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

Ph.D. Thesis

(Abstracts)

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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 region 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.

HISTORY

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.

The name *Catha edulis* was first given to the plant by *Forsskal* in 1775, and the 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.

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

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. Fresh khat leaves are crimson-brown and glossy but become yellow-green and leathery as they age. They also emit 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. 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 the 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.

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 of years the drug has been reported in Great Britain, Italy, The Netherlands, Canada, Australia, New Zealand the USA and even in Hungary.

GENERAL ASPECTS

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.

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. The

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

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$.

CHEMISTRY

The first attempts to isolate the active principle of the plant were made more than 100 years ago by *Fluckiger* and *Gerock* in 1887 and in 1930 *Wolfes* identified *norpseudo-ephedrine* 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 pharma-cological 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. In this work *Szendrei* was one of the leading research workers. (Szendrei, 1980; Kalix, 1988; 1992; *etc.*)

Generally speaking the most important major khat alkaloids are either *phenylalkyl-amines* or *catedulins.* Apart from these khat contains *terpenoids, flavonoids, sterols, glycosides, tannins, amino acids* and *minerals.*

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*".)

Cathinone found mainly in the young leaves and shots. During maturation, cathinone is metabolized to *cathine* and (-)-norephedrine.

Other phenylalkylamine alkaloids found in the khat leaves are *merucathinone, pseudo-merucathine* and *merucathine.* These seem to contribute less to the stimulant effect of khat. (Kalix et al. 1987; *etc.*)

Cathinone is unstable and undergoes decomposition reaction after harvesting and during drying or extraction of the plant material, As cathinone is presumably the main psychoactive component of khat, this explain why fresh leaves are preferred by the users. (WHO, 1980.)

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

The desired 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. 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. (Kalix, 1990; Balint et al. 1990; 2009.)

TOXICOLOGY AND ADVERSE REACTION

Khat use affects almost the whole human organism. (Balint et al. 2009.)

The main toxic effects include: increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men. According to *Raja'a* et al. khat chewing appears to be risk factor for duodenal ulcer. (Raja'a et al. 2000; 2001.) This finding is in conflict and contradiction with *Balint's* works because according to his previous data all the sympathomimetic agents (such as amphetamine and the similar cathine and cathinone;) act against gastric and duodenal ulceration. (Balint, 1998; Balint et al. 2009.)

In addition, khat affects the nervous system and can induce paranoid psychosis and hypomaniac illness with grandiose delusions.

The effects on the nervous system resemble those of *amphetamine*, with differences being quantitative rather than qualitative. (Kalix, 1988; Pennings et a.2008.)

PSYCHOSOCIAL CONSIDERATIONS

Detailed accounts of the psychosocial aspects of khat use are still lacking.

According to Ethiopian authors it appears that the prevalence of khat cheving 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 of khat chewing. (Balint et al. 1990; 1991; Balint and Balint, 1994; 1995.)

DEPENDENCE, TOLERANCE AND WITHDRAWAL

The medical problems that arise from khat chewing are partly due to the sympatho-mimetic effects of the drug and partly to its effects on mental health.

It seems that 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,

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. A real khat withdrawal syndrome has not yet been described.

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, mainly among males.

In Ethiopia khat is freely available and it is a highly valued export commodity as well. The number of khat users has significantly increased in the country during recent decades and the habit has become popular in all sections of Ethiopian society. (Selassie and Gebre, 1996; Bimerew et al. 2007;)

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. On the other hand, khat use can be seen as playing a positive role in supporting the cultural identity of the Somali community.

For some, the daily cost of the habit exceeds their expenditure on food for theis families, which may cause further social and familial problems. (Balint et al. 2009.)

INTERNATIONAL AND NATIONAL CONTROL OF KHAT

Khat is not under international control at present. (WHO, 2003; 2006a,b.)

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*" (UN, 1971;) and cathine in Schedule III. of this Convention. Hungary, as a UN Member -state, follows UN regulations.

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 cathinone is the most important constituent of khat leaves, we have investigated the acute effect of cathinone on different parts of rats' gastrointestinal system.

Investigations on rats' stomach.

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.)

IND-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.

STR-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 mm2 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:

IND-ulcer: Cathinone (CTN; Sigma-Aldrich,) 500 and 1000 µg/kg respectively, at the 0. min and 120th min of the experimental period i.p., (evaluation at 240th min.)

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

It is worth mentioning that during an average human khat session the CTN dose is approximately 80-160 mg, - depending on the quality of khat leaves, - which corresponds about 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 experiments a 500 and a 1000 μg/kg single dose of CTN will be appropriate and informative.

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

The experimental results are presented in a Table: (See below.)

According to the results it seems that CTN showed no ulcerogenic effect, as it was stated by *Raja'a* et al. (2000; 2001;) instead - in accordance with *Kekes-Szabo* (1974;) and our previous results, as a drug with sympathomimetic effect, had antiulcerogenic property.

The Effect of Cathinone on Different Gastric Ulcer Models of Rat.

	IND	Δ%	STR	Δ%
	U.I. mean +/- SEM			
Control	9.7 +/- 1.5	100.0	11.2 +/- 3.8	100.0
CTN 500 μg/kg	8.8 +/- 1.2	90.7	10.8 +/- 2.9	96.4
CTN 1000 μg/kg	6.9 +/- 1.0*	71.1	8.2 +/- 2.2	73.2

* = $p<0.05$

Scanning electron microscopic investigations on rats' stomach

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 scanning electron microscopic results (*Tesla BS-300* scanning electron microscope;) convincingly proof that 1000 μg/kg CTN has no detectable effect on gastric antral and fundic mucosa in the case of acute administration.

Investigations on rats' 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 4^{th} and 8^{th} hour 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 a Table:

The Effect of Cathinone on Cysteamine-induced Duodenal Ulceration of Rats.

	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

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

Investigations on rats' liver

The effect of CTN 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 % 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% ethanol, - and on the sections by leadcitrate. The photomicrographs were taken by a *Zeiss-EM-9S-2* electron microscope.

It seems on the micrographs 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 mitochondrium;) 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 recent literature (Chapman et al. 2010;) there may be an "khat-related" liver disease, we conclude that this, mitochondrial effect may be the first (pathological) sign of the khat-related toxicity.

SUMMING - UP

our experimental work regarding khat's (CTN) effects 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 deleterious effect on the gastrointestinal system, - or some other components of the plant, - *e.g.* tannins, *etc.*, - are responsible for the possible late effects.

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.

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.

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.

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