Review

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What science says about khat (*Catha edulis* Forsk)? Overview of chemistry, toxicology and pharmacology

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Abstract

Catha edulis (khat) is a plant grown commonly in the horn of Africa. The leaves of khat are chewed by the people for its stimulant action. Khat is an evergreen shrub, which is cultivated as a bush or small tree. The leaves have an aromatic odour. The taste is astringent and slightly sweet. The plant is seedless and hardy, growing in a variety of climates and soils.

Khat contains more than 40 alkaloids, glycosides, tannins, amino acids, vitamins and minerals. Many different compounds are found in khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals. The phenylalkylamines and the cathedulins are the major alkaloids which are structurally related to amphetamine.

The major effects of khat include those on the gastro-intestinal system and on the nervous system. Constipation, urine retention and acute cardiovascular effects may be regarded as autonomic (peripheral) nervous system effects; increased alertness, dependence, tolerance and psychiatric symptoms as effects on the central nervous system. The main toxic effects include increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men.

The purpose of this review is to summarize the chemistry, pharmacology, toxicology of khat (*Catha edulis* Forsk).

Key words:
Cathinone; Chemistry; Khat; Pharmacology; Toxicology

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Introduction

Khat is a natural stimulant from the *Catha edulis* plant that is cultivated in the Republic of Yemen and most of the countries of East Africa. Its young buds and tender leaves are chewed to attain a state of euphoria and stimulation [1]. Khat is an evergreen shrub, which is cultivated as a bush or small tree (Fig.1). The leaves have an aromatic odour. The taste is astringent and slightly sweet. The plant is seedless and hardy, growing in a variety of climates and soils. Khat can be grown in droughts where other crops have failed and also at high altitudes. Khat is harvested throughout the year. Planting is staggered to obtain a continuous supply [2]. There is fairly extensive literature on the potential adverse effects of habitual use of khat on mental, physical and social well-being.

Reasons for chewing khat and behaviors associated with the ritual of khat chewing

The vast majority of those ingesting khat do so by chewing. Only a small number ingest it by making a drink from dried leaves, or, even more rarely, by smoking dried leaves. The chewer fills his or her mouth with leaves and stalks, and then chews slowly and intermittently to release the active components in the juice, which is then swallowed with saliva. The plant material is chewed into a ball, which is kept for a while in the cheek, causing a characteristic bulge [3]. Khat chewing usually takes place in groups in a social setting. Only a minority frequently chew alone. A session may last for several hours. During this time chewers drink copious amounts of non-alcoholic fluids such as cola, tea and cold water. In a khat chewing session, initially there is an atmosphere of cheerfulness,

Figure 1. The khat plant with its leaves

optimism and a general sense of well-being. After about 2 hours, tension, emotional instability and irritability begin to appear, later leading to feelings of low mood and sluggishness. Chewers tend to leave the session feeling depleted.

Chewing khat is both a social and a culture-based activity. It is said to enhance social interaction, playing a role in ceremonies such as weddings. In Yemen, Muslims are the most avid chewers. Some believe that chewing facilitates contact with Allah when praying. However, many Christians and Yemenite Jews in Israel also chew khat. Khat is a stimulant and it is used to improve performance, stay alert and to increase work capacity [1, 4]. Workers on night shifts use it to stay awake and postpone fatigue. Students have chewed khat in an attempt to improve mental performance before exams. Yemeni khat chewers believe that khat is beneficial for minor ailments such as headaches, colds, body pains, fevers, arthritis and also depression [5].

Epidemiology of khat

Khat leaves are chewed habitually in the south-western part of the Arabian Peninsula and in the East African countries between Sudan and Madagascar, namely Djibouti, Ethiopia, Somalia, Kenya, Tanzania and Uganda. In addition to the reported health problems, the regular consumption of khat is associated with a variety of social and economic problems affecting the consumers and their families. The impact of khat chewing in Yemen is considerable. It is deep-rooted in the Yemenite society where khat is consumed in social gatherings with family and friends while holding conversations, smoking cigarettes and drinking tea and soft drinks. In Yemen khat users, mostly male, meet after noon and start masticating the leaves thoroughly one by one [2]. In other countries, it is less predominantly a male habit and there is less social pressure to participate in khat sessions [6]. Much time is spent on buying and chewing khat leaves, which affects working hours and time with family [7]. For some, the daily cost of the khat habit exceeds their expenditure on food for their families. Young leaves are preferred because these have the highest stimulant activity. In the last decades, the khat 'habit' has spread to other African countries and to Europe, to Australia and to the United States. In Europe, Australia and the United States, khat use is seen amongst immigrants from Yemen, Somalia and Ethiopia [8-10]. Some authors estimate that 10 million people chew khat worldwide [11]. Khat is freely available in Ethiopia and is a highly valued export commodity in that country. The number of khat chewers has significantly increased in this country and khat consumption has become popular in all segments of the Ethiopian population [12]. Previously, khat was mainly cultivated in the eastern part of Ethiopia. Nowadays, it is grown in all parts of the country. The Ethiopian authorities have recommended the banning of khat consumption from schools and workplace [12].

Chemistry

Khat contains more than forty alkaloids, glycosides, tannins, amino acids, vitamins and minerals [13]. The environment and climate conditions determine the chemical profile of khat leaves. In the Yemen Arab Republic, about 44 different types of khat exist originating from different geographic areas of the country [7, 14].

Many different compounds are found in khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals [15-17]. The phenylalkylamines and the cathedulins are the major alkaloids. The cathedulins are based on a poly-hydroxylated sesquiterpene skeleton and are basically polyesters of euonyminol. Recently, 62 different cathedulins from fresh khat leaves were characterized [18]. The khat phenylalkylamines comprise cathinone [S(–)-cathinone], and the two diastereoisomers cathine [1S,2S(+)-norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R,2S(–)-norephedrine]. These compounds are structurally related to amphetamine and noradrenaline. The plant contains the (–)-enantiomer of cathinone only; the (+)-enantiomer is not found [17]. Thus, the naturally occurring S(–)-cathinone has the same absolute configuration as S(+)-amphetamine (Fig.2). Cathinone is mainly found in the young leaves and shoots. During maturation, cathinone is metabolised to cathine [(+)-norpseudoephedrine] and (–)-norephedrine (Fig.3). The leaves contain [(+)-norpseudoephedrine] and (–)-norephedrine in a ratio of approximately 4:1 [17].

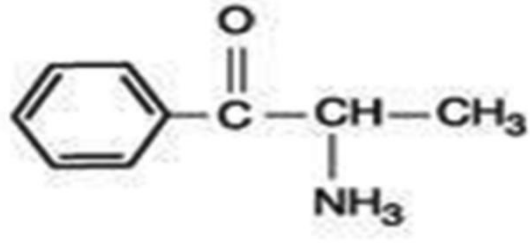

Figure 2. Chemical structure of cathinone

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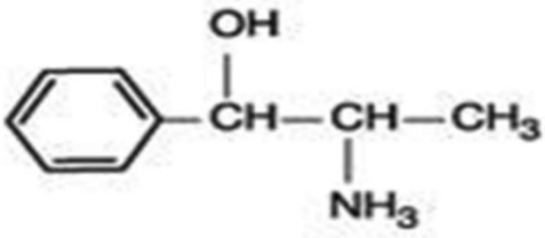

Figure 3. Chemical structure of cathine

Other phenyl-alkylamine alkaloids found in khat leaves are the phenylpentenylamines merucathinone, pseudo-merucathine and merucathine. These seem to contribute less to the stimulant effects of khat [16, 19, 20].

Cathinone is unstable and undergoes decomposition reactions after harvesting and during drying or extraction of the plant material [16, 17, 21, 22]. Decomposition leads to a 'dimer' (3,6-dimethyl-2,5-diphenylpyrazine) and possibly to smaller fragments. Both the dimer and phenylpropanedione have been isolated from khat extracts [21]. As cathinone is presumably the main psychoactive component of khat, this explains why fresh leaves are preferred and why khat is wrapped up in banana leaves to preserve freshness.

The phenylalkylamine content of khat leaves varies within wide limits. Fresh khat from different origin contained on the average 36 mg cathinone, 120 mg cathine, and 8 mg norephedrine per 100 g of leaves [14]. Toennes *et al* found 114 mg cathinone, 83 mg cathine and 44 mg norephedrine in 100 g of khat leaves confiscated at Frankfurt airport [23]. Widler *et al* found 102 mg cathinone, 86 mg cathine and 47 mg norephedrine in 100 g of fresh leaves from Kenya confiscated at Geneva Airport [24]. Al-Motarreb *et al* reported higher levels of cathinone in fresh leaves varying from 78 to 343 mg in 100 g [7]. Khat leaves also contain considerable amounts of tannins (up to 10% in dried material) and flavonoids [7, 25].

Pharmacologic effects of khat

Khat contains many different compounds and therefore khat chewing may have many different effects. The major effects include those on the gastro-intestinal system and on the nervous system. Constipation, urine retention and acute cardiovascular effects may be regarded as autonomic (peripheral) nervous system effects; increased alertness, dependence, tolerance and psychiatric symptoms as effects on the central nervous system. As cathinone, and to a lesser extent cathine, are held responsible for the effects of khat on the nervous system, the effects of the many other constituents of the khat plant are frequently overlooked. As a consequence, much research has been focused on the pharmacological effects of cathinone and cathine, and much less on the other constituents of khat. Because of the large number of different compounds in khat, it is not feasible to include all effects of all components of khat. But this report will focuses on the psychoactive properties of khat and the main psychoactive compounds, cathinone and cathine, found in khat.

Animal studies

Behavioral effects

Rats fed *C.edulis* material (extract or whole) show increased locomotor activity and reduced weight gain [26]. Retardation of growth rate was considered to be due to decreased absorption of food and not due to decreased food consumption. In pregnant rats, khat reduces food consumption and maternal weight gain, and also lowers the food efficiency index [27].

Many reports have confirmed the enhanced locomotor activity. In addition, khat extracts and (–)-cathinone produce stereotyped behavior, self-administration and anorectic effects in animal species [21, 28-32]. Qualitatively, this behavior is similar to that evoked by amphetamine [S(+)-amphetamine] [33, 34].

Both khat extract and (–)-cathinone enhance baseline aggressive behavior of isolated rats [37]. Furthermore, (–)-cathinone is capable of producing conditioned place-preference in rats at the dose (1.6 mg/kg) that produces increased locomotor activity, thus showing the rewarding effect of the drug [36, 37]. A lower dose of cathinone (0.2 mg/kg) that did not increase locomotion, also failed to show conditioned place preference. Cathinone is also able to act as a discriminative stimulus in a food-reinforced operant task [38].

(–)-Cathinone appears to have stronger effects than cathine [(+)-norpseudoephedrine] and norephedrine [(–)-norephedrine] [18, 33]. For example, it was 7-10 times more potent than cathine on a behavioral measure of food intake [39]. Compared to cathine, cathinone also has a more rapid onset of action, which agrees with its higher lipophilic character facilitating entry into the central nervous system, and a shorter duration of action, which agrees with the rapid metabolism of cathinone [17, 33, 39].

Dopaminergic antagonists (*e.g.* haloperidol) and dopamine release inhibitors are able to partially block the activity-enhancing properties of

(–)-cathinone [29, 40], but this has not been confirmed in another study [41]. Generally, cathinone is not considered a direct dopamine agonist but rather a presynaptic releaser and re-uptake inhibitor of dopamine [16]. (–)-Cathinone also releases radioactivity from rat striatal tissue pre-labelled with H-serotonin, similar to (+)-amphetamine although one-third as potent [42]. Apparently, (–)-cathinone shares important effects of (+)-amphetamine on neurotransmission. Further evidence for serotonergic involvement is given in a recent study in which both khat extract and cathinone produced a significant depletion of serotonin and its metabolite 5-hydroxyindoleacetic acid in both the anterior and posterior striatum [35].

Locomotor sensitisation and deficits in prepulse inhibition (PPI) induced by psychostimulants are two paradigms that have been widely studied as animal behavioral models of amphetamine psychosis. Repeated oral administration of a standardised *C.edulis* extract (containing a dose of 1 mg cathinone per kg b.w) or (–)-cathinone (1.5 mg/kg) to rats induced a strong locomotor sensitisation and led to a gradual deficit in PPI [43, 44]. The behavioral sensitisation was long-lasting and persisted after cessation of the treatments, comparable to amphetamine-induced sensitisation. Clozapine, an atypical antipsychotic agent, was able to reverse this behavioral sensitisation and the PPI deficits induced by *C.edulis* extract or cathinone [44]. These results may support the reports on khat-induced psychosis in humans. Neurotransmitter level analyses showed a significant increase in the level of dopamine in the prefrontal cortex. There was also a significant decrease in the level of serotonin in the nucleus accumbens and its metabolite 5-hydroxy-indoleacetic acid in the prefrontal cortex. In the remaining regions (anterior and posterior striatum) no significant changes were found.

Cardiovascular effects

Cathinone has vasoconstrictor activity in isolated perfused hearts from guinea pigs [45]. The effect was unlikely to be due to an indirect action by release of noradrenaline from sympathetic nerve endings or due to a direct action on α_1-adrenoreceptors. (–)-Cathinone is able to potentiate noradrenaline-evoked contractions of the rat right ventricle [46] and to inhibit the uptake of noradrenaline into ventricular slices by a mechanism involving competitive blockade of the noradrenaline transporter [47]. The vasoconstrictor activity of cathinone explains the increase in blood pressure seen in humans [48] and in animals [49], and might be related to the increased incidence of myocardial infarction occurring during khat sessions, *i.e.* during the khat-effective period [50], and associated with heavy khat chewing [51].

Effects on the adrenocortical function

In rabbits, a khat extract given orally for 30 successive days induced a decrease in adrenal cholesterol, glycogen, ascorbic acid and an increase in adrenal phosphorylase activity, serum free fatty acids and urinary 17-hydroxycorticosteroids [52]. These results have been interpreted as a stimulating effect of khat on adrenocortical function. This effect was also seen after oral administration of cathinone and cathine (6.5 mg/kg) [52].

Effects on the reproductive system

Animal data are conflicting. Treatment of male mice with a khat extract over a period of 6 weeks produced a dose-dependent reduction in fertility rate in female mice in the first week after the 6-week khat treatment [53]. In cathinone-treated rats, a significant decrease in sperm count and motility, and an increase in the number of abnormal sperm cells were found [54]. Histopathological examination of the testes revealed degeneration of interstitial tissue, cellular infiltration and atrophy of Sertoli and Leydig cells in cathinone-treated animals. Cathinone also produced 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 [54].

In contrast, rabbits fed khat for three months had an increased rate of spermatogenesis and the Leydig cells were in good condition [45]. In male adult olive baboon, crude khat extract (equivalent to 250 g leaves and shoots) given orally once a week during 2 months produced an increase in plasma testosteron levels and a decrease in the plasma levels of prolactin and cortisol [56]. The testosteron results are in contrast with earlier observations in humans [17] and rats [54]. In biopsies taken 1 month after the last khat administration, no histopathological changes were found in the testis, epididymis, liver, kidney and pituitary gland of the animals. This contrasts with results of cathinone on rabbit liver, which showed increasing chronic inflammation with porto-portal fibrosis in the tissue sections obtained from animals treated with both 20% and 30% *C.edulis* [57]. The doses and administration regimens were different and this may explain the differences.

Khat given to pregnant guinea pigs reduces placental blood flow [58] and produces growth retardation in the offspring [59].

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Human studies

The main effects of khat chewing are on the central and peripheral nervous system, and on the oro-gastro-intestinal system.

Subjective effects

Khat chewing induces a state of euphoria and elation with feelings of increased alertness and arousal. This is followed by a stage of vivid discussions, loquacity and an excited mood. Thinking is characterised by a flight of ideas but without the ability to concentrate. However, at the end of a khat session the user may experience depressive mood, irritability, anorexia and difficulty to sleep [16, 60]. Lethargy and a sleepy state follow the next morning.

Effects on the urinary bladder

Khat induces a fall in average and maximum urine flow rate in healthy men [26, 61]. The urinary effects are probably mediated through stimulation of α_1-adrenergic receptors by cathinone. This is indicated by the complete blockage of this effect by indoramin, a selective antagonist of α_1-adrenergic receptors [61].

Effects on the gal bladder

Khat chewing has no clinically significant effect on gal bladder motility [62].

Cardiovascular effects

Khat chewing induces small and transient rises in blood pressure and heart rate [14, 63-67]. Cathinone (0.5 mg base/kg b.w) has similar effects coinciding with the presence of cathinone in blood plasma [48, 68]. These effects could be blocked by the β_1-adrenoreceptor blocker atenolol, but not by the α_1-adrenorecptor blocker indoramin, indicating mediation through stimulation of β_1-adreno-receptors [65].

In a pharmacokinetic study, diastolic and systolic blood pressures were elevated for about 3 hours after chewing [23]. The rise of blood pressure already started before the rise of alkaloid plasma concentrations, indicating an initial study engagement effect. The dose used was about one quarter (0.6 g/kg) of a traditional khat session dose and chewing was for 1 hour. This resulted in a mean oral dose of 45 mg cathinone. This rather low dose did not affect heart rate, pupil size and reaction to light, and it did not induce rotary nystagmus or impairment of reaction. All participants reported the personal feeling of being alert and ‘energetic’. An impairment of other psychophysical functions could not be objectified [23]. In another study, diastolic and systolic blood pressure, mean arterial blood pressure, and heart rate were raised during the 3 hours of khat chewing and during the following hour [67].

Effects on the adrenocortical function

Nencini *et al* found that khat and cathinone increase adrenocorticotrophic hormone levels in humans [3].

Toxicologic aspect of khat

Khat use affects cardiovascular, digestive, respiratory, endocrine, and genito-urinary systems. In addition, it affects the nervous system and can induce paranoid psychosis and hypomanic illness with grandiose delusions [4]. The effects on the nervous system resemble those of amphetamine with differences being quantitative rather than qualitative [15, 25].

The main toxic effects include increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men [16]. Mild depressive reactions have been reported during khat withdrawal or at the end of a khat session [17, 60]. Frequent use of high doses may evoke psychotic reactions.

Biochemically, khat leaves decreased plasma cholesterol, glucose and triglycerides in rabbits, and increased plasma alkaline phosphatase and alanine aminotransferase in white rabbits [55]. Histo-pathological signs of congestion of the central liver veins were observed with acute hepatocellular damage and regeneration. In addition, some kidney lesions were seen with the presence of fat droplets in the upper cortical tubules, acute cellular swelling, hyaline tubules, and acute tubular nephrosis. Spleen was not affected and the histoarchitecture of the testes and cauda epididymis was normal showing, however, increased rate of spermatogenesis. The amount of khat consumed by the rabbits cannot be evaluated from the details given. The authors reported that, in general, the activity and the behaviour of the animals were observed to be normal [55]. Adverse effects of khat may be summarised according to the system involved [15](Table 1).

Khat-induced psychosis

Khat chewing can induce two kinds of psychotic reactions. First, a manic illness with grandiose delusions and second, a paranoid or schizo-phreniform psychosis with persecutory delusions associated with mainly auditory hallucinations, fear and anxiety, resembling amphetamine psychosis [69]. Symptoms rapidly abate when khat is withdrawn. In fact, khat withdrawal con-sistently

Table 1. Reported and suggested adverse effects of khat in man [15]

System	Adverse effects
Cardiovascular system	tachycardia, palpitations, hypertension, arrhythmias, vasoconstriction, myocard infarction, cerebral hemorrhage, pulmonary edema
Respiratory system	tachypnoea, bronchitis
Gastrointestinal system	dry mouth, polydipsia, dental caries, periodontal disease, chronic gastritis, constipation, hemorrhoids, paralytic ileus, weight loss, duodenal ulcer, upper gastro-intestinal malignancy
Hepatobiliary system	fibrosis, cirrhosis
Genitourinary system	urinary retention, spermatorrhoea, spermatozoa malformations, impotence, libido change
Obstetric effects	low birth weight, stillbirths, impaired lactation
Metabolic and endocrine effects	hyperthermia, perspiration, hyperglycaemia
Ocular effects	blurred vision, mydriasis
Central nervous system	dizziness, impaired cognitive functioning, fine tremor, insomnia, headaches
Psychiatric effects	lethargy, irritability, anorexia, psychotic reactions, depressive reactions, hypnagogic hallucinations

appears to be an effective treatment of khat psychosis and anti-psychotics are usually not needed for full remission [70].

Hypnagogic hallucinations

Hypnagogic hallucinations have been reported in chronic khat users [71]. These consist of continuous visual and/or auditory dreamlike experiences that accompany daily life and are not related to khat sessions. Patients may consider them as normal and do not usually report these hallucinations unless specifically asked about.

Impairment of cognitive functions

Adverse effects of khat chewing include impairment of perceptual-visual memory and decision-speed cognitive functions [72].

Neurological complications

One case history of severe leukoencephalopathy associated with khat misuse has been reported [73]. EEG and MRI findings indicated progressive leukoencephalopathy but the link with khat use is not proven (coinciding).

Cardiovascular complications

Recently, it has been reported that khat chewing is associated with acute myocardial infarction [74]. Khat chewing has also been reported to be a significant risk factor for acute cerebral infarction [75]. The prevalence of high blood pressure was significantly higher in the patient group than in the control group and this higher prevalence was associated with khat chewing.

Oral and gastro-intestinal complications

As a consequence of its mode of consumption khat affects the oral cavity and the digestive tract. A high frequency of periodontal disease has been suggested as well as gastritis [5] and chronic recurrent subluxation and dislocation of the temperomandibular joint [76].

Cancer

In a survey that reviewed cancers for the past two years in the Asir region of Saudi Arabia, 28 head and neck cancer patients were found [77].

Reproductive system

Detailed studies on the effects of khat on human reproduction are lacking. However, the available data suggest that chronic use may cause spermatorrhoe and may lead to decreased sexual functioning and impotence [78].

Genotoxicity and teratogenic effects

Orally administered khat extract induced dominant lethal mutations [53] and chromosomal aberrations in sperm cells in mice [79], and teratogenic effects in rats [27].

Conclusion

Several studies across the globe have reported khat-chewing as a harmful activity on health. Many different compounds are found in khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals the major pharmacologic and toxic effect come from the phenylalkylamines and the

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cathedulins. The major effects of khat include those on the gastro-intestinal system and on the nervous system but also affect cardiovascular, respiratory, endocrine, and genito-urinary systems. The effects on the nervous system resemble those of amphetamine with differences being quantitative. The main toxic effects include increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men. Since this is a major social issue particularly in the East Africa, raising awareness with the general public in terms of the harmful effects of khat-chewing. This can be accomplished via appropriate communication strategies by using printed materials and electronic media.

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