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Modulatory Effects of Natural Honey on Lipid Homeostasis and Hepatic Biomarkers in Albino Rats: Evidence of Hepatoprotective Potential

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Abstract

Background: Natural honey has been the focus of growing attention due to its potential therapeutic effects, especially concerning oxidative stress, liver functioning, and metabolism. The modulatory effects of natural honey on lipid homeostasis and hepatic biomarkers in the albino rats were evaluated in this study.

Methods: A random assignment of twenty male Wistar albino rats was divided into four groups (n = 5): control (distilled water), low dose honey (1 mL/kg), medium dose honey (2 mL/kg) and high dose honey (4 mL/kg). Honey was given orally every day (21 days). Blood samples were taken at the end of the treatment period to analyze the lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C) and hepatic biomarkers (AST, ALT, ALP, total, conjugated and unconjugated bilirubin). The one-way ANOVA with Tukey post hoc test ($p < 0.05$) was used to analyze the data.

Results: Honey administration was seen to significantly decrease the level of AST, ALT, ALP in the treated groups when compared to the control group ($p<0.05$). There was also a significant decrease in total bilirubin and unconjugated bilirubin levels but no significant change in conjugated bilirubin. However, no significant difference was seen among the lipid profile parameters ($p > 0.05$) except for slight differences in triglycerides and VLDL-C and a strong positive correlation was seen between the hepatic markers (AST, ALT, ALP). There was also a significant positive correlation of triglycerides to VLDL-C, and relatively poor correlations of the lipid profile parameters to the hepatic biomarkers.

Conclusion: Under normal physiological conditions, natural honey did not exhibit strong lipid-modulatory activity but displayed strong hepatoprotective activity. These results indicate that the cardiometabolic effects of honey could be mainly mediated by the hepatic stabilization and antioxidant effects of honey instead of direct lipid lowering.

Keywords: *Honey, hepatoprotection, lipid profile, oxidative stress, albino rats, liver enzymes, cardiometabolic health.*

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1. Introduction

Cardiometabolic disorders are a significant health issue in the world, which is caused by a combination of dyslipidemia, hepatic dysfunction, oxidative stress, and chronic low-grade inflammation. An increased level of total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C) and a decreased level of high-density lipoprotein cholesterol (HDL-C) are some of the main causes of atherosclerosis and cardiovascular disease (Du and Qin, 2023; Ference *et al*., 2017). Since the liver is the center of lipid synthesis, lipoprotein metabolism, and cholesterol homeostasis, any disturbance in hepatic functioning is closely associated with the change in the circulating lipid fractions and overall cardiometabolic risk (Lala *et al*., 2023; Thakur *et al*., 2024).

Liver ensures metabolic balance by oxidising fatty acids, synthesising triglycerides, producing bile and detoxification. Therefore, the lipid regulation and the systemic metabolic stability may be impaired because of hepatocellular dysfunction. The most common indicators of hepatocyte integrity and biliary function are biochemical markers (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) (Lala *et al*., 2023; Thakur *et al*., 2024). These parameters are good biochemical surrogates of tissue integrity and changes in them are often indicators of membrane instability, oxidative damage, or inflammatory damage.

Oxidative stress is an important mechanistic connection between hepatic injury and dyslipidemia. The excess of reactive oxygen species (ROS) in the body facilitates lipid peroxidation, cellular membrane disruption, and enzymatic dysfunction, thus contributing to metabolic imbalance and disease progression (Samarghandian *et al*., 2017). Moreover, lipid deposition in hepatocytes can also contribute to the further increase of oxidative stress and inflammation, thus creating a vicious circle worsening the hepatic and cardiovascular outcomes (Younossi *et al*., 2016)

Natural honey is produced by *Apismellifera* and it contains various bioactive compounds such as phenolic acids, flavonoids, enzymes, and vitamins and minerals. These constituents are responsible for its antioxidant and anti-inflammatory properties, with the phenolic fraction playing a significant role in the scavenging of free radicals and the protection of cellular structures (Cianciosi *et al*., 2018; Becerril-Sánchez *et al*., 2021).

A number of studies have been carried out to investigate the effects of honey on lipid metabolism and liver functioning, but the results are still inconsistent. Improvements in lipid profile, including a decrease in total cholesterol, triglycerides and LDL-C, and an increase in HDL-C, have also been reported in experimental studies (Alkhalifah, 2021), although Idrus *et al*. (2020) also noted its cardioprotective effect in the context of lipid metabolism and oxidative stress pathways. Nonetheless, a meta-analysis study by Gholami *et al*. (2022) revealed no significant overall effect, which means that the results might depend on the dose, duration, and botanical origin.

In addition to its lipid modulating property, honey has been shown to have hepatoprotective effects. Nassar *et al*. (2020) demonstrated that honey and related products of bees can decrease biochemical markers of liver damage and oxidative stress in experimental models. There is also emerging evidence that honey may affect gene expression with respect to lipid metabolism and antioxidant defence, and thus has a role to play in maintaining metabolic homeostasis.

Although these findings have been made, very few studies have used lipid profile indices and hepatic biomarkers as combined measures of cardiometabolic health. In the majority of studies these parameters are evaluated independently of each other, which does not allow understanding the interdependence of these parameters. Since the liver plays a key role in the regulation of lipids, a combined test can be considered a more detailed test of the balance of metabolism and integrity of tissues.

Thus, the study examines the modulatory effects of natural honey on lipid homeostasis and hepatic biomarkers in albino rats with the objective of affording the biochemical perspective of its potential use in cardiometabolic protection.

2. Methodology

2.1 Study area

This study was conducted in the Department of Anatomy, Imo State University, Owerri, Nigeria.

2.2 Experimental animals

This study was done using twenty (20) healthy male Wistar albino rats aged 2-3 months and weight of 116.75-130.25 g. The animals were purchased in the Animal House of the College of Medicine, Imo State University. Animals were kept in standard laboratory cages under controlled environmental conditions (temperature: 22-25^{0}C; 12-hour light/dark cycle) and were fed normal pelletized feed and given clean drinking water *ad libitum*. Two weeks acclimatization was noted before the experiment was started. All work was done in compliance with the *Guide to the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, 1986). There was an attempt to reduce the suffering of animals and reduce the number of animals used.

2.3 Ethical approval

All experimental procedures involving animals were conducted in accordance with internationally accepted guidelines for the care and use of laboratory animals. Ethical approval for the study was obtained through the Research Ethics Committee, Faculty of Basic Medical Sciences, Imo State University, Owerri, Nigeria, under institutional oversight for experimental animal research (Approval No.: IMSU/FBMS/REC/2025/014). Animal handling and experimental procedures complied with the principles outlined in the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 2011), and efforts were made to minimize animal suffering and reduce the number of animals used.

2.4 Sample size determination

The size of the sample (n = 5 per group) was calculated with the help of prior experimental studies in which the biochemical and hepatometabolic parameters of rodent models were evaluated using the same sample size (similar group sizes have demonstrated sufficient sensitivity to detect treatment-related differences in the biochemical and hepatometabolic parameters of rodent models) (Erejuwa*et al*., 2012). Moreover, a minimum group size of five animals is generally accepted in exploratory toxicological and biochemical studies to preliminarily assess the effects of treatments.

2.5 Study design and experimental protocol

An experimental design was utilized as a randomized controlled experimental design. The animals were randomly divided into four groups (n = 5/group):

Group A (Control): Distilled water (1 mL/kg body weight)
Group B (Low dose): Honey (1 mL/kg body weight)
Group C (Medium dose): Honey (2 mL/kg body weight)
Group D (High dose): Honey (4 mL/kg body weight)

The doses chosen were based on the past studies that have shown metabolic and hepatoprotective effects of honey in rodent models (Erejuwa*et al*., 2012; Samarghandian*et al*., 2017).

All the treatments were given orally, once a day using a calibrated gavage over a period of 21 consecutive days. This period was chosen due to evidence of observable alterations in lipid and hepatic biomarkers with sub-chronic exposure to natural products within this period (Samarghandian*et al*., 2017).

2.6 Preparation and administration of honey.

Natural honey was sourced out of a certified local supplier and utilized in its natural, unprocessed form to retain its bioactive constituents. The honey was kept in airtight containers at room temperature and kept out of direct sunlight. The calculation of doses was performed depending on the weight of each animal right before the administration. Oral gavage was used to make sure that there was an accurate and consistent dosing across all groups.

2.7 Sample collection

By the end of the 21 days of treatment, animals were fasted overnight with free access to water. The standard protocols were followed to administer anesthesia with intraperitoneal ketamine (80 mg/kg) and xylazine (10 mg/kg) (Flecknell, 2015).

Each animal was sampled (cardiac puncture) to collect approximately 3 mL of blood using sterile syringes. To get serum to carry out biochemical analysis, samples were transferred to plain tubes, allowed to clot and centrifuged at 3000 rpm during 10 minutes.

2.8 Biochemical analysis

2.8.1 Liver enzymes (AST and ALT)

The activities of serum AST and ALT were measured by the Reitman and Frankel colorimetric method modified by Randox Laboratories kits. It is a transamination reaction to the production of ketoacids which react with 2, 4-dinitrophenylhydrazine (DNPH) to form a colored complex that can be measured spectrophotometrically (Reitman and Frankel, 1957).

2.8.2 Alkaline phosphatase (ALP)

The activity of serum ALP was also measured by the colorimetric method described by Roy (1970), which is based on the hydrolysis of thymolphthalein monophosphate to a chromogen that can be measured at 510 nm (Roy, 1970).

2.8.3 Serum bilirubin

The Jendrassik and Grof method was used to measure the total and direct bilirubin concentrations. Diazotized sulfanilic acid reacts with bilirubin to produce azobilirubin which can be measured spectrophotometrically. The subtraction was done to calculate the indirect bilirubin (Jendrassik, 1938).

2.8.4 Lipid profile

Triglycerides: It was determined by an enzymatic colorimetric procedure involving reaction with glycerol phosphate oxidase (Fossati and Prencipe, 1982).

Total cholesterol: Determined by the CHOD-PAP enzyme method (Allain*et al*., 1974)

HDL-C: It is determined after selective precipitation and enzymatic measurement (Warnick*et al*., 1982)

LDL-C: Calculated by Friedewald equation (Friedewald et al., 1972)

$$\textbf{LDL−C=}\ \mathrm{TC}-(\mathrm{HDL}-\mathrm{C}+\frac{\mathrm{TG}}{5})$$

VLDL-C: Estimated indirectly from triglyceride concentrations using the Friedewald approximation:

$$\mathrm{VLDL}-\mathrm{C}=\frac{\mathrm{TG}}{5}$$

This calculation was applied because direct VLDL-C measurement was not performed

2.9 Bias control and quality assurance

Experimental animals were randomly assigned to experimental groups to reduce the selection bias. To minimize measurement bias, biochemical analyses were performed with investigators not knowing to which group they were allocated. All tests were conducted under standardized procedures and calibrated instruments.

2.10 Statistical analysis

IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. The results were presented as mean, standard deviation (SD). The Shapiro-Wilk test was used to test the normality of data distribution, and the homogeneity of variance was tested before analysis. One-way analysis of variance (ANOVA) was used to test the differences between groups followed by the use of the post hoc test (Tukey) to compare the groups. The correlation coefficient (r) of Pearson was used to evaluate the relationships between lipid profile parameters and hepatic biomarkers. The p-value that was regarded as statistically significant was less than 0.05.

3. Results

3.1 Effect of Honey on Serum Lipid Profile.

Table 1 presents the serum lipid profile of albino rats following the administration of natural honey. No statistically significant differences were observed in total cholesterol, HDL-C, and LDL-C across the experimental groups.

Triglyceride levels demonstrated a near-significant variation among the groups (p = 0.059). A borderline statistically significant difference was also observed for VLDL-C (p = 0.050).

Table 1: Serum lipid profile of honey-treated albino rats

Parameter	Group A Control	Group B Low dose	Group C Medium dose	Group D High dose	F-value	p-value
Total cholesterol (mg/dL)	152.80 ± 12.83[a]	155.80 ± 9.36 [a]	165.60 ± 18.84 [a]	150.60 ± 8.11 [a]	1.302	0.308
Triglyceride (mg/dL)	56.40 ± 3.91 [a]	47.20 ± 3.56 [a]	60.40 ± 12.12 [a]	64.00 ± 12.94 [a]	3.044	0.059
HDL-C (mg/dL)	46.60 ± 6.54 [a]	44.20 ± 3.96 [a]	42.60 ± 3.65 [a]	37.80 ± 8.23 [a]	1.973	0.159
LDL-C (mg/dL)	93.40 ± 9.37 [a]	98.00 ± 5.61 [a]	101.00 ± 1.41 [a]	100.60 ± 4.67 [a]	1.708	0.205
VLDL-C (mg/dL)	11.20 ± 0.84[ab]	9.80 ± 0.45 [a]	12.20 ± 1.92 [b]	11.60 ± 1.14[ab]	3.250	0.050

Values are presented as mean ± SD, n = 5 per group. Means with different superscript letters across rows differ significantly at p < 0.05.

3.2 Effect of Honey on Hepatic Biomarker Profile

Table 2 shows the profile of hepatic biomarkers of the experimental animals. AST, ALT and ALP had significant dose-related decreases between the honey-treated groups and control. There were also significant differences in total bilirubin and unconjugated bilirubin and no significant difference in conjugated bilirubin across groups.

Table 2: Hepatic biomarkers of honey-treated albino rats

Parameter	Group A Control	Group B Low dose	Group C Medium dose	Group D High dose	F-value	p-value
AST (IU/L)	8.40 ± 1.52[a]	5.60 ± 0.55 [b]	3.20 ± 0.84 [c]	3.40 ± 1.14 [c]	25.551	<0.001
ALT (IU/L)	6.80 ± 0.84 [a]	4.40 ± 0.55 [b]	2.60 ± 0.55 [c]	2.40 ± 0.55 [c]	52.125	<0.001
ALP (IU/L)	47.40 ± 2.51 [a]	41.40 ± 2.41 [b]	33.00 ± 2.24 [c]	24.00 ± 1.00[d]	114.663	<0.001
Total bilirubin (mg/dL)	0.34 ± 0.11 [a]	0.20 ± 0.00 [b]	0.16 ± 0.05 [b]	0.26 ± 0.05[ab]	6.456	0.005
Conjugated bilirubin (mg/dL)	0.18 ± 0.08 [a]	0.15 ± 0.05 [a]	0.10 ± 0.06 [a]	0.18 ± 0.04 [a]	1.869	0.176
Unconjugated bilirubin (mg/dL)	0.16 ± 0.05 [a]	0.09 ± 0.02[ab]	0.06 ± 0.04 [b]	0.08 ± 0.04 [b]	5.218	0.011

Values are presented as mean ± SD, n = 5 per group. Means with different superscript letters across rows differ significantly at p < 0.05.

3.3 Correlation analysis between lipid profile and hepatic biomarkers was conducted

The analysis showed different level of association of biochemical parameters. The hepatic enzymes showed strong positive correlation among each other, especially between AST, ALT and ALP reflecting the coordinated hepatic biochemical responses. Triglyceride showed a strong positive correlation with VLDL, a relationship which is the expected one physiologically. Most lipid parameter levels, however, only had moderate to weak correlation with hepatic biomarkers indicating that hepatoprotection is mostly independent of significant modulation of lipid parameters in normal physiological conditions.

Table 3: Pearson Correlation Matrix of Lipid Profile and Hepatic Biomarkers

	TC	TG	HDL	LDL	VLDL	AST	ALT	ALP	TB	CB	UB
TC	1.000	-0.370	0.412	0.519	-0.059	-0.048	-0.111	0.095	-0.133	-0.007	-0.144
TG	-0.370	1.000	-0.305	0.038	0.724	-0.296	-0.332	-0.420	0.157	0.060	-0.009
HDL	0.412	-0.305	1.000	0.298	-0.097	0.373	0.410	0.532	0.296	0.309	0.277
LDL	0.519	0.038	0.298	1.000	0.300	-0.285	-0.465	-0.335	0.071	0.366	-0.233
VLDL	-0.059	0.724	-0.097	0.300	1.000	-0.205	-0.266	-0.277	0.243	0.212	0.007
AST	-0.048	-0.296	0.373	-0.285	-0.205	1.000	0.908	0.822	0.610	0.268	0.751
ALT	-0.111	-0.332	0.410	-0.465	-0.266	0.908	1.000	0.849	0.576	0.209	0.730
ALP	0.095	-0.420	0.532	-0.335	-0.277	0.822	0.849	1.000	0.323	0.162	0.494
TB	-0.133	0.157	0.296	0.071	0.243	0.610	0.576	0.323	1.000	0.748	0.733
CB	-0.007	0.060	0.309	0.366	0.212	0.268	0.209	0.162	0.748	1.000	0.220
UB	-0.144	-0.009	0.277	-0.233	0.007	0.751	0.730	0.494	0.733	0.220	1.000

Key: TC = Total Cholesterol; TG = Triglycerides; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; VLDL = Very Low Density Lipoprotein; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; ALP = Alkaline Phosphatase; TB = Total Bilirubin; CB = Conjugated Bilirubin; UB = Unconjugated Bilirubin.

4. Discussion

In the present study, the modulating significance of natural honey on alterations in lipid metabolism and hepatic biomarkers in albino rats was studied. The results showed that the effects of honey on hepatic biochemical parameters were more significant than its effects on lipid profile in the blood. Honey-treated groups showed considerable decrease in AST, ALT and ALP which represent hepatocellular integrity, suggesting a decrease in the leakage of intracellular enzymes into the circulation. Reduction in transaminases is known to result from stabilization of the membrane of the liver cells and maintenance of the functional capacity of the liver (Giannini *et al*., 2005; Pratt & Kaplan, 2000). The results are in accordance with earlier study that showed the hepatoprotective activity of honey. El Rabey *et al*. (2013) found that honey was able to ameliorate liver toxicity in experimental animals following melamine toxicity, while Meligi *et al*. (2020) observed that honey administration significantly decreased liver injury markers in lipopolysaccharide/carbon tetrachloride-induced hepatotoxicity. Likewise, Alfarisi *et al*. (2020) showed

that Trihoney supplementation maintained the integrity of the liver and the biochemical parameters of the liver in rats fed a high-cholesterol diet. This supports the findings of the present study and further enhances the evidence for honey to have hepatoprotective properties. The positive results seen could be related to the antioxidant properties of a honey. The phenolic acids, flavonoids, enzymes, amino acids, vitamins and trace minerals all play a role in the free radical scavenging and cytoprotective effects of honey. Alvarez-Suarez *et al*. (2010) referred to honey as a "biologically active natural product" with significant nutritional and therapeutic properties, and Cianciosi *et al*. (2018) highlighted the properties of anti-oxidation and anti-inflammation of honey phenolics. In addition, Gheldof *et al*. (2002) identified and quantified the major compounds found in honey that are antioxidants, giving some mechanistic support to the role of honey in reducing oxidative damage and maintaining hepatocellular stability. The decrease in unconjugated bilirubin and total bilirubin also indicates an enhanced hepatic metabolic efficiency and bilirubin handling capacity. Bilirubin metabolism is associated with hepatocyte uptake, conjugation and excretion, so lower bilirubin levels may indicate better liver function. But there was no marked effect of honey on biliary excretory function within the period of the experiment, as there was no significant difference in conjugated bilirubin level. This observation confirms earlier reports that biochemical changes in liver enzymes have been reported to precede visible changes in liver structure or on the biliary tract. To support the results obtained in this study, a correlation analysis was used to show strong positive relationships between hepatic biomarkers. AST was positively correlated with both ALT and ALP and ALT was strongly correlated with ALP. The coordinated relationships suggest that the hepatic enzymes responded in a synchronous manner after the administration of honey, suggesting a similar hepatocellular response instead of isolated biochemical fluctuations. Furthermore, the total bilirubin showed strong positive correlations with both both conjugated bilirubin and unconjugated bilirubin, which indicated normal physiological relationships between the bilirubin fractions. The results are consistent and reliable with biochemical data obtained in this study. The changes in the lipid profile parameters were not as significant as those observed in the liver when compared to the other experimental groups. Total cholesterol, HDL-C and LDL-C did not significantly differ, and triglycerides showed a near-significant trend with VLDL-C showing borderline significance.

The present findings indicate that honey has a modulatory effect on lipids in normal physiological conditions, to a certain extent. Partially this observation is in accordance with Chepulis and Starkey (2008) who found that feeding honey for long duration only caused slight changes in lipid profile when compared to the group fed using sucrose, but slightly improved HDL-C in the groups fed using honey. The current results, however, are different from those previously obtained in metabolically stressed or pathological situations. Administration of natural honey led to improvement in lipid parameters in diabetic patients, as reported by Bahrami *et al*. (2009); Yaghoobi *et al*. (2008) reported decreased cholesterol, triglycerides and LDL-C after honey administration. More recently, Yi *et al*. (2024) showed that *Triadica cochinchinensis* honey was effective at improving the hepatic lipid metabolism and decreasing the amount of triglyceride accumulation in aging mice, while Saudi bee honey was seen to significantly lower hepatic triglycerides and cholesterol in rats fed with high fat diet by Al Tamim *et al*. (2025). Correlation analysis showed weak relationships between lipid profile parameters and hepatic biomarker. Most lipid fractions were weakly to moderately correlated with liver enzymes and there was a strong positive correlation between triglyceride and VLDL reflecting the normal physiological lipid metabolism.

The relatively modest lipid response observed in this study suggests that honey might act more like a metabolic stabilizer rather than a strong lipid-lowering agent under normal circumstances. This stabilizing effect is actually quite beneficial, as it shows that honey didn't significantly disrupt lipid balance while still providing positive effects on liver biochemistry. This idea is backed up by Gholami*et al*. (2022), whose meta-analysis of controlled clinical trials found no consistent overall impact of honey on total cholesterol, triglycerides, LDL-C, or HDL-C. They pointed out that lipid outcomes could vary based on factors like dosage, treatment duration, baseline metabolic status, and the type of honey used.

Overall, the findings suggest that honey had a more pronounced protective effect on the liver than on lowering lipids in this experimental model. The coordinated decrease in AST, ALT, and ALP levels indicates better liver cell integrity, while the relatively stable lipid profile suggests that any cardiometabolic benefits might come more from improved liver function and antioxidant activity rather than direct lipid reduction. Since the liver is crucial in lipid metabolism, enhancing liver stability could indirectly support long-term metabolic regulation and cardiovascular health.

5. Conclusion

This investigation showed that natural honey has significant effects on the hepatic biochemical indices in Albino rats, as shown by the significant decrease in serum levels of AST, ALT and ALP. These data suggest that honey has hepatoprotective properties likely due to its antioxidant and membrane stabilizing effects, and enhances hepatocellular integrity. Contrary to this, honey only caused slight changes in lipid profile parameters, not affecting the total cholesterol, HDL-C and LDL-C, and only slightly changing triglycerides and VLDL-C. The other strong and positive relationships obtained between the hepatic biomarkers confirmed the coordinated action of the hepatocytes following the daily administration of honey, and the other weak relationships between lipid parameters and hepatic biomarkers suggested that the effects of honey on the liver were not significantly related. This indicates that, under normal physiological condition, the hepatoprotective action of honey can be achieved independently from the main action on lipid modulation. These results suggest that the effect of honey in healthy animals on hepatic stabilization is more important than on direct lipid regulation. It may, therefore, have a cardiometabolic effect that occurs indirectly via its hepatoprotective effects and its antioxidant action, instead of by a marked effect on lipids.

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