

Khat Use: History and Heart Failure

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ABSTRACT

Recent reports suggest that 20 million people worldwide are regularly using khat as a stimulant, even though the habit of chewing khat is known to cause serious health issues. Historical evidence suggests khat use has existed since the 13th century in Ethiopia and the southwestern Arabian regions even before the cultivation and use of coffee. In the past three decades, its availability and use spread all over the world including the United States and Europe. Most of the consumers in the Western world are immigrant groups from Eastern Africa or the Middle East. The global transport and availability of khat has been enhanced by the development of synthetic forms of its active component. The World Health Organization considers khat a drug of abuse since it causes a range of health problems. However, it remains lawful in some countries. Khat use has long been a part of Yemeni culture and is used in virtually every social occasion. The main component of khat is cathinone, which is structurally and functionally similar to amphetamine and cocaine. Several studies have demonstrated that khat chewing has unfavorable cardiovascular effects. The effect on the myocardium could be explained by its effect on the heart rate, blood pressure, its vasomotor effect on the coronary vessels, and its amphetamine-like effects. However, its direct effect on the myocardium needs further elaboration. To date, there are few articles that contribute death among khat chewers to khat-induced heart failure. Further studies are needed to address the risk factors in khat chewers that may explain khat-induced cardiotoxicity, cardiomyopathy, and heart failure.

Khat is an evergreen shrub cultivated as a bush or small tree native to Ethiopia, East Africa, and the southern Arabian Peninsula.¹ 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 psycho active substances, which produce euphoria and stimulation.²

With the migration of khat users from Africa and Arabia, several health problems have been disseminated to different countries around the globe.^{3,4} A recent report suggested that currently 20 million people worldwide regularly used khat.⁴

Khat chewing is known to cause serious health issues.⁵ 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.⁴ We sought to identify and summarize the adverse cardiovascular

effects, particularly heart failure, associated with chronic khat chewing as well as give a brief review of the history of chewing khat.

Literature search strategy

A traditional narrative literature search was carried out using the PubMed and EMBASE search engines. We used the search terms in different combinations to enhance the retrieval of articles. Additionally, Google Scholar and Google searches for related websites were also performed. Reference lists of appropriate studies were also hand-searched to include further studies for potential inclusion.

A total of 520 articles that met the search criteria were retrieved from different search engines. We excluded videos, errata, letters, and corrections. Finally, 37 articles were deemed suitable for inclusion in the review after the exclusion of 483 articles not relevant to the topic. Table 1 shows the number of articles per type of study included in the review.

Table 1: Number of articles per study type included in the review.

Study type	Countries/region and number of publications	Total number of articles
Cross-sectional	Yemen=4 Ethiopia=2 Saudi Arabia=1 Somalis in Sweden =1 Middle East=2 US=1	11
Prospective	Yemen = 3 Middle East=1 Israel= 1 (Experimental) Yemen = 2 Germany= 1 Switzerland= 1 UK=2	11
Review	Yemen = 2 Ethiopia = 1 US= 2 UK= 1 France= 1 Hungary = 1 Switzerland = 1	9
Case reports*	US = 3 UK =1 Belgium = 1 Scotland = 1	6

*all reported in immigrants

Origin and spread of khat use

The use of psychoactive substances has been known since antiquity. The relationship between humans and substances was shaped by multiple factors including culture, society, religion, beliefs, individual psychology, neurobiology, cognition, and genetics.⁶ Historical evidence suggests khat use existed in the 13th century in Abyssinia (Ethiopia), and was brought to Yemen in the early 15th century.⁷ Its cultivation and use in Ethiopia and the southwestern Arabian areas started earlier than that of coffee.

Khat use varies: the fleshy and thickened parts of the plant can be chewed and then swallowed (the most common form of use), the leaves dried and powdered to make tea known as Abyssinian, African, or Arabian tea, or the powder can be eaten as a paste with honey. Khat was theologically and lawfully accepted as a custom in Arabia and Africa.⁷ Its global distribution has increased dramatically in the past three decades, making khat available in the European and US markets. In the UK, khat worth around £2m was reported as transported from Kenya every week.⁸ The global transport and availability of khat has been enhanced by the development of a capsular form cathinone 200mg (its active ingredient), which

is also known as hagigat. Other synthetic forms that have developed include rakefet, graba, and mephedrone, which are chemically similar to the cathinone compounds found in the khat plant. In slang, mephedrone is known as drone, M-CAT, and meow meow.⁹

Most consumers in the Western world are immigrant groups from Eastern Africa or the Middle East. There is no evidence of uptake by the mainstream population in Western countries, mainly due to the unfamiliar mode of administration. For instance, khat leaves are chewed and a wad of khat is stored in one cheek where it slowly breaks down into the saliva and enters the bloodstream. In addition, the availability of far more active stimulants, such as amphetamine and cocaine, in the Western market might have contributed to the decreased prevalence of use in the native population.^{10,11}

Khat in the Yemeni population

Khat has been a part of Yemeni culture for a long time and is used in virtually every social occasion resulting in animated behavior and lively discussions followed by tranquility and introspection. Nearly 90% of adult males chew khat for between three to four hours daily and 50%, or more, females have taken up the habit.¹² It has been estimated that 73% of women in Yemen frequently chew khat. Notably, 15–20% of children below the age of 12 are also daily consumers.¹² Apart from the various health issues caused, the impact of khat cultivation on the national economy is huge.¹² 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.¹²

Legal status of khat

The spread of khat in new settings raises challenges to regulatory systems across the world where the positive and negative aspects of khat use must be weighed up.¹³ Being both psychoactive and habit forming, khat is considered as potentially risky for the user, family, and the wider community. Moreover, a range of medical conditions associated with khat use are of concern.¹³

The World Health Organization considers khat as a drug of abuse, but less addictive than alcohol or tobacco.¹² Khat is a banned substance in most European countries (including Germany, France,

and the Netherlands), the US and Canada, while it remains lawful in Somalia, Djibouti, Ethiopia, Yemen, and Israel. Cathinone was classified as a Schedule 1 narcotic in the US, placing khat in the same category as heroin and mescaline. On the other hand, the Advisory Council on the Misuse of Drugs (ACMD) in the UK recently opposed the proposal for banning khat based on the lack of evidence for causal linkage between its use and various negative social indicators.¹⁴ However, the UK government decided to ban khat and classified it as a class C drug, in the same category as anabolic steroids and ketamine.¹⁵ Khat use in the Arab Gulf states, other than Yemen, is illegal.

Synthetic cathinones

Synthetic cathinones have recently emerged and have grown to be popular drugs of abuse.¹⁶ These substances are often considered “legal highs” and sold as “bath salts” or “plant food” and labeled as “not for human consumption” to get around drug abuse legislation. It can be obtained through “head shops” (tobacco specialized retailers), internet websites, and local drug suppliers.¹⁶ The synthetic cathinones are most commonly used via nasal insufflation or are ingested. Cardiac, psychiatric, and neurological manifestations are the most common adverse effects reported in synthetic cathinone users who require medical care.¹⁶

Medical harms of khat use

The psychoactive compounds cathinone and cathine are phenylalkylamines present in khat, which are structurally related to amphetamine, and are responsible for most of the effects of khat.² Other constituents identified include cathidine, eduline, and ephedrine, which are less significant in terms of action. Kassim and Croucher¹⁷ have summarized the various adverse effects reported due to the use of khat in humans. However, the causal relationship between khat use and any of these conditions is yet to be proved.

Khat chewing and the heart

The main components of khat are cathinone (α -aminopropiophenone), cathine (norpseudoephedrine), and norephedrine. The phenylpropylamine-type alkaloid cathinone is the major component responsible for the effects of khat on the heart and blood vessels.¹⁸ Cathinone

is structurally and functionally similar to amphetamine. It also exerts pronounced behavioral effects of euphoria, hyperactivity, and restlessness, like ecstasy (MDMA-3,4-methylenedioxy-N-methylamphetamine) and amphetamine. Cocaine and sibutramine have also shown functional similarities with cathinone.¹⁹

Brenneisen et al,²⁰ conducted a study in six healthy volunteers and found that cathinone administration increases blood pressure and heart rate. They concluded that these effects were due to the sympathomimetic activity of cathinone and were similar to the effects of amphetamine. The changes in the heart rate and blood pressure were concomitant with the cathinone level in blood plasma. A study by Kalix,²¹ confirmed the similarity in the mechanism of action between cathinone and amphetamine. These studies suggested cathinone was an indirectly acting sympathomimetic drug having catecholamine-releasing properties at dopaminergic and serotonergic synapses, and at peripheral noradrenaline storage sites.¹⁹

Al-Habori²² pointed out that the habitual use of khat may lead to hypertension. When comparing the blood pressure level of khat and non-khat users Getahun et al,²³ found that chewing was associated with increased mean diastolic blood pressure. The prevalence of hypertension recorded in khat chewers (13%) was significantly higher compared to non-chewers (11%). The proportion of sub-optimal diastolic blood pressure (>80mmHg) among chewers (30%) was higher than that of non-chewers (21%). In addition, khat users had significantly higher heart rates than non-users. However, there was no significant difference in the mean systolic blood pressure between users and non-users. Balint et al,²⁴ also observed that regular khat use caused a rise in arterial blood pressure and pulse rate and these changes were parallel to the levels of cathinone in the plasma.²⁴ The observations of Getahun et al,²³ were consistent with the results of study by Tesfaye et al,²⁵ both which reported increased diastolic blood pressure among regular khat users. A study in Yemen found that the rise in blood pressure corresponded to the duration of khat chewing sessions. Blood pressure remained elevated for about three hours following one hour of chewing with 25% of a traditional khat-session dose.¹⁸ Al-Motarreb and Broadley,²⁶ conducted a laboratory study which confirmed that the peripheral effects of cathinone

were caused by vasoconstriction of coronary arteries. However, they demonstrated that this was not due to indirect or direct sympathomimetic activity. They found that vasoconstrictor effects were not inhibited by prazosin, the adrenoceptor antagonist, and ruled out the role of sympathomimetic action in vasoconstriction. Baker et al,²⁷ also demonstrated that cathinone induced coronary vasoconstriction was via mechanisms other than indirect sympathomimetic activity or α -1 adrenoceptors.

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). Amphetamine also shows vasoconstrictive action by stimulating the release of noradrenaline from sympathetic nerves and may participate in AMI.²⁸ 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.²⁹ Cathinone also plays a role in the development of congenital heart disease.

Al-Motarreb et al,³⁰ conducted a hospital-based matched case-control study in Yemen with 100 AMI cases and 100 control subjects matched for age and sex. They found khat use was significantly higher among AMI patients and heavy khat users had a 39-fold increased risk of AMI. The quantity of khat used and duration of each khat session also contributed to the risk of AMI. Of the 100 cases, 89% were khat users and nearly half of them were considered heavy quantity users. Approximately 90% of patients were using either heavy or moderate quantities of khat. Nearly 27% of the khat users chewed for six hours or more and 85% took more than three hours for their khat sessions. Alkadi et al,³¹ found that 79% of AMI patients in their study were khat users. A further experimental study showed that frequent administration of khat doses resulted in multiple areas of infarcts in rabbit hearts. Moreover, they revealed nearly 70% of AMI events occurred either after completion or during the khat chewing session.

In a study of 347 AMI patients, Al-Motarreb et al,³² confirmed coronary spasm as the main mechanism of AMI in khat users. Of the total AMI cases, 79% were Yemenis. Furthermore, Al-Shami and Al-Motarreb,³³ evaluated the effect of khat chewing on the coronary arteries in patients with history of heart failure and found khat chewing as an independent risk factor for coronary artery disease (CAD).

Khat-associated acute coronary syndrome (ACS) leads to worse outcomes for khat users. Gulf RACE-2, a multicenter study, included 7,399 patients with ACS from six Middle Eastern Gulf countries and reported 1,408 patients (19%) as khat users. The majority of users were Yemeni (75.5%).¹⁹ Khat users were more likely to be associated with AMI and unstable angina. Overall, the study showed that khat users had a higher risk of death, recurrent myocardial ischemia, cardiogenic shock, ventricular arrhythmia, and stroke compared to non-khat users. The researchers concluded that khat use was an independent risk factor of death and for recurrent ischemia, heart failure, and stroke.¹⁹ The study indicated the worsened outcomes in khat users could be related to multiple factors including delay in access to care (attributed to the analgesic effect of khat), reduced efficacy of thrombolytic therapy (due to the prothrombotic effect of cathinone), and increased risk of ischemic cardiomyopathy.

Cardiomyopathy is a disease of the heart muscle that results in abnormal cardiac function and may lead to heart failure or arrhythmias. Synthetic cathinones produce similar effects to amphetamines and cocaine, and its misuse may cause cardiomyopathy.^{34,35} Jacobs³⁶ reported the unexpected death of six young persons who had a history of chronic abuse of amphetamine. Their death was not attributed to a lethal intoxication but to cardiotoxicity, which included cardiomyopathy. Smith et al,³⁷ reported a case of chronic abuse of high doses of dextroamphetamine resulting in congestive heart failure, suggesting a causal relationship between administration of dextroamphetamine and cardiomyopathy.

Neimann³⁸ examined sports-related sudden deaths and found that cases of hypertrophic cardiomyopathy-related deaths resulted from amphetamine abuse. Hong et al,³⁹ reported methamphetamine smoking and its cardiovascular toxic effects. Methamphetamine smoking was associated with the development of pulmonary

edema and a dilated cardiomyopathy. Additionally, smoking crystal methamphetamines was likely to produce diffuse vasospasm and could lead to acute myocardial infarction, cardiogenic shock, and death.³⁹ Cathinone in khat is more likely to have a similar mechanism of action as amphetamines and its derivatives in developing cardiotoxicity or cardiomyopathy.

Saha and Dollery⁴⁰ reported the case of a 33-year-old East African man who having chewed khat almost constantly for two to three days presented with myocardial infarction. The patient had no coronary risk factors other than a history of smoking cigarettes. He continued daily khat chewing for two years and three months. He was later diagnosed with severely impaired biventricular function consistent with ischemic myopathy. In 2004, one study evaluated the role of regular khat chewing, in addition to other cardiovascular risk factors, on 50 Yemeni patients with dilated cardiomyopathy.^{41,42} This study concluded that khat chewing contributes to the occurrence of dilated cardiomyopathy in young patients with an inherited predisposition.^{41,42}

Although the potential link between khat use and increased risk of myocardial ischemia was evident in several studies, a causal relationship between these two is yet to be proved. The Gulf RACE-2 study did not report information about whether users continued to use khat upon admission and at follow-up.

Khat and co-risk factors

The increased prevalence of smoking, diabetes, and hypertension play vital roles in the development of heart failure and makes it difficult to determine the effect of khat.^{14,19} Recently, al'Absi et al⁴³ studied the effects of concurrent tobacco and khat use and suggested that the adverse effects of khat use may lie in its association with tobacco use. Tesfaye et al,²⁵ pointed out that the use of multiple substances caused dramatic effects on the cardiovascular system.

Farmers used to apply pesticide for better khat production. Organophosphate exposure has been found to be another risk factor for cardiac complications among khat users.⁴³⁻⁴⁵ The presence of pesticides in khat was implicated in the inhibition of serum acetylcholinesterase activity⁴⁴ and may contribute to the presence of high levels of free radicals. Another study showed that the production of oxidants, which are responsible for reduction in antioxidant defense system, may be due to khat use.⁴⁶

CONCLUSION

Khat is involved in serious cardiovascular problems among its users, including heart failure, through a mechanism of action on the circulatory system similar to amphetamine and cocaine. Khat increases the catecholamine release, heart rate, and blood pressure, and induces coronary vasospasm. The effect of khat on the myocardium could be explained by its vasomotor effect on the coronary vessels; however, its direct effect on the myocardium still needs further elaboration. There are few reports that contribute death among khat chewers to khat-induced cardiotoxicity, including cardiomyopathy. Further studies are needed to highlight the serious cardiovascular implications of khat.

Disclosure

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