

1 RESEARCH ARTICLE

 2 Effect of Honey on CYP3A4 Enzyme and
 3 P-Glycoprotein Activity in Healthy Human Volunteers

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9 ABSTRACT

10 The activity of cytochrome p450 isozyme 3A4 (CYP3A4) enzyme and P-glycoprotein (P-gp) is modulated
 11 by grapefruit juice and herbal drugs. CYP3A4 is the major phase I drug metabolizing enzyme and P-gp is
 12 an ATP-dependent drug efflux pump that regulates the intestinal absorption of orally administered drugs.
 13 Honey is commonly consumed as a dietary supplement. However, its influence on human CYP3A4 and
 14 P-gp activity is not yet well documented. Therefore, we investigated the influence of a 10-day honey ad-
 15 ministration on CYP3A4 and P-gp activity in healthy volunteers using carbamazepine and digoxin as their
 16 probe drugs respectively. A within-group pharmacokinetic study was done in 12 healthy volunteers. They
 17 were administered single oral dose of carbamazepine (200 mg) and digoxin (0.5 mg) before and after 10
 18 days of honey (10 ml twice daily) intake. Blood samples (5ml) were collected at 0, 0.25, 0.5, 0.75, 1.0,
 19 1.5, 2, 4, 8, 12, 24, 48 and 72 h after drug administration. Concentration of carbamazepine and digoxin in
 20 plasma was measured by HPLC and RIA method respectively. Ten days of honey administration did not
 21 significantly alter the C_{max} , T_{max} and $AUC_{(0-t)}$ of carbamazepine (probe drug for CYP3A4) and digoxin
 22 (probe drug for P-gp). Our results suggest that honey may not significantly modulate the CYP3A4 enzyme
 23 and P-glycoprotein activity. The coadministration of honey with drugs may not result in significant drug
 24 interactions.

 25 **Keywords:** Honey, CYP3A4, P-glycoprotein, carbamazepine, digoxin

26 Honey is a natural saccharine product made by hon- 47 failed to show any significant effect on CYP3A4 [7].
 27 eybees from the nectar of flowers [1]. Being a natural 48 The effect of multiple doses of honey on CYP3A4 in
 28 source of fructose and glucose with some oligosaccha- 49 humans has not been reported to date. It has been well
 29 rides, proteins, vitamins and minerals, honey has be- 50 documented that the CYP3A4 enzyme is involved in the
 30 come a dietary supplement for healthy individuals [2]. 51 metabolism and elimination of carbamazepine [8]. The
 31 Honey is also consumed by many patients with diabetes, 52 pharmacokinetics of carbamazepine is influenced by
 32 hypertension and epilepsy who receive drugs for their 53 alterations in the catalytic activity of CYP3A4 [9].
 33 ailments. This increases the possibility of honey-drug 54 Hence, carbamazepine is used as a probe drug for
 34 interaction. Most of the herb-drug interactions occur at 55 assessing the CYP3A4 enzyme activity in our
 35 the level of metabolism and drug transport mediated by 56 study.

36 CYP 450 group of drug metabolizing enzymes and P- 57 P-glycoprotein (P-gp) is an ATP dependent drug ef-
 37 glycoprotein (P-gp) respectively [3]. 58 flux pump. It plays an important role as a secretory sys-
 38 Among the CYP group of drug metabolizing en- 59 tem in the intestinal barrier and regulates the intestinal
 39 zymes, CYP3A4 is the major phase I drug metabolizing 60 absorption of orally administered drugs [10]. Many
 40 enzyme. It is present in the liver, jejunum, colon and 61 clinically important drugs viz., digoxin, losartan, eryth-
 41 pancreas. It has broad substrate specificity and is re- 62 romycin and rifampin are substrates for P-gp. Some of
 42 sponsible for metabolism of more than 50% of adminis- 63 them besides being a substrate also induce or inhibit the
 43 tered drugs [4]. There are few studies showing the effect 64 P-gp activity. Drugs like fexofenadine, digoxin and lop-
 44 of honey on CYP3A4. Animal studies have shown that 65 eramide are used as probe drugs to assess P-gp activity
 45 multiple doses of honey induced CYP3A4 activity [5,6]. 66 [11]. Among them, digoxin is most commonly used
 46 In a study done in humans, single oral dose of honey 67 [12]. The effect of various dietary derivatives and herbal

Table 1. Pharmacokinetic parameters of carbamazepine (200 mg single oral dose) before and after 10 days of honey administration

Pharmacokinetic parameters	Before honey	After honey
C_{max} ($\mu\text{g.ml}^{-1}$)	4.1 ± 0.28	4.2 ± 0.31
T_{max} (h)	10.1 ± 1.60	9.0 ± 0.90
$AUC_{(0-72)}$ ($\mu\text{g.h.ml}^{-1}$)	203.1 ± 15.30	208.2 ± 17.20

Values are shown as mean \pm SEM. (n=12)

products on the P-gp activity has also been studied. In an *in vitro* study using various fruit extracts, it was found that extracts of strawberry, orange, apricot and mint inhibited the intestinal P-gp [13]. In another *in vitro* study using rat small intestine, extracts of grapefruit juice and orange juice inhibited the transport activity of P-gp [14]. In a study done in humans, grapefruit juice had no effect on P-gp activity [15]. Another human study revealed that St. John's Wort, an herbal product induced P-gp activity [16]. This shows that P-gp is a potential target for drug interactions exhibited by herbal compounds. The effect of honey on P-gp activity has not been studied so far.

Since we wanted to know whether honey, a natural dietary supplement, will interact with concomitantly administered drugs, we investigated the effect of multiple dose administration of honey on CYP3A4 and P-gp activity in humans using carbamazepine and digoxin as the probe drugs respectively. Carbamazepine is a CYP3A4 substrate but it is not a substrate for P-gp [17]. On the other hand, digoxin is a substrate for P-gp only and not a substrate for CYP3A4 [18]. Hence any change in the pharmacokinetic profile of carbamazepine and digoxin due to honey administration may reflect the change in the activity of CYP3A4 and P-gp respectively.

MATERIALS AND METHODS

A within group pharmacokinetic study was done in 12 healthy male volunteers (Age 20-45 years). The mean age of the volunteers was 27.4 ± 1.96 yrs (mean \pm SEM) and their mean body mass index was 23.2 ± 0.94 Kg/m^2 (mean \pm SEM). The study was approved by institutional ethics committee. A written informed consent was taken from all the volunteers. The health of the volunteers was assessed by doing a thorough physical examination and by performing ECG, liver and kidney function tests. Volunteers suffering from chronic diseases or taking concomitant medications were excluded from the study. Similarly, regular users of alcohol and/or tobacco, those with history of vomiting after di-

goxin intake, seizures and drug allergy were also excluded.

Study design

On day 1, single oral dose of 200 mg carbamazepine (Tegrital, Novartis [India] Limited) and 0.5 mg digoxin (Lanoxin, Burrough's Wellcome, [India] Limited) were administered to the volunteers at 7 AM who were fasted overnight. They were not allowed to take food for further 2 h. Blood samples were collected from indwelling venous catheter using heparinised disposable syringes just before and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 4, 8, 12, 24, 48, 72 h after administration of drugs. A standardized breakfast and lunch were given to all the volunteers. From day 5 to day 14, the volunteers were administered 10 ml of honey (Periyakulam Sarwodaya Sangh, Khadi Vastralaya, Theni District, Tamilnadu, South India; Lot No.4/2002) twice daily in empty stomach with 200 ml of water. On day 15, the volunteers were given single oral dose of 200 mg carbamazepine and 0.5 mg digoxin. The blood samples were collected as mentioned before. After separation of the plasma, the samples were stored at -20°C till the drug assays were done. The study protocol is shown as a flow chart in Figure 1.

The honey used in the present study was tested for its purity in Public Health Laboratory, Pondicherry, India. It was found to be within PFA (Prevention of food adulteration act-1955, India) values. It was composed of reducing sugar 71.6%, moisture 24%, sucrose 2.4% and ash 0.3%. The fructose/glucose ratio was 0.97%.

Drug assays

Serum carbamazepine concentration was estimated using a HPLC method [19]. The plasma sample (900 μl) and internal standard (900 μl) were taken in a 2 ml micro centrifuge tube. After vortex mixing, 600 μl was transferred to a conical flask, into which 4:1 mixture of chloroform: methanol was added. After mixing in an orbital shaker, the contents of conical flask were transferred to centrifuging tubes. After centrifugation at 2500 rpm for 10 min, the upper protein layer was transferred into evaporating tubes for evaporation at 50°C . The dried evaporated samples were reconstituted in 400 μl

Table 2. Pharmacokinetic parameters of digoxin (0.5 mg single oral dose) before and after 10 days of honey administration

Pharmacokinetic parameters	Before honey	After honey
C_{max} ($\mu\text{g.ml}^{-1}$)	2.6 ± 0.22	2.5 ± 0.18
T_{max} (h)	1.5 ± 0.26	1.2 ± 0.14
$AUC_{(0-4)}$ (ng.h.ml^{-1})	6.1 ± 0.44	6.2 ± 0.24
$AUC_{(0-72)}$ ($\mu\text{g.h.ml}^{-1}$)	28.9 ± 8.80	27.6 ± 2.20

Values are shown as mean \pm SEM. (n=12)

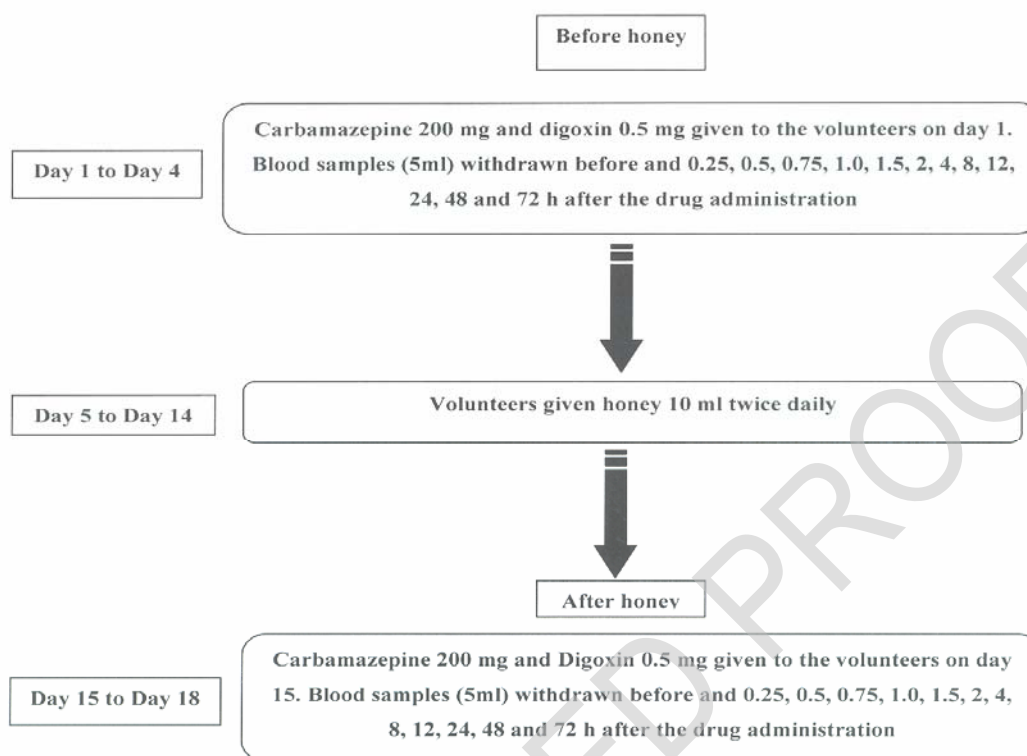


Fig 1. The study plan described as a flow chart.

150 of mobile phase composed of acetonitrile: methanol:174 (T_{max}) were read directly from the actual plasma con-
151 phosphate buffer (12.5:25:62.5, v/v/v) and injected into175 centration data. The area under the plasma concentration
152 HPLC. The inter-day coefficient of variation for car-176 versus time curve [AUC_(0-t)] was calculated by trape-
153 bamazepine HPLC assay was less than 7%. 177 zoidal rule.

154 The digoxin concentration in plasma was measured

155 according to the manufacturer's directions, in duplicate

156 using RIA kits (Orion diagnostics, Finland; Lot No.

157 1588501). Into the appropriate labeled test tubes, 25 µl

158 of calibrators, plasma samples (unknown concentration

159 of digoxin) and 100 µl of antiserum solution were

160 added. All the tubes were mixed on a vortex mixer and

161 then incubated for 1 h at room temperature. One ml of

162 separation reagent was added to all the test tubes and

163 mixed on a vortex mixer. They were centrifuged for 15-

164 20 min at 2000 g. After centrifugation, the supernatant

165 part was decanted and the head of each tube was tapped

166 firmly against absorbent paper. Radioactivity in each

167 tube was counted using gamma counter for 1 min. The

168 measurement range of the kit was 0.5-8.0 nmol/l. The

169 detection limit of the kit was 0.1 nmol/l.

170 Calculation of pharmacokinetic parameters:

171 The pharmacokinetic analysis was done using model

172 independent formulae. The peak plasma concentration

173 (C_{max}) and the time to reach peak plasma concentration

178 Statistical analysis

179 Pharmacokinetic data was expressed as mean ±

180 SEM. The normality of the data was assessed by the

181 Kolmogorov –Smirnov test. The C_{max}, T_{max} and AUC

182 (0-72) were analysed by paired Student's 't' test. All the

183 statistical analyses were carried out by using GraphPad

184 Instat (version 3.05, 2000, San Diego, USA) software

185 system. p<0.05 was considered statistically significant.

186 RESULTS

187 Effect of honey on carbamazepine pharmacokinetic- 188 ics

189 The plasma carbamazepine concentration measured

190 up to 72 h was not significantly altered by honey ad-

191 ministration (Figure 2). After ten days of honey admini-

192 stration, there was no statistically significant change in

193 the mean values of C_{max}, T_{max} or AUC₍₀₋₇₂₎ (Table 1).

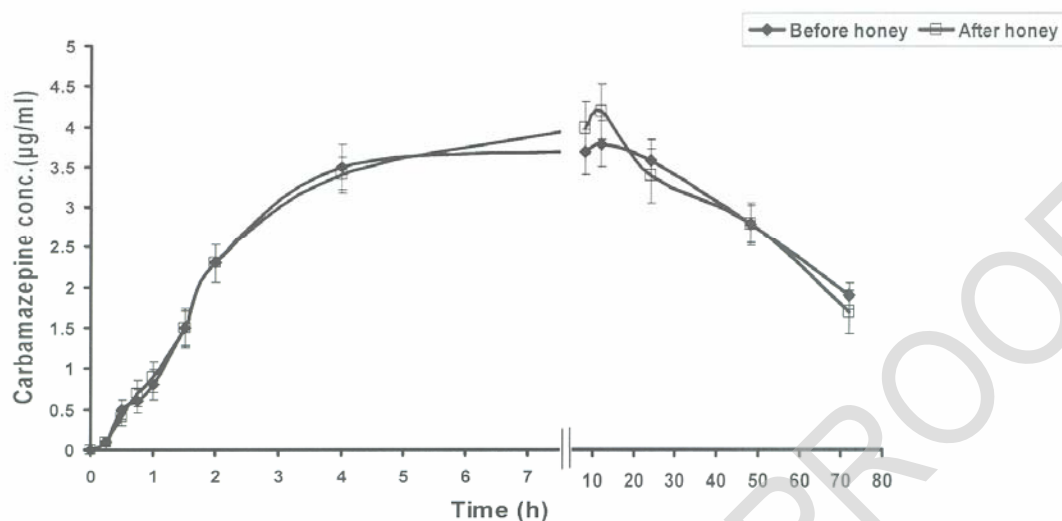


Fig 2. Concentration versus time profile of plasma carbamazepine (AUC_{0-72}) before and after honey. Values are shown as mean \pm SEM.

194 Effect of honey on digoxin pharmacokinetics

195 The plasma digoxin concentrations measured up to
196 72 h were not significantly altered by honey administra-
197 tion (Figure 3). There was no statistically significant
198 change in the mean values of C_{max} , T_{max} , $AUC_{(0-4)}$ or
199 $AUC_{(0-72)}$ (Table 2).

200 DISCUSSION

201 Herbal extracts of garlic [20], grapefruit juice [21],
202 St. John's Wort [22] and milk thistle [23] modulate the
203 activity of CYP3A4 resulting in drug interactions. The

204 extracts of certain herbs used in traditional Chinese
205 medicine like Angelica dahurica [24], Angelica sinensis
206 [25] and Glycyrrhiza glabra [26] modulate the CYP3A4
207 activity. Herbal extracts of Curcumin [27], hawthorn
208 [28], ginseng [29], green tea [30], milk thistle [31],
209 piperine [32], and grapefruit juice [14], orange juice
210 [14] and St. John's Wort [22] modulate P-gp activity.

211 Flavonoids present in herbs have been found to in-
212 teract with CYP3A4 and P-gp [3]. Honey is a natural
213 saccharine product rich in sugars and phytochemicals.
214 The flavonoids present in honey are pinocembrine, pi-
215 nobanskin, chrysin, galangin, quercetin, luteolin and

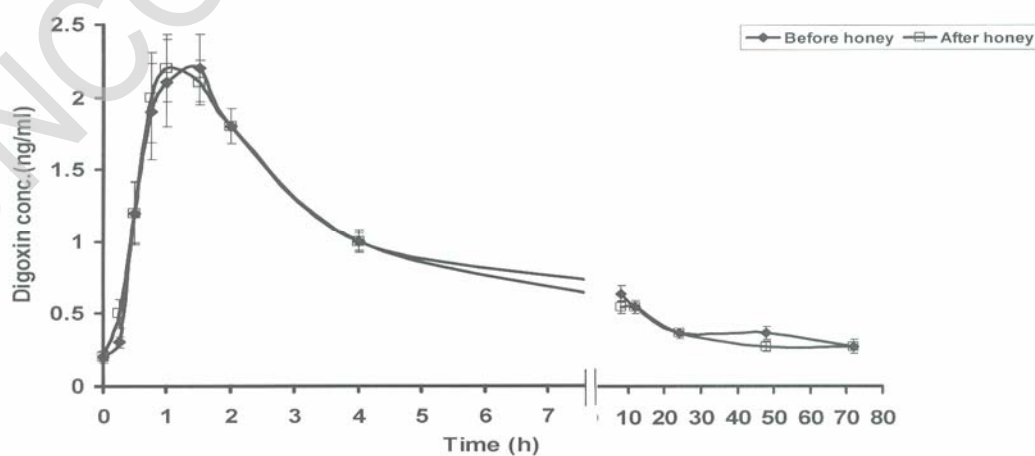


Fig 3. Concentration versus time profile of plasma digoxin (AUC_{0-72}) before and after honey. Values are shown as mean \pm SEM.

- 216kaempferol [2]. Studies in rabbits have shown that
217honey induced the metabolism of diltiazem [5] and car-
218bamazepine [6]. In a human study, where the effect of
219single dose of honey on CYP3A4 was investigated us-
220ing carbamazepine as a probe drug, honey failed to
221show statistically significant effect on carbamazepine
222pharmacokinetic parameters like C_{max} , T_{max} and AUC
223 $(0-72)$ [7]. Hence, we studied the effect of multiple doses
224of honey on carbamazepine pharmacokinetics. In our
225study, multiple doses of honey failed to significantly
226alter the pharmacokinetics of carbamazepine. Hence we
227assume that flavonoids present in honey may not have
228any significant effect on human CYP3A4 activity.
229 Since honey did not change the pharmacokinetics of
230digoxin, it is assumed that the flavonoids present in
231honey may not have any significant effect on P-gp also.
232Becquemont *et al* investigated the effect of grapefruit
233juice on P-gp activity in 12 healthy volunteers using
234digoxin as a probe drug. It was found that grapefruit
235juice did not significantly inhibit the intestinal P-gp ac-
236tivity [15]. Although the C_{max} , T_{max} and AUC $(0-48)$ of
237digoxin did not change significantly, there was a statis-
238tically significant increase in AUC $(0-4)$ of digoxin (i.e. in
239first 4 h) following co-administration with grapefruit
240juice. This correlates with observations made by West-
241phal *et al* that P-gp inhibitors alter the early digoxin
242pharmacokinetics by interfering with the absorption of
243digoxin [33]. In our study, 10 days of honey administra-
244tion did not alter even the early absorption pharmaco-
245netics (AUC $_{0-4}$) of digoxin.
246 Honey and its various derivatives are natural dietary
247supplements consumed commonly all over the world.
248Healthy individuals prefer honey to maintain their
249health and patients with chronic illness take honey along
250with other medications. Hence the possibility of honey
251drug interactions cannot be ruled out. Apart from con-
252suming honey as a single dose along with drugs, some
253patients take honey daily as a nutritional and healthy
254dietary supplement.
255 Since, *in vitro* and *in vivo* studies have reported that
256herbal extracts may modulate CYP3A4 and P-gp activ-
257ity resulting in various types of herb drug interactions;
258the safety of coadministration of honey with drugs
259needs to be studied. This study is an attempt to investi-
260gate the same. To the best of our knowledge, this is the
261first study in humans where the effect of multi dose
262honey administration on CYP3A4 and P-gp activity has
263been investigated. Based upon the present study, it can
264be concluded that honey does not affect the CYP3A4
265mediated metabolism and P-gp mediated transport of
266concomitantly orally administered drugs. The coadmin-
267istration of multiple doses of honey with drugs may not
268produce significant drug interactions.
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