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# A REVIEW OF THE HISTORY, CULTIVATION, CHEMISTRY, PHARMACOLOGY AND ADVERSE HEALTH EFFECTS OF KHAT

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## ABSTRACT

Khat is a term used for fresh leaves and buds of the plant *Catha edulis.* Khat chewing is a social tradition in some countries of eastern Africa, the southern part of Saudi Arabia and Yemen. It is chewed mainly for its intoxicating euphoric effect which is attributed to its active ingredients, cathinone and cathine. These are nervous stimulants that exhibit an effect similar to that of amphetamine. Habitual khat chewing is a growing concern worldwide and has been reported to have various adverse health effects. This review describes the history, cultivation, chemistry, biochemistry and pharmacology of khat. We have mainly focused to review the available literature on the adverse effects on human health. An effort is also made to survey existing regulations on khat use in different countries of the world.

**KEYWORDS:** Amphetamine, Cathine, Cathinone, Khat, Substance Abuse

## INTRODUCTION

*Catha edulis* is an evergreen plant of the family Celestreceae. Its leaves and buds, called Khat, are chewed commonly in certain countries of East Africa and Arabian Peninsula as a social tradition. The habit of khat chewing has spread to many countries including the US and Western Europe on account of the spread of Yemeni, Somali and East African communities to these regions [1, 2]. The leaves are usually eaten fresh but their potency can be preserved by wrapping them in banana leaves immediately after picking [3]. Khat is chewed mainly for its euphoric effect and the 'khat experience' includes increased alertness, concentration, confidence, friendliness, contentment and flow of ideas [4]. Historically, khat has been used for medicinal purposes [5], as an aphrodisiac [6] and also for recreational purposes [4] due to its stimulant effects [7]. Due to its central stimulant effect it has found use in the management of obesity and depression [8]. The main active ingredient of khat responsible for its stimulant effects is cathinone. The habit of khat chewing did not pose serious public health or socio-economic problem a few decades ago as it was restricted to older people particularly Muslim who chewed khat as alcohol was prohibited in the religion [9]. However, more recently its use has spread across populations regardless of faith, ethnicity, age, sex, education etc [10]. With this rise in the prevalence of khat chewing worldwide, the concern to its adverse health has grown [2]. Habitual khat chewing has been reported to have adverse effects on almost all aspects of human health. These effects include impairment of mental health, elevated blood pressure, increased heart rate, increased incidence of acute myocardial infarction (AMI) [11-14], GI problems such as constipation, stomatitis and gastritis [15]. Besides adversely affecting health, khat also has a damaging effect on socio-economic aspects of life [16].

The present review describes the adverse effects of khat chewing on human physiology including the central nervous system, cardiovascular system, digestive system, genitourinary system, reproductive system and fetal and neonatal health.

Other effects on health related to psychosis and psychological dependence and cancer have also been reviewed. The review also includes the current regulations on khat abuse in different countries of the world.

## THE HISTORY OF KHAT PLANT

Khat has its origin in Ethiopia and early spread in to countries of Arabian peninsula, Eritrea, Somalia and Djibouti. Now it is grown in many countries like Kenya, Uganda, Tanzania, the Congo, Malawi, Zimbabwe, Zambia and South Africa [17]. The khat plant was considered a "divine food" by the ancient Egyptians thought to be capable of releasing divinity in humans. The Egyptians used the plant not only as a stimulant but also as a metamorphic tool that could make them transcend into "apotheosis" and make them god-like [15]. An Arabian physician Abu Al-Rihan Bin Ahmed Al-Baironi (973-1051 AD) described the first medicinal use of khat in his book '*Pharmacy and Therapeutic Art'* [18]. Najeeb Al-Deen Al Samargandi, described khat for the treatment of depression in the book '*The Complex Drugs'* written in 1237 AD [8].

## CULTIVATION OF KHAT TREE

The khat plant is perennial, cultivated by grafting and grows for 3-4 years. It has a straight and slender trunk and a thin, smooth, grey-brown bark. Its tap-root grows more than 3 meter deep. The plant is polymorphic, its leaves grow opposite or alternate and are serrated with shapes from ovate-lanceolate to elliptical. The leaves have a slightly sweet astringent taste and a faintly aromatic odour [19]. The flowers are white, five-petal and are produced on short axial cymes. The fruit is an oblong capsule containing 1-3 seeds.

The khat plants are planted 2-3 meter apart in rows. Khat fields on terraced mountains are irrigated by rain water and those on flatlands by shallow trench or pipe irrigation. Heavy watering about a month before harvest makes the leaves and stems soft and moist.

Chewable khat is usually harvested for the first time in 3-4 years. The plant can be harvested up to four times in a year for about 50 years and is a good source of income for the farmer. Crop damage of any economic significance due to plant pathogens is unknown [20]. A tiny green leaf hopper (*Empoasca* species) is considered to be beneficial as it causes older tips to wilt and die off and new shoots to emerge. Khat farmers have used insecticides for crop protection but the consumer response to insecticide treated crops has been negative and more farmers have returned to traditional crop protection means such as fine dust treatment.

## CHEMISTRY OF KHAT

About 44 different varieties differing in their chemical profiles are known to grow in various geographic regions [12, 21]. These have varying tastes due to their tannic acid content. Many different chemical compounds are found in khat and these include alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals [19, 22, 23]. The major alkaloids are phenylalkylamines and cathedulins.

Cathinone [S-(-)-cathinone], and its two diastereoisomers cathine [1S, 2S-(+)-norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R, 2S-(-)-norephedrine] comprise the phenylalkylamines. These compounds have structural similarity to amphetamine and noradrenaline. Only the (–)-enantiomer of cathinone which has the same absolute configuration as S-(+)-amphetamine is found in khat [19]. The young plant contains cathinone which gets converted to cathine [(+)-norpseudoephedrine] and (-)-norephedrine as the plant matures.

Cathinone and cathine at a ratio of 4:1 are found in the leaves [19]. Phenylpentenylamines, merucathinone, pseudomerucathine and merucathine are the other alkaloids belonging to the phenylpentenylamines also found in khat [24-26]. Cathinone is unstable and it decomposes to inactive coumpounds on drying and extraction [22, 27]. Hence, chewing fresh khat is preffered as cathinone is presumably its major psychoactive ingredient. Other (other than cathinone and cathine) have a lesser stimulant effect [22, 27, 28].

Cathedulines is the other major alkaloid group of khat. These are sesquiterpenses which are polymers of euonyminol [29]. Cathedulins from Kenyan khat are named K1, K2, K6 and K15. Of these the most abundant is K2 with an equivalent Y1 from Yemen [30]. Up to 62 different cathedulines may be found in fresh khat. Cathedulines and phenylpentenylamines do not have any significant biological activity [28].

Widely varying content of phenylalkylamines per 100 g khat leaves has been reported.

- 36 mg cathinone, 120 mg cathine and 8 mg norephedrine [21].
- 114 mg cathinone, 83 mg cathine and 44 mg norephedrine [31]
- 102 mg cathinone, 86 mg cathine and 47 mg norephedrine [32].
- Cathinone 78-343 mg [12].

Khat also contains considerable amounts of tannin (7-14% by weight in dried leaves) and small amounts of essential oils, triterpenes, protein, ascorbic acid, thiamin, niacin, riboflavin, iron and amino acids. Of these only tannin may have some biological effect [19, 20, 33].

## PHARMACOKINETICS OF KHAT ALKALOIDS

100-200 g of fresh leaves of the khat are chewed are generally chewed for maximum stimulant effect. 45 g of chewed khat results in an absorption of 45 mg of cathinone. The euphoric effect of khat are felt after about 1 h of chewing when cathinone starts to rise in blood Peak plasma levels of cathinone are reached in 1.5-3.5 hrs [34]. Chewing 60 g fresh khat leaves (cathinone: 0.8-1 mg/kg body weight) can result in a maximum plasma level of 40-140 ng/ml (mean 83 ng/ml) after 1 hr. Cathinone remains detectable in blood for up to 24 hrs. (half-life: 260 min) [32].

Metabolism of cathinone occurs in liver and is rapid. Only 2% of cathinone appears in urine unchanged [22, 35] while 22-52% is excreted mainly as the amino alcohols, norephedrine and norpseudoephedrine. Cathinone is metabolized in the liver by a stereospecific keto reduction to the major metabolites, R, S-(-)-norephedrine from S-(-)-cathinone and R, R-(-)-norpseudoephedrine from R-(+)-cathinone as [31, 35].

## PHARMACOLOGY OF KHAT

Cathinone, the main active alkaloid of khat has amphetamine-like properties [33,36] and like amphetamine it is considered as an indirect dopaminergic agonistic drug [15, 22]. In addition, (-)-cathinone also releases serotonin from its striatal stores, an action similar to (+)-amphetamine [33]. The effect of (-)-cathinone on neurotransmission are similar to that of (+)-amphetamine although at 2-10 times lesser potency. In terms of potency, khat alkaloids lie between caffeine and amphetamine [37]. The central nervous stimulant potency of cathinone is about half of amphetamine [38].

Cathine (norpseudoephedrine) and norephedrine are two other pharmacologically active compounds in khat which are less potent stimulants [27]. Their effect on the nervous system is also qualitatively similar to that of amphetamine [23,39,40]. Chewing a typical amount of khat leaves has been considered as equivalent to an oral dose of 5 mg of amphetamine [41] but this comparison may not be valid [1].

## ADVERSE HEALTH EFFECTS OF KHAT CHEWING

Habitual use of khat affects the cardiovascular, digestive, respiratory, endocrine and genito-urinary systems of the human body. The major effects include those on the gastro-intestinal system (constipation, urine retention), acute cardiovascular and central effects such as increased alertness, dependence and tolerance. Adverse central effects of khat use are the induction of paranoid psychosis and hypomanic illness with grandiose delusions [42].

The adverse effects of khat chewing on human health are described below.

### Effects on the Central Nervous System

Euphoria and elation is an early effect of khat. The chewer feels alert, energetic and aroused. A stage of vivid discussions, loquacity and an excited mood follow. However, a khat session culminates in the user experiencing depression, irritability, anorexia and difficulty to sleep [12, 22]. Temporary anxiety and depression have been reported during khat sessions, but these disappear the following day [43]. Anorexia and insomnia are also associated with khat. [40]. Khat affects the central nervous system in a dose-dependent manner [23, 44]. At a low dose it does not affect pupil size and reaction to light, does not induce rotary nystagmus or impairment of reaction and does not induce any severe adverse reaction.

### Effects on the Cardiovascular System

Abuse of amphetamines is reported to be associated with acute myocardial infarction (AMI) [13, 45]. Coronary spasm has been found to be the main mechanism of AMI in khat chewers [46]. Khat chewing appears to be an independent dose-related risk factor for AMI and a 39-fold increased risk of AMI has been associated with heavy khat chewing [13]. An increased prevalence of AMI has been reported in khat chewers. [47]. In a study in khat administered rabbits, significantly increased serum levels of cardiac enzymes (LDH and CK-MB) and histological changes in heart associated myocardial infarction were observed [47]. A higher incidence of vascular complications like hemorrhoids has also been reported in chronic khat chewers [48].

Higher incidence of acute cerebral infarction has been reported among khat chewers, due to the significantly higher blood pressure [49]. Cases of ischaemic stroke, AMI and cerebrovascular accidents after khat chewing have been reported suggesting increased thrombogenicity caused by khat [50, 51]. However, inspite of these reports a casual relationship between khat chewing and cerebrovascular accidents are yet to be established.

### Effects on Oral-Dental Health

A range of oral and systemic health effects [52,53] associated with habitual khat chewing make it a national and international public health concern [54, 55]. In a cross sectional study of khat chewers from among UK resident Yemeni community symptomatic dental problems were reported [56]. Some other investigators have also described adverse oral-dental issues with khat chewing [57,58]. Long-term khat chewing causes stomatitis with secondary infections which may be due to mechanical strain on oral tissue as well as chemical irritation of the oral mucosa. Periodontal disease and

dental caries have been observed in khat chewers at varying rates. [58]. Hill and Gibson (1987) observed some prevalence of caries and universal attrition, temporomandibular joint pain and increased periodontal pocket depth [59]. Keratosis of buccal mucosa is also reported. Lesions in gums like gingivitis, periodontal pocket formation, gingival recession etc have been reported by some investigators [60]. Oral keratotic lesions at the site of chewing [61] and allergic reaction to khat as plasma cell gingivitis is also described [62]. Some other studies on oral-dental effects of khat chewing have shown contradictory results. In such studies, beneficial rather than detrimental effects on the periodontium have been reported [63, 64]. Mengel et al., (1996) have suggested that bad oral hygiene rather than khat itself might be the cause of periodontal disease [65]. No significant relation between oral leukoplakia and khat could be established [66]. Khat chewing was speculated of inducing a microbial profile compatible with gingival health rather than increasing colonization of gingival plaque [64].

**Effects on the Digestive System**

Habitual khat chewers often have GI symptoms like dryness in mouth, stomatitis, oesophagitis and gastritis. Tannins present in khat are believed to cause these effects due to their astringent action [5, 14, 40]. The tannins are also responsible for gastritis commonly seen in khat chewers [57, 67].

The effect of khat chewing on salivary glands includes mouth dryness, enlargement of salivary glands and inflammation and folding of the parotid papilla at the site of its chewing. Of these, dryness of mouth may be due to the sympathomimetic effect of cathinone [4].

Gastric symptoms are attributed to a hypotonic stomach and delayed gastric emptying due to the sympathomimetic action of khat alkaloids [32, 40]. Manifestation of heartburn (increased rate of gastrooesophageal reflux), acid regurgitation, and an increased risk of Barrett oesophagus are all attributed to delay gastric emptying.

A significant loss of appetite on khat chewing has been reported. Anorexia results after a khat session and khat chewers do not feel hungry [68]. Effect on ghrelin or peptide YY levels is not thought to be responsible for this anorectic effect [69]. It is rather believed to be a direct effect of cathinone on CNS [32]. Plasma levels of leptin increase after 4 hrs of khat chewing at 400 g. Leptin is an anorectic hormone that decreases appetite. Hence, khat chewers are typically underweight [70].

Constipation, probably caused by tannins (astringent) and cathinone (sympathomimetic) is a common complaint of khat chewers [19]. Habitual khat users avoid constipation by eating a high fat meal prior to the khat session [71] or by using laxatives [57]. The mechanisms reported to be involved in constipation are slowing of both the orocaecal transit time [72] and the whole gut transit time [73].

Khat chewing results in malabsorption and low bioavailability of some orally administered antibiotics, like ampicillin [74]. Risk of duodenal ulcers [75] is also associated with khat. No effect on gall bladder contraction has been demonstrated in khat chewing [76].

The liver is particularly vulnerable to the harmful effects of khat [57, 58], and abnormal liver function and anatomy has been described in experimental animals both on short-term [77] and long-term feeding of khat leaves [78]. Khat feeding decreases plasma cholesterol, glucose and triglycerides [79] and increases plasma alkaline phosphatase and alanine aminotransferase [77] in rabbits.

In another study, a significant reduction in total serum cholesterol, HDL- and LDL- cholesterol level and the glucose concentration along with destruction of the normal architecture and hepatocytes of the liver in khat fed animals was observed [80]. Histopathological signs of hepatotoxicity include congestion of the central liver veins and acute hepatocellular damage, acute hepatitis and jaundice [81, 82]. More recently, severe acute liver injury has been attributed to khat chewing in the USA [83]. In UK men of Somali origin who were regular khat chewers, jaundice and deranged liver function has been described based on histology and serum biochemistry [84]. Recently, khat is identified as an etiological risk factor in chronic liver disease and suggested to have a potentiating effect on chronic hepatitis B and delta virus mediated liver damage [85]. In another case study series, PWE-248, khat was observed as a possible cause of drug induced autoimmune hepatitis [86]. In one animal study, hepatotoxicity on heavy khat feeding occured in both male and female SD-rats with hepatic hypertrophy while nephrotoxicity was seen in female SD-rats [87]. Parasitic infection of the liver by *Fasciola hepatica* as a contaminant of the khat leaves has also been reported [88]. Hepatotoxicity in humans has been reported in several other studies [83, 84, 89-91]. Administration of khat extracts at high doses decreased the systemic capacity to handle oxidative radicals and induced cytotoxicity in liver and kidney [92].

**Effects on the Genitourinary System**

Khat induces a decreased urine flow rate in healthy men [40, 93]. Stimulation of α1 adrenoceptors in the bladder neck by the sympathomimetic action of cathinone may be responsible for this effect as the effect is abolished by indoramin, an alpha1-blocker. Khat consumption is considered to induce increased libido, spermatorrhoea and erectile dysfunction an effect that is still not well studied [94].

Kidney lesions have also been observed with the presence of fat droplets in the upper cortical tubules, acute cellular swelling and acute tubular nephrosis [77, 78].

**Effects on Reproductive Function**

Khat chewing affects reproductive functions negatively [95]. It is shown to cause decreased sexual functioning, impotence and spermatorrhoe [57, 95]. Sperm parameters like count, volume and motility are also found to be reduced in habitual chewers [96, 97]. Abnormal sperm morphology like malformed head and flagella, aflagellate heads, headless flagella and multiple heads and flagella have been described in Yemenite khat chewers [96]. The effects are contrary to the beliefs in Yemenites that khat chewing improves sexual desire and excitement [14]. Rather, khat inhibits spermatogenesis and lowers testosterone levels and thereby affects male sexual potency. A reduction in plasma testosterone levels and increase in cortisol has been demonstrated in khat fed male rabbits [98]. Yet, in a study that contrasts the previous study increased testosterone and decreased prolactin and cortisol were observed in olive baboons that were fed khat extracts weekly for 2 months [99]. In another study with khat fed baboons on a dose of 500 g/week for 1 month, reduced testosterone and prolactin (but not cortisol) as well as adverse sperm parameters were observed [100].

**Effect on Fetal and Neonatal Health**

Khat consumption during pregnancy may have detrimental effect on fetal growth and development as it is shown to impair uterine placental blood flow [95]. Increased incidence of lower mean birth weights among full term infants has been reported in in mothers who chewed khat during pregnancy [101,102]. Abd-El-Aziz and Ahmed (1998) have found significantly decreased neonatal parameters including birth weight, length, head circumference and Apgar score at 1 and 5 minutes in neonates born to mothers who ate khat during pregnancy [103].

Nursing mothers frequently complain of Poor lactation in khat chewing nursing mothers has been observed. It is believed to be related to the inhibition of prolactin secretion by khat alkaloids [58]. Cathine has been detected the breast milk of khat-chewing mothers and also in the urine of breastfed infants [104].

**Effect on Diabetes**

The effect of khat on diabetes is not very clear. There are very few and inconclusive reports in the literature on this matter. Yemeni people believe in general that blood sugar can be controlled by khat chewing and khat may have therapeutic role in management of hyperglycemia. Yet, khat has not been shown to affect fasting or postprandial glucose levels in healthy, nondiabetics in one study [105], while in another a decrease in serum glucose was observed [106]. However, blood glucose was found to be raised after 1 and 2 hrs. in diabetics who ate khat [105]. In studies on khat fed rabbits, reports indicate an increase as well as decrease in plasma glucose levels [79,80]. Effect on blood glucose may be indirectly related to decreased appetite in khat chewers. A lowering of plasma cholesterol level was observed through 6-months of khat feeding in rabbits [79].

**Khat and Cancer**

There are a number of studies in the literature on the toxicological properties of khat. Abder-rahman and Modallal (2008) found khat to be is a potent genotoxic agent [107]. As khat is consumed orally, it commonaly affects the oral cavity and digestive tract and that too in a dose dependent manner [94]. Makki (1975) found an association between khat use and oral squamous cell carcinomas particularly in the buccal mucosa and lateral sides of the tongue, these site come into direct contact with the khat during chewing [108]. A similar study in Asir region of Saudi Arabia increased incidence of oral malignancies was shown among habitual, long-term khat chewers [109]. In another study in Yemen on 36 patients of squamous cell carcinoma (including oral cavity, oropharynx, nasopharynx, larynx) 30 were habitual khat chewers since childhood [110].

Keratosis of the oral buccal mucosa, a precancerous lesion, is seen in almost 50% khat eaters [59] Oral keratosis is known to develop into oral cancer [111]. Oral keratotic white lesions have been reported in 22% khat chewers [61]. The prevalence and severity of these lesions is found to increase with the frequency and duration of khat use.

Tannins in khat may be carcinogenic and are known to cause thickening of the mucosa of the oropharynx and oesophagus [112,113]. A high frequency of khat chewing and water-pipe smoking (*mada'a*) was found among both men and women who had 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 [32, 114].

Abnormal mucosal histology of the upper gastrointestinal tract was observed in khat chewing Yemeni patients with dyspepsia [114]. Khat extract, cathinone and cathine were shown to cause rapid, apoptotic cell death in human leukemia cell line [115].

**Physical and Psychological Dependence**

Khat is shown to have slower onset of action and hence a lower addictive potential. Maximal plasma levels of khat alkaloids are reached in about 2-3 hrs. and hence khat has lesser reinforcing properties than other faster acting stimulants like amphetamine and cocaine.

Animal studies have shown khat extracts to induce a long-lasting (10-15 days) behavioral sensitization in rats, an effect similar to that of cathinone and amphetamine [116].

Moderate but often persistent psychological dependence in humans may be caused by khat [42] when khat is eaten on a daily basis [22]. Khat eating does give mild craving but no definite withdrawal symptoms are associated. Habitual khat chewers may feel hot and lethargic [12]. Nightmares are common but these stop after a few nights. Withdrawal symptoms after prolonged use are mild and may consist of lethargy, mild depression, slight trembling and recurrent bad dreams [42], but these symptoms are mild and resolve in short time [94]. Khat dependence has been scarcely reported [117-119]. Khat chewers develop tolerance to the increased BP, heart rate, respiratory rate and body temperature, and also to insomnia [19, 58, 94, 120]. Habitual users after stopping khat have shown improvement in sleep and appetite, and alleviation of constipation [12, 58]. In Somalian khat chewers in UK a moderate dependence has been reported. [121]. Reports of severe medical problems are rare. Khat has not been classified as an inevitably dependence producing drug [57, 122]. The World Health Organization (WHO) has classified khat as a substance that causes psychological but not physical dependence negatively impacting the social and economic life of the user [123]. In conclusion, khat has low abuse potential in humans and khat dependence is mild.

**Khat Induced Psychosis**

Impairment of memory, depression and psychoses have been associated with khat usage. [124]. Two types of psychotic reactions to khat are seen (i) a manic illness with grandiose delusions and (ii) a paranoid or schizophrenic form of psychosis with persecutory delusions associated with mainly auditory hallucinations, fear and anxiety [38,67,125,126]. These reactions are associated with chewing khat in large amounts and are exceptional [127,128]. Khat psychosis may be sometimes be accompanied by depression and violent reactions [67]. Heavy khat chewing precipitates psychosis in those who are already predisposed [23, 129] and might exacerbate symptoms in patients with pre-existing psychiatric disorders [43]. Symptoms rapidly disappear on withdrawal [67, 130, 131]. Hence, withdrawal alone is considered to be an effective treatment of khat psychosis and antipsychotics are rarely needed for full remission [38, 128,130]. Nevertheless, in most cases described in the literature antipsychotic medication has been used to alleviate the symptoms [128].

Some studies on Somalians have revealed a relationship between excessive khat chewing (binge chewing, more than 2 bundles per day) and onset of psychotic symptoms [129]. A positive relation was observed in this study between the number of traumatic events experienced and the average daily consumption of khat. Dhadphale and Omolo (1988) studied psychiatric morbidity among khat users and found it to be associated with consumption of more than two bundles per day [127]. Some case reports also indicate adverse effects of khat at high doses. [44,132]. Some contradictory results have also been reported. The incidence of adverse psychological symptoms was not found to be greater in khat users than in non-users when a large survey among Yemenites was conducted [133]. On the contrary, a negative correlation between the incidence of phobic symptoms and khat use was observed. A report of an attempt of suicide during a khat-induced paranoid psychosis by 34-year-old Somali woman in UK is also found [134]. Among Somali refugees in the UK current khat use was found to be a risk factor for anxiety, depression, suicidal tendency and psychosis [135]. In one study khat use appeared to exacerbate existing psychological problems, there was no clear evidence that implicated khat as a cause of the development of mental illness [136,137]. Khat use is not conclusively linked to psychotic symptoms in population samples of Somali men and women [138].

Hypnagogic hallucinations consisting of continuous visual and/or auditory dreamlike experiences have been reported in chronic khat users [139].

## CONCLUSIONS

In conclusion, it appears that adverse health effects related to habitual, chronic abuse of khat are generally mild in nature. There are very few and inconclusive reports of acute and severe abnormalities resulting from khat use. Though an increased number of cardiovascular events like hypertension and myocardial infarction have been reported in habitual khat users, but no cardiovascular emergencies have been reported as a result of khat use. Some periodontal diseases and gastro-intestinal complaints seem to be associated with khat use, but the effects observed are mild and the epidemiological evidence for an association very weak. On the other hand, there is an alarmingly high prevalence of oral and head and neck cancers in khat users which may be a subject of further investigation. Khat does not appear to cause dependence and has a low abuse potential. There are no definite withdrawal symptoms although mild craving and tolerance to khat effects exists. Whether khat causes psychiatric morbidity is debatable with contradictory evidence of a causal relation. Most evidence is confounded by factors like the presence of post traumatic stress disorder (PTSD), chronic psychotic disorders, social stress [135, 140, 141]. Personal factors such as multi illicit drug use, medication and the relatively low socio-economic background of drug users also complicates any conclusive deduction.

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## APPENDICES

### SUPPLEMENTAL MATERIAL

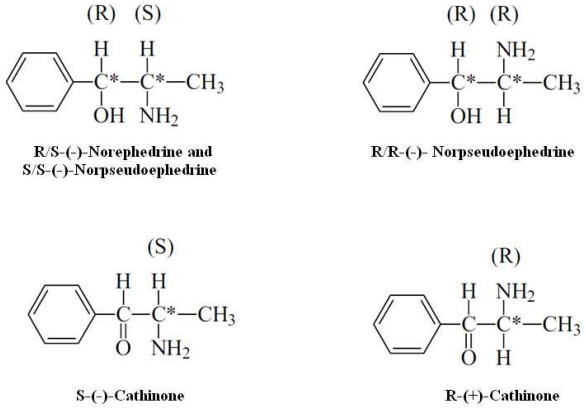


**Figure 1: Chemical Structures of Cathinone and Cathine**

**Table 1: Chemical Composition of Fresh Khat Leaves**

| Cathinone (mg/100 g) | Cathine (mg/100 g) | Norephedrine (mg/100 g) | Reference |
|---|---|---|---|
| 36 | 120 | 8 | [21] |
| 114 | 83 | 44 | [31] |
| 102 | 86 | 47 | [32] |
| 78-343 | - | - | [12] |

**Table 2: Reported Adverse Health Effects of Khat Chewing**

| System | Effects | References |
|---|---|---|
| Cardiovascular and central nervous system | Acute Myocardial Infarction | [13] |
| | Hemorrhoid & Hemorrhoidectomy | |
| | Acute Cerebral Infarction | [49] |
| | Ischemic stroke | [50] |
| | Thrombogenecity | [51] |
| Oral-dental tissue | Stomatitis, Periodontal disease | [58] |
| | Ketatosis of buccal mucosal | [59] |
| | Gingivitis, Periodontal pocket formation, Gingival recession, tooth mobility & mortality | [60] |
| | Oral keratotic lesion | [61] |
| Digestive system | Mouth dryness, Stomatitis, Oesophagititis and gastritis | [40] |
| | Anorexia, Reduced of appetite | [68] |
| | Constipation | [19] |
| | Duodenal ulcer | [75] |
| | Jaundice, Acute hepatitis | [81] |
| | Impaired liver function | [82] |
| | Acute liver injury | [83] |
| Genito-urinary system | Reduced urine flow rate | [40] |
| | Libido, spermatorrhoea, erectile dysfunction | [94] |
| Reproductive, fetal and neonatal health | Spermatorrhoe | [95] |
| | Reduce sperm count and sperm volume, sperm mortality, deformed permatozoa | [97] |
| | Reduced plasma testosterone | [98] |
| | Decreased birth weight | [101] |
| | Poor lactation | [58] |