Adverse Health Effects of Khat: A Review

Molla Abebe1, Samuel Kindie2 and Kasaw Adane3

1Department of Clinical Chemistry, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Ethiopia
2Department of Medical Laboratory, School of Allied Health Sciences, Health Science College, Addis Ababa University, Ethiopia
3Unit of Laboratory Management and Quality Assurance, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Ethiopia

Corresponding author: Molla Abebe, Department of Clinical Chemistry, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Ethiopia, Tel: +251913329707; E-mail: mollish77@gmail.com

Introduction

Khat refers to the leaves and the young shoots of the plant \textit{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.

Definition and epidemiology of khat

Khat refers to the leaves and the young shoots of the plant \textit{Catha edulis} Forsk, which belonging to the plant family Celastraceae \cite{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 \cite{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 \textit{Catha edulis}. There are several names for the plant, depending on its origin: qat-Yemen, tchat-Ethiopia \cite{3}, qaad/jaad-Somalia \cite{4}, miraa-Kenya, mairungi-Uganda, Muhulo-Tanzania and Hagigat-Hebrew \cite{5}.

Fresh leaves from khat trees are chewed daily by over 20 million people on the Arabian Peninsula and East Africa \cite{6}. The khat chewing habit is deeply rooted in the socio-cultural traditions of these countries \cite{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 \cite{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 \cite{10}. The biggest population of chewers is in Yemen, where the plant is used as social stimulant \cite{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 \cite{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 \cite{13}, trace quantities of vitamins including ascorbic acid, thiamine, riboflavin, niacin, and carotene \cite{14,15} and elements including calcium, iron, manganese, zinc, copper and toxic metals like lead and cadmium and a negligible amount of fluoride \cite{16}.

The leaves of khat plant contain alkaloids like cathinone, cathine and norephedrine which are structurally and pharmacologically related to amphetamine \cite{17}. Cathinone is the principal active...
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 Toenness 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 norpseudoephedrine 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 affects 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 β-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].

<table>
<thead>
<tr>
<th>Table 1: A summary of potential adverse health effects of khat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organ/system</strong></td>
</tr>
<tr>
<td>Nervous system</td>
</tr>
<tr>
<td>Cardiovascular system</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>Appetite and body weight</td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
</tr>
<tr>
<td>Liver and kidneys</td>
</tr>
<tr>
<td>Reproductive system</td>
</tr>
<tr>
<td>Free radical homeostasis</td>
</tr>
</tbody>
</table>

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 possibly 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 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 ashes, 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 oesophagus. 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.

References
