# KHAT (*CATHA EDULIS FORESK*)—an updated review

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## SUMMARY

Khat (*Catha edulis* Forsk) is an evergreen plant that grows at high altitudes in East Africa and Arabian Peninsula. Chewing its fresh leaves is a widespread habit in the local populations, with several million people consuming khat regularly in social sessions that often last for hours. This review describes the history, cultivation and chemical composition of khat. The pharmacology of (-)-cathinone (the main active component) in the central nervous system and the peripheral effects are described. (-)-cathinone is regarded as an amphetamine- like sympathomimetic amine and this mechanism of action is discussed in relation to the central stimulant actions. The medical, psychological and social and epidemiological aspects are emphasized, and the current knowledge about the reproductive effects of khat is also presented.

## 1. INTRODUCTION

*Catha edulis Forsk* (Celastraceae), an evergreen shrub or tree grows in certain areas of East Africa and Arabian Peninsula. It belongs to the suborder Rosidae and family Celastraceae. *Catha edulis*, commonly known as "Chat" in Ethiopia but consistently referred to in the literature as khat, is both socially and economically one of the most important plants not only to many countries of Eastern Africa but also for the Middle – East (Figure1). The effects of khat were reported in the literature as early as 1237 by the Arabian Physician Naguib Ad Din, who proposed the use of khat for the treatment of depressive states, and by other writers of the same period who reported that it was effective in blunting the sensation of hunger and fatigue (1).

## 2. HISTORY

Historically, the original source of khat seems to be obscure. However, there is general agreement that its use was prevalent in Ethiopia and from there, around the fifteenth century, the practice spread to the south-west of the Arabian Peninsula (2, 3). Arab sources suggested that khat was in Yemen in the sixth century, when the Ethiopians conquered Yemen. Earliest reference to this plant appears to be dated around 973–1053 AD. by Al-Biurni, who meticulously compiled information on all contemporary drugs, what he called qat that was imported from Turkistan. It was used to relieve biliousness and to cool the stomach and liver3. Haecock and Forrest (4, 5) mentioned (1974) that, it is possible to find a referral to khat as early as 1332 AD in an Arabic manuscript preserved in the Biblioteque National in Paris. The first account of its effects appeared more than seven centuries ago in an Arabic medical textbook (6) in which the leaves of it were recommended for curing depression. The earliest scientific report on khat presented to a Western country was in the eighteenth century, when the botanist, Peter Forskal, identified the plant in Yemen and called it *Catha edulis*. However, he did not live long enough to publish his finding, which were later edited in 1775 by Niebuhr(7), the only survivor of the first European scientific expedition to Arabia. Niebuhr, in his general observation, stated that he "never saw the Arabians use opium like the Turks and Persians. Instead of taking this gratification, they chew kaad (khat). These are the buds of a certain tree, which are brought in small boxes from the hills of Yemen(8). In memory of his friend, Niebuhr labeled khat under the generic name of *Catha edulis* Forsk. Other names were given to the plant by various travelers visiting Arabia and East Africa in the nineteenth century.

## 3. THE KHAT TREE: CULTIVATION

Harvesting of Khat leaves is done in the morning and wrapped in bundles with large fresh leaves such as banana leaves to conserve moisture and keep the khat cool. Since the khat leaf rapidly looses its effect upon wilting, the khat habit has remained, until recently, endemic to the areas where the plant was growing. During the last decades, however, due to development of road networks and the availability of air transport, the habit has spread considerably in those regions and even to countries where the plant does not grow (10).
The plant requires well drained dark red-brown, sandy loam with a low percentage of clay and medium to high amounts of total nitrogen and organic matter. Khat performs best on soils with a pH of 6.0-8.2. Nevertheless, once established, khat grows well under a wide range of soil types and climatic conditions. The optimal altitude for growing khat ranges from 1500-2100 meters above sea level (11).

**Figure 1 Picture of *Catha edulis Forsk* (Khat)**

## 4. SOCIAL AND EPIDEMIOLOGICAL ASPECTS OF KHAT USE

Khat is grown primarily in Ethiopia, Kenya, Yemen, and at high altitudes in South Africa and Madagascar. Millions of people in these countries ingest the stimulant, and its use seems to have expanded considerably in recent years. The Khat plantations occupy scarce arable land, and they compete, for example, with coffee for the well-irrigated terraces (9).

In Ethiopia, khat is widely grown not only for local use but also for export, which provides millions of United States dollars per year to the national economy. Khat chewing is commonly practiced by high school and university students as well as some sector of the population (12). A recent study by N Taffa *et.al* (13) in Addis Ababa, Ethiopia revealed that engagement in sexual activity among young people was associated with khat consumption and alcohol use. A survey of one region in rural Ethiopia placed the prevalence of use at about 50% of the total population (14).

In the rural areas of Yemen, the habit of chewing khat is acquired within the family, usually at the age between 10 and 14 yr, whereas in urban areas, khat use is usually the

result of peer group influence, and abstention can lead to social isolation (9). About 90% of men and 30% of women uses khat, either daily or occasionally (15).

In Djibouti, khat consumption is committed to be a luxurious habit since the material cannot be grown in the country and has to be imported. Mainly because of its availability, about 90% of men and 10% of women uses khat, either daily or occasionally. It is estimated that about 1/3 of all wages is spent on the purchase of khat (9).

In Kenya, khat chewing is a regional phenomenon, with the two centers of consumption being Nairobi and the Meru district, in which khat is cultivated extensively in the foot hills of Mount Kenya (16). Kenya exports quantities of khat valued at approximately two million United States dollars annually (9).

Among the various consequences of khat use are, absenteeism and decreased productivity that frequently lead to unemployment. Furthermore, the purchase of khat puts a strain on family income and the detrimental social effects of the khat habit are felt with in the family. The interaction with the father is adversely affected, since he is irritable and quarrelsome while under the effect of the drug or silent and withdrawn when the effect was worn off. Through its effect on the male reproductive system, the drug leads to progressive estrangement between husband and wife. Thus, the drug has been estimated to be a factor in one out of two divorces in Djibouti (9).

## 5. CHEMICAL COMPOSITION OF KHAT

Khat contains a lot of chemical components that may have different effect on the body system. The first attempts to isolate the active principle of khat were made by Fluckiger and Gerock in 1887. It was Wolfes who in 1930 identified the presence of (+)-norpseudoephedrine (cathine) in the leaves of Khat. Up to 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 present in khat is insufficient to account for the symptoms produced (10). In view of this objection and because of the increase in international problems associated with khat consumption, the United Nations' Narcotics Laboratory put emphasis on the use of fresh material and on the appropriateness of the extraction process. The analytical studies of the laboratory led to the identification of a new alkaloid, S-α- aminopropiophenone, and the name (-)-cathinone was suggested for this compound (17). The spatial configuration of (-)-cathinone was then studied, and the alkaloid was found to have absolute (S) as (+) -amphetamine; the molecule was then reproduced by synthesis (9). Later it became evident that (-)-cathinone is a labile compound that is mainly present in young leaves,

and is biodegraded when the leaves start to dry. This is incomplete agreement with the fact that khat is consumed fresh in the vast majority of the cases and not as dried material (10). A study of the alkaloids distribution in different parts of the plant from materials of various origin (18) revealed that, in few samples, (-)-cathinone accounted for more than two thirds of the total phenylalkylamines, and the market value of the leaves was found to be correlated with the (-)- cathinone content. This study also showed that (-)-cathinone is a phytochemical precursor of (+) - norpseudoephedrine. There is a transformation of (-)-cathinone into (+)-norpseudoephedrine, which is rapid in adult leaves, but slow in young leaves, presumably because in the latter material, the development of the enzyme apparatus is still incomplete. Similarly, the conversion of (-)-cathinone into (+)-norpseudoephedrine occurs when cut leaves wilt (9).

Although most of the (-)-cathinone in khat leaves is converted into (+)-norpseudoephedrine, part of it is transformed into (-)-norephedrine; the leaves contain (+)-norpseudoephedrine and (-)-cathinone in a proportion of approximately 4:1 (9). The plant contains only the (-)-isomer of cathinone; (+)-cathinone is not present. In solution the isomer tend to racemize, and cathinone may cyclize to dimethyldiphenyl pyrazine (19). Analysis of 22 khat samples of different origin has shown that, 100g fresh khat contains on the average 36mg of cathinone, 120mg of cathine and 8mg of norephedrine (19). Furthermore, khat leaves contain another group of alkaloids called the catheduline, with a molecular weight ranging from 600 to 1200 (9). These compounds are polyesters or lactones of sesquiterpenes polyols, and some features of their structure vary with the geographical origin of the plant material (19). In view of these findings, the question arises as to the extent to which the different substances present in the plant contribute to the effects observed after khat chewing. Although only the phenylalkylamines (-)-cathinone and (+)-norpseudoephedrine have so far undergone pharmacological investigation, there is much evidence indicating that the effects observed after khat chewing can be explained by the pharmacodynamics of the two alkaloids alone. The effects of (-)-cathinone and (+)-norpseudoephedrine are qualitatively analogous, but (-)-cathinone is considerably more potent with regard to stimulation of the central nervous system. Nevertheless it would also be of interest to investigate the pharmacology of the other compounds present in khat.

Khat leaves contain small amounts of ethereal oil, they contain sterols and triterpenes, are rich in flavonoids, and have also tannin (20). Although the leaves are reported to contain 5% protein (10), the nutritional value must be considered insignificant. As to vitamins, the leaves have been reported to contain considerable amounts of ascorbic acid (9).

## 6. PHARMACOLOGY OF KHAT ALKALOIDS

Chemically, (-)-cathinone bears a close resemblance to amphetamine, the only difference being that the two hydrogen's on the first carbon of the amphetamine side-chain are substituted by oxygen (Fig. 2). Since the effects of khat had been described earlier as being similar to those of amphetamine, (-) - cathinone has been examined first for amphetamine – like effects (10).

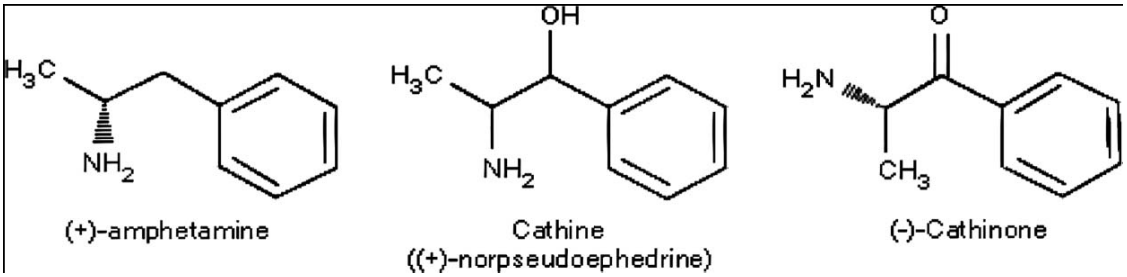


Figure 2 Chemical structures of cathinone, cathine and amphetamine

### 6.1. EFFECT OF CATHINONE IN ANIMALS AND ISOLATED ORGANS

**Peripheral Effects** – It was found that (-)-cathinone when administered to anesthetized rats or cats caused a substantial increase in blood-pressure, and that it showed a positive inotropic and chronotropic effect on isolated guinea pig heart (21). Cathinone has vasoconstrictor properties in the coronary circulation and in a major conducting vessel, the aorta. This vasoconstriction is unlike that of amphetamines as it does not appear to be due to an indirect action by release of noradrenaline from sympathetic nerve endings (not blocked by cocaine) or a direct action on $\alpha_1$- adrenoceptor (not blocked by prazosin). It remains to be established by what mechanism cathinone causes this vasoconstriction and whether it is due to the release of alternative endogenous vasoconstrictor to noradrenaline, such as endothelin or angiotensin. It is possible that the coronary vasoconstriction by cathinone could explain the increased incidence of myocardial infarction in khat chewers that is associated with the timing of the khat chewing session. The cathinone derived from khat could induce coronary vasospasm, which may occlude coronary arteries sufficient to precipitate myocardial infarction (22).

Amphetamine and some of its analogues have analgesic effect that, however, is not sufficiently pronounced to be useful in therapy. Similarly, cathinone was found to have analgesic properties in that it was shown to increase the reaction time of mice in the hot plate and in the tail flick test (19). Amphetamine causes hyperthermia when administered

to rats, an effect that is mainly due to thermogenesis in intracapsular brown adipose tissue. This seems also the case for cathinone, which increases the body temperature of rats with oral administration. The calorigenic action of cathinone is consonant with the fact that it increases, like amphetamine, the metabolic rate and oxygen consumption of rats (19).

**Central Effects** – The IV administration of cathinone to monkeys results in extreme restlessness and tremor (19). This reflects the CNS stimulation expected from an amphetamine – like compounds, an action usually evaluated by quantifying the locomotor activity of rodents. Indeed, the very first report describing the effects of cathinone stated that the alkaloid induces hypermotility in rats and in mice (23). The induction of hyper motility by cathinone can be prevented by pretreating the animals with neuroleptic substances of the butyrophenone type (24), which likewise prevented the motor stimulation produced by amphetamine. Another similarity between cathinone and amphetamine is that high doses of both compounds are capable of inducing stereotyped movements especially of head and face.

In many cases, the use of khat is compulsive and the drug it self is known to be habit forming while inducing moderate psychic dependence. During some of the behavioral experiments, it was observed that cathinone reduced the food intake of the test animals. Thus appeared to have an anorectic effect, as amphetamine (23).

Amphetamine is known to affect serotoninergic pathways in the CNS and has been found, in rat corpus striatum, to release serotonin in a dose-dependent manner (9). In order to determine whether (-)-cathinone can mimic this aspect of amphetamine's action, its effect on the release of radioactivity from rat striatal tissue pre-labeled with $^{3}H$-serotonin was studied. It was found that, in order to produce an effect of an amplitude similar to that produced by a given concentration of (+)-amphetamine, a three times higher concentration of (-)-cathinone was needed. This indicated that with regard to release from serotonin storage sites, (-)-cathinone has no greater specificity than (+)-amphetamine. There are indications, however, that interaction with serotonin pathways might contribute to the CNS effects of (-)-cathinone. There is also interesting observation that, the affinity of (-)-cathinone for serotonin receptors is 4 times greater than that of (+)-amphetamine in the rat fundus preparation (19).

## 6.2. EFFECT OF KHAT IN HUMANS

The effect of khat in group of habitual users were studied by Nencini *et al*., (25) under standard conditions and they noted an increase in blood pressure and pulse rate in all the

participants and they found the subjective effects of cathinone to be consistent with an amphetamine – like action.

The availability of pure cathinone provided the possibility of investigating its effect in humans under clinical conditions. To this end cathinone was administered orally to six healthy volunteers in a double blind random order crossover study (26) at a dose of 0.5mg/kg body weight. In comparison to placebo, cathinone produced a clear-cut increase in blood pressure and heart rate; these changes were manifested in about 30min after administration and they persisted for about 2 hours while being concomitant with the presence of cathinone in blood plasma.

In experiments, in which cathinone was given in a gelatin capsules, cathinone was rapidly absorbed and its plasma level rose to a maximum which persisted from approximately 30 to 90min. after administration and thereafter decreasing with a half-life of about 1.5 h. This is in contrast to amphetamine, which persists much longer in plasma. As far as khat is concerned, however, it must be remembered that the drug is extracted by chewing the leaves and thus being consumed portion wise over a period of 1 to 2 hr. This delayed administration of cathinone from the leaves certainly results in a more gradual evolution of the cathinone plasma levels, and thereby an extended duration of action (9).

Because of the high ionization constant of amphetamine, its effects in humans can be shortened by urine acidification, which leads to an accelerated excretion of the drug. In principle this is also possible for cathinone, which has about the same ionization constant as amphetamine (27), however, due to the short plasma half-life of the alkaloid this approach is of limited usefulness.

It is very likely that the difference in time course of the plasma levels of cathinone versus amphetamine is due to the difference in disposal. Thus, amphetamine is rather stable and to a large part excreted unchanged, the remainder is mainly deaminated while a minor fraction is side-chain as well as ring-hydroxylated. In contrast because of its α-aminoketone structure, cathinone is a labile compound (27).

## 6.3. EFFECT OF KHAT CONSUMPTION ON REPRODUCTIVE FUNCTIONS

There is limited literature on the effects of khat consumption on various reproductive parameters. Hence, there is a need to understand the impact of khat consumption on the health of the society in order to develop intervention strategies to control the abuse. It is

believed to have negative impact on various reproductive health parameters such as fertility, pregnancy, as well as infant survival (28).

**(a) Effect of Khat on female reproductive health**

Khat chewing during pregnancy is on the increase among women of reproductive age and questions have been raised on the potential effects of khat on fetal development. Eriksson and co-workers (29) found out that a khat-chewing mother produces less milk than non-chewers. In another study comparing pregnant khat chewers and non-chewers, it was observed that there was no difference in the rates of stillbirth or congenital malformation (29). It was shown that administration of khat to female pregnant guinea pigs resulted in the birth of smaller pups, which was attributed to decreased blood flow to the uterus (16). The concentration of norpseudoephedrine in pregnant guinea pig urine was found to be directly related to the amount of khat extracts consumed. Khat chewing in the third trimester of pregnancy was also found to significantly reduce the maternal weight gain (30).

## (b) Effect of Khat on male fertility

Long-term and regular consumption of khat may also lead to progressive and diminished sex performance, and this suggests chronic consumption of khat may be the cause of sexual impotence (30). Studies by Islam *et al*., (31) in 1990 revealed that feeding male rats with khat resulted in significant effects on reproduction. These investigators demonstrated that male rats treated with the active constituent, cathinone had smaller testicles, epidydimis and seminal vesicles than do the controls (31). Unlike previous reports suggesting deleterious effects on male reproductive tract, more recently, histopathological examination of sections of male reproductive tract suggested that *Catha edulis* had stimulated spermatogenesis and the cauda epididymides and ledying cells were normal, when compared with equivalent sections from untreated rabbits (32).

Limited experiments have also been performed in humans as reported in the literature. In experiments carried out to determine the effects of khat consumption on semen parameters, El-Shoura *et al* in 1995 (33) used a group of 65 khat addicts and a control group of 50 non-users. In a similar experiment, Hakim examined 214 male patients with history of infertility who, with the exception of 31 people (control group), used khat regularly (34). In both studies, it was established that khat addicts had a reduced semen volume, low sperm count and reduced sperm motility. In addition, there was an increase in the number of abnormal sperm .On the other hand, more recently study done by Adeoya-Osiguwa SA *et al* (35) showed the effects of cathine and norephedrine on mouse and human sperm that they were capable of stimulating the final stage of sperm

maturation (capacitation). In addition both compounds maintained the sperm in a potentially fertilizing state for longer allowing them more time to reach an egg. Moreover, the results suggest that moderate levels of cathine and norephedrine, especially in the female reproductive tract, could have a positive effect on natural fertility (35).

Khat and its alkaloid, cathinone have been reported to affect male sexual potency (9). There are contradictory reports regarding the association between khat chewing and sexuality. However, khat has been reported to be used as an aphrodisiac (1) and a medicament for premature ejaculation. On the other hand, impairment of sexuality, inability to sustain erection and loss of libido (40) has been reported. Endocrinological disturbances including changes in sex hormone level have been observed in khat chewers (41).

A study showed that administration of khat extracts to adult male olive baboons significantly increased testosterone but down-regulated prolactin and cortisol levels in blood plasma compared to the basal levels before khat administration (42). In marked contradiction other study showed that prolonged treatment of cathinone produced a significant decrease in plasma testosterone (31). A recent study by Abdelwahab et al. (43) showed that Low dose (100mg/Kg) has enhanced male sexual behavior, where as higher doses (200, 400mg/Kg) of khat extracts have been shown to inhibit both male and female sexual behaviors (43, 44). More recently, a study on the effect of different concentrations of khat extract on testosterone levels showed that high concentrations of khat extract (30 mg/ml and 60 mg/ml) significantly inhibited testosterone production while low concentrations (0.06 mg/ml, 0.6 mg/ml and 6 mg/ml) significantly stimulated ($P < 0.05$) testosterone production by mouse interstitial cells(45).

## 7. CONCLUSIONS

- Khat chewing is a widespread habit that has a deep-rooted sociocultural tradition in East Africa and in the Middle East with pronounced economic dimensions.
- The sympathomimetic and CNS-stimulating effects produced by khat-chewing are due mainly to cathinone, the ‘natural amphetamine’ present in fresh khat. Compared to amphetamine, however, khat seems to have less potential of inducing tolerance or toxic psychosis.
- The euphoric effects have been demonstrated to arise from the main constituent, (-)-S-cathinone, and there has been abundant research on the involvement of central neurotransmitters in this action.
- khat components have been reported to stimulate the final stage of sperm maturation (capacitation). In addition the khat componenets have maintained the

sperm in a potentially fertilizing state for longer allowing them more time to reach an egg.

- The recently reported effect of low dose of khat extracts on male sexual behavior and more recently the report that low dose of khat extract upregulates testosterone levels may indicate its potential therapeutic use in male sexual dysfunctional disorders.

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