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Mutagenic and Carcinogenic Activity of Khat (*Catha edulis* Forsk) Component

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Khat, *Catha edulis* Forsk, (family Celastraceae), is a shrub or small tree that grows wild or is cultivated in certain regions of Africa and Southern Arabia. Customarily, chewing the leaves and young branches, provides rapid stimulation and euphoria. At least 60% of male and 35% of women chew khat daily. The mutagenic and carcinogenic activities of khat have been poorly examined. The most active components are cathinone, cathine and norephedrine, which are phenylalkylamines type. Apart from the three phenylalkylamines, the khat leaves also contain more than 40 alkaloids, glycosides, tannins, sterols/terpenoids, volatile bases, resins and sugars. This article reviews epidemiological and experimental studies on the mutagenicity, carcinogenicity and teratogenic effects of khat extract and cathinone. The mutagenic, teratogenic, congenital abnormalities, clastogenic activity against the khat extracts and cathinone has been demonstrated in mammalian cell systems and *in vivo* animal tests.

Key words: Khat (*Catha edulis*), mutagenicity, carcinogenic activity

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Introduction

The cultivation and consumption of khat (*Catha edulis*) has been happened for generations in certain areas of the Arabian Peninsula (Yemen) as well as in East Africa (Kenya, Ethiopia and Somalia). These regions have become the main producers and distributing centers of khat (Table 1). Users usually chew the tender and fresh part of the plant. Khat leaves are chewed, the juice is swallowed and the wad of chewed leaves is formed in the cheek and kept there for hours (Soufi *et al.*, 1989). Khat, is classified as a Schedule IV substance by the Drug Enforcement Administration (DEA), of the US Department of Justice (OASAS, 1993). It has a low potential for abuse and has a current accepted usage in treatment as a substitute for amphetamine (Parker, 1999). However, the most active component of khat is cathinone. This ingredient is present only in fresh-picked leaves, (within 48 hours of harvest) and it has recently been classified as a Schedule I narcotic, the most restrictive category.

Khat chewing has been exclusively reported as a male habit, however it has become increasingly popular among women. At least 60% of men and 35% of women chew khat daily (Kennedy *et al.*, 1980. Khat has also been reported to be chewed during pregnancy and lactation (Islam *et al.*, 1991). The investigation on the effect of khat on pregnancy in humans revealed a high rate of prenatal child mortality (Lugman and Donowaski, 1976). The crude extract of khat has been shown to produce anti-implantation, abortifacient activity in laboratory animals (Tariq *et al.*, 1987).

While the side effects of khat and other complications are not clearly understood, the medical problems appear most evident when it is used intensively by poor people, who spend more of their limited resources on purchasing the drug (Halback, 1979)

Effects of khat chewing

Main Effects: Effects of khat chewing sought after by the user, include euphoria (stimulates brain and spinal cord through synapses), diminished hunger (used for suppressing appetite), decreased need for sleep, enhancement and facilitation of associations with others and verbal fluidity (Kalix, 1992). The similarity to amphetamine use also explains the occasional after-effects: apathy, anorexia and depression. Advocates of khat use claim that it eases symptoms of diabetes, asthma, and stomach/intestinal tract disorders (Parker, 1999). Anti-gastric ulcer and anti-inflammatory properties of khat have been reported by Al-Meshal *et al.* (1983; 1985).

Psychological, Social and economic effects: No physical dependence or tolerance has been found, though mild withdrawal reactions have been reported among heavy users. A moderate, but often persistent, psychic dependence has been observed. Social and economic damage has been cited as an unfavorable consequence of the khat chewing habit on communities. The loss of working time and particularly the high proportion of family income devoted to buying khat has been caused emotional stress and economic constraints among khat users (Kennedy *et al.*, 1980).

Side effects: The side effects of the use of khat consist of palpitations, sweating, thirst, drowsiness, constipation and dyspepsia. It interferes with the absorption of iron and other minerals when taken internally (El-Shoura *et al.*, 1995) and heavy khat users become talkative, then depressed and apathetic and its heavy use has been reported to cause loss of appetite, periodontal disease, mucosal lesions and a number of irritative disorders of the upper gastro-intestinal tract (El-Shoura *et al.*, 1995). It is also a cause of stomatitis, gastritis, gastric ulcers and constipation accompanied by hemorrhoids (Kalix, 1984)

Pharmacology of Khat: The pharmacology of khat has been reviewed in detail by HalbacK (1979), and subsequently World health organization (WHO) advisory group, and by Kalix and Brendon (1985). For many years, the active ingredient was thought to be nor-pseudoephedrine, which had been isolated in 1901 and subsequently identified in 1930 by Wolfs. The main pharmacologically active elements of the leaves are the three phenylalkylamines known as cathinone, cathine and norephedrine (Fig. 1). Cathinone is structurally, chemically and pharmacologically similar to d-amphetamine. Cathine is a milder form of cathinone and is considered to be a form of ephedrine (Parker, 1999). The pharmacological studies on these three new compounds leads to the conclusion that the geographical origin, variations in cultivation and timing of the harvest, has remarkable effects on the phenylalkylamines content (Geisshusler and Brenneisen, 1987). The substance has been identified as (-)-a-aminopropiophenone, which had not previously been found in nature and has been named cathinone. Subsequent work identified the labile active compound, cathinone, which is present in fresh leaves but absent from the samples over five days old. This finding corresponds with the observation by khat chewers that the leaves lose their potency after 4 days. Since khat leaves and shoots are consumed fresh, the harvested drug has to be transported quickly to the market, to avoid drying and wilting, which results in a decrease of cathinone content. Khat bundles are usually wrapped in banana leaves, damp papers or plastics. These contents are also affected by the age of the leaves.

A recent analysis of 22 khat samples of different origins showed that, on average, 100g of fresh khat contained 36mg cathinone, 120mg cathine and 8mg norephedrine, although the concentration of these constituents varies within wide limits. It has been found that cathinone is an intermediate in the bio synthesis of cathine and that this intermediate accumulates in young, but not in adult leaves. Similarly, cathinone is transformed into cathine during the wilting of the leaves (Kalix, 1992).

In addition to three phenylalkylamines, the khat leaves also contain more than 40 alkaloids, glycosides, tannins, sterols/terpenoids, volatile bases, resins and sugars (Elmi, 1983). Among the lipid fraction of khat which is rich in fatty acids, the identified esters, hexanoate, heptanoate and octanoate are most prominent. The presence of five flavonoids, together with tritepenes, tannins and alkaloids in powdered khat has also been phytochemically screened (Al-Meshal *et al.*, 1983 and 1991). Khat leaves contain small amounts of ethereal oil, sterols and tritepenes, rich in flavonoids, and have high tannin content (Elmi, 1993).

In vivo and *in vitro* studies revealed that norpseudoephedrine has only 10% of the central nervous system (CNS) effect of cathinone (Kalix, 1980). Together with diasteriomer nor ephedrine, this compound occurs mainly in older plants and is also formed by reduction of cathinone during drying and storage (Brenneisen and Geisshusler, 1985). In addition, a number of alkaloids with a similar structure have been isolated. These are now known as cathedulins. Tannins are also found in varying quantities and tannins thicken the mucosa of the oropharynx and oesophagus (Darke, 1988) and may be carcinogenic (Craddock, 1993).

Toxic effects of khat: In view of the complex nature of khat extract, it is difficult to establish the exact nature of components which is responsible for its teratogenic effects. Cathinone, has been reported to mimic noradrenergic transmission which accounts for the sympathomimetic effects induced by khat chewing (Kalix, 1990). Hyperstimulation of adrenergic receptors is known to increase 3, 5-adenosine monophosphate (cAMP), which in turn causes harmful effects

Table 1: The khatamine content in leaves of Catha edulis of different quality, type and origin (Ethiopia, Kenya Yemen and Madagascar.

			Khatamine content % of total content a,b		
Market	Quality	Type	CA	NPE	NE
Ethiopia	First	Red	1.731 (19.9)	6.495 (74.5)	0.44
Ethiopia	First	White	0.654 (8.0)	7.319 (88.9)	0.24
Ethiopia	Second	Red	0.556 (12.5)	3.656 (82.2)	0.23
Kenya	First	Red	3.324 (58.8)	1.477 (26.1)	0.29
Kenya	First	Red	1.696 (38.0)	1.576 (35.3)	0.841
Yemen	First	White	0.343 (11.3)	2.505 (82.5)	0.18
Yemen	Second	White	0.086 (5.1)	1.516 (88.8)	0.10
Madagascar	?	White	0.119 (66.1)	0.054 (30.0)	0.00

a calculated per dry weight
b CA, (-) cathinone (2). For formulas see Fig 1; NPE, (+) - norpseudoephedrine (6); NE, (-) - norephedrine (5)
Values in parenthesis represent % per dry weight of khatamine content.

on DNA synthesis (Gilbert and Bruyere, 1977).
Quercetine, a flavonoidal fraction of khat (Elmi, 1993), has been shown to induce gene mutation and chromosomal abnormalities in mammalian and human cells (Yoshido and Sugimura, 1980). Other flavonoidal compounds like kaempferol and galangin, have also been shown to possess significant mutagenic potential. It is therefore, appears reasonable to suggest that alkaloidal and/or flavonoidal components of khat may be contributory to its teratogenic effects (Islam and Al-Shabanah, 1994). It is worth noting that the quantitative risk for toxic effects with khat is less than with the better known amphetamines, because the mode of using leaves limits the amount that can be ingested and absorbed (Eddy *et al.*, 1965).
Khat use has been associated with health problems, including oral cancer, dental and oral problems, gastrointestinal disturbances, liver diseases and cardiovascular effects (Kirkorian, 1983) and these associations are not often supported by epidemiological studies. A high frequency of khat chewing and water pipe smoking was found for both men and women and for a group of tumors of gastro-oesophageal junction or cardia. Numbers were insufficient to identify independent effects of each factor individually and its use may also be associated with reaction that is similar to amphetamine psychosis (Critchlow and Seifert, 1987).

Epidemiological Studies: Some of the epidemiological studies give an indication of a correlation between the khat chewing habit and cancer, especially oral cancer.

Khat and Oral Cancer: Oral cancer in the Asir region of Saudi Arabia have been observed to occur mostly among patients who have been long-term khat users (Soufi *et al.*, 1991). In a survey that reviewed cancers for the past two years, there were 28 head and neck cancer patients, 10 of whom presented with a history of having chewed of khat. One of these was a case of metastatic cervical lymph node and unknown primary, one was a parotid tumor, and the remaining eight presented with oral cancers. All were non-smoking khat chewers and all of them had used it over a period of 25 years or longer (Soufi *et al.*, 1991). This review of oral cancers presented over a two years show a strong circumstantial evidence linking the long-term use of khat with increased oral malignancies (Soufi *et al.*, 1991; Macigo *et al.*, 1995)

Khat and Leukoplakia: In Kenya, a case study was conducted to determine the significance of tobacco, alcohol and khat chewing habits in the development of oral leukoplakia among Kenyans aged ranged 15 years and over (Table 2). In a house to house survey, 85 cases and 141 controls matched for sex, age, and cluster origin was identified and compared for these risk factors (Macigo *et al.*, 1995). Smoking unprocessed tobacco (kiraiku) with a relative risk (RR) of 10.0 at (95% confidence interval (CI) = 2.9-43.4), and smoking cigarettes (RR = 8.4; 95% CI = 4.1-17.4) were the most significant factors associated with oral leukoplakia and therefore incriminated tobacco as the most likely principal etiologic factors. In the case group, 18 individuals (14 females and 4 males) had never smoked cigarettes. In another study by Macigo *et al.* (1995) the association of oral leukoplakia and current habit of smoking cigarettes with and without the history of smoking kiraiku (Table 3), the RR associated with smoking cigarettes alone was 4.4 (95% CI = 1.9-10.8). Current habit of smoking kiraiku was increased the RR in current smokers of cigarettes by 3.4 times (RR = 15.2). Previous history of smoking kiraiku was also associated with increased relative risk in cigarette smokers (RR = 14.1). The RR of smoking kiraiku, independent of cigarette smoking, could not be evaluated, because all current smokers of kiraiku in the case group were also current smokers of cigarettes.
The association of oral leukoplakia with khat, chillies, sugarcane and herbal medicines (Table 4), showed no statistically significant association. Khat chewers for instant showed (RR = 1.8), 95%CI = 0.7-5.0). In this study, it was not possible to disentangle the influence of khat from that of smoking tobacco. In addition, the relatively low frequency of khat chewing in the study suggested possible variations in the frequency of this habit among the consumers. This could be attributed to the banning of cultivation, sale and chewing of khat by local administration in the study area (Macigo, 1990). Therefore, it is likely that some individuals may have withheld information concerning this habit.
Other risk habits (Table 5) were explored since tobacco smoking could not explain the occurrence of oral leukoplakia in the 18 cases that had never smoked tobacco. The most frequent habits were consumption of chillies, soup with herbal medicines and chewing of sugar cane. On the other hand, the distribution of other risk habits, that were considered between cases and controls, could not unequivocally explain the occurrence of oral leukoplakia in these cases. The independence of alcohol and khat as risk factors and the possibility of positive interaction with smoking tobacco need further investigation. From a preventive point of view, the prevalence of oral leukoplakia in this case study within the khat, cigarette and alcohol consumers indicates it public health significance in the study community and therefore, should be an issue of consideration in primary health care activities and oropharyngeal examination of members of this community.

Khat and Verrucous Carcinoma: The Miraa (khat) chewing is a popular habit among several ethnic communities in Kenya, especially those of Somali origin, who have been found to show a considerably higher rate of oral cancer. However, a report of two cases of *Verrucous carcinoma*, which is a rare and distinct pathological and clinical variant of well

Table 2: Association of oral leukoplakia with tobacco habits.

Habit	Cases	Control	RR	95% CI.
Cigarettes				
Never smoked	18	78	1.0	-
Current smokers	62	32	8.4*	4.1-17.4
Kiraiku:				
Never smoked	42	120	1.0	-
Current smokers	14	4	10.0*	2.9-43.4
Pipe smoking:				
Never smoked	82	135	1.0	-
Ever smoked	3	3	1.7	0.2-12.6
Cigars:				
Never smoked	84	137	1.0	-
Ever smoked	1	1	1.6	0-128.9

RR= relative risk *P<0.001, Source: Macigo *et al.*, 1995

Table 3: Association of oral leukoplakia and current habit of smoking cigarettes with and without the history of smoking kiraiku

Habit	Cases	Control	RR	95% CI.
Never Smoked either Kiraiku or cigarettes	18	78	Reference Group	-
Currently smokes Cigarettes but never Smoked kiraiku	22	21	4.4*	1.9-10.8
Currently smokes Cigarettes and previously Smoked kiraiku	26	8	14.1*	5.0-40.8
Currently smokes both Cigarettes and kiraiku	14	4	15.2*	4.0-68.6

RR= relative risk *P<0.001

Table 4: Association of oral leukoplakia with khat, chillis, sugarcan and herbal medicines

Independent variables	Cases	Controls	RR	95% CI
Khat:				
Never chewed	66	119	1.0	--
Current chewers	10	10	1.8	0.7-5.0
Sugarcan chewing:				
Currently don't chew	30	32	1.0	--
Currently chewer	55	109	0.5	0.3-1.0
Chilies:				
Never consumed	32	72	1.0	--
Ever consumed	53	69	1.7	0.9-3.1
Soup with herbal **medicines:**				
Currently don't consume	41	53	1.0	--
Current consume	44	88	0.7	0.4-1.2

RR= relative risk

Table 5: Distribution of other suspected risk habits among cases and controls that never smoked tobacco.

	Cases			
		% of Never		
Habits	Number	Smokers	Number	Controls
Oral use of smokers Tobacco	1	5.6	4	5.1
Khat chewing	0	0	3	3.9
Commercial beer	5	27.8	27	34.6
Traditional beer	6	33.3	18	23.1
Wine, spirits & change	2	11.1	7	9.0
Chillies	11	61.1	39	50.0
Sugar cane chewing	9	50.0	56	71.8
Soup with herbal medicines	10	55.6	44	65.4

differentiated squamous cell carcinoma, two case reports of histologically proven oral *Verrucous carcinoma* were presented. One case presented with a history of tobacco chewing, snuff taking and miraa chewing. While the relationship between tobacco chewing, snuff dipping and verrucous carcinoma has been investigated and described, the role played by miraa chewing is still unknown and thus the need for further investigation (Awange and Oyango, 1993).

Khat on Oesophageal and Gastric Carcinoma: Gunaid and Sumairi (1995), investigated the prevalence of oesophageal and gastric carcinoma in the Republic of Yemen with respect to cigarette, water pipe smoking and the khat chewing habit (Table 6). A preponderance of women with carcinoma of the mild-oesophageal was noted, and it was recorded previously only in areas of high prevalence. Unlike the western population, smoking and alcohol consumption were not significant risk factors. A high frequency of khat chewing and water pipe smoking was found for both women and men for a group with tumor of the gastro-oseophageal junction or cardia ($x=2.646$, $p>0.05$). Numbers were insufficient to identify independent effects of each factor individually. Dietary habits alone were insufficient to account for the excess of affected patients.

Khat effects on Animal and Cells Line: Most of the animal studies support the idea of the toxicity of khat. This evidence is supported by the summary of some studies below.

Effect of cathinone compared to amphetamine: Tariq *et al.* (1987) showed that cathinone has clastogenic potential in cells and *in vivo*, the active principle from cathinone and amphetamine have a similar chemical structure and pharmacological activity on the somatic cells of mice. Cathinone and amphetamine produced marked clastogenic activity and affects the cell proliferation in the bone marrow of mice. They also found that cathinone and amphetamine induced a significant increase in the frequency of micronucleated polychromatic erythrocytes at higher doses. Earlier observation by Qureshi and Tariq (1988) on the clastogenic and mitodepressive activity of cathinone on the meristematic region of *Allium cepa,* which indicates that cathinone may be responsible for the mutagenic effect of khat reported by others.

Effect of khat on lymphoid tissue: Al-Meshal *et al.* (1991) demonstrated that treatment of mice with khat resulted in chronic toxicity in mice. Three groups of mice were treated with aqueous solution of khat extract at a dose rate of 50, 100 and 200mg kg^{-1} of body weight daily by oral incubation route for 6 weeks. The result indicated a dose-dependent decrease in body weight, an increase of mortality and induction of site specific body and eye lesions. The histopathological examination of the lesions revealed a reactive hyperplasia and necrosis in the lymphoid tissues. The necrotic areas in the subcutaneous tissues showed the presence of numerous polymorphs.

Effects of chloroform extract on macromolecule biosynthesis: The chloroform ($CHCl_3$) extract of khat leaves were used to study the cytotoxic activity on human epidermoid carcinoma (KB, 1BR.3, and XP2B1) cells. Log phase cell survival curves showed an LD_{50} of 40ng ml^{-1} for KB cells. 1BR. 3 and XP3BI cells were biphasic in their response to the extract during log phase, with an LD_{50} of 20 and 75ng ml^{-1} respectively, while the stationary phase cells were unaffected by the extract. The Radio labeled thymidine and uridine were used to investigate the DNA and RNA synthesis inhibition, by measuring the amount of extract that inhibits the synthesis to 50% of the untreated control cells. The results showed that the DNA synthesis was inhibited by 45, 60, and 200ng ml^{-1} and RNA synthesis by 24, 17, and 58ng ml^{-1} in 1BR.3, XP2B1 and KB cells, respectively. Protein synthesis was inhibited to 15-20% of untreated control cells by a dose of 40ng ml^{-1} in all the cells studied. This study concludes that the main cause of cytotoxicity of khat extract may be the inhibition of *de novo* RNA synthesis. Al-Ahdal *et al.* (1988), suggested that this

Table 6: Proportions of patients with gastric and oesophageal cancers who chewed khat/or smoked the water-pipe (Mada'a) and cigarettes.

		Males					Females					Both sexes			
		Khat or/ + Cigarette					Khat or/ + Cigarette					Khat or + Cigarette			
Site		No	%	No	%	Total	No	%	No	%	Total	No	%	No	%
Stomach (excluding cardia)	42	22	52.4	6	14.3	15	2	13.3	0	--	57	24	42.1	6	10.5
Cardia and gastro-esophagal junction	20	15	72.0	4	20.0	3	0	--	0	--	23	15	65.2	8	7.5
Oesophagus	52	34	65.4	7	13.5	51	17	33.3	1	1	103	51	49.5	8	7.8
Total	114	71	62.3	17	14.9	69	19	27.5	1	1	183	90	49.2	18	9.8
x^2(d.f. = 2)		2.348, p>0.05										2.646, p>0.05			

Source: Gunaid and Sumairi, 1995)

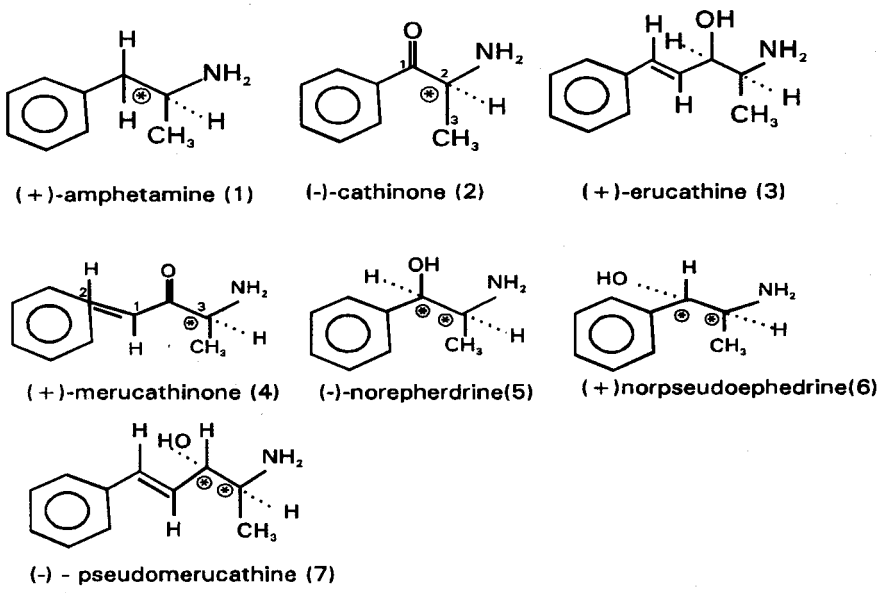

Fig. 1: Structure of amphetamine (1) (dexamphetamine) and of the khathamines cathinone [∝-aminopropiophenone] (2), erucathine (3), merucathinone (4), norepherdrine(5) cathine [norepseudophedrine or phenylpropanolamine] (6), psedomerucathine 7 (Tariq *et al.*, 1987 Geisshusler and Brenneisen, 1987)

inhibition affects all cells used in this study and that KB cells demonstrate a higher resistance to the toxic component.

Effect of Cathinone on Germ Line Cells: Qureshi and Tariq (1988) found that the effect of cathinone on fertility and sterility could be evaluated in the germ cells of male albino mice using a dominant lethal test. They used an aqueous solution of cathinone administrated orally at a dose of 5, 20, or 40mg kg^{-1} body wt, respectively to different group of mice for a period of six weeks. The result of this study showed that treatment of male mice over a period of six weeks produced a dose –dependent reduction in fertility with total sterility at a dose of 40mg kg^{-1} body wt. Cathinone also, show a dose-dependent post-implantation loss during the first week following treatment, and no dominant lethality was detected during the second week of mating. Cathinone accelerated catecholamine release may be responsible for the toxic effect of this compound (Kalix 1980). The cytotoxic effects of caffeine and ephedrine have been associated with stimulation of sympathomimetic system, hyper stimulation of β- receptors is known to increase the 3,5-adenosine monophosphate of (cAMP) which in turn can cause impairment of DNA synthesis, repair and integrity (Thayer and Palmer, 1975 and Kalix and Brendon, 1985). A similar study concluded that cathinone content in khat might be partially or responsible for the reproductive toxicity in khat chewers.
It has been found that cathinone produced a dose-dependent decrease in food consumption and suppressed the gain in body weight (Kalix, 1980). There has been a significant decrease in sperm count and motility and increase in the number of abnormal sperm in cathinone treated animals. Histopathological examination of testes revealed that degeneration of interstitial tissue, cellular infiltration and atrophy of sertoli and leydig's cells in cathinone treated animals. Cathinone also produce a significant decrease in plasma testosterone levels of the rats. Although both enantiomers of cathinone produced deleterious effects on male reproductive system, (-)-cathinone was found to be more toxic than amphetamine (Islam *et al.*, 1991).

Effects of khat on semen ultrastructure: El-Shoura *et al.* (1995) investigated the effects of khat usage on semen parameters and sperm ultrastructure. They reported for the first time, the deleterious effects of khat use on semen parameters in general and sperm morphology in particular for all users, especially those who have consumed khat for longer

periods. The semen parameters and sperm ultrastructural morphology has been observed in semen samples from two groups of Yemeni subjects. The first exposed group comprised 65 khat users, while the second control group included 50 non-khat using subjects. The mean age was 39.94 ±13.85 and 35.72 ± 1.35 years in the exposed and control group respectively. The duration of khat use among the subjects was 25.34 ±12.96 years (range 6.00-48.00). Statistically, significant difference was detected between the semen parameters of the two groups. Such parameters, including semen volume, sperm count, sperm motility, motility index and percentage of normal spermatozoa, were lower among users. Significant negative correlation was also found between the duration of khat consumption and all semen parameters (r ranged from -0.30 to -0.73).

At the transmission electron microscopy level, a counting system was incorporated to compare the number of normal spermatozoa with deformed and dead spermatozoa in ultra thin plastic section (El-Shoura *et al.*, 1995). The total mean percentage of deformed spermatozoa was approximately 65%. Different patterns of sperm deformation were demonstrated, including both the head and flagella. They showed aberrated nuclei with immature nuclear chromatic and polymorphic intranuclear inclusion; these were associated with acrosomal defects. The deformed flagella demonstrated numeric aberration of the axonemal 9+2 configuration and structural defects of their associated elements. Persistent cytoplasmic droplets were observed frequently.

In concluding, khat chewing is associated with toxicity, mutagenity and teratogenicity. The cytotoxic and genotoxic effect of khat extract on a human T lymphoblastoid cell line and on freshly isolated primary buccal cells is still a focal point for investigation. The research is in progress and the result could provide a vital toxicological information necessary especially in those regions where khat is chewed or regularly consumed in the different traditional methods.

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