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EFFECTS OF KHAT *(CATHA EDULIS)* CONSUMPTION ON REPRODUCTIVE FUNCTIONS: A REVIEW
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J.M. MWENDA, M.M. ARIMI, M.C. KYAMA and D.K. LANGAT

ABSTRACT

Objective: **To review research findings on the effects of khat *(Catha edulis)* chewing on reproductive functions.**

Data sources: **Retrieval and critical review of relevant articles and abstracts cited in international and local journals, literature searches on Medline and Medchem from 1961 to 2002.**

Data synthesis: **Analysis of published data and limited interviews of regular khat users revealed that khat chewing lowers libido in humans and may also lead to sexual impotence following long term use. In pregnant women, consumption of khat affects growth of foetus by inhibiting utero-placental blood flow and as a consequence, impairs foetal growth.**

Conclusion: **Detailed studies on the effects of khat on reproduction are lacking. However, the limited available data reveal that chewing of khat has a negative impact on human reproductive health. Khat is genotoxic and has teratogenic effects on the foetus if regularly consumed by pregnant mothers. Since low birth weight is a well-established risk factor for both perinatal and young infant death, khat chewing during pregnancy may be one of the factors contributing to infant mortality in communities where khat is commonly chewed. Khat consumption affects the potency of male sexuality by affecting spermatogenesis and plasma testosterone concentration. However, the precise mechanisms by which khat may affect the male reproductive physiology have not been elucidated.**

INTRODUCTION

Khat *(Catha edulis)* is the name of an evergreen tree grown in the Middle East, Somalia, East Africa and Ethiopia. It belongs to the sub-order *Rosidae* and family *Celastraceae* (the bitter-sweet family of plants). It grows to a height of seven metres and spreads to cover an area three metres wide. The flowers are whitish and are five petalled, occurring in small auxiliary clusters. In Kenya, khat, commonly called *miraa*, is cultivated on a commercial scale around Nyambene hills found in Meru North, 320 km North East of Nairobi. A few khat trees are also grown in Mbooni in Machakos district and in central province of Kenya. Some khat trees were also found to be growing in the wild in Koibatek district in Rift Valley province. 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. Those harvested during dry and sunny season are more potent than those harvested during cool months of the year.

Khat is generally chewed when fresh, although occasionally they are dried and then consumed as pleasantly stimulating beverage. Khat is occasionally consumed with coffee. Habitual khat chewing is mainly a male activity but it has become increasingly popular among women(1). In Muslim countries like Yemen, Ethiopia, and Somalia, khat consumption rate is high because all other drugs are forbidden by religious laws. It is regarded as a gift from God handed over to a monk to enable them pray overnight. Traditionally, consumption of khat is concentrated around Eastern Africa and the Middle East. However, chewing of khat is spreading worldwide and particularly in Europe and North America.

CHEMICAL COMPOSITION

Khat contains a lot of chemical components that have different effects on the body system. Since it is most commonly chewed for its effects on the nervous system, these were the first chemicals studied. Cathine was the first active component to be isolated from dried plant sample as reported by Alles *et al.*, and Zelgher *et al* (2,3). This compound is also called (+)-/-norephedrine, pseudonorephedrine or norpseudoephedrine(3). Khat use results in modest central nervous stimulation effects(3), which is attributed to Cathine(2). Another compound which is more potent

than Cathine was also identified in 1961(2). This new compound was isolated and identified as l(s)-(-)-alpha-aminopriopiophenone or Cathinone(2). Cathinone was believed to be the precursor of Cathine, which degrades to enol derivative on drying. However, cathinone can be found in dry plant material if drying is carefully done(3).

Figure 1

Pseudoephendrine

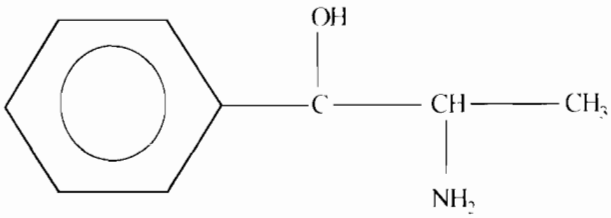
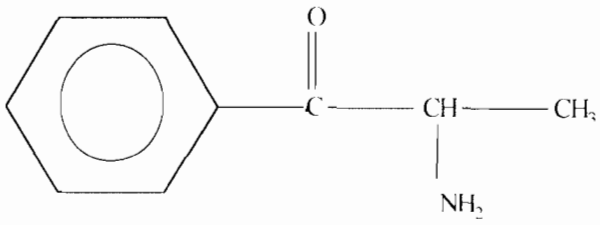


Figure 2

Cathinone



Cathinone is one of the optical isomers of benzylketoamphetamine and has amphetamine-like characteristics(4-6). (-)Cathinone is more potent than its enantiomer (+)cathinone. However both enantiomers have identical absolute stereochemistry in that they possess absolute configuration(4). Cathinone is known to stimulate excess release of dopamine in the central nervous system. Excessive dopamine replenishes the intermediate compound in the synthesis of adrenaline, which is a glycolytic hormone. This results in release of glucose, hence provision of energy for flight(8). Cathinone also affects the production of dopamine in the central nervous system(7,8). The N-methyl analogue of Cathinone is called methcathinone and was shown to be more potent than Cathinone(4,7).

Experiments conducted by Glennon and colleagues in 1987 to compare the drug effect of khat and cocaine using animals trained in behaviour paradigm to discriminate cocaine from vehicles showed that cathinone and methcathinone were indistinguishable from cocaine(4). These investigators further showed that the three compounds could not be distinguished from amphetamine by animals trained to discriminate amphetamine from a vehicle(4). In their studies Zelgher *et al.* argued that Cathinone produced qualitatively similar locomotor stimulation in mice and comparable stereotype in rats similar to amphetamine(3).

Cathinone interacts with brain catecholamines by indirect mechanisms(3,8). Blocking synthesis of catecholamines by alpha-methyl-p-tyrosine completely abolishes the stereotyped behaviour in Cathine and Cathinone treated animals, and these effects mimic those associated with amphetamine(3). It has been suggested that there is a significant association between the habit of khat chewing and both development of haemorrhoidal disease(11) and mental distress(12). Khat chewing may also cause psychosis(13-15). However, conclusive evidence is lacking.

In addition to the chemicals described above, khat also contains other chemicals that have various effects on the body. A recent study showed that khat affects the levels of various enzymes in the liver(16). These investigators showed that there was a significant increase in plasma levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in long-term users (observations made over a six month period). The increase of ALP was more prominent than both ALT and AST at the higher level of 30%. Plasma levels of AST though were only moderately increased at the higher level of 30% at the early stage of treatment (3 months) it significantly increased with all levels of *C. edulis* leaves in the long term (4-6 months). In addition, a time-dependent gradual increase in indirect bilirubin with a concomitant decrease in direct bilirubin levels were observed with the lower level of *C. edulis* (10%) with no signs of haemolysis. Histopathology of tissue sections of liver display evidences of increasing chronic inflammation(16).

KHAT AND REPRODUCTIVE HEALTH

There is limited documentation on the effects of khat consumption on various reproductive parameters (Table 1). There is need to understand the impact of khat consumption on the health of the society and then develop intervention strategies to control the abuse. This is especially important because there are suspected effects of khat on various reproductive heath parameters such as fertility, pregnancy, infant and child survival(17). These effects are discussed.

Table 1

Possible effects of khat on various aspects of reproduction

Reproductive organ/function	Khat extract	Effects	Reference(s)
Semen volume	Cathinone	Reduced	10,18-20
Sperm motility	Cathinone	Reduced	18-20
Sperm motility index	Cathinone	Reduced	19
Sperm count	Cathinone	Reduced	18-20
Abnormal sperm	Cathinone	Increased	18,19
Utero-placental blood flow	Cathine	Reduced	21,22
Post implantation losses	ME	Increased	23
Maternal weight gain	Cathine & ME	Reduced	19,24,25
Placental vascular resistance	Cathine	Increased	21,22
Maternal blood pressure	Cathine	Increased	21,22
Maternal myoendometrial blood flow	Cathine	Reduced	21,22
Sex organs size	Cathine	Reduced	18
Sex ratio	ME	No effects	26
Pup/pup size	ME	Reduced	21,22,24,25
Plasma testosterone	Cathino	Reduced	19
Fertility	ME	Reduced	23
Potency	Cathinone	Reduced	18
Maternal milk production	ME	Reduced	26

ME = Methanolic khat extract.

Effects of khat on female reproductive health: Intrauterine growth retardation, low foetal birth weight and infant mortality are some of the most important reproductive health problems affecting most developing countries. Khat chewing during pregnancy is on the increase among women of reproductive age(1) and questions have been raised on the potential effects of khat on foetal development. In an experiment to determine genotoxic potential of khat, a methanolic khat extract was tested on male germ cells using a lethal assay procedure in Swiss albino mice(23,28). The extract was administered following a regime of 500mg/kg orally once daily, for five days. The effects were studied during the different stages of spermatogenetic cycle, on the of pregnancy rates and post implantation losses. The results showed that khat reduced the percentage pregnancy rates and increased the mean post-implantation losses in the treated groups while there was no change in the controls which received the vehicle (saline) only(23).

The effects of khat alkaloid (+)norpseudoephedrine on utero-placental blood flow in guinea pig was also evaluated by Jansson and colleagues in 1987(21). These investigators found that (+)norpseudoephedrine causes vasoconstriction in the utero-placental vascular bed which may in turn impair foetal growth through reduction of placental blood flow(21). They also showed that in the pregnant pig, the pressure of the regional utero-placental blood increased by 25% and heart rate by 9% during (+)norpseudoephedrine infusions. Myoendometrial blood flow was reduced by 31% and placental vascular resistance increased by 56%(23). In a separate experiment to determine teratogenic potential of khat in rats, a methanolic khat extract was administered orally using different doses, to rats in their 6th to 15th day of gestation(29). It was found out that khat reduced the food efficiency index but had no effect on sex ratio(29). Administration of khat doses of 125mg/kg or higher was found to increase significantly the resorption and foetal wastage(29). Khat administration in utero also produced intrauterine growth retardation.

Examination of the external, visceral and skeletal regions of the foetuses of treated dams showed several types of malformations and variations in the treated animals(29). These embryonic and teratogenic properties were found to be dose related. Eriksson and co-workers found out that a khat-chewing mother produces less milk than non-users(26). In another study comparing pregnant khat chewers and non-chewers, it was observed that there was no difference in rates of stillbirth or congenital malformation(26). It was also shown that administration of khat to female pregnant guinea pigs resulted in the birth of smaller pups(21,22,24,25). This was attributable to decreased blood flow to the uterus(21). The concentration of pseudoephedrine in pregnant guinea pig urine was found to be directly related to the amount of khat extracts consumed(22). Khat chewing in the third trimester of pregnancy was also found to significantly reduce the maternal weight gain(10,24,25).

Effects 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 maybe the cause of sexual impotence(10). Most of the available scientific data available in the literature is derived from animal experiments. Our informal discussions and interviews with regular khat chewers in Kenya suggest that khat consumption may lower libido and sexual performance in men of reproductive age (Mwenda, personal communication).

Studies done by Islam *et al* in 1990 revealed that feeding male rats with khat resulted in significant effects on reproduction(18). These investigators demonstrated that male rats treated with the active constituent, cathinone had testicles, epidydimis and seminal vesicles that were smaller than controls, and had lower circulating testosterone levels(18). Microscopic examination of testicles from these animals showed degenerative changes in the leydig cells (that produce testosterone) and sertoli cells(18). Both enantiomers had deleterious effects on the reproductive system but (-) cathinone, the psycho-stimulant in khat was more toxic(18). In another study with male mice, methanolic extracts derived from khat produced a dose-dependent reduction in the fertility rates in the first week of mating(23,27). Khat extracts also induced post implantation loss during the first weeks of pregnancy, and showed a reversible pattern of dominant lethality(23,27).

Studies in our own laboratory on adult male olive baboons *(Papio anubis)* showed that oral administration of khat extracts significantly increases testosterone but down-regulates prolactin and cortisol levels in blood plasma compared to the basal levels before khat administration(30). In these studies, the animals were given sterile saline for one month and the levels of prolactin, testosterone and cortisol measured daily to obtain the basaline levels. The animals were then fed with khat extracts in saline and the levels of the same hormones monitored daily for two months. Khat administration was then stopped but the levels of hormones monitored for a further two months. The plasma testosterone level was found to be 14.1 ± 0.6 nmol/l, 19.1 ± 1.1 nmol/l and 23.3 ± 0.6 nmol/l in the animals before, during and after oral administration of crude khat extract respectively (Table 2).

Table 2

Concentration of testosterone, cortisol and prolactin before, during and after oral administration of crude khat extract

Hormones	Before khat	With khat	After khat
Testosterone	14.1± 0.6	19.1± 1.1	23.3 ± 0.6
Prolactin	87 ± 5.9	86.3 ± 3.9	64.6 ± 2.4
Cortisol	569 ± 45.3	364 ± 23.7	272 ± 10.8

Note: Values are means ± SE P< 0.05 was considered to be statistically significant

There was significant difference in prolactin concentrations before and after oral administration of crude khat extract. The concentration before and after khat administration was 87 ± 5.9 mIU/l and 64.6 ± 2.4 mIU/l respectively. During the period of khat intake, prolactin concentration was 86.3 ± 3.9 mIU/l. The concentrations of cortisol before and during oral administration of crude khat extract were 569 ± 45.3 nmol/l, and 364 ± 23.7 nmol/l respectively. The concentration was reduced to 272 ± 10.8 nmol/l after withdrawal of oral administration of crude khat extract. It was also observed that khat consumption lowered food appetite and a reduction in body weight.

There was no effect on the histology of the testis, epididymis, liver and pituitary gland of the treated baboons. There was a significant decrease ($p< 0.05$) in the body weight after oral administration of crude khat extract. The average body weights were 23.8 ± 0.06 kg and 23.6 ± 0.07 kg before and during khat administration respectively. The body weight of the animals after withdrawal of crude khat extract was 24.1 ± 0.04 kg. In some of the animals, the mean body weight dropped by as much as 10%. The body weight remained low during this time and an increase was observed from the 13th week after withdrawal of crude khat extract.

Consistent penile erection was observed at different times in the baboons during oral administration of crude khat extract and this recurred twice in the course of sample collection. Pupillary dilation was observed within 30 minutes of oral administration of crude khat extract. An increase in blood pressure (by 36%) was also observed during oral administration of crude khat extract. The mean blood pressure before, during and after khat administration was 93/62, 127/72 and 109/72 respectively. The results of these studies indicate that khat might affect male fertility and libido by interfering with circulating reproductive hormones.

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 and colleagues in 1995 used a group of 65 khat addicts and a control group of 50 non-users(19). In a similar experiment, Hakim (20) examined 214 male patients with history of infertility who, with the exception of 31 people (control group), used khat regularly(20). 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(19,20). El-shoura *et al.* also showed that the sperm motility index decreased(19) and Hakim(20) established that the above effects were more pronounced when khat was taken in conjunction with coffee, alcohol and smoking. Khat consumption was found to modify masculine pattern behaviour(20).

GENERAL PHYSIOLOGICAL EFFECTS OF KHAT CONSUMPTION

Khat appears to have specific effects on reproductive health as well as general physiological effects and behavioral patterns. Some of the instant physiological effects of Cathinone/khat intake are increased blood pressure and respiration, loquacity, thirst after chewing and a tendency of uncontrollable laughter(8,9). The psychological effects of Cathinone/ khat consumption include euphoria, hallucinations, feeling of paranoia and failure of mental clarity. It also causes psychological and physical dependence(9). Excess production of dopamine in the nervous system (stimulated by cathinone) in turn causes hallucinations, bizarre thoughts, schizophrenia, lethargy, mild depression, nightmares and alertness(7,8).

Khat consumption has been implicated in a wide variety of diseases and disorders in humans. It has been suggested that khat consumption may lead to oral cancer(31,32). The effect is enhanced when khat is taken with alcohol and tobacco(32). Research has shown that regular khat-chewing airline flight attendants had less perpetual-visual memory and a reduction in decision-making speed than occasional khat-chewing and non khat-chewing flight attendants(33). Khat chewing was found out to cause a delay in gastric emptying(34). The constipating and antispasmodic effects of khat were found to be similar to that caused by D-amphetamine(35). Nasher *et al.* suggested that khat chewing might have a side effect on the urinary system in reducing the maximum and average urine flow rate(36). It has been reported that there are toxic fungi associated with khat leaves that may be harmful to the khat consumers(37). Attef and colleagues also established that khat consumption might affect the bio-availability of therapeutic drugs that may subsequently be taken after khat(38). The effect is more pronounced when the drug is taken almost two hours after consumption of khat. Yousef also showed that khat consumption may cause psychosis(39). Additionally, a case report in Ethiopia showed heavy khat chewing caused episodic psychosis(40). On the other hand, khat was found to act as a pain reliever, similar to amphetamine, although the mode of action was different(41).

CONCLUSION

Detailed studies on the effects of khat on reproduction are lacking. However, the limited data available show that khat may have drastic negative effects on reproductive health. It is possible that khat use affects both male and female reproductive systems. The mechanisms of action has not been elucidated. Although rodent studies give useful insights to elucidate the mechanism of action of khat/cathinone, there are major differences in the physiology of rodents and humans that place a limitation in the interpretation of data from these experimental animals. Non-human primates are phylogenetically closely related to humans and would form useful models for further studies. The results from our studies on the effect of khat in male baboons strongly suggest this may be an appropriate model to study the medical implications on the use of khat. Further studies are under way to determine the mechanism by which khat affects reproductive functions in baboons.

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