

## Adverse Health Effects of Khat: A Review

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### Abstract

**Introduction:** Khat refers to the leaves and the young shoots of the plant *Catha edulis* Forsk, which belonging to the plant family Celastraceae. Khat is an evergreen shrub or tree found growing wild or cultivated in the east of a region extending from Southern Africa to the Arabian Peninsula. The habit of khat chewing has prevailed for centuries in this part of the world.

**Objective:** To summarize the potential adverse health effects of khat (*Catha edulis*).

**Methodology:** We used 57 different published materials for the compilation of this review article. Google search engine was used for accessing published materials from databases like Google Scholar, PubMed and HINARI.

**Result:** Khat induces disturbance of mood, hallucination, delusions and aggressive behavior. It may also cause elevation of arterial blood pressure and pulse rate with subsequent increase in cardiovascular risk. In addition, khat may be associated with increased risk of carcinoma of the mouth and oesophagitis, anorexia and constipation. It may also have a toxic effect on the liver and kidneys.

**Conclusion:** Many literatures reported that Khat has potential adverse health effects on organs and systems of the body. It affects nervous system, cardiovascular system, reproductive system, gastrointestinal tract, liver, kidneys and others.

**Keywords:** Adverse health effects of khat; *Catha edulis*; Cathinone; Epidemiology of khat; Khat

### Abbreviations:

DNA: Deoxyribonucleic Acid; GSH: Glutathione; MI: Myocardial Infarction; RNA: Ribonucleic Acid; ROS: Reactive Oxygen Species

### Introduction

#### Definition and epidemiology of khat

Khat refers to the leaves and the young shoots of the plant *Catha edulis* Forsk, which belonging to the plant family Celastraceae [1]. Khat is an evergreen shrub or tree found growing wild or cultivated in the east of a region extending from Southern Africa to the Arabian Peninsula [2]. The earliest scientific report on khat in the West was in the eighteenth century when the botanist Peter Forskal identified the plant in Yemen and called it *Catha edulis*. There are several names for the plant, depending on its origin: qat-Yemen, tchat-Ethiopia [3], qaad/jaad-Somalia [4], miraa-Kenya, mairungi-Uganda, Muhulo-Tanzania and Hagigat-Hebrew [5].

Fresh leaves from khat trees are chewed daily by over 20 million people on the Arabian Peninsula and East Africa [6]. The khat

chewing habit is deeply rooted in the socio-cultural traditions of these countries [7,8]. Many of the users originate from countries between Sudan and Madagascar and in the southwestern part of the Arabian Peninsula. Khat use is particularly widespread in Kenya, Ethiopia, Djibouti as well as Yemen [9]. The migration of users of khat from these countries has resulted in the spreading of khat use to countries in other regions of the world like America, Europe and Australia [10]. The biggest population of chewers is in Yemen, where the plant is used as social stimulant [6]. Reports suggest that 80-90% of the male adult and 10-60% of the female adult population in East Africa consume khat on a daily basis [11,12].

#### Active constituents of khat leaf

Several different chemical substances are found in the leaves of khat and these include alkaloids, terpenoids, sterols, flavonoids, glycosides, tannins, more than 10 amino acids including tryptophan, glutamic acid, alanine, glycine and threonine [13], trace quantities of vitamins including ascorbic acid, thiamine, riboflavin, niacin, and carotene [14,15] and elements including calcium, iron, manganese, zinc, copper and toxic metals like lead and cadmium and a negligible amount of fluoride [16].

The leaves of khat plant contain alkaloids like cathinone, cathine and norephedrine which are structurally and pharmacologically related to amphetamine [17]. Cathinone is the principal active

constituent of khat responsible for the stimulant effects that have led khat to be known as a 'natural amphetamine' [18]. Fresh khat is reported to contain an average of 36 mg cathinone, 120 mg cathine and 8 mg norephedrine per 100 g leaves [13]. Considering the nature and content of the various substances known to be present in khat, it is evident that compounds of the amphetamine type and the tannins are those that are particularly relevant to the effects of consumption of khat observed in man [19].

## Methods

We have used Google search engine to access publications from databases like PubMed, Google Scholar and HINARI. Studies (published from 1972 to 2014), focused on epidemiology of khat, active constituents of khat and abuse potential of khat, were browsed using the keywords such as "Adverse health effects of Khat," "*Catha edulis*," "Cathinone," "Epidemiology of khat," and "Khat". Journals, reports, books and related documents published in English language were eligible for inclusion. The review selection process is depicted in Figure 1.

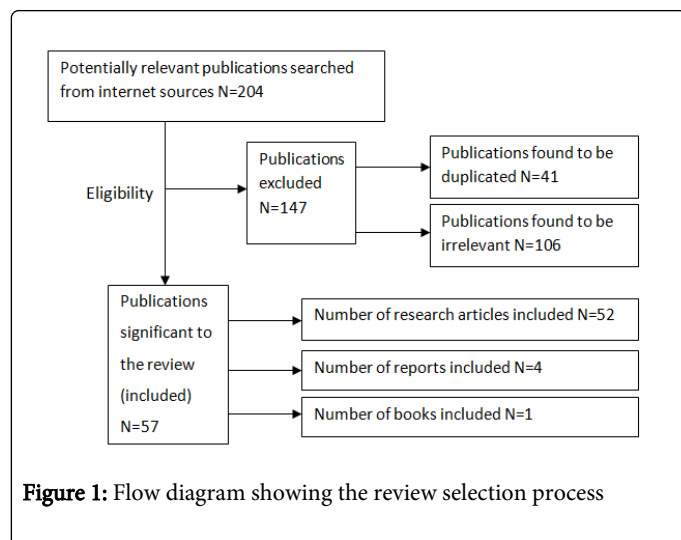


Figure 1: Flow diagram showing the review selection process

## Result and Discussion (Abuse Potential of Khat)

To assess the harm of drugs of abuse, Nutt et al. ranked a range of 20 psychoactive substances in terms of physical harm, social harm and dependence potential. The ranking system positioned khat as the least harmful substance in the group of substances evaluated in the United Kingdom by a panel of experts [20]. There is an emerging consensus among international health authorities that khat has a low abuse potential [21]. In addition, adverse effects of khat use may be aggravated by the use of other stimulants such as tobacco [22].

However, several potentially harmful psychological, physiological, public health and social effects of Khat have been documented [23,24]. These adverse effects to the ingestion of khat may be mild or severe [1,15]. The former includes emotional instability and irritability. More serious side effects have been reported, including impaired cognitive functioning, insomnia, anxiety, psychotic reactions, hypnagogic hallucinations, bronchitis, tachypnea, polydipsia, chronic gastritis, gastric ulcer, constipation, anorexia, weight loss, cirrhosis, urinary retention, impotence, tachycardia, arrhythmia, hypertension, vasoconstriction and myocardial infarction [25].

## Khat and nervous system

Khat is a stimulant with effects similar to amphetamine, because the main active ingredient in khat is cathinone, an amphetamine like substance [26]. Chewers report their subjective experiences of khat use in a positive way when consuming small amounts. They describe a feeling of well-being, increased energy levels, a sense of euphoria, excitement, increased alertness, improvement in self-esteem, increased ability to concentrate, an increase in libido, enhanced imaginative ability, improvement in the ability to communicate, capacity to associate ideas, and subjective improvement in work performance [15].

However, chewers can be seen to show a range of experiences, from minor reaction to the development of a psychotic illness. Minor reactions include over-talkativeness, over-activity, insomnia, irritability, anxiety, agitation and aggression [15]. Broadly, the main psychiatric manifestations linked to the use of khat are a short-lived schizophreniform psychotic illness, mania and, more rarely, depression [27].

## Khat and cardiovascular system

Khat has direct effects on the cardiovascular system due to the indirect sympathomimetic activity of cathinone [6], causing clear increases in heart rate and blood pressure in humans. According to a study by Toennes et al. and Widler et al., significant increases in systolic and diastolic blood pressures persist for between 3 and 4 hours after the onset of khat chewing [28,29]. Similar findings were found by Getahun et al., where the prevalence of hypertension was significantly higher among Khat chewers (13.4%) than non-chewers (10.7%) [30].

In addition, there is evidence of increased risk of myocardial infarction (MI) and cardiac arrhythmias among khat users [31]. However, other studies showed less convincing evidence of the links between cardiac dysfunction and khat use [32]. Khat chewing may be considered as a risk factor for the occurrence of MI especially in persons who are susceptible to the disease. From 120 patients with MI admitted to Al-Thawra Hospital in Yemen, 79% of patients with MI were Khat chewers and only 20.8% were non-Khat chewers. Therefore, it is recommended that Khat chewing should be avoided in persons who have any cardiovascular problems [33].

## Khat and gastrointestinal tract

In the gastrointestinal tract, the astringent characteristic of the tannins account for periodontal disease, oesophagitis, stomatitis, gastritis and duodenal ulcer formation [6]. Tannins and norpseudephedrine contribute to constipation, the most common medical complaint of the khat user. The sympathomimetic action of cathinone in khat may cause the observed delay in gastric emptying [34].

In the oral cavity, khat has been associated with histopathological changes like hyperkeratosis, epithelial hyperplasia and milder dysplasia [35,36]. Oral keratotic white lesions can develop at chewing site. Prevalence of these lesions and its severity increase as duration and frequency of chewing khat increases [36]. A higher incidence of head and neck cancer has been reported among khat chewers compared with non-chewers. Khat has been found to be genotoxic to cells of the oral mucosa [37], to inhibit de novo synthesis of proteins, RNA and DNA [38] and to induce a caspase dependent apoptotic cell death in various leukemic cells [39].

### Effect of khat on human appetite and body weight

The appetite suppressant effects of chewing leaves of the khat plant have been reported for several centuries [19,40]. 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 [34]. In healthy volunteers, khat decreased hunger and increased fullness; this was associated to a prolonged gastric emptying [41]. 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 [42].

### Khat and type II diabetes mellitus

The sympathomimetic actions of cathinone would be expected to raise plasma catecholamine levels. These catecholamines would increase blood glucose levels by activation of glycogenolysis in skeletal muscles and liver. There is also inhibition of insulin release from the pancreatic  $\beta$ -cells which would also elevate blood glucose level [43]. While some studies showed that in healthy non-diabetics, khat did not affect fasting or post-prandial serum glucose levels [44], others have suggested a decrease in serum glucose [45]. In diabetic subjects, however, serum glucose was significantly higher after 1 and 2 hour of khat chewing [44].

Organ/system	Adverse effect	Mechanism
Nervous system	Psychotic illness	Stimulant effects of cathinone
Cardiovascular system	Heart rate and blood pressure increased and myocardial infarction	Indirect sympathomimetic activity of cathinone
Gastrointestinal tract	Oesophagitis, stomatitis, gastritis and duodenal ulcer	Astringent characteristic of the tannins
Appetite and body weight	Appetite and body weight decreased	Decreases hunger and increases fullness
Type II diabetes mellitus	Hyperglycemia	Cathinone would be expected to raise plasma catecholamine levels
Liver and kidneys	Cirrhosis and acute or chronic liver failure	Causes acute hepatocellular degenerative and regenerative activities
	Kidney damage	Causes kidney tissue lesions, acute cellular swelling and acute tubular nephrosis
Reproductive system	Impotence in males	Causes spermatorrhoea and deformed spermatozoa
	Increase sexual desire in females	Increases vaginal secretions and up-regulates estradiol level
Free radical homeostasis	Oxidative stress	Decreases the activities of free radical metabolizing enzyme systems

**Table 1:** A summary of potential adverse health effects of khat

### Effect of khat on liver and kidneys

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 [46].

The histopathology of tissue sections of the liver displayed evidence of congestion of the central liver veins as well as acute hepatocellular degenerative and regenerative activities in the tissue sections obtained from animals treated with both 20% and 30% khat. Similarly, 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 [47].

### Khat and reproductive system

Khat chewing causes impotence. It is known to cause spermatorrhoea usually at the first micturation after the session ends. In a comparison between khat-addicted and non-khat addicted subjects, semen volume, sperm count and sperm motility were found to be lower among the addicts [10]. There were also a greater proportion of deformed spermatozoa present among the addicts [6]. However, its positive effect on sexual desire is more frequently observed in females than in males and occurs when khat is chewed.

Khat extract enhanced sexual motivation, increased vaginal secretions and up-regulated estradiol level in female rats [48].

### Khat and oxidative stress

Reactive oxygen species (ROS) are ions or radicals generated through normal cellular metabolic processes. They comprise free radical species like superoxide anion and hydroxyl radical as well as non-radical species like hydrogen peroxide. These molecules are involved in numerous normal cellular processes like gene expression [49], proliferation and differentiation [50].

Exogenous and endogenous stress may generate excessive amounts of ROS that can damage molecules like nucleic acids, proteins and lipids. This in turn can induce cell cycle arrest and premature senescence [50,51] as well as activation of pathways leading to cell death [52]. Glutathione (GSH) is an essential tripeptide found in mammalian cells where it maintains the intracellular thiol redox status, and detoxifies reactive molecules. Depletion of GSH predisposes cells to proapoptotic stimuli and can also activate apoptosis in the absence of such stimuli. Cellular antioxidant defense systems include superoxide dismutase, catalase, and GSH. They prevent disturbances in ROS homeostasis or reduce the effect of oxidative stress in cells [53].

It was observed that the administration of khat to rats decreased the activities of free radical metabolizing/scavenging enzyme systems,

leading to enhanced free radical concentration and induces oxidative stress, which could be due to khat's alkaloid fraction [38]. The possible effects of sustained oxidative stress induced by khat consumption may lead to the development of several pathologies, notably cancer, hepatotoxicity, nephrotoxicity, cardiovascular toxicity and neurodegenerative diseases [54].

### 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 [55]. In folk medicine, khat is claimed to suppress cough, asthma, epidemic influenza, stomach aches, diarrhea and malaria [56]. It can also relieve pain [57] (Table 1).

### Conclusion

Khat chewing may induce disturbance of mood. In psychotic patients, it may aggravate thought disturbances, induce aggressive behavior and create difficulties in treating these patients. It may cause elevation of arterial blood pressure and pulse rate with subsequent increase in cardiovascular risk, particularly in hypertensive patients. It seems to be a common cause of stomatitis and other problems in the gastrointestinal system. It may be associated with increased risk of carcinoma of the mouth and oesophagitis. It causes anorexia and constipation. It may have a toxic effect on the liver and kidneys. In addition, it may cause impotence in males but increase sexual desire in women. However, there are controversies regarding some potential adverse health effects of khat from previous studies. Therefore, further research need to be undertaken in order to elucidate those disagreements.

### Authors' contribution

MA, designed the review, collected different articles and wrote manuscript. SK and KA also participated in manuscript writing and edition. All authors read and agreed on the final manuscript.

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