

## Catha Edulis Forsk and Its Adverse Effects On Health: Current and Ongoing Factuality

Bereda G\*

Department of Pharmacy, Negelle Health Science College, Guji, Ethiopia

### \*Corresponding author:

Gudisa Bereda,  
Department of Pharmacy, Negelle Health  
Science College, Guji, Ethiopia,  
Tel: +251919622717/+251913118492,  
E-mail: gudisabareda95@gmail.com

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### 1. Abstract

The leaves of khat tree have an aromatic odor and an astringent and slightly sweet taste. It has been widely chewed for its stimulant action by the population in these regions for many years. Its young buds and tender leaves contain amphetamine-like psychoactive substances, which produce euphoria and stimulation. 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 forty alkaloids, glycosides, tannins, amino acids, vitamins, and minerals. The euphoric effects of khat start after about 1 hour of chewing. 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.

### 2. Keywords:

Adverse Effects; Catha Edulis; Forsk; Health

### 3. Introduction

Khat is an herbal product consisting of the leaves and shoots of the shrub *Catha edulis* Forsk, a member (genera) of the evergreen Celastraceae (moonseed or spindle-tree) family or tribe [1].

Khat (*Catha edulis*) also known as Abyssinian tea, Africa salad, Bushman's tea, Gat, Kat, Miraa, Tohai and Chat is a flowering shrub, native to the region extending from Eastern to South Africa, as well the Arabian Peninsula [2-4]. Khat's natural range ex-

tends throughout East Africa from Ethiopia, Eritrea and Somalia, through to South Africa; it is also found in Rwanda, Zaire, Malawi and Zimbabwe [5, 6]. Fresh leaves of khat contain the alkaloids of the phenylpropylamine type of which the two psychoactive constituents are the stimulants cathinone (S-(-)- $\alpha$ -aminopropiophenone) and cathine (S, S-(+)-norpseudoephedrine) [7]. Khat is considered a "natural amphetamine" containing amphetamine-like stimulant substances such as cathinone and cathine [8]. The central stimulant effects of khat are similar to those of amphetamine. The reason is that the main active ingredient in khat is psychoactive alkaloids called cathinone, an amphetamine-like substance [9] (Figure 1).

The psychoactive effects of khat are mainly attributed to cathinone, a potent alkaloid which has a close structural resemblance to amphetamine [10]. The short-lived efficacy of khat leaves is caused by the rapid degradation of (-)-S-cathinone into (+) - norpseudoephedrine and norephedrine within a few days of harvest [11]. Its taste varies from one kind to another and depends on the tannic acid content. Khat leaves have an astringent taste and have an aromatic odour. The young leaves are slightly sweet [12] (Figure 2).

In Ethiopia, khat is commonly used for social recreation and as a recreational drug, the leaves and stem are chewed by people in East Africa and the Arabian countries to elevate mood (as a euphoriant) [11, 14]. Occupational groups such as motor vehicle drivers, truck drivers, who chew khat during long distance driving, to keep awake, also use it under a variety of other conditions [15]. A significant number of students chew khat to be alert especially during examination periods [16]. There is also specific usage of khat by the special sections of the community: craftsmen and

farmers use khat to reduce physical fatigue and traditional healers to heal ailments [17]. Khat is chewed daily by a high proportion of adult population for its Central Nervous System stimulant effect. Furthermore, it is widely masticated among youth Ethiopians, especially high school, college and university students [18]. Recently, khat use became popular among other groups of people, and they used it to increase concentration and performance during trading, farming, academic activities, and for socialization and leisure activities [19, 20]. Factional khat use could also include chewing khat to cope with traumatic experiences elder Muslim men in certain ethnic groups or regions chewed khat for concentration during studying religious writings and to stay alert during night prayer [21, 22]. The khat chewers experience a sense of increased energy

levels, increased alertness and ability to concentrate, improvement in self-esteem and an increase in libido, enhanced imaginative ability, improvement in the ability to communicate, capacity to associate ideas, and subjective improvement in work performance [23, 24]. 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 [25, 26]. The plant material is chewed into a ball, which is kept for a while in the cheek, causing a characteristic bulg [27] (Figure 3).

Widespread use of khat, especially its concurrent use with tobacco, remains a public health challenge in many countries including Asia, Europe, Australia, and the United States [28]



**Figure 1:** Leaf of khat



**Figure 2:** Bundle of khat. The usual length of a bundle is 30–40 cm

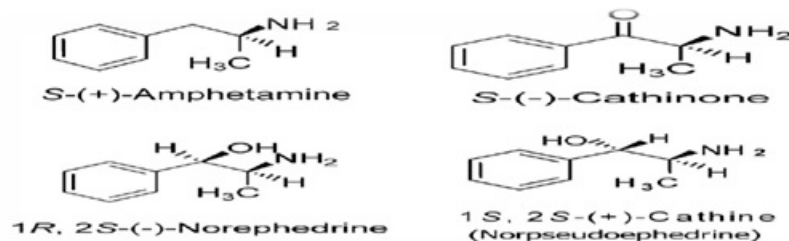


**Figure 3:** Exemplary of Khat chewed into a ball

### 3.1. Chemistry

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 [29]. 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 [30]. 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 noradren-

aline. The plant contains the (-)-enantiomer of cathinone only; the (+)-enantiomer is not found [Cathinone is found mainly in the young leaves and shoots [31, 32]. During maturation, cathinone is metabolized to cathine, and (-)-norephedrine. The leaves contain these two substances in a ratio of approximately 4:1[33]. Chemical Names of cathinone is S(-)-cathinone; S(-)- $\alpha$ -aminopropiophenone; (S)-2-amino-1-phenyl-1-propanone; cathine is 1S, 2S-(+)-norpseudoephedrine; 1S,2S-(+)-phenylpropanolamine; 2-amino-1-phenyl-1-propanol; norephedrine is 1R, 2S(-)-norephedrine; 1R,2S(-)-phenylpropanolamine; 2-amino-1-phenyl-1-propanol (Figure 4).



**Figure 4:** Chemical structure of the phenylpropylamine alkaloid from khat cathinone, norephedrine, norpseudoephedrine (cathine)

### 3.2. Pharmacology

The psychotropic effects of khat are caused by the amphetamine-like compounds [34].

#### MOA

The constituents of khat have been shown to exert their effects on two main neurochemical pathways: dopamine and noradrenalin [35]. It has also been postulated that, like amphetamine, cathinone releases serotonin in the central nervous system [36]. Both cathinone and amphetamine induce release of dopamine from central nervous system dopamine terminals and thus increase the activity of the dopaminergic pathways [37]. Cathinone has a releasing effect on noradrenalin storage sites, which supports the conclusion that cathinone facilitates noradrenalin transmission. Cathinone and cathine cause inhibition of noradrenalin uptake [38, 39].

### 3.3. Pharmacokinetics

The euphoric effects of khat start after about 1 hour of chewing [40]. Blood levels of cathinone start to rise within 1 hour and peak plasma levels are obtained 1.5 – 3.5 hours after the onset of chewing [41]. Metabolism of cathinone is rapid, occurring mainly during first passage through the liver. Only a small fraction (about 2%) appears unchanged in the urine. Most cathinone is metabolized to norephedrine and is excreted in this form [42-44]. The rate of inactivation is about the same as the rate of absorption, which limits the cathinone blood levels attainable by chewing. Cathine has a slower onset of action, with a serum half-life in humans of about 3 hours. It is excreted unchanged in the urine within about

24 hours [45, 46]. When taking khat, large amounts of non-alcoholic drinks are consumed. There is pharmacological synergism with drinks containing Methylxanthines (e.g. tea and cola), which therefore enhances the effects of khat [47, 48].

### 3.4. Adverse Effects of Khat on Health

With the migration of khat users from Africa and Arabia, several health problems have been disseminated to different countries around the globe [49]. 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 [50, 51]. Apart from the various health issues caused, the impact of khat cultivation on the national economy is huge. For instance, almost half a household's income goes towards paying for the khat requirement of the head of the family who often chew it for four to five hours a day. This negatively affects their working hours and the family income [52, 53]

### 3.5. Central Nervous System

Khat is a stimulant with effects similar to amphetamine, because the main active ingredient in khat is cathinone, an amphetamine like substance [54]. Cathinone is more lipids soluble than cathine and it can easily cross the brain blood barrier and enter in the central nervous system that is responsible for adverse effect on the body. It also exerts pronounced behavioral effects of euphoria, hyperactivity, and restlessness, like ecstasy (MDMA-3, 4-methylenedioxy-N-methylamphetamine) and amphetamine [55]

MOA: Stimulant effects of cathinone

### 3.6. Khat-Induced Psychosis

Khat chewing can induce two kinds of psychotic reactions. First, a manic illness with grandiose delusions and second, a paranoid or schizophreniform psychosis with persecutory delusions associated with mainly auditory hallucinations, fear and anxiety, resembling amphetamine psychosis [56, 57]

### 3.7. Schizophreniform Psychosis

The patients typically present with paranoid delusions, fear, a hostile perception of the environment, auditory hallucinations (frequently of a persecutory or threatening type), ideas of reference, thought alienation and a tendency to isolate themselves, or alternatively displaying aggressive behaviour towards others [58].

### 3.8. Manic Psychosis

The patient presented with hyperactivity, shouting, pressure of speech, grandiose delusions with flight of ideas and tangential thought processes, and a labile mood varying from euphoria to anger. The patient had used khat for the first time, chewing about 24 leaves (this is equivalent to a single dose of khat) [59].

### 3.9. Hypnagogic Hallucinations

Hypnagogic hallucinations have been reported in chronic khat users. 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 [60].

### 3.10. Impairment of Cognitive Functions

Adverse effects of khat chewing include impairment of perceptual-visual memory and decision-speed cognitive functions [61]

### 3.11. Cardiovascular Complications

The phenylpropylamine-type alkaloid cathinone is the major component responsible for the effects of khat on the heart and blood vessels [62]. Khat has direct effects on the cardiovascular system

due to the indirect sympathomimetic activity of cathinone, causing clear increases in heart rate and blood pressure in humans [63].

MOA: Indirect sympathomimetic activity of cathinone/ cathinone was an indirectly acting sympathomimetic drug having catecholamine-releasing properties at dopaminergic and serotonergic synapses, and at peripheral noradrenaline storage sites [64]

Another cardiovascular complication of khat chewing is the higher incidence of hemorrhoids and hemorrhoidectomy found in chronic khat chewers (62% and 45%) as compared to non-khat users (4% and 0.5%) khat is hepatotoxic with increases in liver enzymes and there has been histopathological evidence of acute hepato-cellular degeneration [65]

### 3.12. Coronary Vessels, Myocardium, and Heart Failure

Cathinone causes severe coronary vasoconstriction and a severe negative inotropic effect on the cardiac muscle, suggesting coronary spasm contributes to the development of acute myocardial infarction (AMI) [66, 67]. Amphetamine also shows vasoconstrictive action by stimulating the release of noradrenaline from sympathetic nerves and may participate in AMI [68]. Catecholamines induce platelet aggregation and cause transient occlusion of the coronary vessels, which further becomes severe by an increase in myocardial oxygen demand induced by catecholamines. In addition to its role as a risk factor for AMI, amphetamine abuse may lead to chronic cardiomyopathy, pulmonary heart disease, necrotizing vasculitis, and intracranial hemorrhage [69]. Cathinone also plays a role in the development of congenital heart disease [70]

MOA: increased release of catecholamines triggered by the cathinone content of khat, leading to hypertension and acute myocardial infarction (Increased thrombogenicity)/Coronary vasospasm, induced by the cathinone in khat, *causing vasoconstriction may occlude coronary arteries sufficiently to precipitate myocardial infarction* [71] (Figure 5).

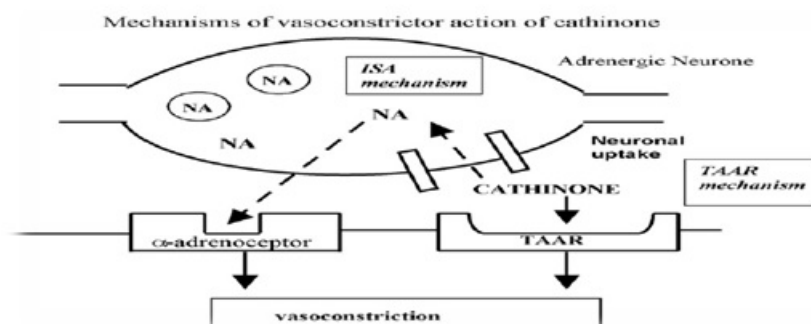


Figure 5: Schematic exemplify of mechanisms of vasoconstrictor action of cathinone

## 4. Metabolic and Endocrine Effects

### 4.1. Hyperthermia (Increased Body Temperature)

The effect of (–)-cathinone on body temperature shares a phenomenon with the effect of (+)-amphetamine and 3, 4-methylenedioxymethamphetamine (MDMA, XTC): hyperthermia at room

temperatures and above, but hypothermia in animals kept below room temperature [72, 73]

### 4.2. Khat and Type II Diabetes Mellitus

MOA: Cathinone would be expected to raise plasma catecholamine levels.

The sympathomimetic actions of cathinone would be expected to raise plasma catecholamine levels. There is also inhibition of insulin release from the pancreatic  $\beta$ -cells which would also elevate blood glucose level [74]. Using khat seems to lower appetite, causing people to skip meals. When eating becomes less routine, people with diabetes may stop following their recommended diet. This could lead to higher blood sugar levels [75].

## 5. Gastrointestinal System

### 5.1. Oral and Gastro-Intestinal Problems

MOA: Astringent characteristic of the tannins

In the gastrointestinal tract, the astringent characteristic of the tannins account for periodontal disease, oesophagitis, stomatitis, gastritis and duodenal ulcer formation. Tannins and norpseudoephedrine contribute to constipation, the most common medical complaint of the khat user [76]. The sympathomimetic action of cathinone in khat may cause the observed delay in gastric emptying [77]. Gastrointestinal adverse effects of khat chewing include anorexia, constipation and stomatitis. Anorexia leads to malnutrition and increased susceptibility to infectious diseases, especially tuberculosis [78]. In the oral cavity, khat has been associated with histopathological changes like hyperkeratosis, epithelial hyperplasia and milder dysplasia [79]

Oral keratotic lesions at the site of chewing and plasma cell gingivitis (allergic reaction to khat) have been reported. The tannins present in khat leaves are held responsible for the gastritis that has been observed [79, 80]

### 5.2. Effect of Khat on Human Appetite and Body Weight

MOA: Decreases hunger and increases fullness

Cathinone affect appetite centrally, by acting in the hypothalamus. Apart from its central effect, it enhances sympathomimetic activity leading to a delay in gastric emptying [81]. A high plasma level of the anorectic hormone, leptin, has been found 4 hour after a heavy khat chewing session (400 g). This hormone may contribute to the decreased appetite and body weight [82]

## 6. Cancer

Keratosis of the oral buccal mucosa is considered as a pre-cancerous lesion that may develop into oral cancer [83]. In human leukaemia cell lines and in human peripheral blood leucocytes, khat extract, cathinone and cathine produced a rapid and synchronized cell death with all the morphological and biochemical features of apoptotic cell death [84]. Buccal epithelial cells experience genotoxic effects in a dose-related way in khat-chewers; this suggests that oral malignancies can be contributed to by khat [85]

## 7. Reproductive System

In chronic chewers, sperm count, sperm volume and sperm motility were decreased and cause impotence [86].

MOA: Impotence in males Causes spermatorrhoea and deformed spermatozoa

*Increase sexual desire in females Increases vaginal secretions and up-regulates estradiol level*

*Khat extract enhanced sexual motivation, increased vaginal secretions and up-regulated estradiol level in female* [87, 88]. In pregnant women, khat consumption may have detrimental effects on uteri-placental blood flow and as a consequence, on foetal growth and development. Khat is genotoxic, having teratogenic effects on the foetus if regularly consumed by pregnant mothers [89]. Neonates have low birth weights – a risk factor for perinatal and young infant death [90]. Currently chewing lactating women have been found to excrete norpseudoephedrine in their breast milk, and traces were found in the urine of a breast-fed infant [91]

## 8. Genotoxicity and Teratogenic Effects

Deaths and haemiplegia (paralysis of half of the body) because of meningeal haemorrhages are reported. The causal mechanism is ruptures of aneurisms following circulatory “coups de fouet” (rupture of the planteris muscle accompanied by sharp disabling pain) engendered by the use of khat same MOA in cerebral haemorrhage, cardiac arrest and pulmonary oedema [92]

## 9. Hepatobiliary System

### 9.1. Effect of khat on liver

MOA: Causes acute hepatocellular degenerative and regenerative activities

Long term chewing of khat leaves can produce repeated episodes of hepatitis and leads to fibrosis and cirrhosis probably through direct toxic effect from reactive khat metabolites, immune-allergic or idiosyncratic causes. Long term users usually develop complications of cirrhosis or acute or chronic liver failure [93]

## 10. Renal System

### 10.1. Effect of khat on kidney

MOA: Causes kidney tissue lesions, acute cellular swelling and acute tubular nephrosis

Kidney tissue showed some lesions and the degree of the lesion increased as the dose of khat leaves increased including: the presence of fat droplets particularly seen in the upper cortical tubules; acute cellular swelling; hyaline tubules and acute tubular nephrosis [94]. Khat induces a fall in average and maximum urine flow rate in healthy men. The urinary effects are probably mediated through stimulation of  $\alpha$ 1-adrenergic receptors by cathinone. This is indicated by the complete blockage of this effect by indoramin, a selective antagonist of  $\alpha$ 1-adrenergic receptors [95]

## 11. Others

### 11.1. Decreased Productivity

Khat chewing leads to loss of work hours decreased economic production, malnutrition and diversion of money in order to buy further khat. Consequently, working hours and possibly productivity can decrease when khat is not used, because of anergia and reduced motivation [96].

## 11.2. Family and Marital Problems

Many men secure their daily portion of khat at the expense of vital needs, indicating dependence. Family life is harmed because of

neglect, dissipation of family income and inappropriate behaviour. Khat is quoted as a factor in one in two divorces in Djibouti. Acquisition of funds to pay for khat may lead to criminal behaviour and even prostitution [97, 98] (Table 1).

**Table1:** The physical adverse effects of khat and its mechanism

System	Adverse effects	Mechanism
Gastrointestinal system	Dry mouth, polydipsia, dental caries, periodontal disease, chronic gastritis, gastric ulcer, constipation, paralytic ileus, anorexia, weight loss, increased risk of upper gastrointestinal malignancy, loss appetite	Astringent characteristic of the tannins Decreases hunger and increases fullness
Genitourinary system	spermatorrhoea, spermatozoa malformations, impotence, libido change in males, changes in sex drive, and inability to get an erection urinary retention, Increase sexual desire in females	Causes spermatorrhoea and deformed spermatozoa Increases vaginal secretions and up-regulates estradiol level
Ocular effects	blurred vision, mydriasis	
Central nervous system	Alertness, dependence, tolerance, and anxiety, sleep disturbance (insomnia), dizziness, impaired cognitive functioning, fine tremor, headaches	Stimulant effects of cathinone
Cardiovascular system	Tachycardia, arrhythmias, palpitations, hypertension, vasoconstriction, ischaemia, infarction, pulmonary oedema, stroke (cerebral haemorrhage). Exacerbation of pre-existing cardiac conditions	Indirect sympathomimetic activity of cathinone
Metabolic and endocrine effects	Hyperthermia, perspiration, hyperglycaemia	Cathinone would be expected to raise plasma catecholamine levels
Obstetric effects	low birth weight, stillbirths, impaired lactation	Cathinone can pass placental barrier and accumulate in fetus blood serum level owing to it is lipid soluble.
Respiratory system	Bronchitis, tachypnoea, dyspnoea, tuberculosis	
Hepatobiliary system	fibrosis, cirrhosis, hepatotoxicity	Causes acute hepatocellular degenerative and regenerative activities
Psychiatric effects	lethargy, irritability, anorexia, psychotic reactions, depressive reactions, hypnagogic hallucinations	
Renal system	Kidney damage	Causes kidney tissue lesions, acute cellular swelling and acute tubular nephrosis

## 11.3. Uses of Khat

Besides its tremendous adverse health effects, khat may have some medical uses that are specially perceived by khat chewers. Leaves of khat have been used in traditional medicine for the treatment of depression, fatigue, obesity and gastric ulcers. In folk medicine, khat is claimed to suppress cough, asthma, epidemic influenza, stomach aches, diarrhea and malaria. It can also relieve pain [99-101].

## 12. Conclusion

Khat (*catha edulis*) is a natural stimulant from the *Catha edulis* plant, found in the flowering evergreen tree or large shrub of *Celastraceae* family, which grows mainly in Ethiopia, Kenya, and Yemen and at high altitude areas in South Africa and Madagascar. Fresh leaves contain both ingredients; those left unrefrigerated be-

yond 48 hours would contain only cathine, which explains users' preference for fresh leaves. Khat loses its potency after 48 hours. The psychoactive effects of khat are mainly attributed to cathinone, a potent alkaloid which has a close structural resemblance to amphetamine. Blood levels of cathinone start to rise within 1 hour and peak plasma levels are obtained 1.5 – 3.5 hours after the onset of chewing. Metabolism of cathinone is rapid, occurring mainly during first passage through the liver. Medical problems associated with khat intoxication include psychiatric manifestations such as deterioration of psychophysical function and schizophreniform psychoses. Khat chewing is also associated with a wide range of health problems including ischaemic heart disease, gastritis, liver toxicity, oral cancer, hypertension, spermatorrhoea and haemorrhoids.

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