



Association between Chewing Khat (*Catha edulis*) and Hematological Indices and *Helicobacter pylori* Infection and Blood Loss in the Gastrointestinal Tract of Yemeni Chewers.

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ABSTRACT

Background: The available data on the effect of Khat chewing on hematological indices are conflicted and mainly based on animal studies. The aim of this study was therefore to investigate the effect of Khat chewing on hematological indices in humans as well as the possible association of Khat chewing with *H. pylori* infection and blood loss in the gastrointestinal tract.

Patients and Methods: This study was a comparative cross-sectional study, carried out on 140 participants aged 18 - 55 years old; 71 were healthy non-Khat chewers serving as a control group and 69 were regular Khat chewers. Complete blood count was analyzed as well as *H. pylori* antigen and occult blood in stool were investigated.

Results: Hemoglobin concentration, MCV, MCH, and PCV were significantly ($p = 0.037, 0.034, 0.043,$ and 0.019 respectively) lower in Khat chewers as compared with non-Khat chewers, whereas platelets count and white blood cells count were significantly ($p = 0.006$ and 0.007 respectively) higher in Khat chewers. Khat chewing was also associated with *H. Pylori* infection (OR: 2.7) and blood loss in the gastrointestinal tract (OR: 3.2).

Conclusion: Khat chewing adversely affects hematological indices and increases the risk of *H. Pylori* infection and blood loss in the gastrointestinal tract.

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1. Introduction:

Helicobacter pylori infection is a common, usually lifelong, infection that is found worldwide.¹ Studies suggest that infection rates vary according to geographic region, but the number of infected people has persisted or even increased over the past three decades because of population growth and because of reinfection and

recrudescence due to unsuccessful eradication.² Globally, it has been estimated that 50% or more of the world's population is infected by *H. pylori*, making it the most widespread infection across the globe.³ Although the majority of infected persons (up to 85%) remain asymptomatic,⁴ infection has been directly linked to several conditions; in particular, peptic ulcer disease and

non-ulcer dyspepsia. as well as mucosa-associated lymphoid tissue lymphoma (MALT) and gastric adenocarcinoma.^{3,5} Based on compelling evidence, the World Health Organization (WHO) has classified *H. pylori* as a group 1 carcinogen leading to gastric adenocarcinoma.^{6,7} The *H. pylori*-induced gastritis can lead to atrophic gastritis. Atrophic gastritis in turn may progress to intestinal metaplasia, dysplasia and neoplasia, gastric adenocarcinoma and MALT lymphoma.^{8,9} Areas with an increased incidence of gastric carcinoma attributable to this infection include the Middle East, Southeast Asia, the Mediterranean, Eastern Europe, Central America, and South America.

Catha edulis (Khat) is an evergreen shrub belonging to the family Celastraceae. The habit of Khat chewing has prevailed for centuries among populations in the Horn of Africa and the Arabian Peninsula including Yemen. It is estimated that 20 million people worldwide are regularly chewing Khat, even though it is known to cause serious health issues. Fresh Khat leaves are customarily chewed by laborers, craftsmen, farmers and students to attain a state of stimulation and reduce physical fatigue.¹⁰ Khat contains variable concentrations of primary amines such as cathinone, cathine, and norephedrine,¹¹ and alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals.¹² The fact that cathinone has a close structural similarity to amphetamine, and both share common pharmacodynamic features, has led to the conclusion that cathinone is an important active ingredient of Khat leaves, which causes the major pharmacologic effects.¹³ The common adverse effects of Khat chewing are wide and variable;^{14,15} including psychoneurological disturbances,^{16,17} vasoconstriction of coronary vasculature,¹⁸ increased carotid intima-media thickness and cerebral stroke,¹⁹ hepatotoxicity in humans²⁰ and animals.²¹⁻²³ Other effects such as delayed gastric emptying,²⁴ delayed intestinal absorption,²⁵ increased prevalence of duodenal ulcer and gastric *H. pylori* colonization.²⁶ Khat has been shown to decrease appetite and reduce

body weight in humans as well as increase leptin concentration²⁷ and decrease serum iron, ferritin and vitamins.²⁸

The available data on the effect of Khat chewing on hematological indices are conflicted and mainly based on animal studies. In addition, there is limited data on the association of Khat with blood loss in the gastrointestinal tract and *H. pylori* infection. Therefore, this study aimed to investigate the effect of Khat chewing on hematological indices in humans as well as the association of Khat chewing with *H. pylori* infection and blood loss in the gastrointestinal tract.

2. Patients and Methods

Study Design, Subjects and Data Collection

This study was a comparative cross-sectional study, performed in Sana'a City – Yemen. Participants were recruited using flyers dispatched to employers of private companies and by word of mouth in Sana'a city. One hundred and forty subjects aged 18 - 55 years were recruited, 71 were healthy non-Khat chewers (49 male and 22 female) who served as a control group and 69 were Khat chewers (47 male and 22 female). Khat chewers had to have been chewing khat on a daily basis for at least 5 years, while the non-khat chewers should have not used khat even once. Before enrolling in the study, participants attended a screening session to assess their suitability for the study and accessibility to participate in this research. The screening session included a brief medical history interview and assessment of current and past Khat use as well as the use of other substances. The participants were non-smokers and matched for age and socioeconomic status, free from any medical conditions (e.g., high blood pressure, diabetes, liver, kidney, or heart diseases) and were not taking any medications or supplements. The study protocol was approved by the institutional review board of the Faculty of Medicine and Health Sciences, Sana'a University. Informed consent was obtained from

all individuals after explaining the purpose and nature of the study.

Anthropometric measurements, including weight and height were recorded. Body mass index (BMI) was computed as weight in kilograms (kg) divided by height in meters squared (m^2). EDTA blood samples and stool samples were collected from each individual. A complete blood count (CBC) was performed on fresh blood using the Automated Hematology Analyzer KX-21N (SYMEX Corporation, Kobe, Japan), occult blood and *H. pylori* antigen were detected by immunochromatographic assay in the stool (Standard Diagnostics Inc, South Korea).

Statistical analysis

The sample size was 140 participants, determined by using the OpenEpi program version 2.3.1 according to Bulletin of the World Health Organization, 2008²⁹ using a 95% confidence interval and expected frequency of Khat chewers in Yemen 90%. The results were analyzed by the Social Package of Statistical Science (SPSS) software version 21 (SPSS Inc., Chicago, IL, USA). General linear model, univariate analyses (ANCOVA) adjusted for BMI as a covariate was used to assess the differences of hematological indices between Khat chewers and non-Khat chewers. The binary logistic regression was used to investigate the association of Khat chewing with *H. pylori* and blood loss in the gastrointestinal tract.

3. Results

Table 1 depicts the mean values of the hemoglobin indices and BMI in both healthy controls and Khat chewers. The hemoglobin (Hb) concentration, mean cell volume (MCV), mean cell hemoglobin (MCH), packed cell volume (PCV) and BMI were significantly ($p = 0.037, 0.034, 0.043, 0.019$ and 0.028 , respectively) lower in Khat chewers with respect to non-Khat chewers, whereas platelets count and white blood cells count were significantly ($p = 0.006$ and 0.007 respectively) higher in Khat chewers.

Table 1: Effect of Khat chewing on hematological indices

Variables	Khat chewers	Non- Khat chewers	p-value
Age (years)	31.4±7.3	30.3±7.6	0.4
BMI (Kg/m^2)	22.1±3.6	23.6±4.3	0.028
Hemoglobin (g/dl) #	13.7±1.7	14.3±1.2	0.037
PCV (%) #	41.1±4.2	42.7±3.8	0.019
MCV (fl) #	82.7±6.7	84.9±4.8	0.034
MCH (pg) #	27.6±3.1	28.6±2.4	0.043
Red blood cell count (no of cells $\times 10^{12}/L$) #	4.9±0.57	5.0±0.51	0.6
White blood cell count (no of cells $\times 10^9/L$) #	6.1±2.1	5.7±1.6	0.007
Platelets count (no of platelets $\times 10^9/L$) #	281±67	258±50	0.006
MPV (fl) #	9.8±1	10.1±1	0.088

The results are presented as mean \pm SD; #, adjusted for BMI. p -value < 0.05 was considered statistically significant. fl: femtoliter; pg: pictogram.

The binary logistic regression analysis in Table 2 showed that the odds ratio of being infected by *H. pylori* was higher among Khat chewers (OR: 2.7), and having occult blood in stool was higher among Khat chewers (OR: 3.2).

Table 2: The association of Khat chewing with *Helicobacter pylori* infection and blood loss in digestive system

Variables	Odds ratio (95% CI)	P value
<i>Helicobacter pylori</i> infection	2.7 (1.3-5.3)	0.005
Blood loss in digestive system	3.2 (1.3-7.9)	0.011

p -value < 0.05 was considered statistically significant

4. Discussion

The results presented in our study show a significant decrease in Hb concentration, MCV, MCH, and PCV in participants chewing Khat leaves which is in agreement with an earlier animal study reporting a significant decrease in PCV and Hb concentration in the blood of rats administered *Catha edulis* hydro-ethanol extract, orally for 28 days.³⁰ However, our results are different from that of another animal study reporting no significant changes in the red blood cell (RBC) count, Hb and PCV values in the blood of rats administered *Catha edulis* crude

methanolic extract, orally for 4 weeks.²³ Our findings could be attributed to the presence of tannins in the leaves of *Catha edulis* which inhibit non-haem iron absorption.³¹ Phenolic compounds (Flavonoids) have been identified as potent inhibitors of iron absorption,^{32,33} presumably by forming insoluble complexes with iron ions in the gastrointestinal lumen and thereby making the iron unavailable for absorption. Iron is an important element for hemoglobin synthesis in bone marrow. Previously, we reported daily Khat chewing to be associated with a decrease in serum levels of iron and ferritin,²⁸ which would lead to a decrease in hemoglobin concentration and consequently decrease in MCH and MCV and subsequently decrease PCV.

On the other hand, our results showed a significant increase in the platelets count and white blood count in Khat chewers, which may be due to stimulation by catecholamines that increase the release of platelets from spleen³⁴ and increase the number of leukocytes.³⁵ Our study is in agreement with an earlier study reporting a significant increase in total leukocytes in rats administered *Catha edulis* crude methanolic extract²³ and different from that in which rats administered *Catha edulis* hydro-ethanol extract.³⁰ This variation in the animal studies could be due to the type of extract used, and possibly the dose of *Catha edulis* selected.

Our results also show Khat chewing to be a risk factor for blood loss in the gastrointestinal tract, which is consistent with previous studies demonstrating Khat chewing to be significantly associated with gastric ulcers, duodenal ulcers and or erosions in the upper gastrointestinal tract.^{36,37} Moreover, Khat chewing has also been associated with the development of hemorrhoid diseases,³⁸ which may lead to increased blood loss. In addition, our study shows Khat chewing to be a risk factor for *H. pylori* infection, which is in agreement with earlier studies reporting the prevalence of *H. pylori* infection to be higher among Khat chewers, indicating that Khat chewing could be a predisposing factor to

gastrointestinal disorders and *H. pylori* infection.^{24,37,39-41} Khat chewers were reported to be four times more likely to have *H. pylori* infection than non-Khat chewers.³⁷ The high prevalence of *H. pylori* with Khat chewing would also be expected to reduce iron absorption,⁴²⁻⁴⁴ since *H. pylori* increases iron uptake and utilization for metabolism⁴⁵ and also leads to blood loss due to gastric lesions as a consequence of infection,⁴⁶ and elevates the pH of gastric juice due to infection.⁴⁷⁻⁴⁹ Lifestyle habits have been recognized as important risk factors for the acquisition of various infections, including *H. pylori* infection. Most of the Khat chewers don't wash or are reluctant to wash the Khat leaves before chewing in the belief that it would cause the plant to lose its taste.

Our study has a number of limitations; first, it is a cross-sectional study that cannot follow up on the future effects of Khat chewing; second, the sample size was small and therefore the findings may not be generally applicable to the overall population.

5. Conclusion

The results of this study demonstrated Khat chewing to induce a significant reduction in hemoglobin concentration, MCV, MCH, and PCV; as well as a significant increase in platelets count and white blood cells count. Moreover, Khat chewers are more susceptible to *H. Pylori* infection and blood loss in the gastrointestinal tract.

Abbreviations

BMI, Body mass index; CBC, Complete blood count; *H. pylori*, *Helicobacter Pylori*; Hb, Hemoglobin; MCH, Mean cell hemoglobin; MCV, Mean cell volume; MALT, Mucosa associated lymphoid tissue lymphoma; PCV, Packed cell volume; RBC, Red blood cell; SPSS, Social package of statistical science.

Data Sharing Statement

The data set generated and/ or analyzed during this study is included in this submitted

manuscript and is available from the corresponding author upon reasonable request.

Ethical Approval

The study protocol was approved by the Institutional Ethical Committee, Faculty of Medicine and Health Sciences, Sana'a university. The study was in compliance with the Declaration of Helsinki for clinical research. All the recruited participants provided written informed consent before participating in the study.

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Disclosure

The authors report no conflict of interest in this work.

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