ORIGINAL RESEARCH ARTICLE

Evaluation of the Effects of Khat Chewing and Cigarette Smoking on Liver and Kidney Functions among Students at Taiz University, Yemen

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Received on: 27 August 2023; *Accepted on:* 04 November 2023; *Published on:* 05 December 2023

Abstract

Aims and background: Khat chewing and smoking are some of the most popular social activities in Yemen. However, little is known about how these habits affect the liver and kidney, so this study was made to examine the potential effects of these habits on the levels of various biochemical parameters to evaluate kidney and liver functions in healthy medical students that were considered as khat chewers and smokers.

Materials and methods: In total, 90 healthy medical students took part in this investigation. The biochemistry of the liver and kidneys was assessed on 30 khat chewers only, 30 khat chewers and smokers, and 30 non-khat chewers and nonsmokers.

Results: The activity of the AST, ALT, and GGT enzymes reveals a significant increase among khat chewers and khat chewers and smokers' groups. A significant correlation was observed between the duration of both khat chewing and cigarette smoking and the levels of creatinine uric acid, albumin, and GGT.

Conclusion: We come to the conclusion that *Catha edulis* with amphetamine-like effect and the cytotoxic effects of cigarette smoking might be responsible for hepatocellular and kidney damage with a correlation to the khat chewing and smoking durations.

Keywords: Khat chewing, Liver function tests, Renal function tests, Smoking.

Indian Journal of Medical Biochemistry (2023): 10.5005/jp-journals-10054-0213

Introduction

The plant *Catha edulis* Forska is a member of the Celastraceae (spindle tree family), it is commonly named Khat.[1] It is most frequently farmed in certain regions throughout various nations in east and central Africa as well as the Arabian Peninsula. Unfortunately, the khat chewing habit carries a significant public health issue in Yemen.[2] Khat consumption has become a common problem that affects health status.

The neurological and gastrointestinal tract systems are two of the khat main targets for adverse health effects. The peripheral autonomic nervous system's side effects might include constipation, urinary retention, and acute cardiovascular problems.[3]

Chronic khat consumption causes subclinical hepatocellular damage depending on how frequently it has been consumed and whether pesticides are used on the plant or not, whereas short-term khat consumption has no effect on liver function.[4]

In both human and animal researches, sustained frequent khat consumption results in hepatocellular damage.[5–7] The hepatotoxicity pathogenesis related to khat chewing is unknown, it can be related to the reactive khat metabolites or an immuno-allergic reaction.[8]

Khat leaves contain many different compounds, including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, vitamins, minerals, and amino acids.[9] Cathinone, cathine, and norephedrine are the main alkaloids present in khat. The most important active ingredient of khat is cathinone, which causes major pharmacological effects.[10] Phenylalkylamines and cathedulins are the two primary alkaloids that share a structural similarity with amphetamine.[11] In comparison to dried leaves, fresh leaves have a greater cathinone-to-cathine ratio.[12] The pharmacological and structural similarities between cathine and amphetamine might lead to the same harmful effects.[13] One of the most common side effects besides khat consumption is tobacco smoking.[14,15] The results of the research that has been done on the health impacts of smoking and khat chewing are generally inconsistent. Khat chewing and smoking have been linked to an increased risk of cardiovascular morbidity[16] and have also been linked to pathological changes in the oral mucosa.[17,18] Khat chewing and smoking have a wide range of distribution in Yemen[15,18] and due to the lack of information about these effects on the liver and kidney, the aim of this study is to assess the combined effects of these habits on liver and kidney biochemical parameters in the healthy Yemeni population.

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How to cite this article: Al-Shamiri SAA. Evaluation of the Effects of Khat Chewing and Cigarette Smoking on Liver and Kidney Functions among Students at Taiz University, Yemen. Indian J Med Biochem 2023;27(1):18–22.

Source of support: Nil

Conflict of interest: None

Table 1: Frequency and percentage of khat chewing and cigarette smoking

				Number	*Percent*
Participants' chew khat *n* = 30 (50%)	Frequency of khat chewing	Per day	One time	18	30
			Two times	42	70
		Per years	1–6	19	32
			7–11	41	68
Participants' smoke cigarette *n* = 30 (50%)	Frequency of cigarette smoking (per years)		1–6	27	90
			7–11	3	10
	Number of cigarette smoking (per day)		1–10	20	67
			11–20	10	33

Materials and Methods

Chemicals

All chemicals used were of highest-grade commercial products. Kits for the biochemical tests were purchased from Spectrum, Egypt.

Study Design, Population, and Grouping

A case–control study was performed on 90 healthy males from the Faculty of Medicine, Taiz University, who were split into three groups.

1. Khat chewers and smokers are those who regularly smoke and consume khat (30 people).
2. Khat chewers are those who regularly consume khat only (30 people).
3. The control group, which consists of 30 nonsmokers and non-khat chewers, who were never smoked or used khat.

The participants of all groups in this study fulfill the following criteria:

- Healthy volunteers aged between 18 and 30 years are excluded from diabetes, cardiovascular, and renal and hepatic diseases.
- This study was performed in accordance with the Helsinki Declarations and approved by the Ethical Committee.

Sample Collection

Blood samples from 90 individuals (30 from each group) were collected between 8 and 10 a.m., 12 hours after the end of khat chewing. The separated serum of all samples was used for biochemical analysis.

Biochemical Assays

The biochemical tests include assays of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total protein (TP), albumin (Alb), globulin (GLOB), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), creatinine (Cr), urea (UR), and uric acid (UA) that were estimated following the instructions of commercial kits provided by Spectrum, Egypt, using a semi-automated spectrophotometer analyzer (Rayto RT-9200).

Statistical Analysis

Data were expressed as mean ± SEM and were analyzed by Mann–Whitney *U* test. The Spearman's rho correlation coefficient was applied for the correlation between different parameters, and the *R*-values were checked using a *t*-test. A *p*-value < 0.05 was considered significant. All analyses were performed using the Stata v13 Software.

Results

Participants Chew Khat

Nineteen (32%) of the participants have been chewing khat for 1–6 years, and 41 (68%) have been chewing it for 7–11 years. In terms of frequency, 42 (70%) of those polled said they chewed khat twice daily, compared with 18 (30%) that they chew khat once daily (Table 1).

Participants Smoke Cigarette

Thirty (50%) of the 60 khat chewers reported being smokers, with 20 individuals (67%) smoking from 1 to 10 cigarettes daily and 10 individuals (33%) smoking 11–20. In terms of smoking duration, 27 (90%) were smokers for 1–6 years and 3 (10%) were smokers for 7–11 years (Table 1).

Table 2 shows that the mean values of AST, ALT, and GGT enzyme levels were significantly increased ($p < 0.05$) in the test groups (khat chewers, khat chewer, and smokers) when compared with the control group (non-khat chewers and nonsmokers), and significant increases in the mean values of these enzymes were also observed in the khat chewers' group when compared with the khat chewers' and smokers' group.

Table 3 shows that there is a statistically significant positive correlation between uric acid levels and both annual smoking frequency and daily cigarette intake ($R = 0.405$, $p < 0.01$, and $R = 0.287$, $p < 0.05$, respectively). Daily khat chewing was found to be positively connected to creatinine ($R = 0.329$, $p < 0.05$) but adversely related to total protein and albumin ($R = -0.323$ and $R = -0.275$, respectively). At (p-value < 0.05), there is a substantial negative connection between GGT and daily cigarette use and smoking duration ($R = -0.276$, $R = -0.278$).

Discussion

Chewing khat and smoking are regarded as social traditional habits. This study observed that cigarette smokers were more prevalent among excessive khat chewers, which is consistent with the study of Kassim et al. They found that 35% of 204 khat chewers solely used khat, 20% were simultaneous smokers and khat chewers, and the rest smoked cigarettes daily,[15] and to the results of Al-hajj et al., showing that the prevalence of smoking was 25.5% among 297 khat chewers.[18]

This is one of the first studies to demonstrate the effects of smoking and using khat on liver and kidney health in Taiz, Yemen. In this study, we found that serum ALT, AST, and GGT were significantly increased in khat chewers and smokers as compared with the control group. Our findings are consistent with previous studies that found a significant increase in the risk

Table 2: Serum levels of biochemical parameters of khat chewers, khat chewers and smokers, and non-khat chewers and nonsmokers

		Test groups (n = 60)				*Control group (n = 30)*		
		Khat chewers (n = 30)		*Khat chewers and smokers (n = 30)*		*Non-khat chewers and nonsmokers*		
Biochemical parameters	*Normal range*	*Mean*	*± SEM*	*Mean*	*± SEM*	*Mean*	*± SEM*	*p-values*
AST	Up to 37	25.77	0.37	24.23	0.43	23.33	0.38	0.000*
ALT	Up to 41	21.40	0.64	20.82	0.47	19.50	0.46	0.009*
AST/ALT	0.7–1.4	1.22	0.014	1.24	0.021	1.25	0.03	0.811
GGT	11–50	28.72	0.80	27.52	0.87	24.14	0.94	0.001*
TP	6.6–8.7	7.14	0.026	7.83	0.019	7.08	0.087	0.800
GlOB	2.0–3.5	3.08	0.035	3.14	0.027	3.16	0.071	0.098
Alb	3.5–5.5	4.01	0.032	3.98	0.039	3.92	0.048	0.173
Alb/GLOB	1.1–2.5	1.27	0.022	1.98	0.017	1.23	0.044	0.143
TBIL	Up to 1.2	0.89	0.024	0.87	0.018	0.87	0.034	0.709
DBIL	Up to 0.4	0.21	0.014	0.24	0.21	0.20	0.019	0.189
IBIL	0.2–0.7	0.66	0.014	0.69	0.016	0.66	0.019	0.939
UR	15–50	25.29	0.47	26.03	0.34	24.46	0.76	0.448
UA	3.5–7.2	4.88	0.11	4.94	0.14	4.53	0.17	0.145
Cr	0.9–1.5	0.86	0.019	0.82	0.024	0.84	0.021	0.596

Results are expressed as mean ± SEM, data were analyzed by Mann–Whitney test. *Significant at *p*-value < 0.05; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alb, albumin; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma glutamyl transferase; GLOB, globulin; IBIL, indirect bilirubin; TBIL, total bilirubin; TP, total protein; UA, uric acid; UR, urea

Table 3: Correlation coefficient (*R*) between biochemical parameters studied (ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alb, albumin; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma glutamyl transferase; GLOB, globulin; IBIL, indirect bilirubin; TP, total protein; TBIL, total bilirubin; UR, urea; UA, uric acid) and variables of (times of khat chewing per day, duration of khat chewing, number of cigarettes per day and duration of smoking) in test group

Biochemical parameters	*Number of cigarettes per day*	*Frequency of smoking [years]*	*Frequency of khat chewing [years]*	*Times of khat chewing per day*
AST (U/L)	–0.045	0.007	0.058	0.163
ALT (U/L)	–0.046	–0.053	0.099	0.157
AST/ALT	–0.096	0.022	–0.096	–0.172
GGT (U/L)	–0.276*	–0.278*	0.133	–0.147
TP (gm/dL)	–0.167	–0.142	0.056	–0.323*
GLOB (gm/dL)	0.005	0.033	–0.002	0.121
Alb (gm/dL)	–0.105	–0.150	–0.111	–0.275*
Alb/GLOB	–0.093	–0.122	–0.062	–0.242
TBIL (mg/dL)	0.131	0.169	0.049	0.155
DBIL (mg/dL)	0.201	0.181	–0.060	0.125
IBIL (mg/dL)	0.038	0.124	0.161	0.160
UR (mg/dL)	0.075	0.083	–0.014	–0.164
UA (mg/dL)	0.287*	0.405**	–0.006	0.195
Cr (mg/dL)	0.221	0.250	0.025	0.329*

Data were analyzed by Pearson correlations coefficient. *Significant correlation at *p*-value < 0.05; **Significant correlation at *p*-value < 0.01

of hepatotoxicity and acute liver injury in khat chewers.[19–21] ALT and AST were increased significantly in the serum of rats after khat feeding for 6 months.[5] Al-Habori et al. observed an increase in ALT, AST, and alkaline phosphatase in rabbits after consuming khat.[6,22] Al-Mehdar et al. demonstrated a considerable increase in ALT, ALP activity, and bilirubin levels, and a significant decrease in albumin levels in rats treated with khat extraction.[22] A case study supports the hypothesis that chewing khat affects liver function.[23] Several mechanisms, including sympathomimetic effect, induction of oxidative stress, cytotoxic action, and promotion of renin–angiotensin system (RAS), may likely be involved in the khat-induced hepatotoxicity. Khat is a potent peripheral indirect sympathomimetic, which works by increasing the release of norepinephrine from adrenergic nerve terminals, inhibiting its reuptake, and inhibition of norepinephrine metabolism inactivation by monoamine oxidase enzyme.[13] The increased norepinephrine concentration in the postsynaptic region of most vascular smooth muscles produces hepatic vasoconstriction via postsynaptic I receptor stimulation.[10] Furthermore, the reduced hepatic blood flow may result in ischemic hepatitis.[24] Khat may stimulate the RAS

via S2 receptor activation as a result of its indirect sympathomimetic action.[25] Renin–angiotensin system activation enhances vascular smooth muscle cell migration, proliferation, and the production of pro-inflammatory chemokines and cytokines.[26]

In our study, we found no discernible change in the levels of urea, uric acid, or creatinine; this is consistent with the study of Mworia et al. that found khat chewing does not increase creatinine levels or cause an electrolyte imbalance, hence having no predisposing influence on renal illnesses.[27] Al-Habori et al. demonstrated that normal renal functions were present in rats after a 6-month exposure to Khat.[6]

The findings of this study were in contrast to the study of Masoud et al. They found a significant increase in creatinine, urea, and uric acid in the plasma of female khat chewers.[28] According to Al-Hashem et al., serum urea was elevated, but albumin level was lowered in rats given extracts of khat.[7] Additionally, Al-Ashwal et al. found that the serum levels of urea and creatinine were considerably higher in the khat users' group than in the control group.[29] Elbendary et al. showed an increase in urea and uric acid but not in creatinine.[30] However, this study demonstrates that the duration of khat chewing and cigarette smoking has a significant effect on uric acid and creatinine levels, implying that khat chewing and smoking have a negative impact on renal function. Al-Habori et al., Brostoff et al., and Masoud et al. proposed that uric acid could act as a protective mechanism against the oxidative stress caused by khat. The oxidative stress generated by chemical compounds found in cigarettes most likely accelerates the decline in antioxidants, particularly serum uric acid.[6,19,28] Trofor et al. found that nicotine increases oxidative stress and decreases antioxidant levels.[31] The negative link that our study observed between albumin and the frequency of khat usage may further indicate albumin's role as an endogenous antioxidant against the khat-induced free radicals that cause their depletion.[32]

Cigarette smoke influences liver function by harmful and toxic compounds on hepatocytes that could lead to the secretion of enzymes from the cells of the liver through the inflammatory pathways and eventually the progression of chronic inflammation.[33] Significant increases in blood activity of ALT, AST, lactate dehydrogenase, alkaline phosphatase, and GGT were observed in the study by Hamad et al., presumably reflecting the deleterious effect of smoking on hepatocyte performance.[34] Cigarette smoking has a high concentration of reactive species, which can cause the formation of cellular oxidants.[35] GSH is essential in airway epithelial cells for protection against oxidants and inflammatory damage.[36] It is the most abundant intracellular antioxidant thiol and has an important role in redox protection under oxidative stress. Although the initial rise in GGT may be compensatory for reduced GSH due to oxidative stress, serum GGT is likely to lower the risk of clinical consequences because the concurrent increase in cellular GGT leads to increased intracellular GSH.[37] However, persistent tobacco smoke exposure can change the expression of many enzymes and transcription factors, resulting in enhanced GSH production.[35] This study found that smoking frequency has a negative correlation with GGT, which may be explained by the possibility of the increase in GSH as an adaptive response to prolonged cigarette exposure. As a result, GGT may not change due to the parallel increase of cellular GGT, and therefore, serum GGT increases proportionally to the amount of GSH.

Conclusion

We demonstrated that *Catha edulis* with amphetamine-like effect and the cytotoxic effects of cigarette smoking, may cause hepatocellular and renal damage, which may be connected to the amount of time spent smoking and chewing khat as well as the quantity of the cigarettes that had been consumed. It is advised to conduct further large-scale randomized controlled researches.

Acknowledgments

The author wishes to thank the entire faculty, staff, and students of the Department of Biochemistry for their contribution to completing this research.

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