Glycemic effects of *Catha edulis*

Samih Abed Odhaib,[1] Butheinah A. Al-Sharafi,[2] Abbas Ali Mansour[3]

[1]Thi Qar Specialized Diabetes Endocrine and Metabolism Center (TDEMC), Thi Qar Health Directorate, Thi Qar, Iraq; [2]Department of Medicine, School of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen; [3]Faiha Specialized Diabetes, Endocrine and Metabolism Center, College of Medicine, University of Basrah, Basrah, Iraq

Abstract

More than 20 million people in the East African horn and the southern Arabian Peninsula chew khat (*Catha edulis*) on a daily basis. The glycemic effect of khat chewing, regardless of diabetes status, is still being debated. Using studies from countries where chewing khat is common, we attempted to discuss the potential glycemic effects of *Catha edulis* in humans and some animal models. This review included a thorough search in PubMed and the Cochrane Library using PRISMA guidelines, with words like (Khat) and (Qat) serving as query indicators for (diabetes) and (glucose), with no language or species restrictions. Khat is chewed for its stimulating and enjoyable properties. Despite a relatively small number of studies on khat's glycemic effect, the debate continues. Many studies have linked the glycemic effect of khat leaves to their freshness and the duration of the stimulant effect. Although only in animal models, khat's destructive effect on pancreatic β-cells could cause some dysglycemic effects. The cathinone cannot be blamed for the glycemic effect.

Correspondence: Samih Abed Odhaib, Thi Qar Specialized Diabetes Endocrine and Metabolism Center (TDEMC). Thi Qar Health Directorate, Thi Qar, Iraq.
Tel.: +9647816787885
E-mail: samihabed@yahoo.com

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Introduction

Khat is one of the names given to the young sprouts of the evergreen shrub *Catha edulis* (Vahl) Forssk. ex Endl., which belongs to the plant family Celastraceae.[1] Khat is grown in Yemen, Ethiopia, Somalia, Malawi, Kenya, Uganda, Tanzania, Zambia, the Democratic Republic of the Congo, Zimbabwe, Madagascar, and South Africa.[2,3] Khat was known by various names, including qat in Yemen, tchat in Ethiopia,[4] qaad/jaad in Somalia,[5] muhulo in Tanzania, mairungi in Uganda, miraa in Kenya, and hagigat in Hebrew.[6] Every day, over 20 million people in the Arabian Peninsula's southern regions and many coastal East African countries chew fresh leaves. Chewing parties or gatherings are a long-standing social-cultural tradition in these countries.[7,8] People chew fresh khat leaves every day, primarily in the afternoon but also occasionally in the morning. Khat chewing has become more popular as a result of various social gatherings.[8] Typically, 100 to 200 g of khat leaves are consumed per session, which is equivalent to an oral dose of 5 mg of amphetamine.[9,10] Yemen has the highest population of Khat Chewers (KCs), where khat is used to induce social stimulation and pleasure.[8,11,12] The effect of khat chewing varies from person to person depending on the type of khat used.[12]

Studies suggest that 80-90% of the adult males and 10-60% of the adult females in East Africa consume khat daily.[13,14]

In this review, we tried to discuss the possible glycemic effects of *Catha edulis* in humans and some animal models using studies from countries where chewing khat is prevalent.

Materials and Methods

To get comprehensive information and data about the effect of khat on blood glucose levels, a thorough search using PRISMA guidelines was done using PubMed and Cochrane Library as search engines.

We used (Khat) and (Qat) as a query indicator for (diabetes)

and (glucose), with no language and species-specific restrictions. During the initial search 52 articles were found. Eleven articles were removed due to duplication. Only 36 articles contained information about the glycemic effects of khat.

Additional search through the references of these 36 articles added an extra 30 references to the search. The final number of the used references in this review included 66 references.

Results

Current state of knowledge

Biochemical constituents and effects of khat leaves

Fresh khat leaves contain several compounds, including phenylalkylamine (alkaloids), Cathine (norpseudoephedrine), and Cathinone (α-aminopropiophenone), which has a similar pharmacological structure to d-amphetamine and is the main active ingredient in khat leaves. Tannins make up 7% to 14% of dried khat.[6,10] Fresh khat leaves contain 120 mg cathine, 36 mg cathinone, and 8 mg norephedrine per 100 grams.[15]

Several other chemical substances are found in khat, like terpenoids, sterols, flavonoids, glycosides, and more than ten amino acids, including tryptophan (Trp), glutamic acid (Glu), alanine (Ala), glycine (Gly), and threonine (Thr),[15] trace quantities of vitamins including ascorbic acid, thiamine, riboflavin, niacin, and carotene[2,16] and elements including iron (Fe), calcium (Ca), manganese (Mn), magnesium (Mg), zinc (Zn), copper (Cu), toxic metals like lead (Pb) and cadmium (Cd), and a negligible amount of fluoride.[17]

Cathinone acts similarly to amphetamine in that it promotes catecholamine release from presynaptic storage sites and induces dopamine release from central dopaminergic nerve terminals.[10,18,19] Cathinone was more lipid-soluble than Cathine, making it more active in the Central Nervous System (CNS).[10,20]

Cathinone exerts noticeable behavioral effects, including excitability, euphoria, anxiety, irritability, restlessness, hyperactivity, and insomnia.[2] These effects arise maximum of 1.5–3.5 hours after initiating the chew, to end afterward with mild dysphoria.[16]

Khat is less likely to cause tolerance than amphetamine, especially for the stimulant CNS effects.[21] Khat consumption may induce certain degrees of persistent psychic dependence rather than physical dependence.[1]

Worldwide spread

Khat chewing is legal in Yemen, Somalia, Djibouti, Ethiopia, Kenya, and Tanzania. There are no age-specific or gender-specific restrictions on khat consumption.[22]

In many Western countries, chewing khat is illegal. Chewing khat has spread significantly to many countries in Asia, Europe, America, and Australia as a result of many waves of migration. Chewing spread to the United States and many European countries, which host a large number of immigrants from countries where khat is widely used.[8,23-27]

The exact prevalence of chewing khat for immigrants and citizens in the host communities remains anecdotal, with more prevalence for immigrants.[23,27,28]

Systemic effects of khat chewing

Khat is chewed for its stimulatory and pleasurable effects. The systemic effects of khat chewing on different body systems rely on its effect on different receptor mechanisms.

Due to its direct action on the 1-adrenoceptor, khat chewing causes a decrease in urinary flow rate.[6,10,15,29] Tannins and the local effects of khat chewing are responsible for its gastrointestinal effects (periodontal disease, stomatitis, esophagitis, and gastritis).[30,31] Heymann *et al.* reported a delay in gastric emptying after chewing khat in a randomized controlled trial.[32] Khat chewing has also been linked to the development of duodenal ulcers.[33] Delays in intestinal absorption contribute to malnutrition and may result in liver cirrhosis. Constipation, the most common medical complaint of khat users, is exacerbated by tannins and norpseudoephedrine.[12,30] Transaminitis with histopathological changes in rabbits has been reported.[34]

Khat increases the desire for active tobacco smoking and is associated with passive smoking. Some people also smoke a common water pipe. This might increase the chance of spreading tuberculosis.[12]

The cardiovascular effect of khat consumption was the subject of exhaustive research, and its causal relationship to acute myocardial infarction is confirmed in many studies.[32-38]

The effect of khat consumption on reproductive function is debatable, and the studies conflicted on whether it improves sexual desire and excitement or causes erectile dysfunction.[12]

El-Shoura *et al.* investigated the effect of khat chewing on spermatogenesis and discovered that KCs had lower sperm volume, sperm count, and sperm motility than non-KCs, as well as a higher proportion of deformed spermatozoa.[39] The effect in khat-fed rabbits for three months showed an increase in spermatogenesis,[34] whereas Islam *et al.* observed degenerative changes in testicular tissues in animals receiving the active ingredient, cathinone.[40]

Khat's effects on blood glucose

The glycemic effect of khat is debated, with supporters claiming a lowering effect on blood glucose, opponents claiming an increasing effect on blood glucose, and authors reporting inconclusive results.

Increase in blood glucose

The traditional consumption of highly sugared drinks alongside khat may aggravate hyperglycemia.[7] Nonetheless, the general belief among Yemeni diabetics is that chewing khat may help with glycemic control. Khat's pharmacological effect involved increased sympathomimetic activity via catecholamines, which counteract insulin action and increase glucagon secretion. Elevated blood glucose is caused by the activation of hepatic and skeletal muscle glycogenolysis. This process is more pronounced in diabetics than in non-diabetics and is mediated by adrenoreceptor-mediated responses 2 and -2.[8,40,41]

Cathinone influences carbohydrate metabolism by increasing cortisol levels. Relative hypercortisolemia reduces insulin secretion while increasing resistin expression. Regardless of diabetes status, this effect was evident.[42]

Khat chewing may increase the risk of developing type 2 diabetes mellitus (T2DM) by various mechanisms, with an odds ratio of 3.5 among KCs.[25]

The long-term exposure to pesticide residues proposed by El-Hadrani and Al-Hoot, who discovered an association with T2DM development in KCs, is one of the theories behind this link. Pesticides inhibit pancreatic secretory action, increase gluconeogenic enzyme activity, and promote hepatic glycogenolysis by activating glycogen phosphorylase. Reduced insulin secretion could also be attributed to decreased calcium permeability.[45]

The theory of nonadherence to a healthy diet and physical

activity could be due to the poor glycemic control in KCs with diabetes, with an odds ratio of more than eight.[46]

Alkhormi *et al.* discovered that KCs from the Jazan region had higher fasting and postprandial glucose levels, as well as higher glycated hemoglobin levels.[47] Al-Sharafi and Gunaid discovered that chewing khat by Yemeni T2DM patients was independently related to lower BMI, poor glycemic control, and diabetes diagnosis at a younger age, with these effects being more pronounced in men.[48]

When chewing khat, individuals with poorly controlled diabetes had higher levels of glucose and C-peptide than non-diabetic KCs, according to Saif-Ali *et al*.[49] The statistical analysis for these two tests, however, was inadequate.

The study by El-Sayed and Amin[42] provided more accurate statistical analyses when comparing KC with and without diabetes. In comparison to non-KCs, khat chewing may cause a significant increase in blood glucose, Insulin Resistance (IR), and serum resistin levels regardless of diabetes status.

KCs with diabetes, on the other hand, had lower insulin levels than KCs without diabetes. The study concluded that chewing khat may be harmful to diabetics because it lowers insulin and induces IR.[42]

The experimental models explained khat's complex direct harmful pathophysiological effect on pancreatic β-cells.[50] After four months, rabbit models fed different concentrations of khat-containing diet showed an initial increase in blood glucose, followed by a significant decrease within six months. The findings mirrored the complex interaction between increased catecholamine-stimulated glycolysis and the effect of increased glucose on insulin secretion and action induced by pesticides. The study's overall blood glucose reduction was explained by compensatory insulin release after periods of high blood glucose.[51]

Alsalahi *et al.* used rat models to confirm the previous study's findings. They discovered that khat has a direct cytotoxic destructive effect on islets of Langerhans and pancreatic β-cells.[52,53]

Reduction in blood glucose

According to another proposed pathophysiology, khat-induced blood glucose reduction was demonstrated. Chewing khat significantly lowers glucose levels in KCs regardless of diabetes status, according to Mengistu *et al.*[54] The glucose reduction in KC groups was attributed to a detectable amount of minerals (magnesium, zinc, iron, chloride, lead, copper) and ascorbic acid in the consumed khat leaves.[54] Their study, however, did not measure these elements in the chewed khat cultivar.

The physiological concentrations of these trace elements have no effect on glucose hemostasis; for example, magnesium influences insulin synthesis and storage, and zinc is required for insulin release.[55] A concentration of 150 mg/100 mg of khat for ascorbic acid may have an anti-oxidant effect in people with T2DM, reducing the destructive effects of free radicals and lowering fasting glucose.[7,56] Tannins, flavonoids, and saponin may also contribute to blood glucose reduction.[7]

Heymann *et al.* proposed that delayed gastric emptying could explain the decrease in blood glucose in KCs due to decreased intestinal glucose absorption.[57] The study is regarded as an important reference for studies that support the resultant blood glucose reduction caused by khat. They did not, however, measure the levels of glucagon-like peptide-1 and corticotrophin-releasing factor, which are important regulators of the gastric emptying process.

In KCs without diabetes, Taleb and Bechyně discovered a 61.22% reduction in blood glucose four hours after consuming 3 gm/kg of fresh khat leaves, compared to the effect of glibenclamide or insulin in diabetic non-KCs.[58] Because they did not investigate the effects mentioned above in KCs with diabetes, their findings are neither comprehensive nor convincing.

Naji *et al.* demonstrated that chewing 200 gm of fresh khat leaves (local cultivar, Sana'a province, Yemen) on a regular basis could significantly lower glucose levels in KCs without diabetes.[59] They offered no explanation for their findings.

Masoud *et al.* found that KCs had significantly lower salivary glucose levels than NKCs. 60 They did not, however, compare the simultaneous blood glucose levels or provide a timeline for the proposed salivary glucose content reduction for the KCs, nor did they specify whether the effect was acute or chronic.[60]

Debecho *et al.* found that crude extract of khat leaves had acute hypoglycemic effects in both healthy and streptozotocin-induced T2DM rat models. The presence of other biologically active constituents responsible for lowering glucose levels was proposed in this study.[61]

When Albaser *et al.* administered weight-adjusted ratios of khat to metformin to diabetic rats, they discovered that this combination was more effective than metformin in the treatment of T2DM and concluded that the metformin-khat combination is much more effective in controlling the insulin-resistant diabetic state.[62]

Nyongesa *et al.*'s findings could explain why KCs have lower blood glucose levels. They investigated the effect of cathinone in monkeys and discovered that cathinone exposure altered cortisol levels in a dose- and time-dependent manner, with cortisol levels decreasing over time.[63] This decrease may have an effect on its insulin-regulatory action.

The ongoing debate on the inconclusive glycemic effect of khat

Elmi conducted a study in Mogadishu, Somalia, that did not directly examine the effect of chewing khat on blood glucose levels in non-diabetic KCs.[5] Regardless of diabetes, Almikhlafy *et al.* found no significant differences in fasting blood glucose levels between KCs and non-KCs. That study's observational design evaluated the glycemic effects of khat leaves in a cohort of 332 Yemeni physicians and found it inconclusive.[64]

The studies that described different glycemic levels in various groups of people explained their findings. Saif-Ali *et al.*[49] and Alkhormi *et al.*[47] both reported an increase in blood glucose and c-peptide levels in KCs with diabetes, but not in KCs without diabetes. These findings could be attributed to the effective release of norepinephrine, which has one-tenth the potency of epinephrine on glucose levels in healthy KCs who do not have diabetes.[8,40]

Because the Cathinone content of fresh and dried leaves differs, it is not always possible to attribute the glycemic effect of Khat solely to Cathinone.[65] The Cathinone content varies from cultivar to cultivar.[43,66]

The study by Murray *et al.* related the proposed changes in blood glucose and body weight to the appetite change during khat chewing. They hypothesized that khat consumption reduces hunger and increases fullness sensations via a central anorexigenic mechanism mediated by Cathinone, with no change in peptide YY and ghrelin levels. Four hours after 400 g of heavy khat chewing, high plasma levels of the anorexigenic hormone Leptin were discovered.[67]

Conclusions

Despite extensive research on the glycemic effect of khat in high prevalence areas, the debate over the net glycemic effect of khat continues. The current inconclusive evidence linked khat's

glycemic effect to the freshness of the leaves and the duration of the stimulant effect. It could be related to its damaging effect on pancreatic cells, as demonstrated in animal models. These effects cannot be attributed solely to the cathinone.

Longer-term real-world observations of khat's effect on glucose, insulin, and counter-regulatory hormones are advised. Experiments could be designed to investigate the effects of cathinone on various endocrine mechanisms that govern glycemic control.

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