Review

Khat (*Catha edulis*): health aspects of khat chewing

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الآثار الصحية لمضغ أوراق القات

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الخلاصة: هناك نسبة مرتفعة من السكان البالغين في اليمن ممن يمضغون أوراق نبات القات بصورة يومية، بالنظر إلى تأثيره المنبِّه الخفيف. ويُعتقدُ أن الكاثينون هي المادة الفعَّالة الأساسية الموجودة في أوراق القات الطازجة، وهي مشابهة، من حيث التركيب البنيوي والتأثير الدوائي للأمفيتامين. وتنتشر عادةُ مضغ أوراق القات انتشاراً واسعاً في اليمن، حيث تُعَدُّ من الموروثات الاجتماعية والثقافية المتأصِّلة، مما يجعلها تمثِّل مشكلة صحية عمومية. ويتمثَّل الغرض من هذا الاستعراض للمواد المنشورة في هذا المجال، في تفحُّص الدراسات التي أُجريت عن القات، ولاسيَّما الدراسات التي أُجريت على البشر، مع الإشارة بوجه خاص إلى تأثير ذلك على الجهاز العصبي المركزي، والجهاز القلبي الوعائي، والجهاز الهضمي، والجهاز التناسلي والبولي، وأنسجة الفم والأسنان، وأمراض السكَّري والسرطان.

ABSTRACT *Catha edulis* Forsk leaves (khat) are chewed daily by a high proportion of the adult population in Yemen for the mild stimulant effect. Cathinone is believed to be the main active ingredient in fresh khat leaves and is structurally related and pharmacologically similar to amphetamine. The habit of khat chewing is widespread with a deep-rooted sociocultural tradition in Yemen and as such poses a public health problem. The objective of this literature review was to examine studies on khat, particularly human studies, with special reference to its effect on the central nervous system, cardiovascular, digestive and genitourinary systems, oral–dental tissues, diabetes mellitus and cancer.

Le khat (*Catha edulis*) : effets de la mastication du khat sur la santé

RÉSUMÉ Les feuilles de *Catha edulis* Forskal, ou khat, sont mastiquées quotidiennement par une forte proportion de la population yéménite pour leur effet légèrement stimulant. La cathinone, structurellement apparentée à l'amphétamine et possédant des propriétés pharmacologiques comparables, semble être la principale substance active contenue dans les feuilles de khat fraîches. La pratique masticatoire du khat est très répandue au Yémen, où elle constitue une tradition socioculturelle profondément enracinée et, en tant que telle, soulève un problème de santé publique. La présente synthèse de la littérature a pour objectif l'analyse des études consacrées au khat, notamment à sa consommation humaine, avec une attention toute particulière sur son action sur le système nerveux central, les appareils cardiovasculaire, digestif et urogénital, les tissus bucco-dentaires, le diabète sucré et le cancer.

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Introduction

The khat plant *(Catha edulis* Forsk*)* is a tree of the family Celastraceae that is frequently cultivated in certain areas of East Africa and the Arabian Peninsula. The leaves of the khat plant contain alkaloids structurally related to amphetamine. They are chewed daily by a high proportion of the adult population in Yemen for the pleasant mild stimulant effect.

Khat appears to have been used first as a drink prepared from dry leaves, but its effect is weak compared with coffee [*1*]. It was found later that drying the leaves results in loss of some active constituents [*2*] and therefore the habit of chewing the green leaves was adopted. For many hundreds of years the custom of chewing khat leaves has been practised for the resulting central stimulant effects [*3*]. In Yemen, the habit is widespread with a deep-rooted sociocultural tradition. The pleasurable central stimulant properties of khat are commonly believed to improve work capacity, and are used on journeys and by students preparing for examinations and to counteract fatigue. In recent years, because of improved air transport, the consumption of fresh khat leaves has expanded considerably, even to communities in Europe.

Early clinical observation suggested that khat had amphetamine-like properties [*4*]. Subsequent chemical analysis confirmed that the fresh leaves contain a number of compounds, including phenylalkylamine compounds (alkaloids) such as norpseudoephedrine (cathine) and alpha aminopropiophenone (cathinone), the latter being structurally related [*5*] and pharmacologically similar to amphetamine [*6,7*]. Khat leaves also contain considerable amounts of tannins (7%–14% in dried material), vitamins, minerals and flavonoids [*4,8*]. Cathinone is currently believed to be the main active ingredient in fresh khat leaves [*7*].

Supporters of khat chewing claim that it is useful in diabetic patients because it lowers blood glucose, it acts as a remedy for asthma, it eases symptoms of intestinal tract disorders [*9*] and maintains social contact as a socializing herb [*10*]. Opponents claim that khat damages health and affects many aspects of life with its adverse social, economic and medical consequences. In Yemen, because of its widespread use, it has become a problem of grave national concern.

The objective of this review of the literature was to examine studies on khat, particularly human studies, with special reference to its effects on the body systems and its relationship with common diseases.

Khat and the central nervous system

The effect that accounts for the popularity of khat is its central nervous system stimulation, believed to be induced by cathinone, an active ingredient of khat leaves [*7*]. Cathinone has a more rapid and intense action compared with cathine due to its higher lipid solubility which facilitates access into the central nervous system.

Several studies have shown that the psychostimulant effects induced by chewing khat leaves include a moderate degree of euphoria and mild excitement resulting in promotion of social interaction and loquacity [*8,11,12*]. While attaining a state of subjective well-being, the chewers feel an increased alertness and energy together with enhanced depth of perception [*7,13*]. These effects were found to be maximum between 1.5–3.5 hours after starting to chew [*14*] and they were progressively replaced by mild dysphoria [*14*], anxiety, reactive

depression [*15*], insomnia [*4,16,17*] and anorexia [*17,18*].

These psychic effects of khat chewing recall those of amphetamine [*19*], but a major role of environmental factors in the expression of khat effects has also been suggested [*14*]. It has been proposed that the differences in the effect of khat and amphetamine are quantitative rather than qualitative [*20,21*]. It has been also reported that the khat-induced behavioural syndrome can resemble hypomania, as it may include hyperactivity and logorrhoea [*4*].

In recent years khat-induced psychosis has become more common in Europe [*22*]. Khat may cause a functional psychosis following consumption of exceptionally potent material, when taken in excess or in a predisposed individual [*4,23,24*]. In the literature reviewed, a number of reports on psychiatric disorders secondary to khat chewing with features of mania-like psychosis [*25*], schizophreniform psychosis [*26*], paranoid psychosis [*27*] or symptoms of acute schizophrenia-like psychosis have been documented [*11,26*]. Moreover, a number of chronic khat chewers experienced persistent hypnagogic hallucinations [*13*]. In one case report from the United Kingdom, khat appeared to induce full-blown paranoid psychosis with the added complication of a suicide attempt [*24*]. In Kenya, grossly excessive chewing led to psychotic states, which were paranoid in type and transitory in nature [*28*]. However, when khat is chewed in moderate quantities, there was no increase in psychiatric morbidity [*28*].

Preliminary data on 65 psychotic male patients admitted for psychiatric care in Sana'a because of symptoms uncontrolled by treatment were analysed [*29*]. They indicated that khat chewing in psychotic patients was likely to be associated with disturbance of mood and behaviour, aggravation of delusional symptoms and diminished response to antipsychotic therapy. Previous similar studies have shown that failure to abstain from khat use might prolong a psychotic episode, even during treatment with psychiatric medication [*11,24–28,30*].

Recently, Alem and Shibre considered khat as a substance of abuse and noted that chewing had the potential to complicate psychiatric conditions and forensic events [*30*].

In comparison with amphetamine, khat is much less likely to cause tolerance [*31*]. In particular, the stimulant central nervous system effects of khat do not seem subject to the development of tolerance [*4*], but some degree of tolerance to insomnia [*3*] and anorexia [*32*] has been observed in most chronic khat chewers.

The issue of dependence on khat has been reviewed by a World Health Organization (WHO) Expert Group on drug dependence, which concluded that khat consumption may induce a persistent psychic dependence rather than physical dependence [*22*] although a certain degree of psychological dependence can occur [*33*]. However, the psychological withdrawal symptoms after prolonged khat use seem to be limited to lethargy, mild depression, slight trembling and recurrent bad dreams [*4,31*]. The lack of physical symptoms of withdrawal suggest that only rebound phenomena rather than a specific abstinence syndrome occurs [*3,34*]. However, the WHO Expert Committee on Drug Dependence recently subjected khat to the preliminary review of psychoactive substances. The Committee reported that khat is believed to be dependence-producing and recommended that there was sufficient information on it to justify a critical review (a fully documented review) at a future meeting [*35*].

Khat use is often accompanied by the use of other substances. Simultaneous ciga-

rette smoking is a common habit that might influence khat-induced symptoms [*4*]. Khat-induced insomnia is frequent and khat users try to overcome this with sedatives or alcohol [*12*]. A report from Ethiopia confirmed the simultaneous use of cigarettes, alcohol, gasoline inhalation and glue sniffing with khat among university students, a pattern similar to that reported for substance abuse in other countries [*36*].

Khat and the cardiovascular system

Recent work on healthy Yemeni adult volunteers provided evidence that khat chewing induced a significant rise of arterial systolic and diastolic blood pressure and pulse rate in comparison with the baseline values [*37*]. The peak effect on the arterial blood pressure and pulse rate was reached 3 hours after starting to chew, followed by a decline 1 hour after spitting the leaves out. These changes run parallel with changes in plasma cathinone levels during and after khat chewing [*38*]. Similar blood pressure changes have also been observed in smaller numbers of subjects when pure cathinone in gelatine capsules was taken orally [*39*] or when khat leaves were chewed [*40*]. These observations support the suggestion that cathinone is the constituent that is mainly responsible for the increase in arterial blood pressure and pulse rate during khat chewing. A possible mechanism is the release of catecholamines from presynaptic storage sites.

To gain further insight into the pharmacological effects of khat chewing, a randomized controlled clinical trial of α_1 and selective β_1 adrenoceptor blockade was conducted on adult Yemeni volunteers [*41*]. The results indicate that selective β_1 adrenoceptor blockade with atenolol prevented the elevation of systolic blood pressure and increase in pulse rate suggesting these effects are mediated by the stimulant effect of cathinone in khat on β_1 adrenoceptors in the heart. By contrast the intake of indoramin, an α_1 adrenoceptor blocker, or placebo premedication failed to antagonize the effects of khat on arterial blood pressure or pulse rate.

It can be concluded from the previous studies that khat-induced blood pressure elevation is probably mediated at least in part through its cardiac action. Therefore, khat chewing carries a potential cardiovascular risk in patients with hypertension and heart disease [*41*], and may precipitate the occurrence of cerebrovascular accidents and myocardial infarction in susceptible individuals [*42*].

The effect of khat chewing on blood pressure and cardiac rhythm among Yemeni patients with hypertension and ischaemic heart disease was also explored using a 24-hour ECG Holter monitor and ambulatory blood pressure monitor [*43*]. The study showed a progressive increase in blood pressure and heart rate that occurred rapidly in the 1st hour of khat chewing; the peak effect was reached at the 2nd and 3rd hours and the blood pressure and heart rate values returned to their baseline values by the 4th or 5th hours after stopping chewing. The normal circadian rhythm and the nocturnal blood pressure drop were well preserved in khat-chewing hypertensive patients. The 24-hour Holter monitor revealed ischaemic changes (ST-segment depression) in 20% of patients with ischaemic heart disease and it was associated with sinus tachycardia and extrasystoles during khat chewing. β1 blockade with atenolol reduced the effect of khat on blood pressure and heart rate among a substantial number of patients with ischaemic heart disease and hypertension [*43*].

The role of khat chewing as a risk factor for acute myocardial infarction in Yemen was investigated by an experimental and clinical study. In the guinea pig, cathinone induced vasoconstriction of the coronary vascular bed which, unlike amphetamine, was not related to a sympathomimetic effect [*44*]. In humans, the circadian rhythm of the timing of acute myocardial infarction was shown to be influenced by khat chewing [*45*]. In non-chewers, there was a progressive increase in number of patients presenting with symptoms of acute myocardial infarction from 03:00 to 09:00 hours, and after 15:00 hours there was a gradual decline until there were none in the last 3 hours of the day. This confirms the previously noted rhythmicity in the timing of the onset of acute myocardial infarction which peaks in the early hours of the day. By contrast, the peak period of presentation of acute myocardial infarction in khat chewers was during the afternoon, commencing at 15:00 hours, continuing until 21:00 hours, and then declining to a trough at 03:00 hours. This finding illustrates the shift in the circadian rhythm of acute myocardial infarction presentation associated with khat chewing [*45*].

Khat and the digestive system

The effects of habitual khat chewing on the digestive system mentioned in older studies were based on the clinical observation that khat chewers often complained of symptoms suggestive of stomatitis, oesophagitis and gastritis. These effects were believed to be caused mainly by the strongly astringent tannins in khat [*17,46*].

Stomatitis is discussed later. Gastric symptoms were attributed to a hypotonic stomach resulting from the sympathomimetic action of cathine and its precursor [*17*]. Recent evidence has shown that khat chewing does indeed delay gastric emptying of a semi-solid meal, probably as a result of the sympathomimetic action of cathinone in khat [*19*]. Delayed gastric emptying may contribute to an increased rate of gastro-oesophageal reflux manifested as heartburn and acid regurgitation, and to an increased risk of Barrett oesophagus, a precancerous condition (see khat and cancer below).

Anorexia frequently follows a khat session and chewers seldom eat a further significant meal on the same day. A significant reduction of appetite after khat chewing was recently noted in a study on the subjective effects of khat chewing [*18*]. This anorectic effect is not due to an effect on ghrelin or peptide YY levels [*47*] but may be attributed to combined direct central and gastric effects of cathinone in fresh leaves of khat [*19*].

A common complaint of khat chewers is constipation, probably caused by a combination of the astringent properties of the khat tannins and the sympathomimetic properties of cathinone [*8*]. Habitual users try to attenuate this undesirable effect by food adaptation, notably by eating a meal with high fat content prior to the khat session in order to facilitate intestinal transit [*48*]. The constipating effect of khat was suggested by the observation that when a ban was imposed on khat in Aden in 1957, the sales of laxatives decreased by 90%, but returned to the original level soon after the ban was lifted [*4*]. Recent evidence has shown that chewing khat leaves significantly slows both the orocaecal transit time [*49*] and the whole gut transit time [*50*]. These 2 mechanisms may contribute to the constipating effect of khat. Moreover, khat chewing was found to interfere with the absorption of some orally administered antibiotics, particularly ampicillin [*51*] and tetracycline [*52*] resulting in low bioavailability. Khat chewing has no effect on gall bladder contraction [*53*].

The liver has been suspected to be particularly vulnerable to the harmful effects of khat use [*3,4*], and a disturbance in liver function and architecture has been described in experimental animals both on short-term [*54*] and long-term [*55*] feeding with *Catha edulis* leaves. Hepatitis B and C viruses are a cause of major health problems in Yemen; however, no significant relationship was found between hepatitis B surface antigen positivity and khat use in one study conducted in a rural community in Taiz province [*56*]. In a recent study on acute sporadic hepatitis in adults in Yemen, it was found that hepatitis viruses A to E accounted for only 48.7% of the cases, and in 51.3% of cases no viral cause was identified. There may be an unknown virus responsible or some environmental toxins, such as pesticides in khat leaves [*57*]. Certainly we have seen patients with abnormal liver function which resolved after khat chewing was suspended and a prospective study is underway.

Khat and the genitourinary system

One of the obvious side-effects of chewing khat leaves in males is temporary interference with micturition with hesitancy and poor flow. Overall urine flow rates were recently found to be significantly lower in khat users [*58*]. This effect is probably mediated through stimulation of α_1 adrenoceptors in the bladder neck by the sympathomimetic alkaloid cathinone. These effects were abolished by the α_1 adrenoceptor blocker, indoramin. The consumption of khat is also said to induce an increase in libido, spermatorrhoea and erectile dysfunction [*7*] but this has not been adequately studied.

Khat and fetal and neoatal health

In the domain of reproductive health, epidemiological data derived from 1181 deliveries in Yemen showed that at birth the mean weight of full-term single infants from mothers who chewed khat habitually or occasionally was below average [*59*]. A study on pregnancy outcome and khat showed a significantly increased incidence of low-birth-weight full-term infants among the offspring of women who chewed khat during pregnancy in comparison to those who were non-chewers during pregnancy [*60*].

Recent evidence indicates that neonates of mothers who chewed khat during pregnancy had a significant decrease in all neonatal parameters such as birth weight, length, head circumference and Apgar score at 1 and 5 minutes in comparison with those of mothers who did not chew khat during pregnancy [*61*]. This effect was found to increase in severity with the increased frequency and duration of khat chewing during pregnancy. Results obtained from the above-mentioned studies indicate that frequent use of khat during pregnancy may impair intrauterine fetal growth. An experimental study in rats has recently proved that khat can affect intrauterine fetal growth by reducing total fetal fat and weight and by inducing some changes in the chemical composition of fetal organs, particularly the liver, heart and kidneys [*62*]. This effect was attributed to depletion of carbohydrate material and suppression of DNA and protein synthesis in the fetal organs.

Nursing mothers in Yemen frequently complain of poor lactation. Some authors believe that this phenomenon may be related to the use of khat as cathine in khat

may inhibit prolactin secretion [*3*]. Interestingly, it has been found that the breast milk of khat-chewing mothers contains cathine, and this compound could even be detected in the urine of one breastfed infant [*63*].

Khat and diabetes mellitus

The effect of khat chewing in diabetic patients is unclear. The very few published papers on this issue make it difficult to draw a conclusion. Some authors believe that the overall effect of khat on diabetic patients is deleterious because the user is less likely to follow dietary advice, and the consumption of sweetened beverages with khat aggravates hyperglycaemia [*3*]. A clinical study was conducted on diabetic patients in Yemen over 20 years ago [*64*]. It showed that when khat-extract was mixed with the glucose given for the glucose tolerance test, there was a significant lowering of blood glucose level in comparison to the non-khat (control) arm of the experiment. This effect was attributed to delayed glucose absorption from the intestine by the action of khat tannins and inorganic ions, particularly magnesium, which produces a substantial inhibitory action upon gastrointestinal function. It seems that khat-induced delay of gastric emptying may also play a role in reducing postprandial hyperglycaemia in patients with type 2 diabetes mellitus [*19*]. By contrast, a similar study on nondiabetic subjects in Somalia showed that khat did not influence to any significant extent blood glucose levels in man [*65*].

Khat and cancer

Since khat use is widespread and often persists throughout adult life, a number of studies have been made on the toxicological aspects of habitual khat use. Owing to its mode of consumption, khat frequently affects the oral cavity and digestive tract. Its effect was found to be clearly dependent on the level of khat consumption [*7*]. Tumours of the oral cavity (lower maxilla, buccal mucosa and lateral surface of the tongue) were reported in 0.13% of patients seeking treatment over a 2-year period in a stomatology clinic in Hodeida, Yemen [*66*]. Most of them had been habitual khat chewers for more than 20 years, and some of them also chewed *shamma* (tobacco powder). A similar review of oral cancers presenting over a 2-year period in Asir region of Saudi Arabia showed strong circumstantial evidence linking the long-term use of khat with an increased rate of oral malignancies [*67*].

Tannins in khat can thicken the mucosa of the oropharynx and oesophagus [*68*] and may be carcinogenic [*69*]. A recent study in Yemen has shown that oesophageal and gastric carcinoma accounted for 6% of all patients who had an upper gastrointestinal endoscopy (183 out of 3064 patients) over a period of 1 year [*70*]. A preponderance of women with carcinoma of the mid-oesophagus was noted, which was previously only recorded in areas of high prevalence of oesophageal carcinoma. A high frequency of khat chewing and water-pipe smoking (*mada'a*) was found among both men and women and among a group with tumours of the gastro-oesophageal junction or cardia. This apparent association of khat with carcinoma of the lower oesophagus might be related to the khat-induced delay of gastric emptying with a subsequent increased risk of gastro-oesophageal reflux and Barrett oesophagus [*19*].

The effect of chewing khat on the mucosal histology of the upper gastrointestinal tract was explored in Yemeni patients presenting with dyspepsia [*71*]. Regular daily khat chewing was not associated with any major effect on the oesophagus or stomach

but duodenal ulcers were common in chewers. This may have been associated with the high prevalence of smoking in this group. Gastric-type mucosa at the lower end of oesophagus is thought to increase the risk of developing adenocarcinoma 30–125-fold. Although its presence was not related to the intake of khat, its overall prevalence in Yemeni patients was comparatively high (18%). To clarify this point, a case–control study on oesophageal carcinoma in Yemen is planned.

Khat and oral–dental tissues

The association with mouth cancer has been discussed earlier.

The adverse effects of khat chewing on oral–dental tissues were first observed by Laurent [*72*], Halbach [*4*] and Luqman and Danowski [*3*]. They reported that long-term khat chewing caused stomatitis followed by secondary infection. These might be related to mechanical strain on the cheek and other oral tissues as well as chemical irritation of the mucosal surfaces. A high rate of periodontal diseases and low rate of dental caries has been observed among male Yemeni khat chewers [*3*]. Mouth dryness, the major complaint following khat chewing, might be due to the sympathomimetic effect of cathinone and/or to excess secretion of saliva during chewing [*73*]. Hill and Gibson observed the effects on oral and dental tissue among Yemeni males with an average age of 35 years who chewed khat for of 20 years [*74*]. They found a low prevalence of caries, but universal attrition, temporomandibular joint pain and increased periodontal pocket depth on the khat-chewing side compared with the non-khat chewing side. They also reported increased keratosis on the buccal mucosa in 50% of the cases. In Kenya, Macigo and his colleagues showed that khat chewing was not significantly associated with leukoplakia compared with tobacco and alcohol consumption [*75*].

Recently, a cross-sectional hospital study among Yemeni khat and non-khat chewers showed an increased risk for a number of oral and paraoral lesions [*76*]. The study revealed that khat chewing caused many lesions to the supporting structures of the teeth, namely gingivitis, periodontal pocket formation, gingival recession, tooth mobility and tooth mortality. Khat chewing caused clicking and pain in the temporomandibular joints and led to attrition and staining of teeth and cervical caries, particularly among crystallized sugar consumers. Due to continuous mechanical friction and/or the chemical content, khat chewing caused white lesions on the buccal and gingival mucosa. Histopathological study revealed changes to the oral mucosa, such as acanthosis, papillomatosis, ortho- and para-keratosis and intercellular oedema, but not leukoplakia.

Concerning saliva and salivary glands, khat chewing results in mouth dryness, enlargement of salivary glands, inflammation and folding of the parotid papilla at the site of khat chewing. Khat chewing also causes obvious facial asymmetry of facial tissues.

Conclusion

To conclude, khat chewing appears to pose the following potential health risks.

- It may induce disturbance of mood (anxiety and/or depression, insomnia).
- In psychotic patients, it may aggravate thought disturbances (hallucination and delusions), induce aggressive behaviour and create difficulties in treating these patients.
- It may cause elevation of arterial blood pressure and pulse rate with subsequent

increased cardiovascular risk, particularly in hypertensive patients.

- It seems to be a common cause of stomatitis and other problems in the mouth as well as gastro-oesophageal reflux.
- It may be associated with increased risk of carcinoma of the mouth and oesophagitis.
- It may interfere with absorption of some orally administered antibiotics.
- It causes anorexia.
- It causes constipation.
- It may have a toxic effect on the liver, possibly as a result of pesticides used in khat cultivation.
- It is associated with an increased risk of low birth weight infants in khat-chewing pregnant women.

Recommendations

Since khat chewing is widespread in Yemen, the following actions are recommended.

1. Increase public awareness of the potential health hazards of khat chewing.
2. Support scientific research on khat in different institutions and universities to explore the different effects of khat on public health.
3. Integrate education about khat into the curricula of primary and secondary schools.
4. Legislate on the use of pesticides in the cultivation of khat in view of their potentially harmful effects on human health.

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