The Significance of the Effects of Catha edulis Forsk on Electrical Activities of the Heart and some Lung Function Indices

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By

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### Abbreviations

<table>
<thead>
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<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>HPLC</td>
<td>High pressure liquid chromatography</td>
</tr>
<tr>
<td>DA</td>
<td>Dopamine</td>
</tr>
<tr>
<td>NEP</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>VCIN</td>
<td>Inspiratory Vital Capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital capacity</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced Expiratory Volume in one second</td>
</tr>
<tr>
<td>FEV1%</td>
<td>% Forced Expiratory Volume in one second</td>
</tr>
<tr>
<td>PEFR</td>
<td>Peak Expiratory Flow Rate</td>
</tr>
<tr>
<td>FMF</td>
<td>Forced mid Expiratory Flow Rate</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>MEF50%</td>
<td>50% of maximal expiratory flow rate</td>
</tr>
<tr>
<td>LFI</td>
<td>Lung Function Indices</td>
</tr>
<tr>
<td>LFT</td>
<td>Lung Function Tests</td>
</tr>
<tr>
<td>CREB</td>
<td>C-AMP dependent response element binding protein</td>
</tr>
<tr>
<td>FOSB</td>
<td>Factor of sensitization (immediate early gene)</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>V/S</td>
<td>Vital signs</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
</tbody>
</table>
ABSTRACT

The chewing and ingestion of fresh and young leaves of khat produces observable alterations in the physical, physiological and psychological wellbeing of man. The aim of this study was to assess the effects of Khat 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 kgs, their BMI was 22.3±0.6 kg/m². 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 a normal P/E and history and normal V/S, LFI and ECG prior to the khat session. Each of the subjects was given 200 gm of fresh Beleche leaves to chew for a period of two hours. All vital signs including arterial blood pressure, heart rate, and respiratory rate increased significantly (P<0.001). 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). Khat alkaloids apparently activate β-adrenergic receptors in the respiratory system and bring about the overall changes seen on lung volume and capacities, which reflect bronchial dilation. Other important changes observed in this study were ECG changes. Following chewing and ingestion of khat the overall ventricular depolarization and conduction velocity (QRS) increased by 11%; the cardiac cycle length (R-R interval) was shortened by 9% and this hastened the ventricular depolarization and repolarization time (QT interval) by 4.5%. The effects observed on the cardiovascular variables possibly are mediated through activation of α- and β-adrenergic receptors localized in the atria and ventricles, respectively. The active ingredients of Khat have sympathetic- like effects on conductivity, rhythmicity and excitability of the heart.

Other observations in this study were increased energy level and alertness in almost all study subjects following khat ingestion for two hours. These could be parts of the central actions of cathinone, a lipophilic ingredient of khat that can easily traverse the Blood-Brain-Barrier. The cardiopulmonary responses to khat use and the objectively observable behavioral (central) effects are significantly marked in the present investigation but further studies must be conducted to get an insight into:

a) The effects of long-term and chronic use of khat on cardiopulmonary functions,

b) The peripheral and central effects of quick ingestion of khat juice.
1. LITERATURE REVIEW

1.1 The Khat plant and its constituents

*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 (Rudolf, Brenneisn, 1985; Dagne, 1984). 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 (Ethiopia, Kenya, Somalia), Madagascar and the Arabian Peninsula (North Yemen) to attain a state of euphoria and stimulation (Al Meshal et al, 1985; Kalix, 1996).

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. Shipments of *Khat* have been observed by custom authorities in France, Italy, Switzerland, Great Britain and United States (Kalix and Braenden, 1985). Its use is largely confined to those ethnic communities accustomed to its traditional use.

It is estimated that each day, 2-8 million *Khat* portions are chewed worldwide (Kalix and Braenden, 1985). And the growing use of *Khat* has motivated an interest in further knowledge of its active ingredients. Its biological effects are both central and peripheral. It affects the CNS, the cardiovascular and the
The acute cardio-respiratory responses to khat use.

Several *in-vitro* and *in-vivo* experiments have been conducted to characterize pharmacodynamic and pharmacokinetic properties of *Khat*amines (phenylpropyl, phenylpentylamine) and *Khat* in animals and humans (Johansen, Schuster, 1981; Widler *et al*., 1995; WHO; Kalix and Braenden, 1985). Extraction and isolation of major khat ingredients are as shown in figure 2. By using HPLC technique, it is found that *(-)-s-cathinone* is the main active ingredient of *Khat* (Kalix and Braenden, 1985; Geisshusler and Brenneisen, 1987; Zelger, Schorno, Carlini, 1980; Kalix and Braenden, 1985). *Khat* also contains another alkaloid known as *cathine* or *(+) norpseudoephedrine*, which is predominantly responsible for most of the peripheral/somatic effects (Kalix and Braenden, 1985, Patel, 2000; Dagne 1983; Crombie, 1980; Peterson, Maitail and Sparber, 1980).

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. *In-vitro* experiments concluded that cathinone, a potent amphetamine-like compound with indirect sympathomimetic action has the same mechanism of action as amphetamine; including the release of neurotransmitters (dopamine and noradrenaline) from storage sites in the central and peripheral nervous system (Patel, 2000; Kalix, 1996; Brenneisen *et al*., 1990; Khan and Kalix, 1984). In confirmation of this view, cathinone is considered to be a natural amphetamine (Rivier *et al*., 1991).
Evidence in favor of the pharmacological similarity between cathinone and amphetamine is overwhelming (Kalix, 1980; Halbach, 1972; Johanson, 1981; Goudie and Newton, 1985). This pharmacological similarity brought the use of Khat leaves in East Africa and the Arabian Peninsula under the scrutiny of the League of Nations in 1964 and 1971 (Kalix, 1988; and WHO Advisory Group, 1980).

Fig 1 The khat plant and plant parts, Dagne 1984.
1.2 **The Chemistry of phenylalkylamines**

1.2.1 **Cathinone (aminopropriophenone)**

Starting materials for the isolation of cathinone as well as for the other phenylpropylamines were fresh and dried plants from catha cultivations in the area of Meru, Kenya. The phenylpropylamines have been isolated predominantly as oxalates or as N-acetates using various extractions procedures. Subsequently single components were separated using preparative thin layer chromatography (Schorno, 1979).

1.2.2 **Extraction and isolation**

The ether–chloroform extract resulting from the standard extraction procedure for *Khata*amines (Fig.2) was further separated with preparative thin layer chromatography (TLC). Subsequent fractional crystallization of hydrochlorides produced the diastereomers, (+)-norpseudoephedrine and (-)-norephedrine in pure form (Fig. 4).
The acute cardio-respiratory responses to khat use.

**Fig. 2**

**Extraction and Isolation Scheme**

PHENYLPROPYLAMINES

FRESH PLANT MATERIAL
 (= CATHA EDULIS "MERU/KENYA")

POWDERED LEAVES

TURBO EXTRACTION
 (ULTRA TURRAX)

HCL EXTRACT

10% NaOH/PH 10
ETHER/CHLOROFORM
CONC.

ETHER-CHLOROFORM EXTRACT

OXALIC ACID

1. CATINONE OXALATE

2. NORPSEUDOEPHEDRINE OX.
 + NOREPHERDINE OX.

ACETYLATION

ACETATE MIXTURE

NORPSEUDOEPHEDRINE +
NOREPHERDINE

PREP. TLC

CATHINONE ACETATE

PREP. TLC

HCL
FRACT. CRYST.

1. NOREPHERDINE-HCL
2. NORPSEUDOEPHEDRINE-HCL

(SCHORNO, 1979)
1.2.3 Structure and metabolism

The structure of cathinone (Fig. 3) follows unambiguously from its spectroscopic data.

The absolute configuration and the predominant conformation of cathinone are shown to be S- (-) alpha aminopropriophenone by circular dichroism (CD), using the quadrant sector rule.

Little is known, at present, regarding the metabolic fate of (-) cathinone, which is likely to be different from that of (+) amphetamine because of cathinone’s amino acetone structure. Preliminary studies in man by Geisshusler, 2000, however, showed that after oral administration, (-) cathinone is rapidly metabolized into (-) norephedrine, and that it is excreted almost exclusively in this form. Only 2% of the (-) cathinone absorbed appears in urine. Unchanged small quantities of (-) NPE also appears in the urine (Kalix and Braenden, 1985).

The rate of absorption of (-) cathinone is also rapid during mastication of Khat leaves that would limit the cathinone blood levels after chewing Khat (Kalix and Braenden, 1985).

In contrast to (-) cathinone; absorption of (+) NPE is slow and serum half-life is almost 3 hours and it is excreted unchanged within about 24 hrs (Forsch, 1977).
The acute cardio-respiratory responses to khat use.

Fig. 4  Structure and metabolism of Khat alkaloids, Dagne 1983.
Fig. 3 Spectroscopic data, Dagne 1983.
Table 1. The content of khatamines in dependence on origin, plant tissue and age.

<table>
<thead>
<tr>
<th>Plant tissue and age</th>
<th>CATHINE</th>
<th>NORPSEUDOEPHRINE</th>
<th>NOREPHEDRINE</th>
<th>PERCENTAGE OF TOTAL CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catha Variety Yemen Bot. Garden Lausanne/Switzerland</td>
<td>0.517</td>
<td>0.037</td>
<td>0.032</td>
<td>0.449</td>
</tr>
<tr>
<td>Catha Variety (Yemen?) Bot. Garden Teneriffa</td>
<td>0.515</td>
<td>0.001</td>
<td>0.025</td>
<td>0.488</td>
</tr>
<tr>
<td>Catha Variety Nairobi Arboresum Nairobi</td>
<td>0.030</td>
<td>0.003</td>
<td>0.011</td>
<td>0.016</td>
</tr>
<tr>
<td>Catha Leaves Meru 78 Kenya</td>
<td>1.679</td>
<td>0.036</td>
<td>0.306</td>
<td>1.337</td>
</tr>
<tr>
<td>Catha Thick Stems Meru 78 Kenya</td>
<td>1.956</td>
<td>0.012</td>
<td>0.170</td>
<td>1.822</td>
</tr>
<tr>
<td>Catha Thick Stems Meru 78 Kenya</td>
<td>0.233</td>
<td>0.002</td>
<td>0.012</td>
<td>0.219</td>
</tr>
<tr>
<td>Catha Bark of Branches Meru 78 Kenya</td>
<td>0.385</td>
<td>0.007</td>
<td>0.012</td>
<td>0.366</td>
</tr>
<tr>
<td>Catha Short Tops Meru 78 Kenya</td>
<td>1.912</td>
<td>0.968</td>
<td>0.183</td>
<td>0.771</td>
</tr>
<tr>
<td>Catha Leafy Tops Meru 78 Kenya</td>
<td>2.875</td>
<td>0.527</td>
<td>0.786</td>
<td>1.562</td>
</tr>
<tr>
<td>Catha Streetmarket, Upper Parts Nairobi 78</td>
<td>5.077</td>
<td>0.656</td>
<td>0.660</td>
<td>3.161</td>
</tr>
<tr>
<td>Catha Streetmarket, Lower Parts Nairobi 78</td>
<td>2.603</td>
<td>0.110</td>
<td>0.142</td>
<td>2.351</td>
</tr>
<tr>
<td>Catha Streetmarket, 24 H Old Nairobi 78</td>
<td>5.199</td>
<td>2.127</td>
<td>0.401</td>
<td>2.672</td>
</tr>
<tr>
<td>Catha White Madagascar 83</td>
<td>0.181</td>
<td>0.119</td>
<td>0.007</td>
<td>0.054</td>
</tr>
<tr>
<td>Catha Red Madagascar 78</td>
<td>0.735</td>
<td>0.059</td>
<td>0.015</td>
<td>0.661</td>
</tr>
<tr>
<td>Catha Variety Ethiopia Harare 83</td>
<td>1.745</td>
<td>0.275</td>
<td>0.128</td>
<td>1.342</td>
</tr>
</tbody>
</table>

(Schorn and Brenneisen, 1982)
1.3 The effects of Khat chewing

The majority of studies with (-) cathinone were performed after a single administration to animals and, on the basis of this single dose experiments, far reaching conclusions have been drawn concerning the actions of Khat.

The syndrome induced by Khat chewing consists of stimulating effects on the central nervous system and various peripheral sympathomimetic effects (Kalix and Braenden, 1985; Amaha, 1983; Halbach, 1972 and WHO Advisory Group Report, 1980).

The subjective effects reported during double blind, placebo-controlled experiments with cathinone and Khat indicated its psychostimulant and euphorogenic properties, which can be expected to reinforce the habit of chewing Khat. (Rivier, Soejarto, Waller, 1991). Cathinone is the keto-analogue of cathine. It is, therefore, more lipophilic and penetrates easily to its sites of action in the CNS. Indeed, cathinone has been found to be a highly potent Central Nervous System stimulant (Patel, 2000; Rivier, Soejarto, Waller, 1991).

Intraperitonial administration of high doses of (-) cathinone to rats was found to cause not only marked changes of electroencephalographic (EEG) pattern but also to induce stereotyped behavior and stereotyped oral activities such as licking and gnawing (Kalix and Braenden, 1985 and Zelger, Schorno, Carlini, 1980).

Similar studies on mice by Mekonnen et al (1998) showed significant impairment of memory as early as the second day of repeated Khat ingestion. However,
tolerance quickly develops to the performance disrupting and memory dulling effects of *Khat*. It is not clear whether sensitization occurs after a much more prolonged use of whole *Khat* leaves. Nevertheless, development of tolerance to the sympathomimetic effect of *Khat*, as demonstrated by the non-significant changes in blood pressure and heart rate, has been observed in human subjects who chew *Khat* frequently (Nencini *et al*, 1984).

Although most research done so far employed (-) cathinone, the major amphetamine like central nervous system stimulant, it is known that there are more than 20 pharmacologically active compounds in the leaves (Mekonnen *et al*, 1998). Moreover, results from experiments where cathinone alone was given parenterally to experimental animals may not wholly reflect the behavioral toxicity observed after administrating *Khat* in a dosage similar to that used traditionally (Mekonnen *et al*, 1998).

### 1.4 The molecular basis of Addiction

Addiction can be viewed as a form of drug-induced neural plasticity. In addiction, the central pathways shown in **figures 5 and 6** are established. One of the best-established molecular mechanisms of addiction is up regulation of the cAMP second messenger pathway, which occurs in many neuronal cell types in response to chronic use. This up-regulation and the resulting activation of the transcription factor CREB appear to mediate tolerance or dependence (Jennifer and Eric, 2004).
Tolerance refers to drug-induced adaptation that leads to diminishing effects of a constant drug dose. And dependence refers to drug induced adaptation that compensates for drug exposure and leads to an array of withdrawal symptoms (negative affective state or diaphoresis) when drug use ceases. In contrast, induction of another transcription factor, termed FOSB, exerts the opposite effect and may contribute to sensitized response to drug exposure (reverse tolerance). FOSB are early class of genes whose expression is induced within minutes of exposure to a stimulus (Jennifer and Eric, 2004).
Other studies suggest that (-) cathinone and (+) norpseudoephedrine which are active ingredients of *Khat* have peripheral side effects of the sympathomimetic type, in different organ system of the body (Rudolf and Brenneisn, 1985; Kalix and Braenden; Duke, 1985 and Widler *et al.*, 1985). At the cardiovascular level, there is arrhythmia, tachycardia and dose-dependent increase in blood pressure (Kalix and Braenden, 1985; Ayana *et al.*, 2002). Habitual use of *Khat* may lead to chronic hypertension, which, upon abstinence from the drug, can change into a transient hypotensive state (Kalix and Braenden, 1985). An increase in the incidence of acute myocardial infarction is reported among other risk factors associated with *Khat* chewing (Al-Meshal *et al.*, 1985).
Effects of *Khat* in the respiratory system are mainly increased respiration, increased oxygen consumption and hyperthermia (Rudolph and Braensen, 1985 and Kalix and Braenden, 1985).

In general NEP and EP, have an inhibitory effect on the non-sphincter smooth muscles of the GIT, bladder, and lungs (Kalix; 1996). Smooth muscles of skeletal blood vessels and glands are excited by NEP and EP. Neurotransmitters released from the sympathetic axon terminals generate inhibitory post sympathetic potential on effector smooth muscle cell membrane, which causes relaxation of smooth musculature. In the body, these transmitters are inactivated soon after release, by decomposition and reabsorption into the nerve endings.

Since *Khat* leaves have high tannin content, *Khat* chewing frequently causes periodontal disease, mucosal lesions, and a number of disorders of the upper gastro-intestinal tract including constipation (Kalix, Braenden, 1985; Mekonnen, 2000 and Heymann et al., 1995).

*Khat* is also known to impair male sexual function and to lead to a high incidence of spermatorrhoea which is sometimes accompanied by testicular pain. Long-term chronic use may lead to permanent impotence (Rudolph and Braensen 1985; El-Shaura et al., 1995).

*Khat*-induced analgesia has been reported recently (Connor, Mekonnen and Rostom, 2000) but it is not known whether the mechanism is central or peripheral. Previously Nencini *et al.*, (1984) reported that (-)-cathinone has analgesic
The acute cardio-respiratory responses to khat use.

properties in mice. This is ascribed to monoaminergic and endogenous opioid mechanisms.

1.5  **Cellular mechanisms that underlie the central and peripheral effects of khat alkaloid (-)cathinone.**

1.5.1 Central effects

(-) Cathinone (amphetamine analog) can inhibit the re-uptake of physiologically released DA, i.e. it prolongs the action of DA on its receptors. Another possibility is that cathinone acts by inducing the release of DA from periaqueductal storage sites (Kelly and Iversen, 1976). Therefore, the effect of (-) cathinone on the efflux of radioactivity from isolated rabbit caudate nucleus pre-labeled with $^3$H-DA was studied. It was found that the superfusion of the tissue with (-) cathinone produced a rapid and reversible increase of the efflux of radioactivity).

1.5.2 Peripheral effects

The mechanism underlying the peripheral effects of (-) cathinone is studied on isolated tissues of animal models pretreated with $^3$H-NEP (Knoll, 1979).

(-)Cathinone superfusion caused increasing efflux of radioactivity. Therefore, it was understood that (-) cathinone’s effect peripherally is mediated by increasing NEP release from peripheral storage sites (Knoll, 1979).
1.6 **Epidemiological aspects of Khat use**

In Kenya, *Khat* chewing is a regional phenomenon with the two center of consumption being Nairobi and the Meru district, in which *Khat* is cultivated extensively in the foothills of Mount Kenya. Statistics on production and consumption are not available, but it is known that, until recently, Kenya annually exported quantities of *Khat* valued at approximately 2 million USD (Kalix and Braenden, 1985; Shahandeh et al., 1983).

In Ethiopia, *Khat* is commonly used for social recreation, but occupational groups such as motor vehicle drivers, who chew *Khat* during long distance driving, to keep awake, also use it under a variety of other conditions. A significant number of students chew *Khat* especially during examination periods to be less sleepy and get mental alertness. There is also specific usage by some members of the community: craftsmen and farmers use it to reduce fatigue and traditional healers to cure some ailments (Duke, 1985). Ethiopia earns more than 16 million USD annually from *Khat* export (Kassaye et al., 1999).

*Khat* has a bitter taste and it is usually chewed in combination with sugar. A good number of *of khat* chewers smoke cigarette during *Khat* session. This is believed to enhance the degree of excitement (Kassaye et al., 1999; Kebede, 2002). Most often alcoholic beverages are taken after *Khat* chewing to terminate excitation (*Mirkana Chipsa*).
The acute cardio-respiratory responses to khat use.

The growth in the number of Khat chewers of different types, Beleche, Awedai, Kolombia, Gunchire, Abo Mismar, Gemeto, Wondo and Sebale as observed in Ethiopia and elsewhere in the world, has attracted farmers in the country in general, and those in western and eastern parts of the country in particular, to turn much of their farmland over to growing Khat (Ethiopian Fortune Newsletter, vol.15, sun., Sep., 2004).

According to a survey from the Ethiopian Federal Statistics Authority, in 2002, farmland covered by Khat reached over 1.5 million hectares of which 242,616 hectares are located in Harar, the highest of khat growing area in the country. Others such as the Somali Regional State, with 411,000 hectares, and the Oromia Regional State with 910,000 hectares follow. Annually, over 46,000tn of of khat is produced in the country.

In Harar alone, the survey discloses, that 70% of the farmland, which is used to grow coffee has been turned into growing Khat, following the collapse of coffee in the international market. Khat now claims the third place, next to coffee and hides and skins, in earning foreign currency for the country. According to data from the Ethiopian Export Promotion Agency, in the last five years alone, an average of 11,000 tons of Khat has been exported each year. The export earnings for 2002 and 2003 were 418 million and 500 million Birr, Djibouti and Somalia being the largest importers. Djibouti, for instance, buys an average of over 60 tons of Khat everyday (Ethiopian Fortune Newsletter, vol.15, sun., Sep., 2004).
1.7 **Socio-economic impact**

Apart from the ever-increasing health problems, the habit of *Khat* chewing has caused serious socio-economic repercussion (Belew *et al.*, 2000; Shahandeh *et al.*, 1983).

The major consequences of *Khat* use are absenteeism and decreased productivity frequently leading to unemployment. Furthermore, the purchase of *Khat* puts a strain on family income, and the detrimental social effects of the *Khat* habit are felt mainly within the family. The interaction of family members with the father is adversely affected because he is irritable and quarrelsome while under the influence of the drug he may be silent and withdrawn when the effect has worn off. Through its effect on the male reproductive system, the drug also leads to progressive estrangement between husband and wife. It is estimated that the drug leads to one out of two divorces in Djibouti (Kalix, Braenden, 1985 and Shahandeh *et al.*, 1983).

Mainly because of the social and economic problems associated with *Khat* use, international organizations have been showing concern in the issue since 1935 (Kalix and Braenden, 1985). In 1935, the Advisory Committee of the League of Nations discussed technical reports on the traffic of dangerous drugs but no action was taken. In 1956, the question was raised again during a session of the United Nations Commission on narcotic drugs; the Commission later recommended that the UN Economic and Social Council invite the World Health Organization to
study the medical aspects of the habitual chewing of Khat (Kalix and Braenden, 1985). WHO then began to collect relevant data and made the necessary assessment. From this it could be seen that a reinvestigation of the active constituents of Khat was necessary for a rational study of the plant’s effects.

1.8 Rationale for further study

The growing use of Khat has motivated an interest in getting further knowledge of its active ingredients and the pharmacological as well as biological effects. A number of studies have therefore been made in an attempt to throw more light on the effect of chewing and ingestion of khat. The investigation led to the discovery of the alkaloid (-) cathinone, which is now considered to be the constituent that is mainly responsible for the psycho-stimulant properties of Khat leaves (Guantai and Maitai, 1982). It is fortunate perhaps, that Khat is also very rich in ascorbic acid, which is an excellent antidote to amphetamine type compounds (Mustard, 1952).

It appears that Khat’s effects on the central nervous system includig talkativeness, alertness, psychosis and dependence are well documented (Yousef et al., 1995) 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 (Nencini *et al.*, 1984) as a result of tolerance, subjects in the present work are those who chew *Khat* casually.

Although there have been several other research works done 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 clearing on khat as a habit-forming drug. Some disturbances of rhythm and conduction velocity of cardiac impulse could be developing as a consequence of *Khat ingestion*. 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, FVC, FEV1, FEV1%, FEF and PEFR following the ingestion of *Khat*. No work relating to lung function indices has been undertaken to date.
2. **OBJECTIVE OF THE STUDY**

2.1 **General Objective**

To assess the effects of *Khat* (Catha edulis Forsk) on **lung function indices** and some **cardiovascular variables**.

2.2 **Specific Objectives**

2.2.1 To assess changes in vital signs including, respiratory rate, pulse rate and blood pressure following ingestion of khat

2.2.2 To characterize electrical activities of the heart associated with the ingestion of *Khat* juice.

2.2.3 To estimate the changes in mechanical lung function indices (FVC, FEV, FEV1%, FEF25%-75%, PEFR) associated with ingestion of *Khat* juice.

2.2.4 To assess the general socioeconomic implication of khat cultivation and the regular use of it.
3. **SUBJECTS AND METHODS**

3.1 **Study Subjects**

A sampling frame of *Khat* session places (Mufferaj) in each Woreda of Addis Ababa was obtained from informants of 10 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
The acute cardio-respiratory responses to khat use.

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

3.2 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 was 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. It is the quantity approximated to bring a state of euphoria and excitement in the user. According to sources from literature (Kalix, 1987; Schrono et. al, 1983) 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.

3.3 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
The acute cardio-respiratory responses to khat use.

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 cardio-respiratory 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.

3.3.1 Lung Function Tests

The measurements of VCIN, FVC, FEV1, FEV1 %, 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 °C, 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.

### 3.3.2 ECG tracing

A self-interpreting ECG machine was used for the tracing of surface cardiac electrical changes. 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.

### 3.3.3 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.

3.4 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.

Multiple logistic regression model was applied to assess the relative effect of each explanatory variable to the outcome of variable in question.

3.5 Ethical consideration

The study was carried out only after it was cleared by the Ethical Committee of AAU. 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.
4. RESULTS

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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>80%</td>
</tr>
<tr>
<td>Effect size</td>
<td>0.2+2SD</td>
</tr>
<tr>
<td>Significance level</td>
<td>0.05</td>
</tr>
</tbody>
</table>

We studied 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.

4.1 Effect of *Khat* on clinical parameters

During the first part of the *Khat* session, there was an atmosphere of cheerfulness characterized by optimism, high spirit, and a general sense of wellbeing. The excitement brought about by the consumption of *Khat* reduced social inhibitions and caused loquacity. After about one and half hours, certain degree of tension that reflected emotional instability and irritability became apparent. The talking became louder, less relevant to the subject under discussion, and there was greater awareness of problems (Table 2).
The acute cardio-respiratory responses to khat use.

The desirable effects as perceived by most subjects under study were relief from fatigue, increased alertness and energy levels, feelings of elation, improved ability to communicate, enhanced imaginative ability and capacity to associate ideas, and heightened self-confidence.

The objectively observed central effects in most study subjects following two hours of Khat chewing and ingestion were mild euphoria and excitement accompanied by episodes of logorrhea and then verbal aggressiveness.

Table 2. Clinical effects of Khat observed on 60 voluntary male subjects two hours after Khat chewing and ingestion, AA, Ethiopia, 2004

<table>
<thead>
<tr>
<th>No.</th>
<th>Symptom</th>
<th>Frequency of occurrence(%)</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Body warmth</td>
<td>99</td>
<td>Increased BMR</td>
</tr>
<tr>
<td>2</td>
<td>Dryness of mouth</td>
<td>90</td>
<td>Astringent property of tannin</td>
</tr>
<tr>
<td>3</td>
<td>Palpitation</td>
<td>70</td>
<td>Chronotropic effects</td>
</tr>
<tr>
<td>4</td>
<td>Euphoria</td>
<td>84</td>
<td>Psychostimulant effect</td>
</tr>
<tr>
<td>5</td>
<td>Increased working capacity</td>
<td>86</td>
<td>Increased DA releasing effect and VO2 Max.</td>
</tr>
<tr>
<td>6</td>
<td>Pseudoexophthalmia</td>
<td>78</td>
<td>Sympathetic effect on the levator palpebrae superioris muscle of the eyelids.</td>
</tr>
</tbody>
</table>
4.2 Effects of Khat on BP, HR

Arterial blood pressure (BP) and respiratory rate (RR) were all increased significantly (P<0.001) after 2 hours of Khat chewing and ingestion (Table 3 and 4). This finding is in agreement with related studies done on experimental animal models where the SBP and DBP were found to be higher than the resting baseline values following one hour of administration of Khat extract (Expert Committee Report on HPT Control, WHO Technical Report Geneva, 1996, 86:1-77).

Table 3. Changes in BP, HR and RR after Khat chewing and ingestion at 2 hours interval in 60 normotensives. AA, Ethiopia. Values are presented as mean ± SE.

<table>
<thead>
<tr>
<th>Testing condition</th>
<th>SBP(mmHg)</th>
<th>DBP(mmHg)</th>
<th>Mean BP</th>
<th>HR(beats/min)</th>
<th>RR(breaths/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before chewing</td>
<td>107.38±0.77</td>
<td>76.33±0.63</td>
<td>89.47±0.81</td>
<td>80.56±1.53</td>
<td>16±0.22</td>
</tr>
<tr>
<td>2 hours after</td>
<td>128.28±144</td>
<td>84.90±0.51</td>
<td>99.33±0.71</td>
<td>90.15±2.13</td>
<td>25±0.49</td>
</tr>
<tr>
<td>Paired difference</td>
<td>20.89±0.37</td>
<td>8.58±0.11</td>
<td>9.86±0.10</td>
<td>9.59±0.70</td>
<td>9±0.27</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt; 0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 4. Observed mean vital signs for the 60 study subjects before and two hours after chewing Khat

<table>
<thead>
<tr>
<th>V/S</th>
<th>Before</th>
<th>After</th>
<th>% change</th>
<th>P-Value</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>80.56</td>
<td>90.15</td>
<td>12</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
<tr>
<td>RR</td>
<td>16</td>
<td>25.5</td>
<td>59</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
<tr>
<td>SBP</td>
<td>107.38</td>
<td>128.28</td>
<td>19</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
<tr>
<td>DBP</td>
<td>76.33</td>
<td>84.9</td>
<td>11</td>
<td>&lt;0.001</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

4.3 Effect of Khat on lung function indices

Measurements of VCIN, FVC, FEV, FEV1%, and FEF25%-75% made in 60 eligible adult men showed statistically significant differences between pretest and post-test values (Table 5). The bronchial dilation measurement showed significant % change (P<0.001). Although the actual value of the post-test measurement of FEF50% and FEV1% showed significant increase, the % change was lower in 46% and 29% of the study subjects, respectively as reflected by the mean values of the lung function indices (Table 5 and Fig 7). The pattern of % difference appears to be essentially the same in almost all study subjects.

The change in VCIN, FVC and PEFR appear to be relatively more consistent and significant (see Table 5.). The acute changes observed in lung function were similar in all age groups (Table 5.).
Table 5. Means and SD of the LFI before and 2 hours after khat ingestion in 60 volunteer study subjects. P value represents level of significance and the magnitude of effect size- small (0.2-0.5), medium (0.5-0.8), large (0.8+).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre (mean +SD)</th>
<th>Post (mean +SD)</th>
<th>% change (mean)</th>
<th>Effect size</th>
<th>Magnitude of ES</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCIN (L/sec)</td>
<td>2.52±0.59</td>
<td>2.91±0.78</td>
<td>15.6</td>
<td>0.67</td>
<td>Moderate</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.40±0.45</td>
<td>3.70±0.53</td>
<td>9</td>
<td>0.66</td>
<td>Moderate</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 (L/sec)</td>
<td>2.98±0.40</td>
<td>3.27±0.51</td>
<td>10</td>
<td>0.74</td>
<td>Moderate</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1%</td>
<td>87.50±7.84</td>
<td>88.96±6.56</td>
<td>2</td>
<td>0.18</td>
<td>No effect</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PEFR</td>
<td>6.01±1.93</td>
<td>7.23±1.58</td>
<td>20</td>
<td>0.63</td>
<td>Moderate</td>
<td>0.001</td>
</tr>
<tr>
<td>FEF75%</td>
<td>1.90±0.84</td>
<td>2.05±0.99</td>
<td>8</td>
<td>0.18</td>
<td>No effect</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEF50%</td>
<td>4.14±1.23</td>
<td>4.54±1.47</td>
<td>10</td>
<td>0.33</td>
<td>Small</td>
<td>0.043</td>
</tr>
<tr>
<td>FEF25%</td>
<td>5.51±1.72</td>
<td>6.39±1.10</td>
<td>16</td>
<td>0.51</td>
<td>Moderate</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
FVC change is positively correlated with FEV1 at a significance level of P<0.001 and a coefficient of r=0.602 (Fig.8 A). Similarly PEF change and FEF % change are significantly correlated (P<0.001) with r=0.601.

4.4. **Effect of Khat on ECG profile**

The mean duration (ms) of the PR, QRS, RR and QT intervals measured before and 2 hours after the chewing of Khat leaves is shown in Table 6.

*Khat* mainly increased HR and the rate of ventricular depolarization (QRS), P<0.001 while ventricular depolarization and repolarization time (QT) was only slightly but significantly shortened (Table 6) PR interval prolonged (P<0.001) and the RR interval (Cardiac cycle length) was significantly shortened (P<0.001). 16% of the study subjects had arrhythmia and 25% sinus tachycardia and 3% atrial fibrillation in the post-test.

**Table 6. Pre/post Khat ECG profile. The data are expressed as the means ±SE**

<table>
<thead>
<tr>
<th>Variable parameters</th>
<th>Pre Mean ±SE</th>
<th>Post Mean ±SE</th>
<th>% Change Mean ±SE</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR(bpm)</td>
<td>80.56 ± 1.53</td>
<td>90.16 ± 2.12</td>
<td>12.54 ± 0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-R</td>
<td>0.75 ± 0.01</td>
<td>0.68 ± 0.01</td>
<td>-9.41 ± 0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-R</td>
<td>0.12 ± 0.002</td>
<td>0.13 ± 0.01</td>
<td>8.86 ± 0.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS</td>
<td>0.10 ± 0.01</td>
<td>0.09 ± 0.002</td>
<td>-11 ± 0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QT</td>
<td>0.35 ± 0.01</td>
<td>0.33 ± 0.01</td>
<td>-4.5 ± 0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Axis QRS</td>
<td>51.98 ± 1.23</td>
<td>49.49 ± 1.19</td>
<td>-15 ± 0.32</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Fig. 7. Mean % change of lung function indices 2 hours after ingestion of khat leaves in different age groups.

(a) VCIN
The acute cardio-respiratory responses to khat use.

(b) FVC

(c) FEV1
The acute cardio-respiratory responses to khat use.

(d) FEV1%

(e) PEF
The acute cardio-respiratory responses to khat use.

(f) FEF75%

(g) FEF50%
The acute cardio-respiratory responses to khat use.

AGE

(h) FEF25%
Fig.8 (A) Correlation between % change PEF and % change FEF.

(B) Correlation between % change FVC and % change FEV1
5. DISCUSSION

5.1 General

The central effects of khat including talkativeness, alertness psychosis and dependence have been well documented (Yousef et al.; 1995). The peripheral effects are relatively less emphasized. Khat-induced analgesia has been reported recently (Connor et al., 2000). Although it is not known whether the mechanism is central or peripheral, acute autonomic responses, such as elevated blood pressure and tachycardia, have been reported (Duke, 1985; Widler et al., 1994). Gastric ulcer (Iwu, 1993) and abnormal spermatogenesis (El-Shaura., 1995) have also been observed in Khat users. One clinical trial on Khat showed delay in gastric emptying after Khat chewing (Heymann and Bupulan., 1995).

Khat contains a number of alkaloids known collectively as Khatamines, the major components being (-) cathinone and cathine (Guantai and Maitai, 1982). Both alkaloids are believed to be responsible for most of the pharmacobiological actions of Khat. The fact that cathinone has a closer structural similarity with amphetamine and that both share common pharmacodynamic features, led to the conclusion that cathinone is the most important active ingredient of Khat that causes the major pharmacological effects (Kalix, 1980). The chewing of freshly harvested Khat results in effects indistinguishable from those of amphetamines (Mekonnen et.al; 1998).
Khate and Amer; 1995, indicated that the leaves of Khat are chewed because of the CNS stimulating and sympathomimetic effects. It was also stated, in one of the previous studies that tolerance developed to the sympathomimetic effects of Khat (Nencini et al 1984). All these data indicate that Khat has sympathomimetic action. As there is close structural similarity between amphetamine and cathinone, the objectively observable changes in the aforementioned variables of interest two hours following the chewing of Khat might be attributed to (-) cathinone. (-) Cathinone may act by facilitating the release of adrenergic transmitters from adrenergic nerve terminals. The fact that similar actions have been observed with amphetamine could substantiate such an assumption. Although the exact mechanism that underlie the alterations in cardiorespiratory variables have not yet been established, one may suggest the possible mechanisms from the pervious studies. For instance, the urinary retention observed with Khat has been suggested to be mediated through activation of \(\alpha\)-adrenoreceptors (Patel NB, 2000). The effects observed on the heart possibly are mediated through activation of \(\alpha\) and \(\beta\)-adrenergic receptors localized in the atria and ventricles, respectively. By the same token Khat alkaloids might activate \(\beta\)-adrenergic receptors in the respiratory system to cause the changes seen on lung volume and ventilatory capacities (Table 5, Fig.7 a-h).
5.2 Specific

The desirable effects of khat as perceived by most subjects (86%) under study were relief from fatigue, increased alertness and energy levels, feelings of elation, improved ability to communicate, enhanced imaginative ability and capacity to associate ideas, and heightened self-confidence (Table 2). The observed central effect following two hours of Khat chewing and ingestion was mild euphoria and excitement (84%) accompanied by episodes of logorrhoea and then verbal aggressiveness (Table 2). The effects clearly observed on study subjects would substantiate our understanding of the psychostimulant action of (-)-cathinone contained in the leaves.

In addition, the objectively observed behavioral effects such as verbal aggression and alertness following Khat chewing could be cathinone’s central action mediated by brain monoaminergic system. This active Khat ingredient is lipophilic and can traverse the blood brain barrier (Kalix and Braenden, 1985).

There might as well be specific receptors for cathinone in these organ systems, which might open another avenue for further investigation on the mechanism of action.

The general understanding is that most study subjects had good mastication efficiency and attained full state of euphoria. Some individuals with poor mastication efficiency took a little longer time to manifest the expected sympathomimetic effect.
The acute cardio-respiratory responses to khat use.

The explanation for the significant rise in BP (systolic, diastolic and mean) and acceleration of HR (P<0.001) could be that (-)-cathinone; the lipophilic active ingredient of Khat extract stimulates the release of NEP centrally.

Alternatively, (-) cathinone and cathine together induce the release of NEP from storage sites of peripheral sympathetic nerve endings (terminal button).

In the present study the chewing and ingestion of khat leaves caused significant post-test increment in the measurement of VCIN (P<0.001), FVC (P<0.001), FEV1 (P<0.001), PEFR (P<0.001) and FEF25-75% (P<0.001) (Table 5).

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 5, do clearly indicate a reduction in airway resistance or an increased expiratory pressure.

Pulmonary indices that were consistently increased were VCIN, FVC, and FEV1 and 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
The acute cardio-respiratory responses to khat use.

(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.

According to Lippincott and Wilkins, 1995; the control of airway diameter involves:

a) Sympathetic nerve stimulation to the airways causes bronchodilation
   
i) Direct sympathetic nerve activation causes only slight bronchodilation because in humans the adrenergic nerve do not actually innervate the bronchial smooth muscles.
   
   ii) Circulating adrenergic substances (eg. EPN) bronchodilation because bronchial smooth muscles contain large number of $\beta_2$adrenergic receptors that produce smooth muscle relaxation in response to adrenergic drugs.

b) Non-cholinergic activity: VIP causes bronchodilation and inhibits mucus secretion.

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:
The acute cardio-respiratory responses to khat use.

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 7 and Fig.8 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.

(-)Cathinone increases metabolic rate and oxygen consumption (Halbach, 1972). 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%.
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The acute changes on ECG intervals and duration of waves associated with Khat use are summarized on Table 6. The PR interval, a measure of A-V dephosphorization wave was significantly increased two hours after Khat ingestion (P<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 6). 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 shortening 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 (Kalix and Braenden, 1985).

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.

In summary, the present overall increment in lung volumes and ventilatory capacities and some of the cardiovascular parameters were considerable. And these findings ie; acute cardio-respiratory responses to the use of khat, is in agreement with the hypothesis that Khat alkaloids have sympathetic-like effect.
6. CONCLUSION AND PERSPECTIVE

Experiments have shown a correlation between the symptoms of stimulation observed after *Khat* consumption and those seen in animals after administration of the *Khat* alkaloid, (-)-cathinone (Kalix and Braenden, 1985). Similarly it is now possible to explain the compulsiveness of *Khat* intake observed in some of the chewer by the reinforcing properties of (-) cathinone, which have been demonstrated in self-administration experiments with monkeys. (Nencini *et al*., 1984).

Furthermore (-) cathinone can be considered a potent amphetamine like compound, since in almost all respects its effects are analogous to those of (+) amphetamine (Eddy *et al*., 1965). Indeed, no major pharmacological difference between the *Khat* alkaloid and the synthetic stimulant has been discerned (Kalix and Braenden, 1985). The key observation demonstrating this is the finding that (-) cathinone and (+) amphetamine have the same mechanism of action (Kelly and Iverson, 1976 and Knoll, 1979). Both substances induce the release of dopamine from CNS terminals and thus increase the activity of dopaminergic pathways. These results confirm the assumption that *Khat* is an amphetamine- like substance (Eddy *et al*., 1965).

The somatic effects observed after *Khat* consumption are characterized by sympathomimetic syndrome.
Since *Khat* leaves usually contain more cathine than (-) cathinone (Schorno *et al.*, 1983), the peripheral and central effects induced by a portion of *Khat* can be considered to be predominantly due to (+) NPE. The greater the contribution of (+) NPE to the CNS effects, the more will be the pronounced sympathomimetic side effects of a given batch of *Khat*. The *Khat* chewer, therefore, will prefer leaves that contain a high proportion of (-) cathinone, not only because these are better stimulant, but also because they are less prone to producing the undesired peripheral effects.

In view of the usually chronic use of *Khat*, it seems necessary to give more attention to the possibility of long-term adverse effects on cardio-respiratory functions and the carcinogenic and teratogenic potential of this substance.

Acute and immediate medical problems arising from *Khat* consumption are infrequent (Kalix and Braenden, 1985), probably because the alkaloids are diluted in the bulk material of the leaves and because of the fact that *Khat* is rich in ascorbic acid that acts as a potent antidote to amphetamine toxicity (Mustard, 1952).

The main concern with regard to *Khat* chewing is the wide range of indirect health, social and economic consequences of the habit. It must be granted, however, that the *Khat* habit has certain positive aspects. It furthers social interaction and structures social life. This is the predominant reason for its long tradition and wide social acceptance as the main recreational activity. . It must also be recalled that some *Khat* chewers have non-recreational motives since,
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particularly among the rural population. Farmers also use Khat to relieve fatigue and increase work performance and to suppress the feelings of hunger.

Considering the problem in this perspective, the limits between use and abuse of Khat become difficult to discern.

During the last two decades the use of khat has spread considerably, probably because of more efficient transportation of this perishable commodity as well as because of the pattern of habitual Khat use. The serious socio-economic repercussions of these developments, as well as the resulting increase in health problems, have stimulated efforts to restrain the cultivation and use of Khat. It has been found, however, that prohibition of Khat is difficult to enforce. More gradual approaches such as reducing the availability of Khat by reducing the marketing of the leaves may have better chances of success. This has already been tried in North Yemen, where Khat markets have been moved to the outskirts of the population centers and in south Yemen, where Khat is sold on holidays only. Of course, such regulatory measures should be supported by crop substitution program for those who derive their income from Khat, and by creating alternative recreational activities.

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. These include increased HR, SBP, DBP, conduction velocity, 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.

Further research 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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Declaration

I, the undersigned, declare that this thesis is my original work, has not been presented for a degree in any other university and that all sources of material used in the thesis have been duly acknowledged.

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