether. Blood samples were then collected from the orbital sinus of the mice at the medial canthus of the eye using a haematocrit tube. The samples were analysed for liver enzymes, glucose, insulin, and lipid profile (Roche Cobas, INTEGRA 400 plus). All biochemical assays were performed in triplicate by a certified diagnostic laboratory to ensure analytical precision.

Homeostatic model assessment of insulin resistance

The homeostatic model assessment of insulin resistance (HOMA-IR) is applied as a physiological indicator of insulin resistance. It is calculated using the following formula:

HOMA-IR=[Fasting Glucose (mmol/L)×Fasting Insulin (mIU/L)]/22.5

Histological study

At the end of 24 weeks, the rats were euthanised, and their livers were collected, weighed, and examined macroscopically before being fixed in 10% neutral buffered formalin for histological analysis. Liver tissues were processed using an automated tissue processor (Leica TP 1020) and embedded in paraffin blocks (Leica EG1160). Sections were then cut at a thickness of 3 μm and stained with haematoxylin and eosin (H&E) as well as Masson's trichrome for histological evaluation. The histological grading and staging of NASH were performed based on the Brunt Schema.[12] Brunt schema for NASH grading considers four parameters (steatosis, hepatocytes ballooning degeneration, lobular and portal inflammation) and based on these, NASH is graded into Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe). As for staging, it ranges from Stage 0 to Stage 4 (absence of fibrosis to peri-sinusoidal fibrosis, periportal fibrosis, bridging fibrosis, and cirrhosis). The NAFLD activity scoring was also performed using a scoring system developed by the Nonalcoholic Steatohepatitis Clinical Research Network.[13] The scoring systems take into account three parameters: steatosis (0-3); lobular inflammation (1-3), and ballooning (1-2).

Statistical analysis

Data analysis was carried out using SPSS statistical software version 18.0. A significance level was set at a 95% confidence interval ($p < 0.05$). Mean comparisons were assessed using analysis of variance (ANOVA), and differences between group pairs were further determined using Duncan's and Tukey's post hoc tests.

RESULTS

Biochemistry results

Liver enzymes

All animal groups with TH supplementation (T1, T2, and T3) showed lower mean serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) levels as compared to the 12% CD group. However, only the T2 group ($p=0.025$) exhibited a significant reduction in the ALT level. As for the AST, both groups T2 ($p=0.002$) and T3 ($p=0.010$) showed significant differences with that of the 12% CD group. The mean serum ALP levels between the groups were not statistically significant (Table II).

Fasting blood glucose level

Table II shows the fasting blood glucose level in each of the experimental groups. The mean fasting blood glucose levels were lower in the TH-supplemented groups compared to the 12% CD group. The T2 ($p=0.018$) group exhibited a significantly lower mean fasting blood glucose level.

Fasting insulin level

The mean serum fasting insulin levels were also lower in the T1, T2, and T3 groups as compared to the 12% CD group. The differences were statistically significant in T2 ($p=0.001$) and T3 ($p=0.001$) groups (Table II).

Homeostatic model assessment of insulin resistance

The mean HOMA-IR index for each of the TH groups was lower than that of the 12% CD group. The differences were statistically significant when comparing the 12% CD group with T2 (p=0.001) and T3 groups (p=0.001) (Table II).

Lipid Profile

There was no significant difference in both serum total cholesterol (TC) and triglycerides (TG) throughout the groups. Although all the TH supplemented groups had lower LDL-c levels than the 12% CD group, only groups T1 (p=0.006) and T3 (p=0.013) exhibited a significant difference in the level, respectively. The serum high-density lipoprotein (HDL-c) level showed a significant increment in all groups compared to the 12% CD group (T1 group p=0.001; T2 group p=0.001; T3 group p=0.001) (Table II).

Table II: Blood biochemical parameters of 12% CD and TH-supplemented groups of the NASH animal model.

Group/ Parameter	12% CD (n=4)	T1 (n=4)	T2 (n=4)	T3 (n=4)	Significance
Liver enzymes					
ALT (U/L)	77.25± 16.32	58.75± 6.08	50.25± 10.56	57.00± 12.14	$p<0.05^{b}$
AST (U/L)	193.25± 43.95	140.00± 17.38	106.75± 24.46	122.75± 15.65	$p<0.05^{b,c}$
ALP (U/L)	94.00± 19.20	94.00± 18.57	89.75± 17.23	84.50± 11.27	NS
Glucose, Insulin & HOMA-IR					
Fasting glucose (mmol/L)	5.55± 0.71	4.03± 0.34	3.65± 0.91	4.63± 0.74	$p<0.05^{b}$
Fasting insulin (mU/L)	4.61± 1.38	2.83± 1.38	0.18± 0.18	0.30± 0.40	$p<0.05^{b,c}$
HOMA-IR	1.14± 0.38	0.53± 0.44	0.03± 0.03	0.09± 0.08	$p<0.05^{b,c}$
Lipid profile					
TC (mmol/L)	3.53±0.40	2.58±0.88	3.20±1.14	2.60±0.29	NS
TG (mmol/L)	0.64±0.18	0.73±0.26	0.68±0.21	0.43±0.19	NS
LDL-c (mmol/L)	2.71±0.75	1.10±0.70	1.54±0.68	1.23±0.21	$p<0.05^{a,c}$
HDL-c (mmol/L)	0.27±0.06	1.15±0.24	1.35±0.41	1.18±0.13	$p<0.05^{a,b,c}$

CD = cholesterol diet; TH= Tualang honey; T1 = 0.2g/kg/day TH; T2 = 1.2g/kg/day TH; T3 = 2.4g/kg/day TH; HOMA-IR = homeostatic model assessment of insulin resistance; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatise; TC = total cholesterol; TG = triglycerides; LDL – c = low-density lipoprotein cholesterol; HDL – c = high-density lipoprotein cholesterol. a: 12% CD vs T1; b: 12% vs T2; c: 12% vs T3 ; NS: Not significant.

Pathology results

Gross morphology of the livers

The livers of rats in the 12% CD group appeared enlarged, with a yellow and greasy surface, consistent with hepatic steatosis. In contrast, the livers of TH-treated groups appeared less yellow, less greasy, and more reddish in colour (refer to Figure 1).

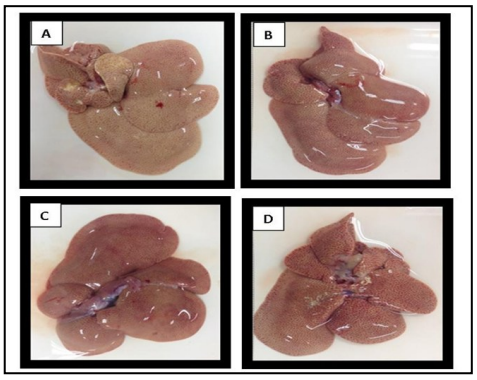

Figure 1: Gross morphology features of livers from (A) 12% cholesterol diet, (B) T1 = treatment dose (0.2g/kg/day); (C) T2 = treatment dose (1.2g/kg/day); (D) T3 = treatment dose (2.4g/kg/day)

The relative liver weights were lower in the T1, T2, and T3 groups compared to the 12% CD group, although there were no significant statistically (Table III).

Table III: Relative liver weight, NASH grading, staging, and NAFLD activity scores in experimental groups.

Group/ Parameter	12% CD (n=4)	T1 (n=4)	T2 (n=4)	T3 (n=4)	Significance
Relative liver weight	3.67±0.30	3.29±0.68	3.09±0.29	3.34±0.47	NS
NASH grading	2.25±0.50	1.25±0.50	1.25±0.50	1.25±0.50	$p<0.05^{a,b,c}$
NASH staging	1.50±0.58	1.00±0.00	0.50±0.58	0.50±0.58	NS
NAFLD activity score	7.50±0.58	4.25±0.96	3.50±1.00	4.50±2.08	$p<0.05^{a,b,c}$

CD = cholesterol diet; TH= Tualang honey; T1 = 0.2g/kg/day TH; T2 = 1.2g/kg/day TH;
T3 = 2.4g/kg/day TH. a: 12% CD vs T1; b: 12% vs T2; c: 12% vs T3 ; NS: Not significant.

Non-alcoholic steatohepatitis grading, staging, and activity scores

The mean grading of each of the TH groups was significantly lower than the 12% CD group (Group T1 p=0.044; Group T2 p=0.044; Group T3 p=0.044). The staging did not significantly differ between the non-TH supplemented group (12% CD group) and the supplemented groups (T1, T2and T3). As for the mean NAFLD activity scores, they were significantly lower in the TH groups (Group T1 p=0.010; T2 p=0.002; Group T3

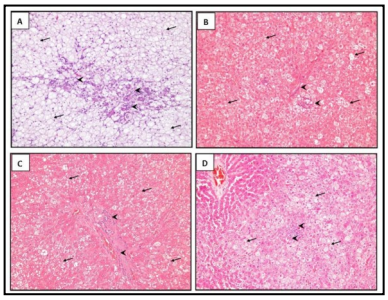

Figure 2: Pictomicrograph of liver sections stained with Haematoxylin and Eosin with x20 objective. A: (12% CD group); B: T1 group; C: T2 group; D: T3 group. The section showed areas of steatosis with portal inflammation. Arrow = steatosis, arrow head = inflammation.

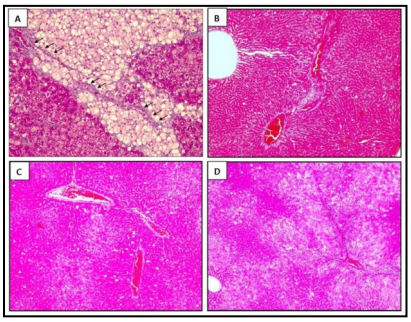

Figure 3: Pictomicrograph of liver sections stained with Mason trichrome. A: 12% CD group (x20 objective). The arrows indicate fibrosis. B: T1 group (x10 objective). C: T2 group (x10 objective). No area of fibrosis is seen in T1, T2, and T3.

Liver histology of the 12% cholesterol diet group

The liver sections exhibited extensive micro vesicular and macro vesicular steatosis affecting nearly the entire hepatic tissue. Occasional ballooning degeneration of hepatocytes was observed. Lobular inflammation was characterized by infiltration of neutrophils and mononuclear cells. Moderate portal inflammation was evident [Figure 2(A)], along with regions of perisinusoidal and periportal fibrosis identified through Masson Trichrome staining [Figure 3 (A)].

Liver histology of 12% cholesterol diet with 0.2 g/kg/ day Tualang honey group (T1)

The sections of the liver showed mixed areas of steatosis, predominantly of the micro vesicular type. Occasional hepatocyte ballooning degeneration was seen. There were areas of mild lobular and portal inflammation [Figure 2 (B)].

Liver histology of 12% cholesterol diet with 1.2 g/kg/ day Tualang honey group (T2)

The liver sections showed patchy areas of steatosis, predominantly of the micro vesicular type. Very occasional hepatocytes with ballooning degeneration were observed. Mild areas of portal and lobular inflammation were seen [Figure 2 (C)].

Liver histology of 12% cholesterol diet (12% CD) with 2.4 g/kg/day Tualang honey group (T3)

The sections of the liver showed patchy areas of steatosis with very occasional hepatocyte ballooning. The liver exhibited mild portal and lobular inflammation [Figure 2 (D)].

DISCUSSION

In our previous study, we demonstrated that a 12% cholesterol diet successfully induced mild to moderate NASH in the rat model.[9] With this established NASH animal model, we further investigated the effects of TH on this animal model. NASH development is believed to be "multiple–hit" in nature, and insulin resistance is proposed to be the first hit that subsequently sensitizes the liver to oxidative stress, inflammation, fibrosis, and cirrhosis.[14] Based on this pathogenesis, TH is seen to have potential benefits in improving NASH because honey has been shown to have antioxidant, anti-inflammatory, antidiabetic, as well as hepatoprotective properties and is known to improve lipid profile.[15–18]

In this study, we have demonstrated that TH supplementation in the NASH animal model improved the liver function profile, HOMA-IR, lipid profile, and histology of the liver. The improvement in liver function was indicated by the significant reduction in both serum ALT and AST levels in the TH-supplemented groups. Our results are consistent with the study by Onochie et al. (2018), which reported that honey exerts hepatoprotective effects, as evidenced by significant reductions in ALT, AST, and ALP levels in male Wistar rats treated with honey. Additionally, several other studies in the literature have also highlighted the hepatoprotective properties of natural honey.[19–22]

In our NASH animal model (CD 12%), the elevation of the AST and ALT is deemed to be related to the underlying pathogenesis of NASH, in which there is destruction to the hepatocytes. Hepatocyte injury in this condition has been associated with oxidative stress. According to Takaki et al. (2017), excessive accumulation of long-chain fatty acids activates the mitochondrial β-oxidation pathway in NASH, resulting in increased production of reactive oxygen species and subsequent cellular damage.[23] TH has been shown to have higher antioxidant activity than other local and commercially available honeys, and this is attributable to the high phenolic and flavonoid content, which may explain the reduction in the liver enzymes seen in this study.[15]

The rats that received TH supplementation showed improved insulin sensitivity, as indicated by decreased fasting insulin levels and lower HOMA-IR values. Insulin resistance is considered a key factor in the progression of NAFLD to NASH. Hepatic steatosis triggers the activation of liver macrophages, including Kupffer cells, which aggravates insulin resistance through the release of inflammatory mediators such as tumour necrosis factor (TNF)-α and interleukin (IL)-1β. These pro-inflammatory cytokines impair hepatic insulin sensitivity by activating inflammatory signalling pathways and suppressing insulin receptor signaling.[3]

Hence, honey most likely modulates insulin resistance in these NASH animal models through its hypoglycaemic effect, attributed to its fructose constituent.[24] Fructose stimulates glucokinase activity, which facilitates the conversion of glucose into glucose-6-phosphate, thereby lowering blood glucose levels.[25] Fructose has also been shown to stimulate insulin from the pancreas,[26] which leads to a decrease in blood glucose. TH has been shown to suppress the activity of protein tyrosine phosphatase 1B (PTP1B), an enzyme that negatively regulates insulin receptor signalling. This inhibition enhances the expression of insulin receptors and stimulates glucose uptake in liver cells, thereby improving glycaemic control.[27]

One of the approaches to the management of NASH involved addressing the dyslipidemia condition, which is one of the criteria of metabolic syndrome known to be closely associated with NASH.[28] We have demonstrated in our animal study that TH supplementation leads to improvement in the lipid profile. Our results are in agreement with those of El-Shafey et al. (2015), who reported that animals supplemented with natural honey exhibited increased HDL-c levels and decreased LDL-c levels.[29] Other studies have also reported that rats given natural honey showed elevated HDL-c levels.[30] Overall, it has been shown that honey supplementation improves lipid abnormalities in both animals and humans, and therefore, it has the potential to improve the lipid profile in NASH patients with metabolic syndrome.[16,17,31–33] Evidence suggests that TH regulates genes associated with lipid metabolism. It decreases the expression of fatty acid binding protein 1 (FABP1) and increases the expression of hepatic lipase (HL) and apolipoprotein A1 (APOA1), thereby supporting better lipid profile outcomes.[34]

In this study, notable improvements in histological grading and NAFLD activity scores were observed across all three groups of animals treated with varying doses of honey compared to the 12% CD group. Both the extent of steatosis and the levels of lobular and portal inflammation showed improvement relative to the 12% CD group. The anti-inflammatory activities of the honey have been linked to its ability to lower the prostaglandin E2 level and the inhibitory effect on nitric oxide, and hence may partly explain the findings in the TH supplemented groups.[35] These histologic changes parallel the changes observed in the biochemical parameters, the effects of TH, which cause a reduction in the liver enzymes and improvement in the insulin resistance and lipid profile.

CONCLUSION

Our study reveals that TH supplement improves the liver function tests, insulin resistance, and the abnormal lipid profile of the NASH animal models. This is further supported by the changes observed in the histological characteristics of the liver of the NASH animal model supplemented with TH. These findings pave the path for further research to be undertaken, one of which is to study the molecular mechanisms by which TH improves NASH biochemically and histologically in the NASH animal model.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

All procedures related to animal handling, treatment, and experimental protocols were approved by the Institutional Animal Care and Use Committee of the International Islamic University Malaysia (IACUC-IIUM), Kuantan Campus (Approval No.: IIUM/IACUC Approval/2014/(4)(17)), and were conducted in accordance with the Malaysian Code of Practice for the Care and Use of Animals for Scientific Purposes.

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CONFLICT OF INTEREST:

No

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