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On Some Gastrointestinal Effects of Khat (*Catha edulis*)

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Abstract

Background: The possible gastrointestinal effects of khat (*Catha edulis*) chewing still under debate. Some authors are on the opinion that khat has a gastric and/or duodenal ul-cerogenic effect, while others denies this effect. Considering the absolutely different standpoints in this case, we have decided to investigate this contradiction in different experimental ulcer models of rat.

Materials and Methods: It is known that the main effective (amphetamine-like) constituent of the khat is cathinone, we have investigated the effect of 500 and 1000 ug/kg of its dose in stress (restrain) and drug (indomethacine) induced gastric, as well, as cyste-amine induced duodenal ulcer-models. It seems that in indomethacine and in stress induced models cathinone showed no ulcerogenic effect, moreover in the indomethacine induced model it showed a significant anti-ulcerogenic effect. Moreover, scanning electron microscopic investigations verified that the acute cathinone treatment has no detectable effect on gastric mucosa. In the cysteamine-induced duodenal ulcer-model cathinon showed neither ulcerogenic, nor anti-ulcerogenic effect.

Discussion and Conclusion: Moreover, our scanning electron microscopic investigations showed that basically no structural changes can be seen in the treated animals' liver; the only visible change is that the mitochondrial surface area of the treated liver is enlarged. According to our opinion our experimental results presented, gave evidence that khat, at least its cathinone content, have no gastrointestinal (ulcerogenic) effect.

Keywords: Gastrointestinal; Indomethacine; Ulcerogenic; Cathinone

Introduction

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

Chewing the leaves of the plant ("khat session") for their pleasurable stimulant effect is a habit that is widespread in the mentioned geographical areas. It is estimated by the WHO that about 5-10 million people chew it every day. 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. The chewing of (fresh) khat leaves has a stimulating effect and causes a certain degree of euphoria. It is worth mentioning that the chewing of the leaves probably pre-dates the use of coffee.

During the past decades khat chewing has gained global prominence as the result of migration. 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 already. As a consequence of rapid and relatively inexpensive air transportation, during the past couple of years the drug has been reported in Great Britain, The Netherlands, Canada, Australia, New Zealand, the USA and even in Hungary [1].

The first attempts to isolate the active principle of the plant were made more than 100 years ago by Fluckiger and Gerock in 1887. It was Wolfes who in 1930 identified (+)-norpseudoephedrine (NPE) 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 NPE present in the khat is insufficient to account for the effects [1]. In the view of this objection the plant was reinvestigated. These pharmacological studies culminated in the isolation of the keto-analogue of NPE

from khat leaves and the name (-)-cathinone (CTN) was suggested for this new alkaloid [2,3]. Chemically CTN bears a close resemblance to amphetamine (AMA). Since the effects of khat had been described earlier as being similar to those of AMA, CTN was examined first for AMA-like effects [4,5]. The observations suggest that CTN is responsible for the sympathomimetic symptoms observed after khat consumption. The effects of the many other constituents of the plant still are either over-looked or even unknown.

As noted khat contains many different compounds and therefore khat chewing may have many different effects. The major effects include those on the gastro-intestinal system and the nervous system. Constipation, urine retention and acute cardiovascular effects may be regarded as peripheral, autonomic nervous system effects, while increased alertness, dependence and to a lesser extent CTN are held responsible for the effect of khat on the nervous system [1]. It is worth mentioning that data on khat's effect on animals' gastrointestinal systems are somewhat scarce, relatively more data can be found in human studies. (Mainly only as simple observations and not in the form of a planned and detailed clinical investigation.) "Follow-up" type investigations are almost unknown.

Considering Raja'a et al. publications in which they stated that khat has an ulcerative effect in the gastrointestinal tract, moreover Chapman et al. work in which they reported their observation on six patients (who were not related with each other, neither geographically, nor temporally) whose use of khat was associated with severe acute hepatitis [6,7]. According of the mentioned authors no other cause for their liver disease was found than khat consumption. On the basis of the above-mentioned publications we have decided to perform some animal investigations in those fields.

Materials and Methods

We have investigated the acute effect of CTN on different parts of rat gastro-intestinal system.

It should be noted 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 to 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 all investigations a 500 and a 1000 µg/kg single (rapid) dose of CTN will be appropriate and informative [8].

A. Investigations on rats' stomach

1. Gastric ulcer models: Six groups of adult 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: Indomethacine (IND) and Stress (STR) induced ulceration [9].

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 [10].

The following drug has been tested and the single doses (in aqueous solution,) were as it follows:

IND ulcer: CTN, 500 and 1000 µg/kg i.p., respectively, at the 0 min and 120th min of the experimental period, evaluation at 240th min.

STR ulcer: CTN, 500 and 1000 µg/kg i.p., respectively, at the 0 min, and 6th, 12th and 18th hour of the experimental period, evaluation at 24th hour.

Within each animal group mean ± SEM was calculated and analysed statistically using Student's (two tailed) t-test. The experimental results are presented in **Table 1**.

Table 1 The effect of cathinone in different gastric ulcer models of rat.

Variables	IND ulcer U.I. mean ± SEM	Δ%	STR ulcer U.I. mean ± SEM	Δ%
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				

According to the results it seems that CTN showed no ulcerogenic effect, in effect, it had antiulcerogenic property.

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 to 220 g were used. Prior to investigation the animals were fasted for 24 hours but allowed water ad libitum. The rats were assigned in groups consisting each of 10 animals. The control animals received in appropriate amounts water only.

After 120 min of treatment with CTN (1000 µg/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 hours 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 2000x.

The scanning electron microscopic results convincingly proof that CTN has no detectable effect on gastric mucosa in the case of acute administration [11].

B. Investigations on rats' duodenum

Experimental duodenal ulcer: The acute duodenal ulcer model described by Selye and Szabo was employed [12]. 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 48h 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 [13]. The oral 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 2**.

Table 2 The effect of cathinone on cysteamine induced duodenal ulceration of rats.

Variables	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 anti ulcerogenic effect in rats' CEA induced ulcer model.

C. Investigations on rats' liver

The effect of CTN on liver tissue during these investigations 45 Wistar rats of both sexes were used. Their body weight was 200 to 230 g and they were treated as follows:

The animals in the control group (n=15) received 0.5 ml sterile, pyrogen free, normal saline solution, intraperitoneally (i.p.). The treated animals received i.p. 500 (n=15) and 1000 (n=15) µg/kg CTN respectively. After 24 hours 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 lead citrate. The photographs were taken by a Zeiss-EM-9S-2 type electron microscope.

According to the results it seems on the micrographs that basically no structural changes can be seen in the treated animals. The basic structure of the treated liver is normal compared to the control. The only visible change is that the

mitochondrial surface area of the treated liver is enlarged [11]. The results are presented in **Table 3**.

Table 3 The effect of cathinone on rats' hepatic mitochondria.

Mitochondrial surface area, mm ² (11700x)*	
Control	58.77 ± 8.17
CTN 500 µg/kg	92.46 ± 12.39
CTN 1000 µg/kg	128.40 ± 14.68 (▲)
* =mean values ± SEM	
▲ =p<0.02	

As it is documented in **Table 3** the average surface area of the mitochondria in the untreated liver was 58.77 mm², counted minimally 100 mitochondrium, if the magnification was 11700x, while in the case of 500 µg/kg CTN dose the surface grew to 92.46 mm² and in the case of 1000 µg/kg CTN treatment it was 128.40 mm², (among the same experimental circumstances) which latter is a significant enlargement (Student's t-test, p<0.02). This result is in complete agreement with our previous, preliminary results.

Discussion and conclusion

According to Raja'a et al. [6] khat chewing appears to be a risk factor for duodenal ulcer. This finding is in conflict and contradiction with Kekes-Szabo's and our own works because according to the latter data all the sym-pathomimetic agents

such as AMA, and the similar CTN, -act against gastric and duodenal ulcerations in humans and in animals, e.g. albino rats [14,15] Tariq et al. also have received negative results regarding khat's ulcerogenic effect [16].

According to our present and detailed investigations it seems that khat has no ulcerogenic effect neither on the stomach nor in the duodenum. Moreover the scanning electron microscopic investigations proved that CTN has absolutely no deleterious fine effects on the gastric mucosa. These results correspond and strengthen our previous investigations as well. On the other hand on the basis of our present investigations we may strengthen those opinions that khat chewing at least because of its CTN content, may have an effect on the liver.

It is known that CTN, similarly to NPE and AMA, has a mainly enzymatic degradation outside of the liver, but we cannot rule out that CTN has a direct effect on the liver as well. (Other compounds of the leaves, for example tannins, terpenoids etc., during their metabolism definitely have a direct effect on the liver).

According to our opinion, based on our above discussed result, the significant mitochondrial enlargement, seems to be a consequence of the applied CTN treatment, which represented the well-known khat chewing sessions, and which sessions after a (very?) long time (as the khat chewing habit is) may cause inflammatory, pathological changes, (perhaps only among special circumstances in special persons?) resulting in such pathological conditions what Chapman et al. have reported [7]. Further, mainly long-lasting "follow-up" type clinical investigations seem to be needed along this line, what we would like to complete.

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