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**KHAT (*CATHA EDULIS*) A CONTROVERSIAL PLANT:
BLESSING OR CURSE?**

(History, Survey, Critical Review and Our New Results.)

**A Thesis submitted for the Degree of Doctor of Philosophy in
University of Szeged, Szeged, Hungary**

by

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ARTICLES, THE THESIS IS BASED ON

- I. Balint GA, Desta B, Balint EE , Ghebrekidan H, Katema H: Investigation of the traditionally used Ethiopian medicinal plants with modern up-to-date pharmacological methods. Addis Ababa University, School of Pharmacy, Dept. of Pharmacology. Report to the WHO, 1990. (A joint WHO/UNDP/World Bank project.) **IF: -**
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- III. Balint GA, Balint EE (1994) On the medico-social aspects of khat (Catha edulis) chewing habit. *Hum Psychopharmacol Clin.* 1994 9(2): 125-128. **IF: 2.607**
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LIST OF ABBREVIATIONS

APA	amphetamine
CEA	cysteamine-hydrochloride
CTN	(-)-cathinone
DEA	Drug Enforcement Administration
GER	granular endoplasmic reticulum
Ind	indomethacin
M	mitochondrion
Mb	microbody
NPE	norpseudoepinephrine
SER	smooth endoplasmic reticulum
STR	stress
U.I.	ulcer index
UNDCP	United Nations International Drug Control Program
WHO	World Health Organization

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*“The basic thing nobody asks is:
Why do people take drugs of any sort?”
(John Lennon)*

*“Drug misuse is not a disease, it is a
decision, like the decision to step out in
front of a moving car. You would call
that not a disease but an error of
judgment.”
(P.K. Dick)*

1. Introduction

Fresh leaves of khat (*Catha edulis*) are customarily chewed by the inhabitants of East Africa and Southern Arabia to attain a state of stimulation.

Although the use of khat is widespread, until recently it has remained mostly confined to the regions where the plant is grown since only the fresh leaves have the potency to produce the desired effects.

Considering that during the last decade(s) khat chewing became more common in the so-called “western or developed countries” - for example due to migration, - and given the possible abuse potential of the herb, - which is prohibited by law in several European and American countries, - knowledge of its properties may be useful.

2. History and Survey of Literature

Khat (*Catha edulis*, *Celestraceae*) is a flowering plant indigenous to tropical East Africa and the Arabian Peninsula. The origins of the plant are often argued. Many believe its origins are Ethiopian, others state that khat originated in Yemen before spreading to Ethiopia and the nearby countries Arabia, Kenya, Somalia, Uganda, Tanzania, Malawi, Congo, Zambia, Zimbabwe and South Africa; it has also been found in Afghanistan and Turkestan.

Our view, based on personal knowledge collected in Ethiopia, is that the Ethiopian origin is more likely.

Sir Richard Burton, the renowned British explorer, stated in his contemporary (1856) book "*First footsteps in East Africa*" that khat was introduced to Yemen from Ethiopia in the 15th century.

According to some authors, the earliest medical use of khat is recorded in the *New Testament*. The ancient Ethiopians considered the plant a "divine food", while the Egyptians used the plant for more than its stimulating effects. They used it in a metamorphic process to transcend into "apotheosis", thus the human being was made "god-like".

The medical use of khat goes back to antiquity, when *Alexander the Great* used khat to treat his soldiers for an unknown "epidemic disease".

The earliest documented description of khat dates back to the "*Kitab al-Saidana fi al-Tibb*", an 11th century work on pharmacy and materia medica, written by *Abu Rayhan al-Biruni*, a Persian scientist (Kiple and Ornelas, 2001).

In 1924 Lewin gave a brief account of khat and how it was used (Lewin, 1931).

The name *Catha edulis* was first given to the plant by *Forsskal* in 1775, and this name has since been used by most authors. Other, locally used names are: Ethiopia: chat, khat; Saudi Arabia, Yemen: qat, q'at; Somalia: jaat; Kenya: kat, khat, muringi, meongi, muraa, chat, tschat, miraa, murungu; Uganda: musutate, mutabungwa, ngongo, kitandwe; Tanzania: mlonge, mulungi, warfo, mzengo, ikwa; Malawi: mutsawiri; Mozambique: mutsawhari, m'tianali; South Africa: bushman tea; - and many other names which indicate that the plant is well known across the eastern part of Africa. The dried leaves of the plant are known as Abyssinian tea, Arabian tea or Bushman tea (Balint and Balint, 1995).

The plant is a shrub or decorative tree growing 1 - 25 m tall and is widely distributed in Africa (*Figure 1*).

The leaves are elliptic to oblong, pendulous, leathery, bright green and shiny above, paler below with an evenly toothed margin. They are 5 - 10 cm long and 1 - 4 cm wide (*Figure 2*). Fresh khat leaves are crimson-brown and glossy but become yellow-green and leathery as they age. They also emit a strong smell. The most favoured part of the leaves are the young shoots near the top of the plant. However, leaves and stems at the middle and lower sections are also used.

Khat grows in habitats varying from evergreen submontane forest to deciduous woodland at 800 - 2000 m altitude and is now indigenous in Ethiopia, Kenya, Uganda and Tanzania, and from East Congo southward to South Africa. More recently it has also been introduced to Somalia.

Chewing the leaves of the plant for their pleasurable stimulant effect is a habit that is widespread in the mentioned geographical areas. It is estimated that about 5 - 10 million people chew it every day. In Yemen for example, 60% of the males and about 35% of the females were found to be khat users and had chewed daily for long periods of their lives (*Figure 3*). The chewing of khat leaves probably pre-dates the use of coffee. (There is even a well-known Ethiopian proverb: "*Coffee is the poor man's khat.*")

The chewing of khat leaves has a stimulating effect and causes a certain degree of euphoria. Since only fresh leaves have the desired effect, the chewing habit until the present time has remained in those areas where the plant is indigenous.

Khat is harvested in the early hours of the morning and sold in markets in the late morning. It is presented as a bundle of twigs, stems and leaves, and is wrapped in banana leaves to preserve freshness (*Figure 4*).

During the past two decades khat chewing has gained global prominence as the result of migration, an increase in its use and the associated socioeconomic and health problems among its users. Khat already has a global market and a recognized economic value comparable to other crops such as tea, coffee and cacao. The khat trade has a complex distribution network and therefore efforts to control it would require recognition of its potential to develop into a black market if criminalized.

As a consequence of rapid and relatively inexpensive air transportation, during the past couple years the drug has been reported in Great Britain, Italy, The Netherlands, Canada, Australia, New Zealand, the USA and even in Hungary (Kassim and Croucher, 2006; VPOP, 2008).

The recent controversies and problems regarding khat result from contradictions inherent in the findings of past and recent scientific studies on the plant. A large body of literature mainly focuses on the negative consequences of its use from a health perspective, while ignoring the socioeconomic perspectives and social significance of the plant among users.



Figure 1. Khat (*Catha edulis*) plant.



Figure 2. Fresh young khat leaves.



Figure 3. Khat cewing.



Figure 4. Fresh khat leaves, ready for sale and chewing.

3. General Aspects

In the context of the UNDCP study on illicit drug trends in Africa (UNDCP, 1999), field research was undertaken in Ethiopia in early 1998, confirming that the cultivation of khat is financially attractive and is spreading into new areas, apparently at the expense of traditional staple and cash crops, and there is an increasing trend in cultivation and consumption of khat, which is legal in Ethiopia. There are no laws restricting its use, although the government discourages it.

Traditionally, khat has been used as a socializing drug and this is still very much the case. It is mainly a recreational drug in the countries where it grows, though it may also be used by farmers and agricultural and other laborers for reducing physical fatigue and by lorry drivers and high-school students for improving attention.

Children very often start chewing khat around the age of 10. At present in Yemen it is so popular that about 40% of the country's water supply goes towards irrigating it, with the percentage increasing by about 10 - 15% every year (Kirby, 2007).

In Somalia the demand for khat is so heavy that 20 tons, - worth US\$ 800.000, - were shipped daily from Kenya before the ban by the Supreme Islamic Courts Council (Wax, 2006). The Kenyan government banned all flights to Somalia, prompting protest by Kenyan khat growers that the local land in Meru North District had been specialized for khat cultivation and that the ban could devastate the local economy. With the victory of the Provisional Government at the end of 2006, khat has returned to Mogadishu, though Kenyan traders have noted that demand has not returned to pre-ban levels. Taking into consideration the newer and further political changes in Somalia, the present situation is unknown.

The trade of khat in one Somali city alone, - Hargeisa, the capital of breakaway Somaliland, - is estimated at 300.000 US\$ a day (Wax, 2006).

In the USA khat is being sold for 300 - 500 US\$ a kilo, - with a bundle of leaves selling for 30 - 50 US\$. It appears that there is an increase in use of khat in the upstate New York area, probably due to return of the drug from Somalia.

In July 2006 the USA Drug Enforcement Administration (DEA) executed "*Operation Somalia Express*," an 18-month investigation that resulted in the coordinated takedown of a 44-member international trafficking organization responsible for smuggling more than 25 tons of khat from the Horn of Africa to the USA. According to DEA estimation the khat was worth more than 10 million US\$ (DEA, 2006).

4. Chemistry

The environment and climate conditions determine the chemical profile of khat leaves.

Its taste varies from one type to another and depends on the tannic acid content. The leaves have an adstringent taste and a characteristic aromatic odor. The young leaves are slightly sweet. Many different compounds are found in khat, including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, minerals and others (Kalix and Braenden, 1985; Nencini and Ahmed, 1989; Kiple and Ornelas, 2001). The *phenylalkylamines* and *cathedulins* are the major alkaloids (*Table I*).

The first attempts to isolate the active principle of the plant were made more than 100 years ago by *Fluckiger* and *Gerock* in 1887 (Balint et al. 1991) and in 1930 *Wolfes* identified *norpseudoephedrine* in the leaves. Until the beginning of the 1960s this substance was generally believed to be the active principle of khat, although it had been stated in 1941 by *Brucke* that the amount of *norpseudoephedrine* in khat was insufficient to account for the symptoms produced (Szendrei, 1980).

In view of this objection the plant was reinvestigated and chemical and pharmacological studies culminated in the isolation of the keto-analog of *norpseudoephedrine* from khat leaves; *cathinone* (beta-keto-amphetamine) was suggested as the name for this new alkaloid (Szendrei, 1980; Kalix, 1984; 1988; 1990; 1992).

Alkaloids	<i>Phenylalkylamines</i>	Norpseudoephedrine
		Cathinone
		Cathine
		Merucathinone
		Pseudomerucathinone
		Merucathine
	<i>Cathedulins</i>	More than sixty different cathedulins, (WHO, 2006a.)
Terpenoids		
Flavonoids		
Sterols		
Glycosides		
Tannins		
Amino acids		
Minerals		

Table I. The most important compounds found in *Catha edulis*.

The khat phenylalkylamines comprise cathinone [(S-(-)-cathinone) and the two diastereoisomers cathine (1S,2S-(+)-norpseudoephedrine or (+)-norpseudoephedrine) and norephedrine (1R,2S-(-)-norephedrine)].

These compounds are structurally related to amphetamine and noradrenaline (norepinephrine).

The plant contains the (-)-enantiomer of cathinone only; the (+)-enantiomer is not found. Thus, the naturally occurring S-(-)-cathinone has the same absolute configuration as S-(+)-amphetamine. Hence the name of *Catha edulis*: “A plant, with naturally occurring amphetamine” but nowadays in the USA sometimes it is mentioned as “herbal ecstasy” (Kuczkowski, 2005).

Cathinone is found mainly in the young leaves and shoots. During maturation, cathinone is metabolized to cathine, and (-)-norephedrine. The leaves contain these two substances in a ratio of approximately 4:1 (Kalix and Braenden, 1985).

Other phenylalkylamine alkaloids found in khat leaves are the phenylpentenylamines *merucathinone*, *pseudomerucathine* and *merucathine*. These seem to contribute less to the stimulant effects of khat (Maitai, 1977; Kalix et al. 1987; Nencini and Ahmed, 1989; Al-Hebshi and Skaug, 2005).

Cathinone is unstable and undergoes decomposition reactions after harvesting and during drying or extraction of the plant material (WHO, 1980; Brenneisen and Geissshusler, 1985;

Krizevski et al. 2007). Decomposition leads to a dimer (3,6-dimethyl-2,5-diphenylpyrazine) and possibly to smaller fragments. Both the dimer and phenylpropanedione have been isolated from khat extracts (WHO, 1980). As *cathinone is presumably the main psychoactive component of khat, this explains why fresh leaves are preferred by the users.*

The phenylalkylamine content of khat leaves varies within quite wide limits. On average, 100 g fresh khat leaves contain 36 - 114 mg cathinone, 83 -120 mg cathine and 8 - 47 mg norephedrine (Geissshusler and Brenneisen, 1987; Widler et al. 1994; Toennes et al. 2003).

Khat leaves also contain considerable amounts of tannins and flavonoids (Al Motarreb et al. 2002; Hassan et al. 2002).

According to our own investigations 100 g fresh khat leaves (Addis Ababa region Ethiopia;) contain approximately 40 mg cathinone, 120 mg cathine 5 mg norpseudoephedrine, plus more than 30 minor compounds (Balint and Balint, unpublished data, 1990).

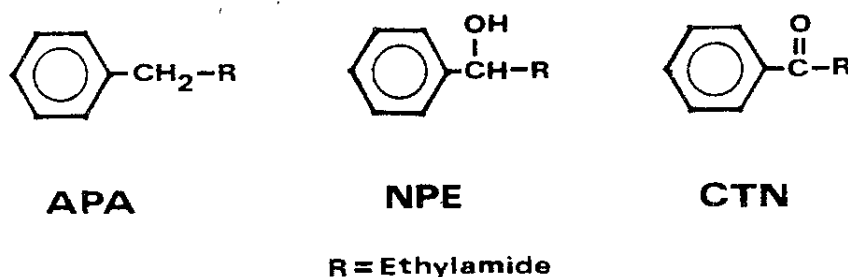


Figure 5.: The chemical structure of amphetamine (APA), norpseudoephedrine (NPE) and (-)-cathinone (CTN).

5. Pharmacology and Pharmacokinetics

As noted khat contains many different compounds and therefore khat chewing may have many different effects.

The major effects include those on the gastrointestinal system and the nervous system, Constipation, urine retention and acute cardiovascular effects may be regarded as peripheral, autonomic nervous system effects; increased alertness, dependence and to a lesser extent cathine are held responsible for the effect of khat on the nervous system. The effects of the many other constituents of the plant are either overlooked or even unknown.

5.1. Animal Studies

Behavioral effects:

Albino rats fed with khat material show increased locomotor activity and reduced weight gain. Retardation of growth rate was considered to be due to decreased absorption of food and not to decreased food consumption. In pregnant rats, khat reduced food consumption and maternal weight gain (Maitai, 1977; Islam et al. 1994).

Many reports have confirmed enhanced locomotor activity with enhanced baseline aggressivity of isolated rats. (Banjaw et al, 2006.) Khat extracts and (-)-cathinone produce a stereotypic behaviour, - together with an anorectic effect, - similar to that evoked amphetamine (Zelger et al. 1980; Goudie,1985). (-)-cathinone appears to have stronger effects than cathine and norephedrine. Compared with cathine, cathinone also has a more rapid onset of action, in accordance with its higher lipophilic character facilitating entry into the central nervous system (CNS), and shorter duration of action, which relates to its rapid metabolism (Zelger et al. 1980; Peterson et al. 1980; Kalix and Braenden, 1985).

Dopaminergic antagonists (e.g. haloperidol) and dopamine-release inhibitors [e.g. CGS-10746B: *i.e.* 5-(4-methyl-1-piperazinyloxy)-1H-imidazo[2,1-b][1,3,5]-benzothiadiazepine- maleate; Ciba-Geigy, USA] able to partially block the activity-enhancing properties of (-)-cathinone (Schechter, 1986; Calcagnetti and Schechter, 1992; Patel, 2000).

Cardiovascular effects:

Cathinone has a vasoconstrictor activity on isolated perfused guinea-pig heart (Al-Motarreb and Broadley, 2003). The effect is unlikely to be due to an indirect action by release of noradrenaline (norepinephrine) from sympathetic nerve endings or to a direct action on *alpha*-1-adrenoreceptors. The vasoconstrictor activity of cathinone explains the increase in blood pressure seen in humans, and in animals might be related to the increased incidence of myocardial infarction occurring during khat "sessions" (Kohli and Goldberg, 1982; Brenneisen et al. 1990; Al-Motarreb et al. 2002b).

Gastrointestinal effects:

Data on khat's effect on animals' gastrointestinal systems are somewhat scarce (Al-Habori et al. 2002). More data can be found in human studies.

Other effects:

In rabbits, a khat extract given orally for a longer period of time (30 successive days,) induced a decrease in adrenal cholesterol, glycogen and ascorbic acid and an increase in adrenal phosphorylase activity, serum free fatty acids and urinary 17-hydroxy- corticosteroids. These results have been interpreted as a stimulating effect of khat on adrenocortical function (Ahmed and El-Qirbi, 1993).

Animal data on the effect of khat on the reproductive system are conflicting. In cathinone-treated rats, a significant decrease in sperm count and motility and an increase in the number of abnormal sperm cells were found (Islam et al. 1990). The drug also produced a significant decrease in plasma testosterone levels. In contrast, rabbits fed khat for 3 months had an increased rate of spermatogenesis, and in the male adult olive baboon, khat extract, - given orally once a week during a 2-month period, - produced an increase in plasma testosterone levels and a decrease in plasma levels of prolactin and cortisol (Al-Mamary et al. 2002; Mwenda et al. 2006). Khat given to pregnant guinea pigs reduced placental blood flow and caused growth retardation in the offspring (Jansson et al. 1988a, 1988b).

5.2. Studies in Humans

The main effects of khat chewing are on the central and peripheral nervous systems and on the gastrointestinal system, *Table II* and *III* give a summary of the pharmacological effects of khat in humans.

Subjective effects:

Khat chewing induces a certain state of euphoria and elation with feeling of increased alertness and arousal. This is followed by a stage of vivid discussions, loquacity and an excited mood. Thinking is characterized by a flood of ideas but without the ability to concentrate. However, at the end of khat session the user may experience depressive mood, irritability, anorexia and difficulty of sleeping (Nencini and Ahmed, 1989; Al-Motarreb et al. 2002a).

It is notable that local khat consumers sometimes distinguish between “stimulant” (“*miraa*”) and “calmant” (“*hereri*”) khat varieties. At present there is no explanation for this “tranquillizing” effect of khat (Balint et al. 1994; Summers, 2006).

Effects on the urinary bladder:

Khat induces a fall in the average and maximum urine flow rates in healthy men. These effects are probably mediated through stimulation of *alpha*-1-adrenargic receptors by cathinone (Nasher et al. 1995; Hassan et al. 2002).

Cardiovascular effects:

Khat chewing induces a small and transient rise in blood pressure and heart rate (Nencini et al. 1986; Kalix et al. 1991; Kalix, 1992; Hassan et al. 2000; 2005; and Al-Motarreb et al. 2002b). According to Tesfaye et al. (2008) regular khat chewing together with smoking was associated with a significantly elevated mean diastolic blood pressure in adult Ethiopians. These effects could be blocked by the *beta*-1-adrenoreceptor blocker atenolol, but not by the *alpha*-1-adrenoreceptor blocker indoramine, indicating mediation through stimulation of *beta*-1-adrenoreceptors (Nencini et al.1986).

Effects on the adrenocortical function:

Nencini et al. (1984) found that khat and cathinone increase ACTH hormone levels in humans.

Gastrointestinal system:

It has been reported that khat chewing delays gastric emptying of a semi-solid meal (Gunaid et al. 1999).

Some evidences of chronic liver disease suggest that long-term use of khat may be associated with repeated episodes of subclinical hepatitis with evolution to chronic liver disease over time. The mechanism of "khat-related" hepato-toxicity is unknown (Chapman et al, 2010).

Moreover it is worth mentioning that in the field of the gastrointestinal system we had still unpublished results, of which (among others) we want to give a report in this Thesis.

The euphoric effects of khat start after about an hour of chewing. Blood levels of cathinone start to rise within 1 hour and peak plasma levels are obtained 90 - 120 min after the onset of chewing. Cathinone was barely detectable at 30 min and 450 min (*i.e.* 7 1 h) and not detectable at all after 24 hours (Halket et al. 1995). It seems that metabolism is rapid and occurs during the first passage through the liver. Only 2% of administered cathinone was found unchanged in the urine (Brenneisen et al. 1986; Nencini and Ahmed, 1989). In humans, norephedrine and norpseudoephedrine are absorbed slowly and excreted (almost) unchanged in the urine (Maitai and Mugeru, 1975; Kalix and Braenden, 1985).

Acute effects	Relief of fatigue, increased alertness, reduced sleepiness
	Mild euphoria and excitement; improved ability to communicate, loquacity
	Tachycardia, hypertension
	Moderate hyperthermia
	Mydriasis, blurred vision
	Anorexia, dry mouth
	Constipation
	Psychotic reactions (at high doses)
	Irritability and depressive reactions at the end of khat session
	Lethargy and sleepy state (later)

Table II. Acute pharmacological effects of khat in humans.

<i>Long-term effects</i>	Malnutrition
	Psychotic reactions after chronic use
	Depressive reactions
	Irritative disorders of the (upper) gastrointestinal tract, gastritis, enteritis
	Cardiovascular disorders
	Hemorrhoids
	Impaired male sexual function, spermatorrhea, impotence
	Periodontal disease, mucosal lesions, keratosis

Table III. Long-term pharmacological effects of khat in humans.

6. Toxicology and Adverse Reactions

Khat use affects almost the whole human organism as it is seen in *Table IV*.

Cardiovascular system	Tachycardia	Genitourinary system	Urinary retention	
	Palpitations		Spermatorrhea	
	Hypertension		Spermatozoa malformations	
Gastrointestinal system	Arrhythmias	Respiratory system	Impotence	
	Vasoconstriction		Libido change	
	Myocardial infarction	Obstetric effects	Tachypnoea	
	Cerebral hemorrhage		Bronchitis	
	Pulmonary edema		Low birth weight	
	Metabolic and endocrine effects	Dry mouth	Ocular effects	Stillbirths
		Dental caries		Impaired lactation
Periodontal disease		Central nervous system	Blurred vision	
Polydipsia			Mydriasis	
Chronic gastritis			Dizziness	
Constipation		Psychiatric effects	Impaired cognitive function	
Hemorrhoids			Fine tremor	
Paralytic ileus			Insomnia	
Weight loss			Headache	
Hepatobiliary system		<u>Duodenal ulcer: (?)</u>	Psychiatric effects	Lethargy
	Upper gastrointestinal malignancy	Irritability		
Metabolic and endocrine effects	Hyperthermia	Anorexia		
	Perspiration	Psychotic reactions		
	Hyperglycemia	Depressive reactions		
Hepatobiliary system	Fibrosis	Psychiatric effects		Hypnagogic hallucinations
	Cirrhosis			

Table IV. The adverse effects of khat.

The **main toxic effects** include increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men (Nencini and Ahmed, 1989; Cox and Rampes, 2003). In addition, khat affects the nervous system and can induce paranoid psychosis and hypomaniac illness with grandiose delusions. (Halbach, 1972).

The effects on the nervous system resemble those of amphetamine, with differences being quantitative rather than qualitative. (Tariq et al. 1983; Kalix, 1988; Hassan et al. 2002; Cox and Rampes, 2003; Dhaifalah and Santavy, 2004). In their recent investigation Pennings et al. (2008) also found that the main psychoactive compounds in khat leaves are cathine and cathinone, which are some to 2- to 10-fold less active than amphetamine.

Cardiovascular complications:

An increased incidence of acute myocardial infarction occurring during or after khat sessions has been found. (Al-Motarreb et al. 2002b; Kalix et al. 1991; Al-Kadi et al. 2002.) The authors concluded that khat chewing is an independent dose-related risk factor for the development of acute myocardial infarction with a very significantly, - 39-fold, - increased risk. (Kalix et al. 1991).

Khat chewing has also been reported to be a significant risk factor for acute cerebral infarction. (Mujilli et al. 2005).

The prevalence of high blood pressure was also significantly higher among khat chewers than among non-chewers.

Another cardiovascular complication of khat chewing is the higher incidence of hemorrhoids found in chronic chewers. (Al-Hadrani, 2000).

Hyperthermia:

Pronounced hyperthermia has been observed in rabbits treated with (-)-cathinone. This response was blocked by haloperidol and strongly inhibited by pimozide, two well known antagonists of amphetamine hyperthermia (Knoll, 1979; Kalix, 1980). These results are in complete accordance with our previous results (Balint et al. 1990).

Gastrointestinal complications:

Khat chewing affects the oral cavity and certain parts of the digestive tract (Hill and Gibson, 1987; Kalix, 1990). Periodontal disease and gastritis have been reported but other studies have indicated no such detrimental effect of khat (Kennedy et al. 1983; Jorgensen and Kaimenyi, 1990).

No significant association could be found between khat chewing and oral leukoplakia in a Kenyan study (Macigo et al. 1995).

The tannins present in the leaves are held responsible for the gastritis that has been observed in khat chewers. Chewing khat reduces the absorption of ampicillin and to a lesser extent that of amoxicillin but the effects are minimal 2 hours after khat chewing stops (Halbach, 1972; Pantelis et al. 1989a).

According to *Raja'a et al.* khat chewing appears to be a risk factor for duodenal ulcer (*Raja'a et al.* 2000; 2001). This finding is in conflict and contradiction with *Kekes Szabo's* and our own works, because according to the latter data all the sympathomimetic agents such as amphetamine, - and the similar cathine and cathinone, - act against gastric and duodenal ulceration in humans and in animals, e.g. albino rats (*Kekes Szabo*, 1974; *Balint*, 1987; 1998). *Al-Meshal et al.* (1983) also have received negative results regarding khat's ulcerogenic effect. Constipation and hemorrhoids have been reported as unwanted side-effects of khat chewing (*Al-Hadrani*, 2000; *Cox and Rampes*, 2003).

Reproductive system:

Detailed studies on the possible effects of khat on human reproduction are lacking. However, the few available data suggest that chronic use may cause spermatorrhea and may lead to decreased sexual function and impotence (*Halbach*, 1972; *Mwenda et al.* 2003).

Cancer:

It has been reported that about 50% of khat chewers develop oral mucosal keratosis (*Hill and Gibson*, 1987). This pathological change is considered a pre-cancerous lesion that may develop into oral cancer (*Goldenverg et al.* 2004). The prevalence of this lesion and its severity increased with frequency and duration of khat use. *Makki* stressed (1975) the importance of khat after finding that most of the oral squamous cell carcinomas in her study patients were located in the buccal mucosa and lateral sides of the tongue, which come into direct contact with khat during chewing.

In a survey in Saudi Arabia about 50% of the patients with head and neck cancer presented with a history of khat chewing and all of them had used khat over a period of 25 years or more (*Soufi et al.* 1991). In some cases, - similarly to *Makki's* observation, - the malignant lesion occurred at exactly the same site as where the khat bolus was held. The authors concluded that a strong correlation existed between khat chewing and oral cancer.

Khat-induced psychosis:

Khat chewing can induce two kinds of psychotic reaction: manic illness with grandiose delusions, and a paranoid or schizophreni-form psychosis with persecutory delusions associated with mainly auditory hallucinations, fear and anxiety, and resembling amphetamine psychosis (*Dhadphale et al.* 1981; *Critchlow and Seifert*, 1987; *Dhaifalah and Santavy*, 2004). Both reactions are exceptional and associated with chewing large amounts of khat (*Dhadphale and Omolo*, 1988; *Jager and Sireling*, 1994). Symptoms rapidly abate when khat is withdrawn and

anti-psychotics are usually not needed for remission (Pantelis et al. 1989a, 1989b; Jager and Sireling, 1994; Nielen et al. 2004).

Hypnagogic hallucinations:

Hypnagogic hallucinations have been reported in chronic khat users; interestingly, patients may consider these as “normal” (Granek et al. 1988).

Genotoxicity and teratogenic effects:

The effects of khat, smoking and alcohol have been found to be additive. Results suggest that khat consumption, especially when accompanied by alcohol and smoking, might be a potential cause of oral malignancy (Kassie et al. 2001).

7. Psychosocial Considerations

Detailed accounts of the psychosocial aspects of khat use are still lacking. Ethiopian authors have attempted to describe some of the psychosocial effects of khat chewing, and have made a preliminary survey to provide insight into drug use, including khat, among university and highschool students, since there is no adequate information on the pattern of khat and drug abuse in Ethiopia and for most African and Arabian countries (Elmi, 1983; Zein et al. 1984; Belew et al. 2000; Kebede et al. 2005; Beckerleg, 2006; 2008; Aden et al. 2006; Hassan et al. 2007; Carrier, 2008).

On the basis of the cited investigations it appears that the prevalence of khat chewing is higher among the younger age groups. Alcohol, smoking, glue-sniffing and khat are the drugs that are most commonly used either separately or in combination, and their use has gained social acceptability.

According to the available objective data there is no convincing evidence that moderate, - e.g. once a week, which is a rare practice, - khat chewing has any adverse effect on the physical health of the user. However, one must take into consideration the poor economic situation of such countries (*i.e.* very limited medical budget) moreover there are no long-term follow-up studies to establish the possible chronic effects (such as chronic changes in the cardiovascular system, gastrointestinal activity, central nervous system) of khat chewing (Balint et al. 1990; 1991; Balint and Balint, 1994; 1995). Further studies are clearly required.

Recently *Odenwald* et al. reported (2007) on the consumption of khat and other drugs among Somali combatants, indicating that drug-related problems among armed mercenaries and other

groups have reached formerly unknown levels. Moreover, in recent years khat use in Somalia has become a risk factor for psychotic disorders (Odenwald et al. 2005).

8. Dependence, Tolerance and Withdrawal

Several authors have argued that regular khat consumption (seriously) affects the social and economic life of the user (Balint et al. 1991; Kalix, 1991).

The medical problems that arise from khat chewing are partly due to the sympathomimetic effects of the drug and partly to its effect on mental health. According to *Kalix*, khat chewing may induce a moderate but often persistent psychological dependence (Kalix, 1994). Withdrawal symptoms after prolonged use are mild and may consist of lethargy, mild depression, slight trembling and recurrent bad dreams. There are very few reports on khat dependence, and habitual users do not show serious problems when stopping use (Giannini et al. 1992; Patel, 2000).

Tolerance is difficult to evaluate because chewing sets an upper limit to the amount of khat that can be consumed. It seems that a certain degree of tolerance is developing to the increases in blood pressure, heart rate, respiratory rate and body temperature (Luqman and Danowski, 1976; Nencini et al. 1984; Kalix and Braenden, 1985; Kalix, 1990; Feyissa and Kelly, 2008). A real khat withdrawal syndrome has not yet been described.

9. Epidemiology of Use and Abuse

In addition to the health problems, (regular) khat consumption is associated with a variety of social and economic problems affecting not only the consumers but their families as well.

The impact of khat consumption in Yemen is the most considerable, in that it is deeply rooted in Yemenite society, mainly among males. At least one life-time episode of khat use was reported in 81.6% of men and in 43.3% of women. Male users tended to use more frequently (Numan, 2004; Graziani et al. 2008). In other countries it is less predominant and there is less social pressure to participate in khat sessions (Kalix, 1990).

Khat is freely available in Ethiopia and is a highly valued export commodity, particularly to neighbouring Djibouti. The number of khat users has significantly increased in Ethiopia during recent decades and the habit has become popular in all sections of Ethiopian society (Selassie and Gebre, 1996; Bimerew et al. 2007). According to estimations the average prevalence of khat use is about 32% in Ethiopia. Unfortunately it now appears more common to combine khat

chewing with smoking, and consumption of alcohol and other drugs, particularly among professional people. Traditionally khat was mainly cultivated in the eastern part of Ethiopia, - Harar and its surroundings, - nowadays it is grown in all parts of the country.

Among Somali refugees in the UK, war-related experiences, occupational status before migration and current khat use were found to be risk factors for anxiety, depression, symptoms of psychosis and suicidal tendencies (Bhui et al. 2003). Medical problems associated with the habit were rare. Khat was traditionally chewed by Somali men, - it was until recently taboo for Somali women to chew - in a gathering place, known as a *mafrish* (Summers, 2006). On the other hand, khat use can be seen as playing a positive role in supporting the cultural identity of the Somali community (Griffiths et al. 1997).

In all countries involved, much time is spent on buying and chewing khat leaves, which affects working hours, productivity and time with family. For some, the daily cost of the habit exceeds their expenditure on food for their families, which may cause further social and familial problems.

10. International and National Control of Khat

Khat is not under international control at present. In 1965 the WHO Expert Committee on Dependence-producing Drugs (14th Report) stated: “*The Committee was pleased to note the Resolution of the Economic and Social Council with respect to khat, confirming the view that the abuse of this substance is a regional problem and may best be controlled at that level.*” (WHO 2003; 2006a; 2006b). This is, - even today, - the reason why khat was not scheduled under the “*Single Convention of Narcotic Drugs,*” but in 1980 WHO classified khat as a drug of abuse that can produce mild-to-moderate psychic dependence. Generally speaking, this is the present international situation, but individual countries may regulate the problem quite differently (*Table V*).

Cathine and cathinone, two substances present in khat, have been under international control since the early 1980s, like all amphetamine-like substances.

Cathinone was included in Schedule I. of the “*UN Convention of Psychotropic Substances*” and cathine in Schedule III. of this Convention (UN, 1971). Hungary, as a UN Member-state, follows UN regulations.

Canada	Controlled substance under Schedule IV
France	Prohibited as a stimulant
Germany	Controlled substance, ownership and sale illegal
Hong Kong	Cathine and cathinone are regulated under Schedule I
Israel	Currently legal, khat leaves are sold in open markets
Netherlands	Khat use <i>i.e.</i> chewing, is tolerated
Norway	Classified as a narcotic drug and illegal to use, sell and possess
Sweden	Classified as a narcotic drug and illegal to use, sell and possess
Switzerland	Prohibited as a stimulant
United Kingdom	Not a controlled substance. A recent British study suggests that khat chewing is less dangerous than tobacco and alcohol. No convincing evidence that khat use is a gateway to the use of other stimulant drugs. Strong association between khat use and smoking tobacco, - and consumption of sugary drinks.(Graw, 2006.)
USA	See text

Table V. Regulations regarding khat in some countries.

In the United States until very recently khat was classified as a Schedule IV. substance by the DEA. Cathinone has now been classified as a Schedule I. narcotic, the most restrictive category used by the DEA, which means that without a DEA licence it is illegal to manufacture, buy, possess or distribute, sell, trade or give cathinone. In the USA cathine is still classified as a Schedule IV. substance, one that has low potential for abuse.

It is worth mentioning that illegal laboratories have been discovered already using a synthetic form of cathinone: 2-(methylamino)-1-phenyl-propan-1-one (*MCTN*), which is the N-methyl-derivative of cathinone, known on the street as “cat”. The substance is readily manufactured from ephedrine by oxidation and is assessed as having a high abuse liability (Belhadi-Tahar and Sadeq, 2005; Balint et al. 2009). In 1995 the WHO Expert Committee on Drug Dependence recommended classification of MCTN as a Schedule IV. compound (WHO, 1995).

11. Possible Therapeutic Use

In the Kenyan region where most of the plant originates today (North Meru area) khat use is reported among the Meru tribe for the treatment of erectile dysfunction, malaria, influenza, vomiting and headache. In other places and countries khat does not belong to the group of commonly used medicinal plants.

In traditional Ethiopian medicine a mild tea made of the leaves reduces swelling in the mouth and may lower (?) blood pressure. Poultices of khat leaves have a curative effect on wounds. Dried *Catha edulis* is an important medicine with anti-infective and anti-aging qualities (Balint and Balint, unpublished data, 1990).

12. Investigations Regarding Khat's Acute Gastrointestinal Effects

According to the generally accepted tenet that the most important effects of khat include those on the gastrointestinal system and the nervous system, moreover that CTN is (presumably) the most important (psychoactive) constituent of khat leaves, we have investigated the acute effect of the CTN on different parts of rats' gastrointestinal system.

12.1. INVESTIGATIONS ON RATS' STOMACH

12.1.1. Gastric ulcer models

Six groups of female Wistar rats (n=15/group) weighing 190 -210 g were used. Prior to the investigations the animals were fasted for 24 hours but allowed water *ad libitum*. The following gastric ulcer models were investigated: indomethacin (IND) and stress (STR) induced ulceration, (Balint and Varro, 1985).

Indomethacin ulcer

The animals received 30 mg/kg IND suspension intraperitoneally (i.p.) at the beginning of the experimental period (0 min). After 4 hours following IND treatment the animals were killed and their stomachs were removed.

Stress-induced ulcer

The animals were immobilized lying on their backs. After 24 hours the animals were killed and their stomachs were removed. The removed stomachs were opened in both experimental series and the changes were evaluated using an *Ulcer Index* (U.I.). The U.I. was determined as follows:

each mm ² lesion	1 point	
bleeding	further 5 points	
perforation	further 10 points	(Karacsony et al. 1986)

The following drug has been tested and the single oral doses - in aqueous solution, -were as follows:

Indomethacin ulcer: Cathinone /CTN, S-(-)-cathinone.HCl, Sigma-Aldrich, #: C-3196/ 500 and 1000 µg/kg respectively, at the 0 min and 120th min of the experimental period i.p., (evaluation at 240th min).

Stress-induced ulcer: CTN, 500 and 1000 µg/kg respectively, at the 0 min, and 6th, 12th and 18th h i.p., (evaluation at 24th h).

/It is worth mentioning that the average quality Ethiopian khat leaves contain approximately 40 mg of CTN per 100 g of weight, - and during an average khat-session the users use to chew 200 - 400 g of leaves. Therefore the CTN dose is approximately 80 - 160 mg (which corresponds about a 1 - 2 mg/kg of body weight dose) during a 4 - 6 hour long session. Considering that CTN's metabolism is rapid we have concluded that in our experimental investigations a 500 and a 1000 µg/kg single (rapid) dose of CTN will be appropriate and informative/.

Within each animal group *mean* +/- *SEM* was calculated and analysed statistically using *Student's t-test*.

Results: The experimental results are presented in *Table VI*.

	Indomethacin	Δ % U.I. mean +/- SEM	Stress	Δ %
Control	9.7 +/- 1.5	100.0	11.2 +/- 3.8	100.0
CTN 500 μ g/kg	8.8 +/- 1.2	90.7	10.8 +/- 2.9	96.4
CTN 1000 μ g/kg	6.9 +/- 1.0 (a)	71.1	8.2 +/- 2.2	73.2

(a) = $p < 0.05$

Table VI. The effect of cathinone in different gastric ulcer models of rat.

According to the results it seems that CTN showed no ulcerogenic effect, instead - in accordance with the previous results, - as a drug with sympathomimetic effect - had antiulcerogenic property.

12.1.2. Scanning electron microscopic investigations.

In this part of our study investigations were performed to elucidate the possible fine morphological changes of rat gastric mucosa under the effect of CTN.

Adult female Wistar rats weighing 200 - 220 g were used. Prior to investigation the animals were fasted for 24 h but allowed water *ad libitum*. The rats were assigned in groups consisting each of 5 animals. The control animals received in appropriate amounts water only. After 120 min of treatment with CTN (1000 μ g/kg, given orally by gastric tube) the animals were sacrificed, their stomachs were removed and opened. The isolated antral and fundic (oxyntic cell area) parts were fixed for 24 h in *Karnovsky's* solution and consequently dehydrated. Afterwards the specimens were dried and contrasted by gold with routine methods for further investigation. A *Tesla-BS-300* scanning electron microscope was used with a magnification of x2000. The experimental results are presented on micrographs.

On *Figure 6* and *7* the pictures of the untreated, - *i.e.* control, - antrum and fundus can be seen while the *Figure 8.* and *9* shows the antrum and fundus of the treated animals.

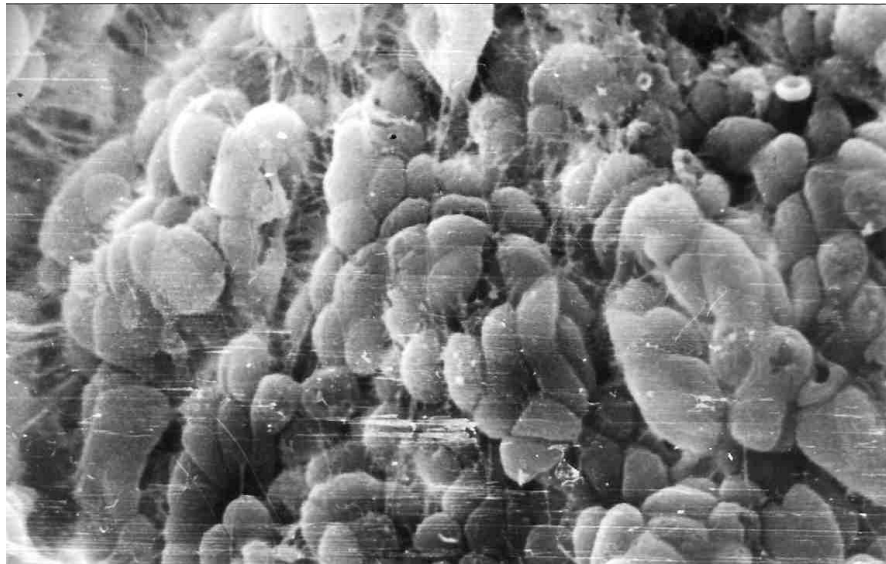


Figure 6. Rat stomach, antral mucosa, control.

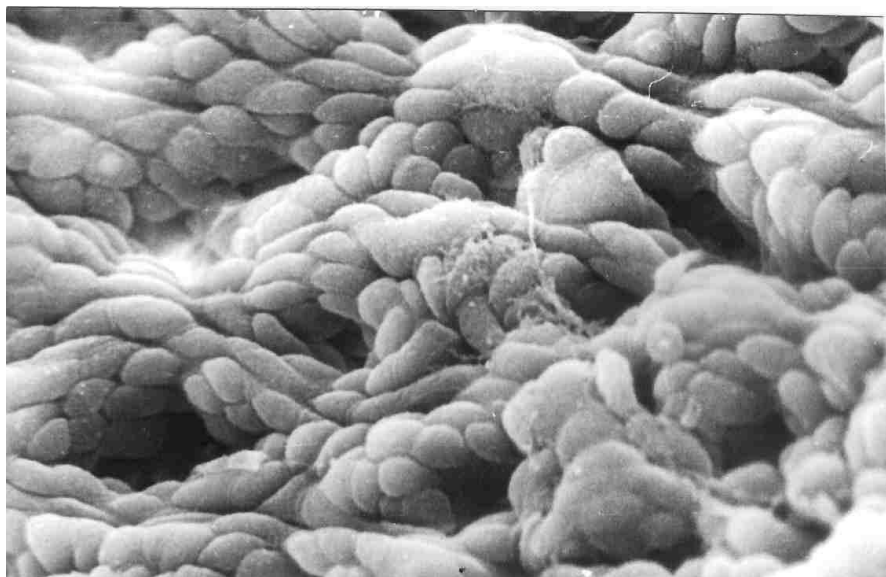


Figure 7. Rat stomach, fundic mucosa, control.

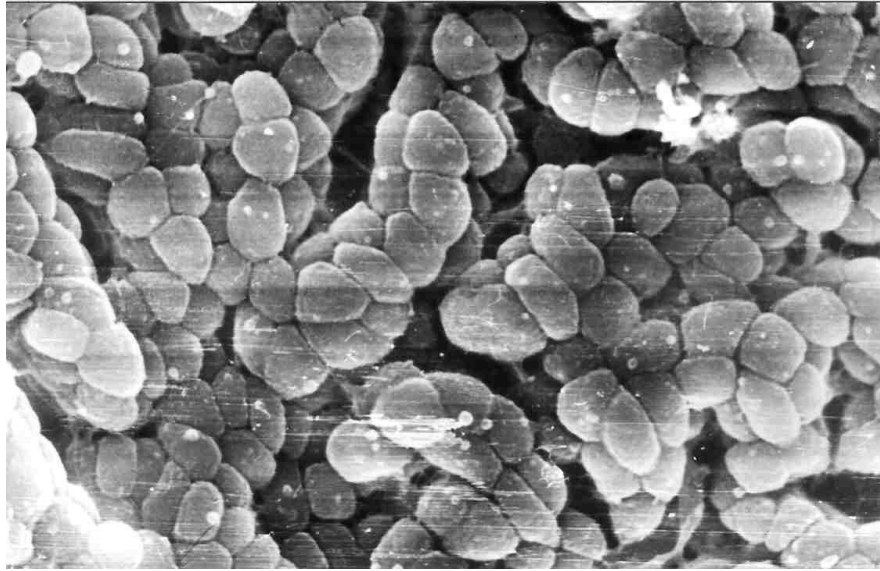


Figure 8. Rat stomach, antral mucosa, 1000 µg/kg CTN treated

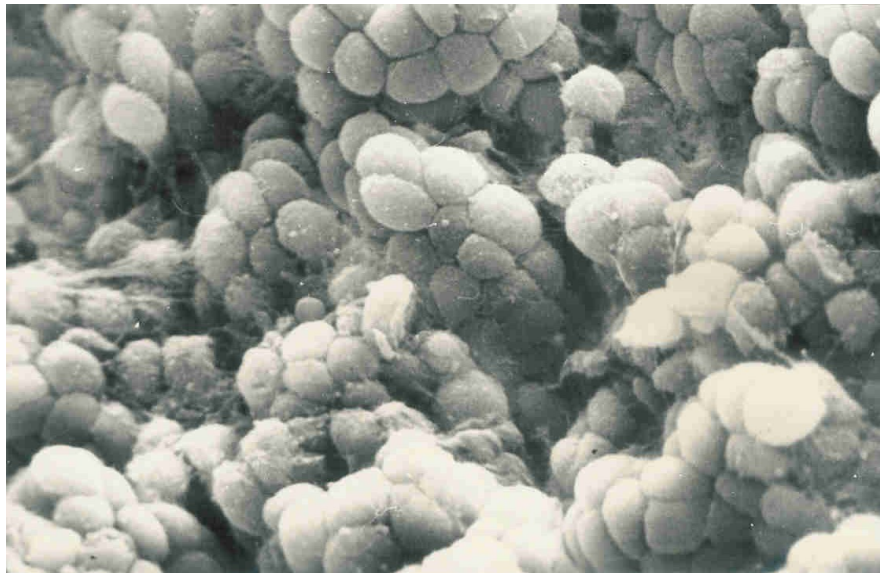


Figure 9. Rat stomach, fundic mucosa, 1000 µg/kg CTN treated

The scanning electron microscopic results convincingly prove that CTN has no detectable effect on gastric mucosa in the case of acute administration.

12.2. INVESTIGATIONS ON RAT'S DUODENUM

Experimental duodenal ulcer

The acute duodenal ulcer model described by *Selye* and *Szabo* (1973) was employed. Female Wistar rats of 210 - 230 g body weight were used. The animals were assigned in groups consisting each of 15 animals. The experimental design was as follows: Cysteamine-hydrochloride (CEA) 300 mg/kg in a single dose was given orally by gastric tube in 10 % aqueous solution at the beginning (0 min) and in the 4th and 8th h of the experiment. The animals were fed throughout, - water *ad libitum*, - and were killed 48 h after the first CEA-treatment. The stomach and the duodenum were taken out as a single unit, opened along the greater curvature for the stomach and the antimesenteric side for the duodenum, and examined for the presence of ulceration. The alterations were evaluated by U.I. counting according to *Szabo* (1978). The treatment with CTN (500 and 1000 µg/kg respectively) was carried out in every 6th hour until the animals were killed. The experimental results are presented in *Table VII*.

According to the experimental results received, CTN showed neither ulcerogenic nor antiulcerogenic effect in rats' CEA-induced ulcer model.

	U.I.*	Δ %	Incidence	Δ %	Mortality	Δ %
Control	2.8	100.0	15/15	100.0	7/15	46.7
CTN 500 µg/kg	2.5	89.3	14/15	93.3	8/15	53.3
CTN 1000 µg/kg	2.3	82.1	13/15	86.7	8/15	53.3

* = mean values

Table VII. The effect of cathinone on cysteamine induced duodenal ulceration of rats

12.3. INVESTIGATIONS ON RATS' LIVER

The Effect of Cathinone on Liver Tissue

During these investigations 15 Wistar rats of both sexes were used. Their body weight was 200 - 230 g. and they were treated as follows:

The animals in the control group (n = 5) received 0.5 ml of sterile, pyrogen-free, normal saline solution intraperitoneally. The treated animals received i.p. 500 (n = 5) and 1000 (n = 5) µg/kg CTN respectively. After a 24 h waiting period all of the animals were killed by decapitation.

Within 60 seconds after decapitation samples were taken approximately from the same part of the liver, - right lateral lobe, - for electron microscopic investigation.

The liver slices were fixed in 2.5 per cent glutaraldehyde solution at 0 - 4 °C. After the fixation they were dehydrated in alcoholic-series, then were embedded in araldite. In the blocks, - during dehydration, - they were contrasted by uranyl-acetate, - dissolved in 70 per cent ethanol, - and on the sections by leadcitrate. The photomicrographs were taken by a *Zeiss-EM-9S-2* type electron microscope. The results are presented in the *Figure 10* and *11*.

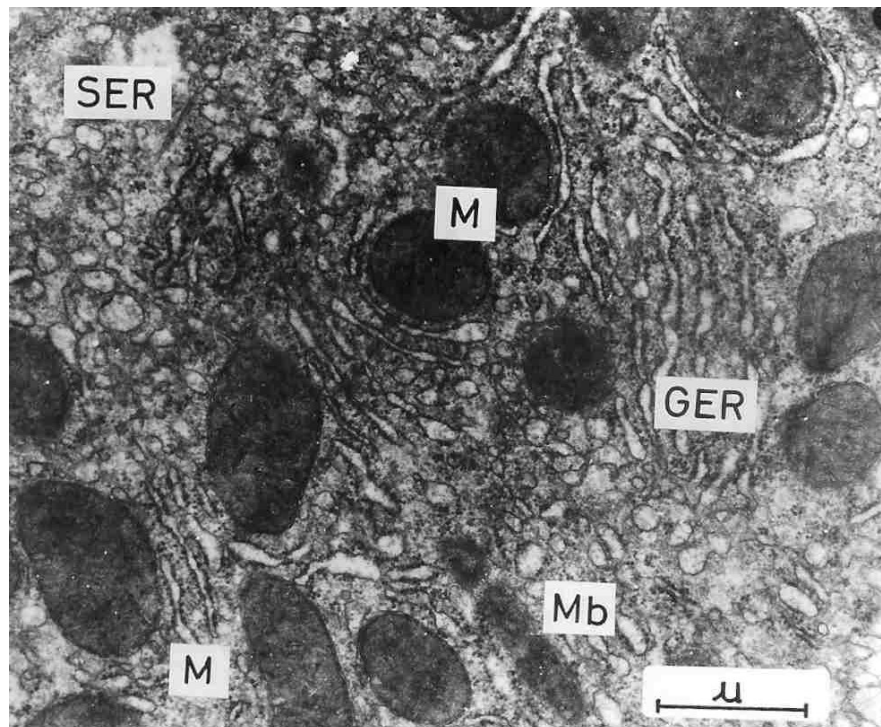


Figure 10. Rat liver, control. Abbreviations: GER: granulated endoplasmic reticulum, SER: smooth endoplasmic reticulum, Mb: microbody

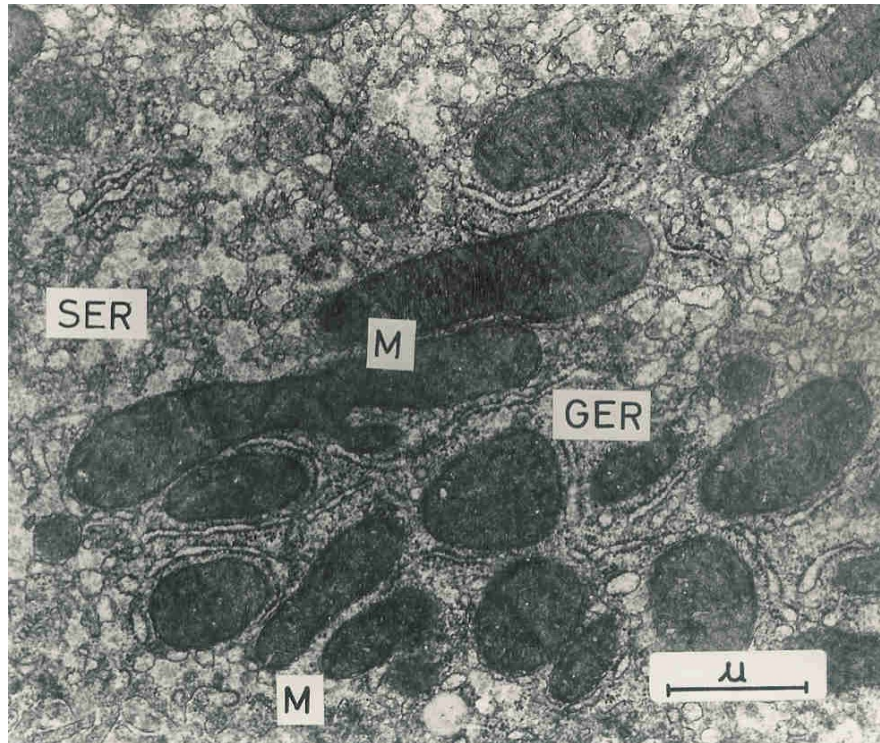


Figure 11. Rat liver, 1000µg/kg CTN treated. Abbreviations: GER: granulated endoplasmic reticulum, SER: smooth endoplasmic reticulum, M: mitochondrion

It seems on the micrographs presented that basically no structural changes can be seen in the treated animals. The basic structure of the liver is normal compared to the control. The only visible change is that the mitochondrial surface area of the treated liver is enlarged. The average surface area of the mitochondria in the untreated liver was 58.77 mm² (counted minimally 100 mitochondrion) if the magnification was x 11.700, while in the case of 1000 µg/kg CTN treatment the surface of the mitochondria grew to 128.40 mm² (among the same experimental circumstances;) which is a significant ($p < 0.02$) enlargement. Considering that according to some data in the literature (Chapman et al, 2010) there may be a “khat-related” liver disease, we conclude that this, mitochondrial effect may be the first (pathological) sign of the khat-related toxicity.

12.4. SUMMING - UP our experimental work regarding khat's (CTN) effect on rats' gastrointestinal system, we conclude that its single, acute effect is negligible and further, long-term follow-up studies seem to be needed to establish convincingly whether khat (CTN) has a deliterious effect on the gastrointestinal system, - or some other components of the plant - e.g. tannins, etc. - are responsible for the possible late effects.

13. Khat, - a Blessing or a Curse?

The answer is not easy. One must take into consideration not only the severe medical and public health problems but undoubtedly also the concerned societies' customs and traditions. (Belew et al. 2000; Carrier, 2008; Bentur et al; 2008; BBC, 2009; Dizikes, 2009).

In our view (Balint et al. 2009) it is clear that khat use has negative consequences on the economic development of a country, through its effects on the health, time and finances of the most productive section of human resource, the young people. Now is an important time for policy makers to revise rules and regulations regarding control of the use of illicit drugs, including khat.

As the world faces the reality of khat use as a phenomenon, efforts to bring it under international conventions and possible control at national levels should and hopefully will increase. However, these efforts will require in-depth consideration of all the aspects that underpin the evolution of khat production and consumption as a global phenomenon.

In the opinion of the author, perhaps the most acceptable solution would be similar to that for coca-leaf chewing in South America: thus, in the countries where khat is indigenous and the habit is an old custom of the society, it should be tolerated; in other regions of the world khat chewing should be (strictly) controlled.

14. DISCUSSION

Khat (*Catha edulis*) commonly called “Arabian tea”, “qat”, or “miraa”, etc., is a flowering plant native to the Horn of Africa and the Arabian peninsula. The plant is a shrub or decorative tree growing 1 - 25 m tall and widely distributed in Africa, - particularly in the eastern side of the continent. The origins of the plant are often argued. Many believe its origins are Ethiopian others state that khat originated from Yemen before spreading to Ethiopia and the nearby countries on the African continent. Our view, based on personal knowledge collected in Ethiopia, is that the Ethiopian origin is more likely. The earliest documented description of khat dates back to the 11th century's work of Abu Rayhan al-Biruni. The name *Catha edulis* was first given to the plant by Forsskal in 1775 and this name has since been used by most authors.

Chewing the leaves of the plant for their pleasurable stimulant effect is a habit that is widespread in the mentioned geographical areas. The chewing of khat leaves probably pre-dates the use of coffee. There is even a well-known Ethiopian proverb: “Coffee is the poor man's khat”.

Traditionally, khat has been used as a socializing drug and this is still very much the case. It is estimated by the WHO that about 5 - 10 million people chew it every day. The chewing of khat leaves causes a certain degree of euphoria (together with some excitement and loss of appetite). Since only the fresh leaves have the desired effect, the chewing habit until the present time has remained in those areas where the plant is indigenous.

During the past decades khat chewing has gained global prominence as the result of migration, an increase in its use and the associated socioeconomic and health problems among its users.

The plant already has a global market and a recognized economic value with a potential to develop into a black market if criminalized.

As a consequence of fast and relatively inexpensive air transportation, during the past decade(s) the drug has been reported in a number of countries all over the World, e.g. in Great Britain, the USA, Canada, Australia, The Netherlands, etc. and even in Hungary.

The first attempts to isolate the active principle of the plant were made more than 100 years ago, in 1887, and in 1930 norpseudoephedrine was identified in the leaves. Until the beginning of the 1960s this substance was generally believed to be the active principle of khat. Later, in the 1980s the plant was reinvestigated and chemical and pharmacological studies culminated in the isolation of different phenylalkylamine derivatives from khat leaves, particularly cathine and cathinone. These compounds are structurally related to amphetamine and noradrenaline

(norepinephrine). Cathinone was (and is) suggested as the main psychoactive component of khat.

Considering that khat chewing is usually a common, permanent and almost a lifelong habit, which starts in adolescence until the late senescence; - in Yemen for example 60% of males and about 35% of the females were found to be regular khat users and had chewed daily for long periods of their lives - it is absolutely understandable that it may have acute and long-term effects moreover it influences the organism's all systems.

It should be noted that while there are publications that relate to the geographical use of khat, detailed accounts of the medical and psychosocial aspects of khat use are still lacking. On the basis of some investigations, - particularly in Ethiopia, - it seems that the prevalence of khat chewing (sometimes together with alcohol and other drug abuse;) is higher among the younger age groups.

According to the (scarce) available objective data there is no evidence that moderate, - once a week, which is a (very) rare practice, - khat chewing has any adverse effect on the physical health of the abuser. However, one must take into consideration the poor economic situation in such countries. Because of the very limited medical budget there are no long-term follow-up studies to establish the possible chronic effects (e.g. changes in the cardiovascular system, gastrointestinal system, etc.) of khat chewing.

There are reports that khat chewing may cause a pre-cancerous lesion i.e. mucosal keratosis in the buccal cavity which is the first place where khat has a direct connection to the organism.

Considering that following the oral cavity the next obvious place, where khat may exert its effect among acute circumstances, is the gastrointestinal tract, and there are some data regarding khat's effect on this system we have concluded that investigation of the possible effects of khat chewing (which is virtually an acute cathinone effect) could be important.

Yemeni authors have reported that khat chewing appears to be a risk factor for duodenal ulcer. This finding is in conflict and contradiction with the common medical belief, i.e. according to the data in the literature all sympathomimetic agents, such as amphetamine and cathinone, etc. act against gastric and duodenal ulceration in humans and in animals, e.g. albino rats. Therefore, to clear this controversial situation we have decided to perform investigations on albino rats regarding cathinone effects on different gastric ulcer models.

Two different experimental gastric ulcer models were investigated, according to the internationally accepted manners, namely:

Indomethacin ulcer and
Stress-induced ulcer.

In both ulcer models the effect of cathinone was observed on the ulcer-formation (against untreated control group) and the applied dose were as follows: 500 and 1000 µg/kg intraperitoneally in a sterile, pyrogen-free aqueous solution.

It is worth mentioning that the average quality Ethiopian khat leaves contain approximately 40 mg of cathinone per 100 g of weight, - and during an average khat- session the users chew 200 -400 g of leaves. Therefore the cathinone dose is about 80 - 160 mg, which corresponds to about a 1 - 2 mg/kg of body weight dose, during a 4 – 6 hour long session. Considering that the cathinone has a rapid metabolism we have concluded that in our experimental investigations a 500 and a 1000 µg/kg single dose will be appropriate and informative.

Within each bunch of the experiments mean +/- SEM was calculated and analysed statistically using Student's t-test.

According to the results it seems that cathinone showed no ulcerogenic effect, instead as a drug with sympathomimetic effect showed antiulcerogenic properties.

Considering that cathinone may cause fine morphological changes (less than ulcerogenesis) rat gastric mucosa scanning electron microscopic investigations were performed to elucidate this possibility. After 120 min of 1000 µg/kg oral treatment of cathinone the animals were sacrificed and their stomach were removed. The isolated antral and fundic (oxyntic cell area) parts were fixed in Karnovsky's solution and after dehydration they were contrasted with gold for further investigation.

The scanning electron microscopic results convincingly proof that cathinone has no detectable effect on gastric mucosa in the case of acute administration.

Taking into consideration that Yemeni authors stated that khat chewing can be a risk factor for duodenal ulcer formation we have investigated cathinone's effect on experimental duodenal ulcer model as well.

The well known acute duodenal ulcer model described by Selye and Szabo was employed.

According to the experimental results received cathinone showed neither ulcerogenic nor antiulcerogenic effect in rats' cysteamine-hydrochloride - induced duodenal ulcer model.

Considering that the liver is also a part of the gastrointestinal system, moreover according to some data in the literature there may be a "khat-related" liver disease, we have investigated the possible acute effect of cathinone on the liver. During these investigations adult Wistar rats of both sexes were used and apart from control ones the treated animals received 500 and 1000 µg/kg cathinone (in sterile, pyrogen-free aqueous solution) i.p. After 24h waiting period the animals were killed and within 60 seconds samples were taken from the same part of the liver (right lobe) for electron microscopic investigation. After the routine glutaraldehyde - araldite - uranyl-acetate process, the photomicrographs were taken by a Zeiss electron microscope.

It seems on the micrographs that basically no structural changes can be seen in the treated animals. The only visible change is that the mitochondrial surface area has significantly enlarged in the case of 1000 µg/kg cathinone treatment. On the basis of this result we conclude that this, mitochondrial effect may be the first acute (pathological) sign of khat-related toxicity in the gastrointestinal tract.

On the basis of our experimental results we conclude that khat's (cathinone) single, acute effect on rats' gastrointestinal system is negligible.

Further, long-term (months, years?) follow-up studies seem to be needed to establish convincingly whether khat (cathinone) has a deleterious effect on the gastrointestinal system, - or some other components of the plant, - e.g. tannins, etc., - are responsible for the possible late effect.

But on the other hand, it is evident from these (limited) studies that the medical and psychosocial effects of khat chewing are hazardous both to the individual and the community. For this reason, those countries in which khat consumption is widespread are now beginning to take steps , with the help of the United Nations and the World Health Organization, to reduce the availability of the drug.

In the opinion of the author, perhaps the most acceptable solution would be similar to that of coca-leaf chewing in South America: thus, in the countries where khat is indigenous and the habit is an old custom of the society, it should be tolerated; while in other regions of the world khat chewing should be (strictly) controlled. (This latter statement seems to be valid even for Hungary because khat has already appeared in our country as well.)

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