Effect of Khat (Catha edulis) Use on the Bioavailability, Plasma Levels and Antimalarial Activity of Chloroquine

*Faiza H. Issa,1 Molhem Al-Habori,1 Michael L. Chance2
1Department of Biochemistry & Molecular Biology, Sana’a University, Sana’a, Yemen; 2Department of Parasitology, Liverpool School of Tropical Medicine, Liverpool, UK

ABSTRACT: Objectives: This study aimed to evaluate the effect of khat (Catha edulis) on chloroquine (CQ) bioavailability in healthy Yemeni adults and its effect on CQ plasma levels and parasite clearance among malaria patients.

Methods: This study took place between January and April 2007 in Baijl and Sana’a, Yemen. Two CQ doses (600 mg each) were given to 15 healthy males on separate occasions; the first dose was followed by a khat-chewing session (phase one) while controls abstained from khat-chewing for the second (phase two). Additionally, 103 patients with Plasmodium falciparum-induced malaria, including both regular khat chewers (n = 57) and non-khat chewers (n = 46), were treated with CQ (25 mg/kg) over three days. Pharmacokinetic parameters were analysed among both controls and malaria patients. Parasite clearance was also investigated for the latter group.

Results: The mean area under the concentration-time curve (AUC) was 2,108.9 versus 2,797.4 ng/hour/mL, mean peak plasma concentration (Cmax) was 415.6 versus 508.7 ng/mL and mean time to reach Cmax was 3.8 versus 3.6 hours for controls in one phase versus phase two, respectively; both AUC and Cmax levels were significantly reduced by khat-chewing (P < 0.050). For khat- versus non-khat-chewing malaria patients, mean plasma CQ concentrations were 266.4 ng/mL versus 427.5 ng/mL (P < 0.001). Furthermore, CQ was effective in 71.7% and 75.4% of non-khat and khat-chewing malaria patients, respectively (P = 0.823).

Conclusion: Khat-chewing was found to significantly reduce plasma CQ levels among healthy volunteers and malaria patients.

Keywords: Khat; Catha edulis; Malaria; Plasmodium falciparum; Chloroquine; Yemen.

Advances in Knowledge
- This is the first study to reveal that the use of khat (Catha edulis) significantly reduces plasma chloroquine (CQ) levels among malaria patients receiving CQ treatment.
- The results of this study may be used as a reference for future research on possible interactions between khat and other drugs.

*Corresponding Author e-mails: faiza.issa@uta.edu and f.eyssa@hotmail.com
GROUPS and malaria patients made up the control and patient groups, respectively. A total of 15 healthy males >18 years old and between 45–64 kg were recruited from Sana’a, the capital city of Yemen, which is free of malaria. The healthy volunteers were selected from a group of respondents to an advertisement requesting participants for an unpaid pharmacological study. Volunteers with blood film examinations negative for malaria parasites, normal standard laboratory test results (including haemoglobin [Hb] levels, a complete blood count and kidney and liver function tests) and who were otherwise healthy with no history of clinical illness were included in the control group. Individuals with a history of taking antimalarial or prophylactic drugs over the preceding 12 months and those who were unwilling to abstain from khat-chewing for a period of 72 hours were excluded. For the patient group, all patients >18 years old who presented to the National Malaria Control Centre in Bajil, Al-Hudaydah Governorate, West Yemen, with microscopy-confirmed Plasmodium falciparum-induced malaria were recruited (n = 103). This area was identified as a meso- to hyperendemic area for malaria between January–April 2007. All patients had a P. falciparum-positive thick or thin blood smear and were seeking treatment for uncomplicated malaria with no signs of severe malaria, such as an inability to drink/eat or sit/stand upright, repeated vomiting, convulsions, lethargy or unconsciousness and Hb levels of <7 g/dL. The presence of a documented fever was not required for enrolment in the study.

The control group underwent two phases of CQ administration. In the first phase, a single dose of CQ (600 mg) was administered orally to the healthy volunteers immediately before a khat-chewing session which involved chewing ~250 g of fresh khat leaves for 4–5 hours. The second phase occurred four weeks later; participants received a second single dose of CQ (600 mg) after having been instructed to abstain from khat-chewing for the preceding 48 hours. In addition, they were also requested to refrain from khat-chewing for 24 hours on the day of dosing. All of the participants clearly understood the purpose of the study and had agreed to abstain from khat-chewing for the required period of time. The principle investigator contacted all of the volunteers two days before their second CQ dose to reiterate the necessity of abstaining from khat-chewing. For both stages, 3

Methods
This study was carried out between January and April 2007 in Bajil and Sana’a, Yemen. Healthy volunteers and malaria patients abided by the study rules and had a complete blood count and kidney and liver function tests (including haemoglobin [Hb] levels, a complete blood count and kidney and liver function tests) and who were otherwise healthy with no history of clinical illness were included in the control group. Individuals with a history of taking antimalarial or prophylactic drugs over the preceding 12 months and those who were unwilling to abstain from khat-chewing for a period of 72 hours were excluded. For the patient group, all patients >18 years old who presented to the National Malaria Control Centre in Bajil, Al-Hudaydah Governorate, West Yemen, with microscopy-confirmed Plasmodium falciparum-induced malaria were recruited (n = 103). This area was identified as a meso- to hyperendemic area for malaria between January–April 2007. All patients had a P. falciparum-positive thick or thin blood smear and were seeking treatment for uncomplicated malaria with no signs of severe malaria, such as an inability to drink/eat or sit/stand upright, repeated vomiting, convulsions, lethargy or unconsciousness and Hb levels of <7 g/dL. The presence of a documented fever was not required for enrolment in the study.

The control group underwent two phases of CQ administration. In the first phase, a single dose of CQ (600 mg) was administered orally to the healthy volunteers immediately before a khat-chewing session which involved chewing ~250 g of fresh khat leaves for 4–5 hours. The second phase occurred four weeks later; participants received a second single dose of CQ (600 mg) after having been instructed to abstain from khat-chewing for the preceding 48 hours. In addition, they were also requested to refrain from khat-chewing for 24 hours on the day of dosing. All of the participants clearly understood the purpose of the study and had agreed to abstain from khat-chewing for the required period of time. The principle investigator contacted all of the volunteers two days before their second CQ dose to reiterate the necessity of abstaining from khat-chewing. For both stages, 3

Clinical and Basic Research | 0183

**Application to Patient Care**
- Chewing khat was found to significantly reduce plasma CQ levels among malaria patients. Health workers and medication manufacturers should be educated regarding the potential risk of CQ and khat co-administration and patients should be advised to abstain from khat-chewing whilst undergoing CQ treatment.
- The rate of CQ resistance noted in this study was above the threshold recommended by the World Health Organization. This indicates that current antimalarial drug practices in Yemen need to be modified.
Effect of Khat (Catha edulis) Use on the Bioavailability, Plasma Levels and Antimalarial Activity of Chloroquine

mL of venous blood was collected from the subjects before and during CQ administration, at 0.5, one, two, three, four, six, eight, 12 and 24 hours after each dose. Samples were transferred to heparinised tubes and the plasma was separated and stored at -75 °C until analysis. Several studies have shown that CQ levels are negligible four weeks after a single dose. Furthermore, active components of khat, cathine and cathinone are reportedly undetectable 24 hours after chewing. As a result, residual levels of either the first dose of CQ or khat would not interact with the CQ dose administered during the second phase.

Malaria patients were divided into regular khat chewers and non-khat chewers. Patients were considered khat chewers if they reported chewing khat more than three days a week. For khat-chewing patients, the amount and type of khat used and the timing of the khat-chewing sessions was not controlled by the researchers. On average, khat chewers reported using 230–350 g of fresh khat leaves for 4–5 hours per session. All of the malaria patients received oral CQ tablets administered over three days, at 10 mg/kg for the first two days and 5 mg/kg on day three, resulting in a total dose of 25 mg/kg. The full dose was readministered if the patient vomited within 30 minutes of the initial dose. A total of 3 mL of venous blood was drawn and transferred into heparinised tubes the day before CQ dosing (day zero) and during CQ treatment (days 1–3), 24 hours after the dose had been administered. Body temperature was recorded during treatment as a marker of illness/clinical cure. In addition, parasitaemia was routinely assessed on each visit by counting the number of asexual parasites against at least 200 white blood cells (WBCs) in thick blood films, assuming a normal WBC count of 8,000/µL. Patients were followed-up for three days after the first dose of CQ.

A validated high-performance liquid chromatography (HPLC) method was used to determine plasma CQ concentrations in the blood samples of both healthy controls and malaria patients using the LC-2010HT system (Shimadzu Corp., Kyoto, Japan) with an auto sampler. Ultraviolet detection of eluted peaks was performed at 340 nm. Chromatographic separation was carried out using the reversed-phase 150 mm x 4.6 mm HypersilTM BDS C18 HPLC Columns (Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA) with a 5 µm particle size. The mobile phase contained a mixture of water and acetonitrile (ratio: 85:15%) as well as 1% triethylamine adjusted to a pH of 2.8 with concentrated phosphoric acid and a flow rate of 1 mL/minute. The pharmacokinetic parameters of CQ were determined by measuring the area under the concentration-time curve (AUC) from time zero (before the CQ dosing) to 24 hours after CQ dosing, maximal plasma drug concentration (Cmax) and time taken to reach maximum plasma concentration (Tmax). These parameters were calculated using the compartmental/trapezoidal method with Kinetica Software for PK/PD Data Analysis, Simulation and Reporting, Version 4.4 (Thermo Fisher Scientific Inc.). Values were reported as means ± standard deviation.

Among the malaria patients, parasitological and clinical responses to CQ treatment were classified according to different treatment protocols devised by the World Health Organization (WHO) and Osorio et al. In terms of parasitological response, the 1973 WHO protocol was utilised—patients were deemed to exhibit sensitivity (S)/resistance level I (RI) if the P. falciparum parasites had cleared by day two of CQ treatment; RI if there was incomplete clearance of parasites by day two; and RIII if parasite density on day two was ≥25% that of the parasite density observed on day zero. Clinical responses to CQ were classified according to definitions used within the 1996 WHO treatment protocols and methods of Osorio et al. Early treatment failure (ETF) was defined as (1) the development of any danger signs, such as fever and vomiting, severe malaria or parasite positivity on days 1–3 of CQ administration; (2) higher parasitaemia levels on day two than day zero; or (3) parasite density on day three ≥25% that of day zero. Treatment success (TS) was classified as negative parasitaemia on day three. Late treatment failure (LTF) was defined as the development of any danger signs, severe malaria, parasitaemia or fever after day three or an unscheduled return to seek medical help because of clinical deterioration or parasitaemia on any scheduled follow-up day on or after day seven. In this study, follow-up after three days was not possible. Patients who failed to respond to CQ treatment were prescribed sulfadoxine/pyrimethamine. During follow-up, patients received a single dose of primaquine (0.75 mg/kg) at the end of the follow-up period if they were found to have gametocytanya.

The t-test for paired values was used to compare pharmacokinetic parameters of CQ obtained after the two phases of the control group trial and to compare results between khat-chewing and non-khat-chewing malaria patients. Geometric means were used to summarise parasite densities for malaria patients. Parastate clearance and the association with khat use were analysed with a two-sided Fisher’s exact test. A P value of <0.050 was used as the level of significance.

This study was approved by the institutional review boards of the Faculty of Medicine & Health Sciences at Sana’a University and the National Malaria Control Programme (NMCP) in Sana’a. In addition, ethical
permission was granted by the Liverpool School of Tropical Medicine in Liverpool, UK. Informed consent was obtained from all individuals before participation in the study.

Results

The control group ranged in age from 20–30 years old and had a mean Hb level of 16.2 g/dL and mean body weight of 62.86 kg. In phase two versus phase one, there was a significant reduction in mean Cmax and AUC among the healthy controls (415.6 versus 508.7 ng/mL and 2,108.9 versus 2,797.4 ng/hour/mL; \( P < 0.001 \) and 0.002, respectively) [Figure 1]. However, no significant difference was seen in mean Tmax (3.8 versus 3.6 hours; \( P = 0.81 \)) [Table 1]. The malaria patient group ranged in age from 20–45 years old and there were 57 khat chewers and 46 non-khat chewers. Of the khat and non-khat chewers, 25 (43.9%) and 27 (58.7%) were female and 32 (56.1%) and 19 (41.3%) were male, respectively. All patients had a temperature of >37 °C prior to treatment and had normal axillary temperatures by day three of CQ treatment. Plasma CQ levels among khat- and non-khat-chewing malaria patients according to day of treatment are presented in Table 2. Plasma CQ levels were significantly reduced among khat-chewing malaria patients compared to their non-khat-chewing counterparts (266.4 ± 164.3 and 427.5 ± 125.6, respectively; \( P <0.001 \)).

Before CQ treatment, parasite density among the malaria patients ranged from 48–256,800 to 32–111,760/µL for non-khat and khat chewers, respectively. No danger signs or severe malaria symptoms were recorded for any of the patients. Geometric mean parasitaemia before treatment was 1,494/µL (95% confidence interval [CI]: 771–3,837/µL) and 1,861/µL (95% CI: 902–2,890/µL) for khat and non-khat chewers, respectively. On day three of CQ treatment, the geometric mean parasite density was 3/µL (95% CI: 1.7–5.2/µL) and 4/µL (95% CI: 1.9–7.9/µL) for khat and non-khat chewers, respectively. There was no significant difference in mean parasite density (\( P = 0.652 \) and 0.563, respectively) and axillary temperature (\( P = 0.140 \) and 0.145, respectively) between khat and non-khat chewers before treatment and on day three [Table 3].

Among the malaria patients, parasitaemia had cleared completely (S/RI) by day two of CQ treatment for 61 patients (59.2%) while the remaining 42 patients (40.8%) showed resistance at either the RII or RIII levels. Among non-khat chewers, 27 (58.7%) patients were completely clear of parasites by day two, while 19 (41.3%) showed parasitological resistance. However, CQ was effective for 34 khat chewers (59.6%) while 23 non-khat chewers (40.4%) were not clear of parasites by day two. There was no significant difference in overall resistance (RII and RIII) between the two groups (\( P = 0.394 \)). Among the patient group, 76 (73.8%) had

Table 1: Effect of khat-chewing on the pharmacokinetic parameters of chloroquine* among healthy adult males in Yemen (N = 15)

| Parameter               | Mean ± SD | \( P \) value |
|-------------------------|-----------|--------------|
|                         | After 48-hour khat-chewing abstinence period | After khat-chewing session† |
| AUC in ng/hour/mL       | 2,797.4 ± 845.9 | 2,108.9 ± 682.3 | 0.002 |
| \( C_{max} \) in ng/mL  | 508.7 ± 106.4 | 415.6 ± 103.1 | <0.001 |
| \( T_{max} \) in hours  | 3.6 ± 0.5 | 3.8 ± 0.4 | 0.810 |

SD = standard deviation; AUC = area under the time-concentration curve; \( C_{max} \) = peak plasma concentration; \( T_{max} \) = time to reach peak concentration.

*Single dose of 600 mg. †Approximately 250 g of fresh khat leaves for 4–5 hours.

Table 2: Effect of khat-chewing on chloroquine plasma levels among malaria patients in Yemen after chloroquine treatment* (N = 103)

| Day of treatment | Mean plasma level ± SD | \( P \) value |
|-----------------|------------------------|--------------|
|                 | Non-khat chewers (n = 46) | Khat chewers (n = 57) |
| Day one         | 216.5 ± 94.8 | 145.4 ± 73.8 | <0.001 |
| Day two         | 313.3 ± 123.4 | 202.7 ± 130.1 | <0.001 |
| Day three       | 427.5 ± 125.6 | 266.4 ± 164.3 | <0.001 |

SD = standard deviation.

*Total dose of 25 mg/kg over three days.
Effect of Khat (Catha edulis) Use on the Bioavailability, Plasma Levels and Antimalarial Activity of Chloroquine

**Table 3:** Parasitaemia and axillary temperature before (day zero) and after (day three) chloroquine treatment* among khat- and non-khat-chewing malaria patients in Yemen (N = 103)

|                          | Mean† parasitaemia per µL (95% CI) | Mean axillary temperature in °C ± SD |
|--------------------------|------------------------------------|-------------------------------------|
|                          | Day 0                              | Day 3                               |
| Khat chewers (n = 57)    | 1,494 (771–3,837)                  | 3 (1.7–5.2)                         |
|                          | 37.5 ± 0.54                        | 36.8 ± 0.11                         |
| Non-khat chewers (n = 46)| 1,861 (902–2,890)                 | 4 (1.9–7.9)                         |
|                          | 37.4 ± 0.66                        | 36.8 ± 0.14                         |

CI = confidence interval; SD = standard deviation. *Total dose of 25 mg/kg over three days. †Geometric mean.

TS/LTF while 27 (26.2%) had ETF. Overall, rates of TS/LTF were 71.7% and 75.4% among non-khat- and khat-chewing malaria patients, respectively (P = 0.823). There was no significant difference between khat and non-khat chewers in terms of ETF (P = 0.823) [Table 4].

### Discussion

The co-administration of CQ and khat was found to significantly affect the pharmacokinetics of CQ among both healthy controls and malaria patients in Yemen. This was comparable to reported reductions in the pharmacokinetic activity of tetracycline hydrochloride and the low bioavailability of ampicillin and amoxicillin when co-administered with khat. A possible drug-plant CQ-khat interaction exists, as indicated by the significantly reduced CQ AUC and C max values observed with khat use in the present study. The mechanisms underlying this interaction are unknown; however, one possible mechanism may relate to the interaction of the drug with some of khat’s components—tannic acid, cathinone and cathine—which are known to cause the formation of insoluble complexes and non-absorbable compounds. In particular, it has been hypothesised that tannins in khat may interfere with absorption processes in the gastrointestinal tract. Changes in gastric acidity and motility or the delay of gastric emptying may slow absorption of CQ, as these changes will prolong the duration of time that the drug remains in the stomach. Finally, increased diuresis is often reported among khat chewers, possibly due to fluid intake during khat-chewing sessions; this may lead to increased urinary excretion of CQ. Other possible mechanisms of pharmacokinetic interactions between khat and CQ require further investigation.

In the current study, CQ plasma levels were significantly reduced among khat-chewing malaria patients in comparison to non-khat-chewing patients. This may be associated with the general health of this patient group with regards to malnutrition, anaemia and parasitic infestation; Tulpule et al. found faster clearance of CQ in undernourished subjects. In general, khat-chewing-induced symptoms include loss of appetite and malnutrition. This may also affect digestion or absorption of CQ. In addition, differences in plasma CQ levels between healthy controls and malaria patients could be related to the age differences between the two groups. Edwards et al. reported that CQ blood concentrations and AUC were significantly higher in malaria patients receiving oral CQ treatment than in healthy subjects, suggesting that malaria induces absorption changes and increases systemic exposure to CQ. In the current study, reduction in the plasma CQ levels among khat-chewing malaria patients could be related to impaired gastrointestinal absorption due to the effect of khat on CQ absorption.

In the current study, the rate of CQ resistance among the malaria patients was above the acceptable level of resistance determined by the WHO. Several studies conducted in different governorates of Yemen have also demonstrated high to medium rates of CQ treatment failure, including rates of 61% in the

### Table 4: In vivo Plasmodium falciparum response to chloroquine treatment* in khat- and non-khat-chewing malaria patients in Yemen (N = 103)

|                        | S/RI † | RII † | RIII † | Overall R † | TS/LTF ‡ | ETF § |
|------------------------|--------|-------|--------|-------------|----------|-------|
| Khat chewers (n = 57)  | 34 (59.6) | 17 (29.8) | 6 (10.6) | 23 (40.4) | 43 (75.4) | 14 (24.6) |
| Non-khat chewers (n = 46) | 27 (58.7) | 10 (21.7) | 9 (19.6) | 19 (41.3) | 33 (71.7) | 13 (28.3) |
| Total                  | 61 (59.2) | 27 (26.2) | 15 (14.6) | 42 (40.8) | 76 (73.8) | 27 (26.2) |

S = sensitivity; R = resistance level; TS = treatment success; LTF = late treatment failure; ETF = early treatment failure.

*Total dose of 25 mg/kg over three days. †According to the 1973 treatment protocol of the World Health Organization. ‡According to values obtained on day three of treatment and the 1996 treatment protocol of the World Health Organization. §According to values obtained on day three of treatment and the methods of Osorio et al. *P = 0.394; ‡P = 0.823.
Al-Musaiem district of Lahj Governorate and 16.1% in the Hethran and Al-Mafatch districts of Taiz Governorate. In addition, Al-Mekhlafi et al. observed a high frequency of *P. falciparum* CQ resistance transporter T76 mutations, suggesting considerable CQ resistance among cases of *P. falciparum*-induced malaria in Yemen. In the current study, parasite densities differed between *khat*- and non-*khat*-chewing malaria patients, although this finding was not significant. Ketema *et al.* similarly observed the mildly antiplasmodial characteristics of *khat* leaves. Antimicrobial activity has also been reported. Several studies have shown that plant alkaloids, flavonoids and tannins demonstrate *in vivo* and *in vitro* antimalarial activity against CQ-sensitive and -resistant strains of *P. falciparum*. However, further studies are needed to investigate the antimalarial activity of *khat*. The limited reduction in parasite densities observed in the current study might be attributed to the antiplasmodial activity of certain compounds in *khat* leaves.

With regards to treatment outcomes, no significant differences were found between *khat*- and non-*khat*-chewing malaria patients in the current study. However, rates of successful treatment may have been overestimated, as certain patients might have been classified as cases of LTF instead of TS had they been followed-up for a longer period of time (e.g. 14–28 days). The lack of follow-up and utilisation of non-age-matched control and patient groups are limitations of the present study. Additionally, the difference between cases of S or RI could not be distinguished at day two; CQ resistance may therefore have been underestimated due to the short follow-up period. A further limitation was the use of CQ over artemisinin-based combination therapy (ACT). In 2005, the NMCP in Yemen replaced CQ with ACT as the first line of antimalarial therapy. Unfortunately, however, this policy was not implemented in practice until 2009. Nevertheless, regardless of current antimalarial treatment guidelines, CQ remains the second most common antimalarial drug prescribed by physicians in public and private health facilities in Yemen. As such, the results of this study should be utilised to educate health workers and medication manufacturers in Yemen as to the potential risk of CQ co-administration among *khat*-chewing patients. Current anti-malarial drug practices in Yemen should be modified accordingly and physicians should advise patients not to chew *khat* whilst undergoing CQ treatment.

**Conclusion**

The findings of this study revealed that CQ plasma levels were significantly reduced by *khat*-chewing; however, *khat*-chewing had no significant influence on rates of *P. falciparum* parasite clearance among malaria patients. The rate of CQ resistance among the patient group was above the acceptable levels determined by the WHO, indicating high CQ resistance in these areas of Yemen. Based on these preliminary findings, patients should be advised not to chew *khat* whilst undergoing CQ treatment.

**CONFLICT OF INTEREST**

The authors declare no conflicts of interest.

**References**

1. Ali BH, Al-Qarawi A, Mousa HM. Effect of grapefruit juice on plasma chloroquine kinetics in mice. Clin Exp Pharmacol Physiol 2002; 29:704–6. doi: 10.1046/j.1440-1681.2002.03722.x.
2. Crevoisier C, Handschin J, Barre J, Boumenov D, Kleinbloesem C. Food increases the bioavailability of mefloquine. Eur J Clin Pharmacol 1997; 53:135–9. doi: 10.1007/s002280050351.
3. Mahmoud BM, Ali HM, Homeida MM, Bennet JL. Significant reduction in chloroquine bioavailability following coadministration with the Sudanese beverages Aradaib, Karkadi and Lemon. J Antimicrob Chemother 1994; 33:1005–9. doi: 10.1093/jac/33.5.1005.
4. Rotan PE, Mercer AJ, Weatherley BC, Holdich T, Meire H, Peck RW, et al. Examination of some factors responsible for a food-induced increase in absorption of atovaquone. Br J Clin Pharmacol 1994; 37:13–20. doi: 10.1111/j.1365-2125.1994.tb04232.x.
5. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. Eur J Clin Pharmacol 1982; 23:271–3. doi: 10.1007/BF00547567.
6. Welling PG. Effects of food on drug absorption. Pharmacol Ther 1989; 43:425–41. doi: 10.1016/0163-7258(89)90019-3.
7. Izzo AA. Herb-drug interactions: An overview of the clinical evidence. Fundam Clin Pharmacol 2005; 19:1–16. doi: 10.1111/j.1472-8206.2004.00301.x.
8. Kennedy JG. The Flower of Paradise: The institutionalized use of the drug qat in North Yemen. Dondrecht, Netherlands: Springer; 1987. Pp. 783–9.
9. Kalix P. Khat: A plant with amphetamine effects. J Subst Abuse Treat 1988; 5:163–9. doi: 10.1016/0740-5472(88)90005-0.
10. Attef OA, Ali AA, Ali HM. Effect of khat chewing on the bioavailability of ampicillin and amoxycillin. J Antimicrob Chemother 1997; 39:523–5. doi: 10.1093/jac/39.4.523.
11. Hamed FF, Ali AO, Ahmed AA. The influence of khat on the in-vitro and in-vivo availability of tetracycline-HCl. Res J Pharm dosage Forms Technol 2015; 7:1–6. doi: 10.5958/0975-4377.2015.00001.4.
12. Middle East Health. Regional profile: Yemen - The burden of poverty. From: www.middleeasthealthmag.com/jan2006/yemen_profile.htm Accessed: Jan 2016.
Effect of Khat (Catha edulis) Use on the Bioavailability, Plasma Levels and Antimalarial Activity of Chloroquine

13. World Health Organization. Yemen: Neonatal and child health profile. From: www.who.int/maternal_child_adolescent/epidemiology/profiles/neonatal_child/ym.pdf Accessed: Jan 2016.

14. Ketema T, Yohannes M, Alemayehu E, Ambelu A. Effect of chronic khat (Catha edulis, Forsk) use on outcome of Plasmodium berghei ANKA infection in Swiss albino mice. BMC Infect Dis 2015; 15:170. doi: 10.1186/s12879-015-0911-2.

15. Ketema T, Bacha K, Alemayehu E, Ambelu A. Incidence of severe malaria syndromes and status of immune responses among khat chewer malaria patients in Ethiopia. PLoS One 2015; 10:e0131212. doi: 10.1371/journal.pone.0131212.

16. Bin Ghouth AS. Availability and prescription practice of antimalarial drugs in the private health sector in Yemen. J Infect Dev Ctries 2013; 7:404–12. doi: 10.3855/jidc.2528.

17. National Malaria Control Programme of Yemen. Report on the final results of the national malaria indicator survey: 2009. From: www.mophp-ye.org/arabic/docs/Report2009.pdf Accessed: Jan 2016.

18. Na-Bangchang K, Limpaibul L, Thanavibul A, Tan-Ariya P, Karbwang J. The pharmacokinetics of chloroquine in healthy Thai subjects and patients with Plasmodium vivax malaria. Br J Clin Pharmacol 1994; 38:278–81. doi: 10.1111/j.1365-2125.1994.tb04354.x.

19. Walker O, Salako LA, Alván G, Ericsson O, Sjöqvist F. The disposition of chloroquine in healthy Nigerians after single intravenous and oral doses. Br J Clin Pharmacol 1987; 23:295–301. doi: 10.1111/j.1365-2125.1987.tb03048.x.

20. Halket JM, Karasu Z, Murray-Lyon IM. Plasma cathinone levels following chewing khat leaves (Catha edulis Forsk). J Ethnopharmacol 1995; 49:111–13. doi: 10.1016/0378-8741(95)90038-1.

21. World Health Organization. Basic malaria microscopy: Part 1 - Learner’s guide. 2nd ed. From: apps.who.int/bitstream/10665/44208/1/9789241547826_eng.pdf Accessed: Jan 2016.

22. Bell DJ, Nyrongo SK, Molynieux ME, Winstanley PA, Ward SA. Practical HPLC methods for the quantitative determination of common antimalarials in Africa. J Chromatogr B Analyt Technol Biomed Life Sci 2007; 847:231–6. doi: 10.1016/j.jchromb.2006.10.020.

23. World Health Organization. Chemotherapy of malaria and resistance to antimalarials: Report of a WHO scientific group. World Health Organ Tech Rep Ser 1973; 529:1–121.

24. World Health Organization. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria, December 2003. From: www.who.int/malaria/publications/atoz/whohtmrbm200350/en/ Accessed: Jan 2016.

25. Osorio LE, Giraldo LE, Grajales LF, Arriaga AL, Andrade AL, Ruebehus TK 2nd, et al. Assessment of therapeutic response of Plasmodium falciparum to chloroquine and sulfadoxine-pyrimethamine in an area of low malaria transmission in Colombia. Am J Trop Med Hyg 1999; 61:968–72. doi: 10.1590/S0074-02762000000400020.

26. Halbach H. Medical aspects of the chewing of khat leaves. Bull World Health Organ 1972; 47:21–9.

27. Edwards G, Looaereesvan S, Davies AJ, Wattanagoon Y, Phillips RE, Warrell DA. Pharmacokinetics of chloroquine in Thais: Plasma and red cell concentrations following an intravenous infusion to healthy subjects and patients with Plasmodium vivax malaria. Br J Clin Pharmacol 1988; 25:477–85. doi: 10.1111/j.1365-2125.1988.tb03322.x.

28. Mubjer RA, Adeel AA, Chance MLM, Hassan AA. Molecular markers of anti-malarial drug resistance in Labj Governorate, Yemen: Baseline data and implications. Malar J 2011; 10:245. doi: 10.1186/1475-2875-10-245.

29. Alkadi HO, Al-Maktari MT, Nooman MA. Chloroquine-resistant Plasmodium falciparum local strain in Taiz Governorate, Republic of Yemen. Chemotherapy 2006; 52:166–70. doi: 10.1159/000093592.

30. Al-Mekhlafi AM, Mahdy MA, Al-Mekhlafi HM, Azary AA, Fong MY. High frequency of Plasmodium falciparum chloroquine resistance marker (pfcrt T76 mutation) in Yemen: An urgent need to re-examine malaria drug policy. Parasit Vectors 2011; 4:94. doi: 10.1186/1756-3305-4-94.

31. Al-beshi N, Al-baroni M, Skaug N. In vitro antimicrobial and resistance-modifying activities of aqueous crude khat extracts against oral microorganisms. Arch Oral Biol 2006; 51:183–8. doi: 10.1016/j.archoralbio.2005.08.001.

32. François G, Bringmann G, Dochez C, Schneider C, Timperman G, Aké Assi L. Activities of extracts and naphthylisoquinoline alkaloids from Triphyophyllum peltatum, Ancistrocladus abbreviatus and Ancistrocladus barteri against Plasmodium berghei (Anka strain) in vitro. J Ethnopharmacol 1995; 46:115–20. doi: 10.1016/0378-8741(95)01240-E.

33. Garavito G, Rincón J, Arteaga L, Hata Y, Boudry G, Gimenez A, et al. Antimalarial activity of some Colombian medicinal plants. J Ethnopharmacol 2006; 107:460–2. doi: 10.1016/j.epharm.2006.03.033.