

## Khat (*Catha edulis*) as a risk factor for cardiovascular disorders: Controversies and facts

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### ABSTRACT

The leaves of khat (*Catha edulis*) are chewed as a social habit for the central stimulant action of their cathinone content. There is growing concern about the health hazards of chronic khat chewing. Many authors have addressed the adverse effects of khat chewing on the cardiovascular and other systems. Based on a limited number of case reports and few prospective controlled studies, associations between khat chewing and the occurrence of myocardial infarction, dilated cardiomyopathy, and vascular diseases such as hypertension and cerebrovascular ischemia have been proposed. This review outlines the current knowledge on the adverse health effects of khat chewing on the cardiovascular system, assesses the strength and the limitations of the studies, and identifies the questions that the future studies should address.

**Key words:** Cardiomyopathy, Cardiovascular disorders, Coronary artery disease, Hypertension, Khat

**K**hat (or Qat) is the traditional plant consumed mainly in Yemen and some of the East African countries such as Ethiopia, Somalia, Djibouti, Kenya, and Uganda (known as African horn countries), and with the growing immigration rates from the middle east region toward Europe and America [1] and growing communities of these countries, it becomes a more common habit in these geographical zones that brings out health attention and social recognition. In Yemen, people chew fresh khat leaves daily on a regular basis mainly in the afternoon, although some people start to chew khat in the morning. Social gatherings such as wedding parties, funerals, and at election time have made khat chewing more popular. Moreover, khat is consumed by students when they wish to study for long hours especially during examination periods [2].

As a medicine, khat leaf is used for diabetes, muscle strength, to the lower the need for food and sleep, and to increase aggression, but there is no good scientific evidence to support these uses. Khat chewing, however, has been reported to have adverse effects on various human body systems. Many authors have addressed the adverse effects of khat chewing on the cardiovascular system (CVS). Links have been proposed between khat chewing and the incidence of myocardial infarction, dilated cardiomyopathy, and vascular disease such as hypertension and cerebrovascular ischemia. The fresh leaves of khat contain over 40 compounds of which the amphetamine such as chemicals cathine and cathinone

and are reported to be responsible for its central nervous system (CNS) and CVS effects [1,3]. The effects of these compounds on the CVS are expressed by an increment in heart rate (HR), blood pressure (BP), and vasomotor effects on the coronary vessels [3]. The aim of this review is to outline the current knowledge on the adverse health effects of khat chewing on the CVS, it assesses the evidence and the limitations of the studies and identifies the questions that the future studies should address.

### CONSTITUENTS OF KHAT

Pharmacologically khat belongs to a group of plants which has an amphetamine-like effect (amphetamine-like substances) and are known to have psychostimulant effects, which include euphoric, anorectic, empathogenic, entactogenic, and hallucinogenic effects. Khat leaves contain three main alkaloids: Cathinone, Cathine (norpseudoephedrine), and norephedrine [4]. These compounds are structurally related to amphetamine and noradrenaline.

Cathinone is the main active component of fresh khat leaves (soon after harvesting), and most of the pharmacologic and biological effects of khat belong to this substance, and with time, it is converted into less active substances such as norpseudoephedrine and norephedrine [1]. These substances interact with the dopaminergic pathways in the CNS similarly to amphetamines and induce psychotropic effects [4].

On the CVS, cathinone increases BP, has positive inotropic and chronotropic actions in isolated atria, and increases HR in

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anaesthetized rats [5] and dogs [6]. Direct vasoconstriction of isolated blood vessels does not appear to have been demonstrated, but there is potentiation of the vasoconstriction due to electrical field stimulation. The peripheral responses to khat are due to enhanced release of noradrenaline with an action and potency similar to those of amphetamine [7].

## THE EFFECTS OF KHAT ON CVS

Regular and repeated intake of Khat has recently been proposed to be associated with increased risk of cardiovascular disease. For descriptive purposes, the proposed effect of repeated khat intake is divided into two groups: (1) Indirect effects by exaggerating the effect of well-known risk factors such as hypertension, diabetes mellitus (DM), and dyslipidemia and (2) direct effects as independent risk factor for cardiovascular disease.

### Indirect Effects of Khat-Chewing on CVS

#### Hypertension

One of the major risk factors for cardiovascular morbidity and mortality is both systolic and diastolic hypertension [8]. Elevated BP has many risk factors that are of behavioral, dietary, or genetic origin. Among the main modifiable risk factors of hypertension are overweight and obesity, cigarette smoking, physical inactivity, unhealthy diet, stress, dietary salt intake, and alcohol use [9]. Regular and repeated intake of Khat has recently been proposed to be associated with high BP because of its amphetamine-like substances effect [9,10].

The validity of these reports is disputed as most of these studies have focused on the Yemeni and Ethiopian populations [9-12]. In Yemen, most people smoke cigarettes (or Hubble Bubble) and drink caffeinated soft drinks while chewing khat. Cigarettes and caffeine are risk factors for hypertension [9] and these confounding factors may not be equally redistributed among study groups. Moreover, available data indicate that different dosages of khat can affect BP differently [13]. However, in most of these studies, the authors did not really standardize or mention participants' khat consumption in terms of dose or quantity, which makes the results of these studies a matter of debate.

#### DM

Another risk factor, which has a strong relation to cardiovascular disease, is DM. There is a growing evidence of the effect of khat chewing on Type 2 DM (T2DM) and glycemic control. However, the role of khat chewing in T2DM is not fully understood as the available data are non-conclusive. A systemic review and meta-analysis study included 25 studies from 1976 to 2016, suggested that khat is predisposing factor contributing to the development of T2DM [14]. Alkhormi *et al.* [15] found that khat chewing increases fasting blood glucose, post-prandial blood glucose, and HbA1c levels in patients with diabetes in the Jazan region, Saudi

Arabia, and Yemen. Moreover, an experimental study in Malaysia suggested that the cytotoxic effect of khat induced DM through the destruction of pancreatic  $\beta$ -cells and changing the structures of the islets of Langerhans [16] in addition. Badedi *et al.* [17] concluded that there was an association between khat chewing and the development of T2DM. However, the cause-and-effect relationship has not yet been directly investigated. Therefore, the role of khat chewing as a risk of T2DM development has not yet been elucidated. Further studies are needed to clarify the effect of khat and its chemical substances on pancreatic cells.

#### Dyslipidemia

Dyslipidemia is a term referring to the disorders of lipoprotein metabolism and is clinically characterized by elevated plasma levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. Available data exploring khat effects on lipid profile are scarce, and conflicting [18].

### The Direct Effects of Khat on Cardiovascular Disease

#### Coronary artery disease

Some authors proposed that khat chewing can be considered as independent risk factor for cardiovascular diseases. In an attempt to assess the cause and effect relationships of khat with coronary artery diseases, two mechanisms were suggested [19]: (a) Indirect effect through tension, insomnia, loss of appetite, and lack of physical activity, which are associated with khat chewing, that consequently affects the CVS negatively. (b) Direct affect through coronary vasoconstriction due to amphetamine like effect of cathinone. The direct effect of khat-chewing on coronary artery diseases was derived from two sources. The first source was experimental. A laboratory study was performed on the Langendorff heart preparation isolated from guinea pigs and showed that cathinone causes coronary vasoconstriction and has negative inotropic effects [11]. It is not clear, whether the cathinone effect is dose dependent and whether cathinone can affect human being in the same manner. The second source of this information was based on case reports and few number of observational studies [20-23], which were conducted in Yemen without being supervised by a research committee or any independent organization to guarantee its reliability and validity. Moreover, despite most of Yemeni population chew khat daily, it is unclear why some people develop acute myocardial infarction while others do not. Therefore, we urge for cautious interpretation of the study findings and there is also a need for conducting further studies with high quality design, to assess the effect of khat-chewing on coronary artery disease.

#### Heart Failure and Cardiomyopathies

It was proposed that khat chewing can affect the heart leading to acute cardiomyopathy [19,24-26]. This suggestion was

based on few reports which described the occurrence of acute cardiomyopathy secondary to intravenous amphetamine abuse [24,25], and on one study conducted in Yemen, which involved 50 Yemeni patients with dilated cardiomyopathy who were regular khat chewers. The histopathological study of the heart muscle showed myocyte hypertrophy and interstitial fibrosis [19,26]. In fact, it is unclear when this study was conducted, as there is no reference has been found. Moreover, was cardiac biopsy performed in Yemen?. Moreover, is the effect of intravenous amphetamine similar to oral cathinone available in khat?

### Arrhythmias

Khat chewing was suggested to increase the risk of cardiac arrhythmias [27]; however, data on this association are very limited.

### CONCLUSION

There is no solid evidence to believe that khat-chewing can affect the coronary artery or the heart directly. At best, we can conclude that khat-chewing can indirectly affect the CVS through increase HR, insomnia, loss of appetite, and lack of physical activity. There is a need for conducting further studies with high quality design, to assess the effects of khat-chewing on the coronary artery and the heart or other systems.

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