

Modulation of cytochrome P450 3A4 mediated quinine metabolism in healthy volunteers by two honey samples from different floral and geographical sources

Sharon Iyobor Igbino^{1*}, Cyprian Ogbonna Onyeji², Moses Atanda Akanmu³

¹Department of Clinical Pharmacy and Pharmacy Administration, ²Department of Pharmaceutical Chemistry, ³Department of Pharmacology, Obafemi Awolowo University, Ile-Ife, Nigeria

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***Correspondence to:**

Dr. Sharon Iyobor Igbino, Email: sharonomo2002@yahoo.co.uk

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ABSTRACT

Background: Honey is widely used both for its nutritional and medicinal benefits and reports exist to suggest it may alter the disposition of conventional drugs whose metabolism is mediated by CYP3A4. The study aimed at investigating the effect of multiple dose administration of honey sourced from two different geographical zones in Nigeria, on an antimalarial, quinine and its CYP3A4 mediated metabolism.

Methods: In a randomized cross-over study, twenty healthy volunteers divided into two groups A and B [A used honey (HA) from Northern and B used honey (HB) from Eastern Nigeria; n=10 respectively] received single oral doses of 600 mg quinine sulphate tablet alone and after 7 days administration of 10 ml of honey (HA or HB) twice daily. Blood samples collected at the 16th hour following quinine administration were subjected to HPLC analysis.

Results: Compared to baseline, 10 ml of honey HA significantly increased (0.86±0.22 versus 1.36±0.43) (p<0.05; Wilcoxon test); mean metabolic ratio of quinine (3-hydroxyquinine/quinine) in group A subjects. On the other hand, administration of honey HB resulted in a non-significant reduction (p>0.05) (0.84±0.19 versus 0.69±0.34) of the metabolic ratio of quinine in group B volunteers. Also, the geometric mean [95% CI: 0.63(0.45, 0.91)] of quinine metabolic ratio in the presence of honey HA alone was significantly increased (p=0.02, t-test).

Conclusions: Honey sample from Northern Nigeria significantly stimulated CYP3A4-mediated quinine metabolism as reflected by an increased metabolic ratio of quinine. In conclusion some honey samples may have the potential to significantly modulate CYP3A4 activity, thus honey effects cannot be generalized.

Keywords: Quinine, Honey, CYP3A4, Metabolic ratio, Drug-food interactions

INTRODUCTION

In recent years, there is a tremendous interest in the possible role of nutrition in prevention of diseases leading to a growing demand of natural products in human diet.¹ Increasing consumption of medicinal herbs and dietary supplements suggest that, when they are administered in combination with conventional therapeutic drugs, it is likely that constituents in herbal preparations may be substrates, inhibitors, or inducers of Cytochrome P450 and this may have significant impact on the pharmacokinetics of any co-administered drugs metabolized by this system.²

From ancient time, honey a natural product has been widely used in traditional medicine to treat a wide range of ailments and complaints and in recent years there is a rise in its use as household nutritional supplement and as sweetener instead of sugar.³⁻⁶ Honey, apart from being primarily composed of sugar, also contains flavonoids and phenolic compounds such as chrysin, kaempferol, quercetin, pinobanksin, pinocembrin, luteolin, apigenin, genistein, naringenin, hesperetin, P-coumaric acid, gallic acid, ellagic acid, ferulic acid, syringic acid, caffeic acid and vanillic acid, some of which have been shown to increase the activity of CYP3A4 in vitro.⁷⁻¹¹ Few studies have investigated the influence of honey sourced from different geographical regions on the activities of some

CYP450 in rats and humans. It is well known that the composition of natural honey varies, depending on many factors such as the geographical areas, source of honeybee food or florals, climate, environmental conditions and the processing it undergoes.^{1,9,12,13} For instance, honey from India has been reported to significantly induce CYP3A in animal models and in man.¹⁴⁻¹⁷ However two studies in man have found no significant modulating effect of a German and a Nigeria honey on CYP3A4 activity in humans.^{18,19} There is a resurgence of the use of quinine in the treatment of malaria because of resistance development to the other amino quinolones.²⁰ There are numerous evidences that suggest metabolism of quinine to 3-hydroxyquinine is mediated by CYP3A4 and may be used for phenotyping CYP3A4 activity.²¹⁻²⁴ Björkhem-Bergman et al recently demonstrated that quinine metabolic ratio was comparable to midazolam clearance in plasma as a measure of CYP3A4-activity and midazolam is a well validated and recommended probe drug for CYP3A4 activity.^{25,26}

This interaction study has dual rationale. Firstly since honey is a highly popular food supplement in Africa, it is necessary to determine its influence on the metabolism of quinine which is useful in the treatment of severe and complicated malaria in sub-Sahara Africa where malaria is endemic.²⁰ Secondly, quinine has been validated against midazolam, a well-established probe for CYP3A4 activity.²⁵ Modulation of activity of this enzyme by honey provides information on the potential for the honey to influence other CYP3A4 substrates which constitute over 60 % of conventional drugs.²⁷ The only available drug-honey interaction study of honey from Africa by Igbinoba et al suggested that honey sample from western region of Nigeria did not significantly alter CYP3A-mediated metabolism of quinine in healthy human volunteers though a dose-dependent biphasic effect on the pattern of quinine metabolism was observed.¹⁹ Indeed Nigeria is a very large country with different climatic condition and vegetation along the different region and geographical spread. Knowing that numerous factors such as climate and floral sources may affect the honey constituents with

attendant variation in honey, it was deemed necessary to study samples of honey from other geographical region within Nigeria to know how it will modulate CYP3A4 metabolism of quinine. This present study set out to investigate how honey harvested from beehives in the Northern and Eastern geographical region of Nigeria may affect CYP3A4 mediated metabolism of quinine. The metabolic ratio of quinine (3- hydroxyquinine/quinine) in a 16th hour plasma sample collected in healthy volunteers after quinine administration with and without multiple honey intake was used to assess the influence of honey on CYP3A4 metabolism of quinine.^{23,28}

METHODS

Before the commencement of the study, ethical approval was obtained from the Obafemi Awolowo University teaching hospital complex research ethics board and safety committee. Twenty apparently healthy subjects, comprising of 14 males and 6 females (range; mean±SD: age, 19-29 years; 24.16±2.87 years and weight, 45-74 kg; 61.5±9.92 kg) who gave a written informed consent to comply with the study protocol participated in this study. All subjects were healthy according to medical history, laboratory (liver and kidney function test) and clinical investigations. Potential subjects were excluded if on alcohol, on tobacco, pregnant, breast feeding, suffering from chronic disease, on quinine therapy or with known hypersensitivity reaction to quinine or similar agent. From two weeks until the end of the study, the volunteers were told to abstain from taking honey, fruits juices or herbal supplements and quinine.

Honey samples used in the present studies were sourced directly from the beekeepers thus information was obtained about the major floral sources (Table 1) within about 5-10 km of the beehive, presumably the floral the bees fed on. The bees’ major floral source for honey sample from Eastern Nigeria was palm tree; Northern Nigeria Honey sample was produced by bees which fed from about four floral sources (Table 1). The honeys were coded: HA (from Kaduna in Northern Nigeria) and HB (from Umudike in Eastern Nigeria).

Table 1: Major flora within the immediate vicinity of the beehive for the honey samples.

Place/(honey code)	Honey colour	Scientific name	Family	Common name
Northern Nigeria (HA)	Light brown	Butyrospermum parkii	Sapotaceae	Sheabutter tree
		Parkia biglobosa	Mimosaceae	Locustbean tree
		Pennisetum glaucum	Poaceae	Pearl-millet
		Sorghum bicolor	Poaceae	Sorghum
Eastern Nigeria (HB)	Light brown	Elaei guineensis	Aracaceae	Palm tree

Twenty volunteers were randomly divided into two groups (A and B) of ten (n=10) each based on the honey

type (HA or HB) to be taken. To investigate the effect of the selected Nigeria honey samples on CYP3A4 activity

using quinine as the probe drug, a randomized, open label two periods cross over pharmacokinetic design was used with a two-week wash out period allowed between drug administrations. On day 1 of the study, after an overnight fast, each subject in the respective groups (A and B) received a single oral dose of 600 mg of quinine sulphate tablet (Maderich Ltd, Surrey, England) alone or after taking approximately 10 ml of either honey HA or HB, respectively, twice daily for 7 days. In each period, blood samples (5 ml) were collected at the 16th hour post quinine administration.

Method of analysis

A validated HPLC method reported by Babalola et al but modified by Igbinoba et al was employed in the analysis of quinine and its metabolite, 3 hydroxyquinine in plasma.^{19,29} The Agilent HPLC machine (Agilent 1200 series, Agilent Technologies, Santa Clara, California) used in the analysis was fitted with an isocratic pump (model G1341A) coupled with variable wavelength detector [Agilent Technologies; standard version (model G1341B)] set at 254 nm. Drug and metabolite extraction from 1ml of plasma (to which had been added 3.0 µg/ml of primaquine as internal standard) was achieved by precipitating with 200 µl of perchloric acid (70% w/w) and alkalisation with NaOH, followed by extraction with diethylether and subsequent back-extraction into 0.1 M HCl. Chromatographic run was done with a mobile phase composition of methanol: acetonitrile: 0.02 M potassium dihydrogen phosphate buffer (15:15:70) and 74 mmol/l perchloric acid (0.64 ml), adjusted with 10 M NaOH to a pH 2.6 and separation was achieved with an Eclipse XDB-C18 reverse phase HPLC column (150x4.6 mm internal diameter) with a 5-µm particle size (Agilent USA). Linear curves were obtained over a range of 1.25-80 µg/ml with a coefficient of determination (R²) of over 0.998 for standard curves for quinine and its metabolite, 3-hydroxyquinine. The calibration procedures were as previously reported.¹⁹ The limit of quantitation was 0.37 µg/ml and 0.5 µg/ml for quinine and 3-hydroxyquinine, respectively. At concentrations of 0.25 and 4.0 µg/ml, the

intra-day and inter-day coefficient of variation was not greater than 4 % for both quinine and 3-hydroxyquinine. The recovery was at least 93.9 % for quinine and 73.4 % for 3-hydroxyquinine. The accuracy was between 93.1 % and 105.9 %.

Data and statistical analysis

The effect of honey on CYP3A4 metabolism of quinine was estimated using the 16th hour metabolic ratio (MR) of quinine in plasma as defined below.

$$\text{Metabolic ratio} = \frac{\text{Plasma concentration of 3 - hydroxyquinine at the 16th hour}}{\text{Plasma concentration of quinine at the 16th hour}}$$

Statistical analyses were generated using SPSS for Windows, Version 16.0. Chicago, SPSS Inc. Data were generally expressed as mean±SD. In each groups of volunteer (A and B respectively) a non-parametric statistical test (Wilcoxon matched-pairs signed rank test) was used to determine any significant difference in the mean metabolic ratio of quinine at baseline and in the presence of the respective honey. Also the individual metabolic ratios were log-transformed and the mean difference between pairs of data (log MR quinine alone - log MR quinine and honey) was calculated and presented with the antilog. Corresponding 95% confidence intervals for the MR were calculated from the antilog of the mean. Statistically differences in the mean MR of the two set of log transformed data was determined with paired t-test. P value below 0.05 was considered statistically significant.

RESULTS

The study started with twenty volunteers but three subjects (two subjects from group A and one from group B) withdrew from the study because of non-compliance to study protocol. (Tables 2 and 3) show the metabolic ratio (mean±SD) for quinine both at baseline and with ingestion of honey. In group A, quinine mean metabolic ratio significantly increased by 57.63% (P<0.05) while in group B it reduced by 17.4% and this reduction was not significant (P>0.05) (Table 2).

Table 2: Summary of mean metabolic (MR) ratio of quinine (3-hydroxyquinine/quinine) following oral administration of 600 mg of quinine sulphate tablets alone or after intake of 10 ml of respective honey samples twice daily for seven days to groups A and B healthy volunteers respectively.

Honey Type and dose	MR (3-HQN/QN) (No honey)	MR (3-HQN/QN) (With honey)	MR (% change)	P-value
HA; Northern Nigeria (10 ml twice daily)	0.86±0.22	1.36±0.43	↑57.63	0.01*
HB; Eastern Nigeria (10 ml twice daily)	0.84±0.19	0.69±0.34	↓17.40	0.29

3-HQN/QN 3-hydroxyquinine/quinine; Values are expressed as mean ± SD, (Group A; n=8: Group B; n=9), Wilcoxon matched-pairs signed rank test, *P<0.05;

Table 3: Log-transformed mean metabolic ratio of quinine (3-hydroxyquinine/quinine) following oral administration of 600 mg of quinine sulphate tablets alone or after intake of respective honey.

Honey Type and dose	Mean difference (3-HQN _{log} - QN _{log})	(95% CI)	P-value
HA; Northern Nigeria (10 ml twice daily for 7 days)	0.63	0.45, 0.91	0.02*
HB; Eastern Nigeria (10 ml twice daily for 7days)	1.35	0.81, 2.24	0.20

(Group A; n=8; Group B; n=9); 3-HQN/QN 3-hydroxyquinine/quinine;

Paired t-test calculated for log-transformed MR of quinine (with and without honey), *Statistically significant P < 0.05; CI-confidence interval.

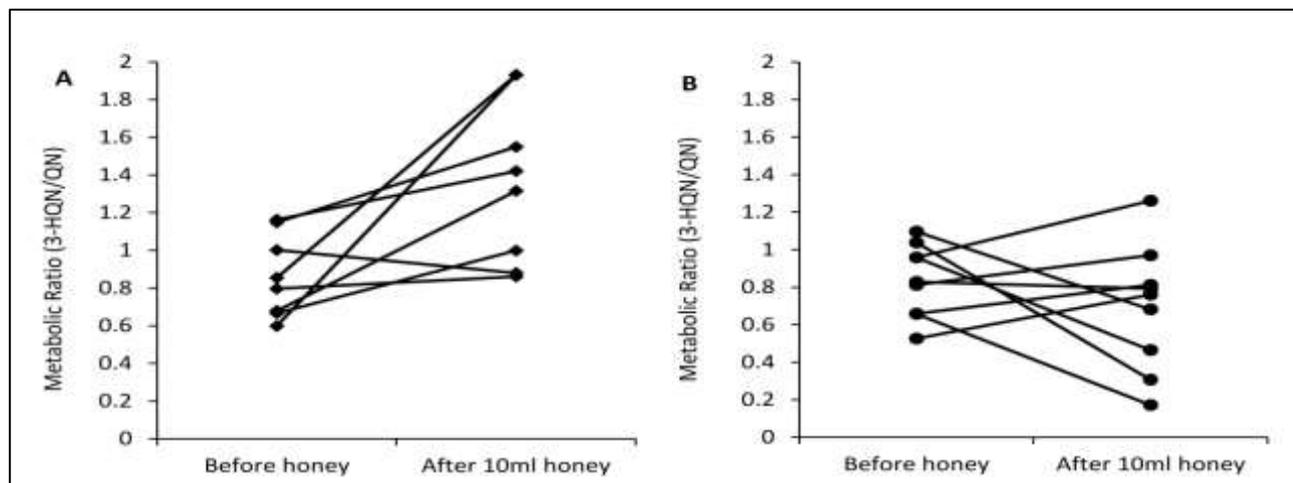


Figure 1: Metabolic ratio of quinine (3-hydroxyquinine/quinine) following oral administration of 600 mg quinine sulphate tablet to healthy volunteers before and after administration of 10 ml of Northern (A) and 10ml of Eastern (B) Nigeria honey twice daily for 7 days [Groups; A: n = 8; and B:n=9].

In (Table 3), the 95% confidence interval (CI) for the log-transformed mean in group A was 0.63 (0.45, 0.91) and was significantly different (p=0.02) from the metabolic ratio in the absence of honey. In group B, the metabolic ratio of quinine pre- and post-honey intake were comparable (P>0.05). (Figure 1) shows the metabolic ratio of quinine in the two groups (A and B) before and after repeated honey (HA and HB) intake respectively. Six out of eight subjects (group A; northern honey) showed increased enzyme activity as reflected by a higher metabolic ratio observed. In volunteers who used eastern honey (group B), less marked stimulatory effect on enzyme activity was observed in about fifty six percent of the volunteers while the remaining forty four percent of the subjects demonstrated inhibitory activity that was more marked (Figure 1).

DISCUSSION

Using quinine as a marker for CYP3A4 activities, we investigated the effects of two honeys from two different geographical zones in Nigeria on CYP3A4 mediated metabolism in healthy volunteers. A broad range of climate and environmental conditions have been shown to alter the levels of plant chemical composition and their secondary metabolite.^{30,31} Variation in honey composition is well established in literature and the chemical constituents of honey generally reflects the flora of plants that the honey producing bee feed on.^{9,12,13} Thus the two

honey samples used in this study were empirically presumed to be different in constituents coupled with the knowledge that the bees that produced the respective honey fed on different floral. The bees which produced the honey from Northern region fed on four different plants while the one from the eastern region was obtained from a research Institute were the bees fed on only palm tree. Determination of the constituents of honey sample used in this study is beyond the scope of the present investigation.

Our results showed that while multiple doses of the honey sample from Northern Nigeria region significantly increased the mean metabolic ratio of quinine at the 16th hour by over fifty seven percent when compared to baseline, the change in mean metabolic ratio of quinine in the presence of honey sample from Eastern Nigerian was not significantly altered. Since quinine has been validated against the clearance of midazolam, a well-established probe for assessing CYP3A-activity in man, findings in this present study may suggest that the honey sample from Northern Nigeria caused a significant induction of CYP3A4 mediated quinine metabolism but honey from Eastern Nigeria did not significantly inhibit CYP3A4 activity.²⁵ The result of the honey sample from Northern Nigeria is in agreement with earlier studies where honey from India revealed a significant induction of CYP3A-mediated metabolism in rabbits and in healthy volunteers.¹⁴⁻¹⁷ In the group that used honey from Eastern

Nigeria, a non-significant inhibitory effect of honey on CYP3A4 activity observed is similar to previous report by Feztner et al where multiple doses of German-sourced honey did not significantly inhibit or alter intestinal or hepatic CYP3A4 metabolism of midazolam in healthy human subjects.¹⁸

Contrary to the result of honey sample from Northern Nigeria, a very recent quinine-honey interaction study of Nigeria honey sample from western region of Nigeria indicated a non-significant dose dependent biphasic effect on quinine metabolism with a lower dose of honey suggesting stimulation and a higher dose indicative of inhibition in CYP3A4 activity in the same group of healthy volunteers.¹⁹ Furthermore, six out of the eight subjects (group A) who used Northern honey showed increased enzyme activity as reflected by a higher metabolic ratio post honey intake (Figure 1). In group B (used eastern honey); stimulatory and inhibitory activity on CYP3A4 was comparatively spread among the volunteers. This observed non-uniform pattern of effect of honey on CYP3A4 activities is similar to a previous report on the effect of honey on the activities of CYP2C19 where five volunteers showed increase in metabolic ratio and seven volunteers a decrease in metabolic ratio of dextromethorphan.¹⁷

Thus far, studies on interaction between honey and CYP3A4 substrates have been carried out using honey from different geographical zones and climatic conditions. Putting together our present results and evidences from previous reports in literature, honey seems to have a potential to exact either a stimulatory or inhibitory effects on CYP3A4 activity with or without significant effect. Thus generalization of effect of honey on CYP3A4 substrates may not be appropriate, more so as literatures abound to support that variation in honey constituents exist.^{9,12,13}

CONCLUSION

In conclusion, the results of this study have shown that the two honey samples studied suggest a variable modulatory effect on CPY3A4 mediated metabolism of quinine to 3-hydroxyquinine activity in man. Honey sample from Northern Nigeria alone significantly altered the metabolic ratio of quinine. Potentially, this alteration may affect the therapeutic action of quinine in malaria patient. Making generalization on the effect of honey from a country can be misleading since honey constituents is influenced by the geographical and floral source that produced it.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee, (ERC/2011/11/01)

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