EFFECTS OF *KHAT* (Catha edulis Forsk) ON ELECTROPHYSIOLOGIC PROPERTIES OF THE HEART AND OF THE LUNG FUNCTION INDICES

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Summary

The aim of this study was to assess the effects of Catha edulis Forsk on vital signs, lung function indices and electrocardiographic profile of the casual user.
Sixty healthy adult men who were casually chewing Khat leaves were randomly selected from 10 localities in Addis Ababa using inclusion and exclusion criteria. The mean age (±SD) was 31±2 years; their mean body weight was 70.8±3.8, their BMI was 22.3±0.6 kg/m^2. None were smokers and their frequency of chewing and ingestion of khat leaves was on the average 1.7 times per week. All study subjects had normal history, vital signs, LFI (lung function indices) and ECG profile prior to the khat session. Each of the subjects was given 200 gm of fresh "Beleche" Khat leaves which was chewed over a period of two hours.
Measurements of VCIn, FVC, FEV1, FEF and PEFR showed statistically significant differences between pre-test and post-test values ($P<0.001$). The mean value of the post-test FEV1% showed significant increment in only about 70% of the study subjects. The changes in VCIN, FVC, FEV1 and PEFR appeared to be relatively more consistent and significant ($P<0.001$). Other important changes observed in this study were ECG profiles. The ventricular depolarization and conduction velocity (QRS) increased by 11%; the cardiac cycle length (R-R interval) and the ventricular depolarization and repolarization time (QT interval) was shortened by 9% and 4.5%respectively.
The active ingredients of Khat have sympathetic- like effects on conductivity, rhythmicity and excitability of the heart, and lung volume and ventillatory capacity.

Key words:

Adrenergic, Electrical activities of the heart, *Khat* (Catha edulis Forsk), Sympathomimetic.

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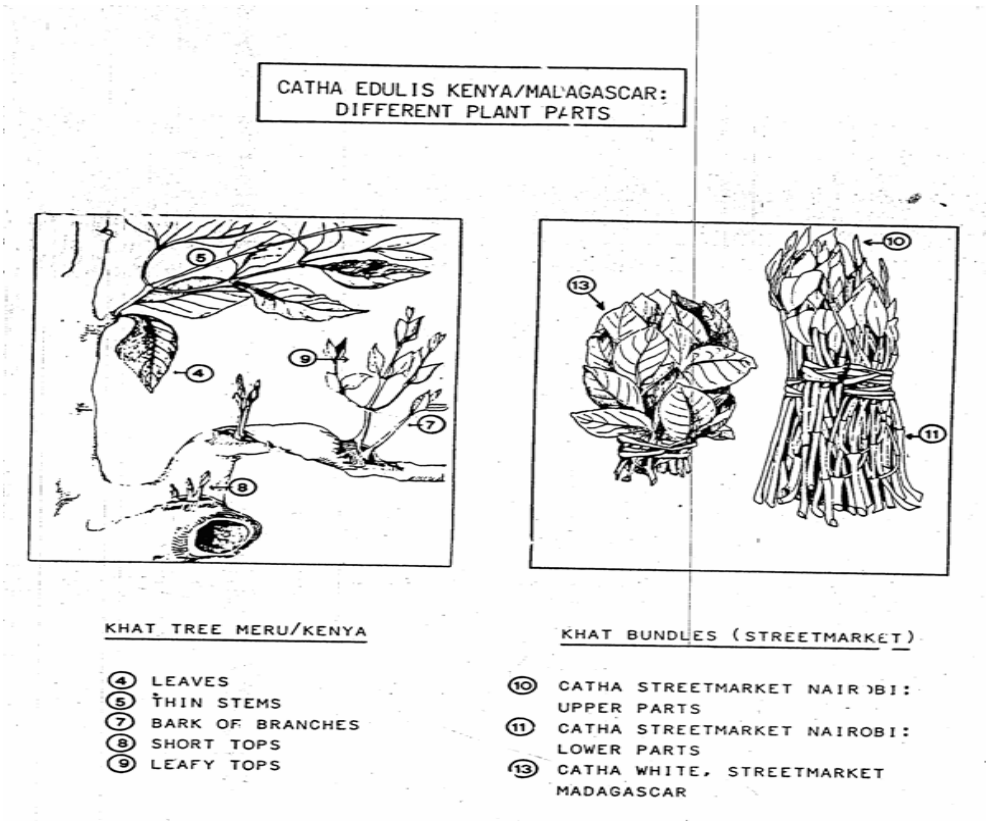
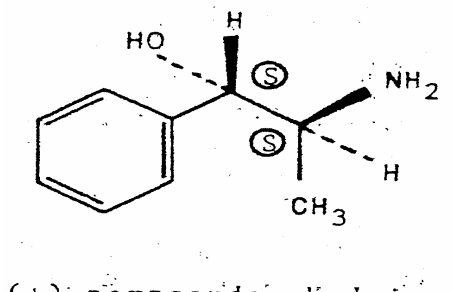
Introduction

Khat (chat, qat, mirra, etc) commonly known as the leaves, young shoots or stem tips of Catha edulis Forsk is an evergreen shrub of the celastraceae family (1,*2*). Parts of the shrub are as shown in figure 1. The fresh leaf is traditionally chewed mainly by people living near the cultivation areas in East Africa and the Arabian Peninsul
to attain a state of euphoria and stimulation (3,4).

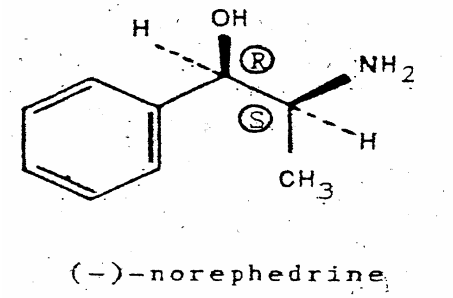


Since the *Khat* leaf rapidly loses its effect upon wilting, the *Khat* habit has remained, until recently, endemic to the areas where the plant is grown. During the last decades, however, due to the development of road networks and the availability of air transport the habit has spread considerably in those regions and countries where the plant doesn't grow.

And the growing use of *Khat* has motivated an interest in further knowledge of its active ingredients and their biological effects. By using HPLC technique, it is found that **(-)-s-cathinone** is the main active ingredient of *Khat* (5,6,7). *Khat* also contains another alkaloid known as **cathine** or **(+) norpseudoephedrine**, which is predominantly responsible for most of the peripheral/somatic effects (2,5,8,9,10).



(+)-norpseudoephedrine



(-)-norephedrine

There are more than 20 pharmacologically active compounds extracted from Khat. Of these, emphasis has been given mainly to cathinone and, to a lesser extent, to cathine.
It is fortunate perhaps, that *Khat* is also very rich in ascorbic acid, which is an excellent antidote to amphetamine type compounds (11).

It appears that *Khat*'s effects on the central nervous system includig talkativeness, alertness, psychosis and dependence are well documented (12) but further clearing on its peripheral effects seem to be needed.

The present study is intended to describe the effects of *Khat* on electrical activities of the heart and lung function indices in 60 apparently healthy adult men who have the habit of chewing *Khat* leaves occasionally.

Since *Khat*- induced changes appeared to be less pronounced in chronic users (13) as a result of tolerance, subjects in the present work are those who chew *Khat* casually.
Although there have been other researches Conducted on the cardiovascular effects of *Khat*, the use of electrocardiogram to learn electrical activity of the heart, among regular *Khat* chewers and a concomitant study of the effects associated with *Khat* on lung function indices have not been done to date.
The present study will apparently enrich previous findings and give further clearings on khat as a habit-forming drug. It should be emphasized, however, that the ECG measurement gives no direct information concerning the mechanical performance of the heart.

Measurement of the duration of QRS complex and QT interval allows clinical evaluation of drugs and diseases on the time dependent properties of the ion channels responsible for the ventricular depolarization and repolarization of waves.

In addition, this work is designed to examine the changes observed on lung function indices including VCIN (Inspiratory vital capacity), FVC (Forced vital capacity), FEV1 (Forced expiratory volume in one second), FEV1% (Flow rate in the first one second), FEF (Expiratory flow rate) and PEFR (Peak expiratory flow rate) following the ingestion of *Khat*. No work relating to lung function indices has been undertaken to date.

Subjects and Methods

Study Subjects

A sampling frame of *Khat* session places (Mufferaj) in each Woreda of Addis Ababa was obtained from informants of sevem different individual sub-city representatives. Systematic sampling technique was used to select 60 volunteer adult men who have the habit of chewing *Khat* leaves casually. Clinical examination and inclusion / exclusion criteria were set for the selection of eligible study subjects.

The study protocol was reviewed and approved by the ethics committee of the medical faculty of the AAU, and each man gave informed consent before entering the study.

1. Entry Criteria

1.1 Male, age > 25 years
1.2 Willingness to fully cooperate In the proposed study.
1.3 Occasional *Khat* chewer

2. Exclusion Criteria

2.1 Previous history of cardio-respiratory disease
2.2 Significant cardiac dysfunction requiring maintenance therapy
2.3 Chronic obstructive pulmonary disease (COPD)
2.4 History of hypertension
2.5 Past history of treatment with anti-TB medication for open pulmonary tuberculosis
2.6 Medication shortly before experiment
2.7 Athletes and permanent residents of high altitude.
2.8 Chronic regular khat chewer

Plant material preparation

"Beleche" *Khat* leaves were purchased from various local markets in Addis Ababa. The *Khat* bundles usually arrive Addis Ababa a few hours after harvest and transportation from the farm

(Wondogenet area) by Isuzu light trucks. The packaging in plastic bags or wrapping in banana leaves were understood to retain the *Khat* moisture and freshness. Quantity and dosage form management for individual study subjects mostly correlated with price. A bunch of Beleche khat worth Eth. Birr 20 is estimated to be equivalent to about 200gm. According to sources from literature (14,15) and information obtained from experienced *Khat* users, about 200gm of 'Beleche' *Khat* chewed over a period of 2 hours is known to bring about a peak state of euphoria and excitement in the casual user.

Measurement of study variables

Initial ECG, mechanical lung function tests (FVC, FEV, FEV% and PEFR) and clinical examination were conducted on men age >20 years and in apparent good state of health. The volunteers comprised merchants, civil servants, students and essentially sedentary subjects from different localities in Addis Ababa.

After routine clinical examination, normal subjects were selected by means of a standard questionnaire of cardiorespiratory symptoms, based on the recommendation of the British Medical Research Council and the aforementioned exclusion criteria. The measurements of study variables were conducted before and two hours after the *Khat* session.

Lung Function Tests

The measurements of VCIN, FVC, FEV1, FEV1 %, FEF200-1200, FEF25-75% and PEFR were derived from three successive forced expiratory spirogram recorded by the SpiroPro, a portable spirometer with latest technological development

Subjects were instructed to practice the breathing maneuver before being attached to the instrument. Nose-clips were used; and the test was performed in a standing position. After the practice blow, the recording was made three times and the best of the three readings was automatically recorded. All volumes were recorded at an ambient T^0 of 22 ^oC, pressure 990pha and relative humidity of 45%.

The SpiroPro was regularly checked for a constant ambient condition prior to every measurement. The spirometer gives automatic interpretation of the measured data of the pre/post dilation test.

Student's t-test was used for statistical analysis. The 5% probability level was taken as significant.

ECG tracing

A self-interpreting ECG machine was used for the tracing of surface cardiac electrical potential. This was recorded against time for the 60 volunteer adults who were considered eligible. Procedures of ECG tracing were explained and demonstrated to subjects for better cooperation

and accuracy. Pre-test measurement was conducted on each study subject three hours after meal and following half an hour rest in the examination room i.e. *Muffraje*.

The machine was set to make the tracing at a standard recording speed of 25mm /sec and a calibration deflection of 1mv=1cm.

The mean ± SE, t-values and a one-tailed P-value for paired observations were calculated using SPSS version of computer software package. A probability of <0.05 was considered significant.

Measurement of vital signs

The conventional Riva-Rocci method was used to estimate arterial blood pressure. Two readings were taken in each subject just before and two hours after *Khat*. The mean ±SD of systolic and diastolic blood pressure was considered. The overall mean BP was not considered because it is understood that systolic and diastolic BP could show different responses to the change in testing conditions. Pulse Rate was taken from the ECG and respiratory rate was estimated by inspection of the chest movement.

Data processing and Statistical Analysis

Descriptive statistics including mean, SD, and correlation coefficients were computed. Data were statistically compared using Pearson's correlation test and student's t-test where appropriate. The significance level was considered at P<0.05.

Ethical consideration

The study was carried out only after it was cleared by appropriate committee Informed consent was first sought from individual respondents. Privacy and confidentiality were maintained. Those found diseased were given appropriate treatments or referred for better investigation and workup.

Results and Discussion

A sample size of 60 was needed in this quantitative study to establish the cause-effect relationship of the chewing and ingestion of *Khat leaves* and certain defined clinical parameters including LFI, ECG and vital signs.

Power	80%
Effect size	0.2+2SD
Significance level	0.05

The study included 60 normal men, whose mean age (±SD) was 31±2 years; their mean body weight was 70.8 ±3.8, their BMI (weight in Kg divided by height in Mt squared) was 22.3±0.6. None were smokers and their habit of chewing khat leaves based on a one-week ingestion or use recall is 1.7 times. All study subjects had normal V/S, LFI and ECG profile prior to the khat session.

In the present study the chewing and ingestion of khat leaves caused significant post-test increment in the measurement of VCIn (P<0.OO1), FVC (P<0.001), FEV1 (P<0.001), PEFR (P<0.001) and FEF25-75% (P<0.001) (Table 1).

Fig. 1 **Mean % change of lung function indices 2 hours after ingestion of *khat* leaves in different age groups.**

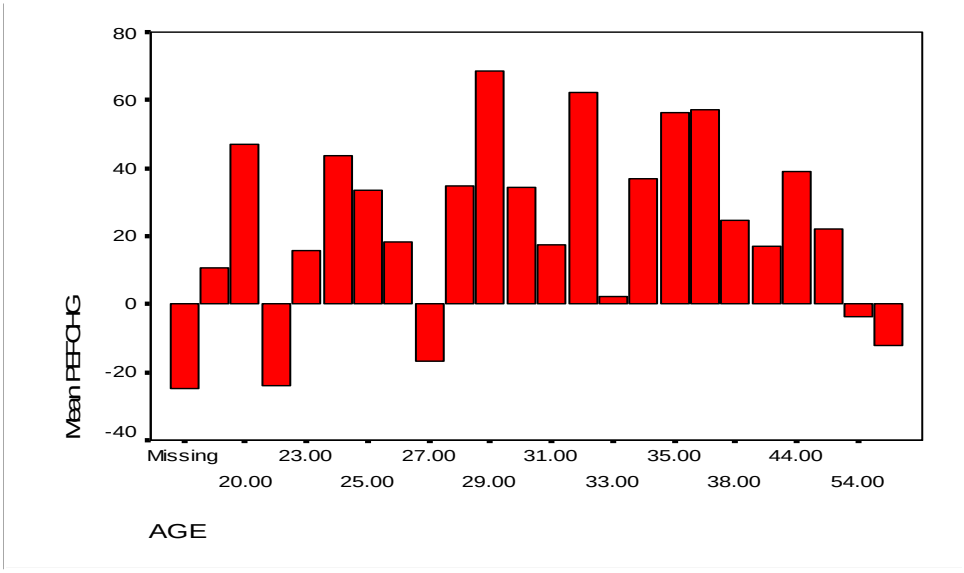


Table1. Means and SD of the LFI before and 2 hours after khat ingestion in 60 study subjects. P value represents level of significance and the magnitude ofeffect size- small (0.2-o.5), medium (0.5-0.8), large (0.8+).

Variable	Pre (mean +SD)	Post (mean +SD)	% change (mean)	Effect size	P-value
VCIN (L/sec)	2.52±0.59	2.91±0.78	15.6	0.67	<0.001
FVC (L)	3.40±0.45	3.70±0.53	9	0.66	<0.001
FEV1 (l/sec	2.98±0.40	3.27±0.51	10	0.74	<0.001
FEV1%	87.50±7.84	88.96±6.56	2	0.18	<0.001
PEFR	6.01±1.93	7.23±1.58	20	0.63	0.001
FEF75%	1.90±0.84	2.05±0.99	8	0.18	<0.001
FEF50%	4.14±1.23	4.54±1.47	10	0.33	0.043
FEF25%	5.51±1.72	6.39±1.10	16	0.51	<0.001

The FVC which is a measure of the forced expiratory volume could possibly be explained by an increase in total lung volume as results of sympathetic-like effects of (-)cathinone on small and intermediate sized airways. Although the individual contribution of each variable to the overall increase in total lung volume and ventilatory capacity is yet to be studied by further research, the post- test measurement of FEV1, PEFR and FE25-75% ($P<0.001$) as seen on Table 1, do clearly indicate a reduction in airway resistance or an increased expiratory pressure.
Pulmonary indices that were consistently increased were VCIn, FVC, and FEV1and PEFR. These findings reflect an overall increase in the total lung volume and functional capacities. This probably is due to the sympathomimetic effect of (-) cathinone and cathine on small and medium sized air passages that lead to an overall increase in functional surface area of the lungs. In other words, there is induction of physiological dead space. The significant increase in PEFR ($P<0.001$) reflects not only dilation of small and intermediate sized bronchi but also reabsorption of mucus fluid within smaller air passages probably due to (-)cathinone's aroma and astringent effect decreasing airway resistance and hence improved PEFR ($P<0.001$). This might be the reason why many asthmatic patients experience ventilatory improvement during and after *Khat use*.

The correlation paired t-test for pulmonary indices FEV1% and FEF50% was low but still significant (P-value 0.01 and 0.043) respectively.
The possible explanation includes the following:

1. The reduction in airway resistance following *Khat* chewing was not so marked as the change seen on FVC.
2. Large airways have limited elasticity because of cartilage.
3. Poor cooperation for a complete expiratory effort by the study subjects.

Post- test FVC score has shown significant correlation at $P< 0.01$ level in a 2-tailed t- test with most of the lung function indices (Table 1 and Fig.2 a, b). The explanation given for the increment in FVC 2 hours after Khat chewing and ingestion is that active Khat ingredients (cathinone and cathine) have sympathetic-like effect on small to medium sized air passages to cause bronchodilation thereby increasing the total lung volume (9% change). The trachea and large bronchi might not be affected by the sympathomimetic effect of khat, probably due to poor elasticity of large airways with high cartilage composition.

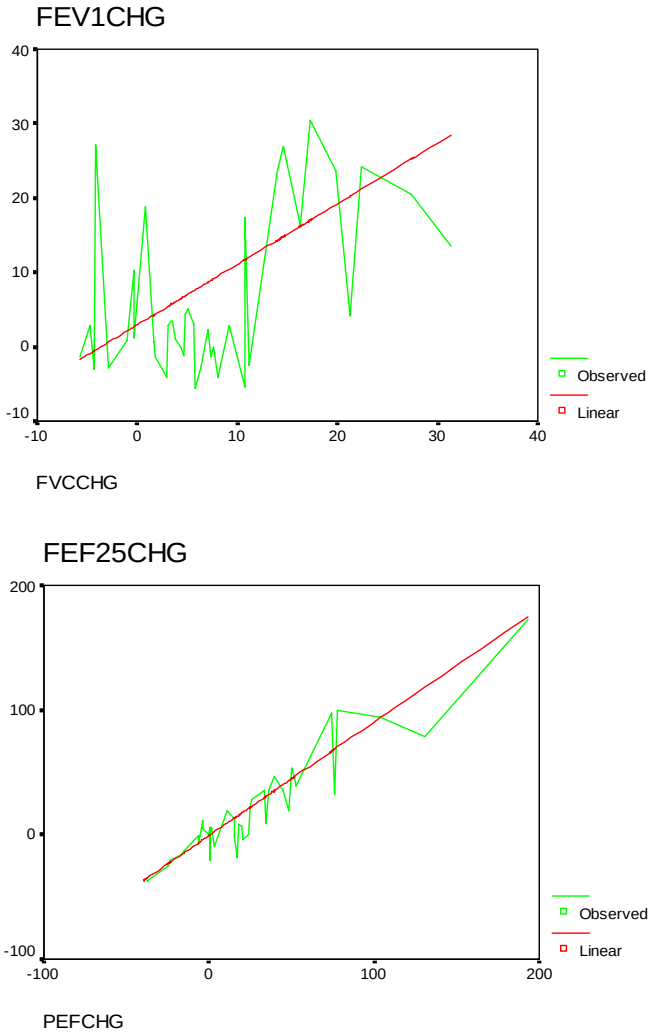


Fig.2 (a, b) Correlation tests.

(-)Cathinone increases metabolic rate and oxygen consumption (16). This might explain the enhanced respiration caused by *Khat* chewing and ingestion although this might also be a consequence of the hyperthermia which occurs during *Khat* consumption (Nencini etal , 1984).

About 200gm of *Khat* chewed and ingested over a period of two hours increased the overall ventricular conduction velocity of depolarization wave (QRS) by 11%, shortened the R-R interval (cardiac cycle length) by 9% and shortened the duration of ventricular depolarization and repolarization time (QT interval) by 4.5%.

The acute changes on ECG intervals and duration of waves associated with Khat use are summarized on Table 2. The PR interval, a measure of A-V deplorization wave was significantly increased two hours after Khat ingestion ($P<0.001$).

Table 2 Pre/post *Khat* ECG profile. The data are expressed as the means±SE.

Variable parameters	Pre Mean	SE	Post Mean	SE	% Change Mean	P-Value
HR (bpm)	80.56	1.53	90.16	2.12	12.54	=0.001
R-R	0.75	0.01	0.68	0.01	-9.41	<0.001
P-R	0.12	0.002	0.13	0.001	8.86	<0.001
QRS	0.10	0.01	0.09	0.002	-11	<0.001
QT	0.35	0.01	0.33	0.01	-4.5	<0.001
Axis QRS	51.98	1.23	49.49	1.19	-15	<0.001

Acceleration of the HR after Khat ingestion (P< 0.001), could be attributed to stimulation of β-adrenergic receptors by NEP from sympathetic nerve terminals of the heart (released under the influence of Khatamines). Another possibility is that Khatamines might directly affect the sino-atrial node in a way that probably induces an increase in heart rate.

The mean of PR interval in the 60 study subjects following the chewing and ingestion of khat leaves over a period of about two hours was increased by 8% (Table 4). This was significant at P<0.001. This increase may be attributed to an increased delay in the A-V node.
Similarly, the RR interval (cardiac cycle length) was shortened by 9%. This is again significant at P<0.001.
The decrease in the duration of QRS complex suggests an increase in the rate of propagation of action potential in the ventricles. The finding that there is a significant increase in the HR and hortening of the cardiac cycle length reflected by significantly reduced RR interval is in agreement with the hypothesis that khat alkaloids have sympathomimetic effects on the heart (5).
The mean of the post-test HR score in the 60 study subjects is correlated to the post- test score of RR and QRS with a significance level of 0.000 and 0.026, respectively see Table 7. As the HR increased by 12% following the chewing and ingestion of Khat leaves, the RR-interval, which is a measure of the duration between two successive QRS waves decreased by 11%. The rate of ventricular depolarization also increased parallel to the increase in HR.

Conclusion and Perspectives

(-) Cathinone can be considered a potent amphetamine like compound, since in almost all respects its effects are analogous to those of (+) amphetamine (17). The key observation demonstrating this is the finding that (-) cathinone and (+) amphetamine have the same mechanism of action (18,19), in that both substances induce the release of dopamine from CNS terminals and thus increase the activity of dopaminergic pathways.

The somatic effects observed after *Khat* consumption are characterized by sympathomimetic syndrome. Observations in the present study were all in agreement with previous assumptions.

In the present study we have observed substantial changes on cardio-respiratory variables of the sympathomimetic type in response to acute ingestion of khat extract ,including increases HR, SBP, DBP, conduction velocity and also causes arrhythmia and changes in the duration of waves and intervals. Nevertheless, the present study can only suggest the possible underlying mechanisms, which are yet to be substantiated by further investigations.

However, further researches should be conducted to find out the effect of long-term use of khat on cardiorespiratory functions, taking into consideration the frequency of use and the quantity and quality of *Khat* to be used.

In addition, the effects of quick ingestion of khat juice must be studied.

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