

Association of Khat Chewing With Increased Risk of Stroke and Death in Patients Presenting With Acute Coronary Syndrome

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OBJECTIVE: To evaluate the prevalence and significance of khat chewing in patients with acute coronary syndrome (ACS).

PATIENTS AND METHODS: From January 29, 2007, through July 29, 2007, 8176 consecutive patients presenting with ACS were enrolled in a prospective, multicenter study from 6 adjacent Middle Eastern countries.

RESULTS: Of the 8176 study patients, 7242 (88.6%) were non-khat chewers, and 934 (11.4%) were khat chewers, mainly of Yemeni origin. Khat chewers were older (57 vs 56 years; $P=.01$) and more likely to be men (85.7% vs 74.5%) compared with non-khat chewers. Non-khat chewers were more likely to have diabetes mellitus, hypertension, dyslipidemia, obesity, and prior history of coronary artery disease and revascularization. Cigarette smoking was more prevalent in khat chewers, and they were more likely to present greater than 12 hours after onset of symptoms compared with non-khat chewers. At admission, khat chewers had higher heart rate, Killip class, and Global Registry of Acute Coronary Events risk scores. Khat chewers had a significantly higher risk of cardiogenic shock, stroke, and mortality. After adjustment of baseline variables, khat chewing was an independent risk factor for in-hospital mortality (odds ratio, 1.9; 95% confidence interval, 1.3-2.7; $P<.001$) and stroke (odds ratio, 2.7; 95% confidence interval, 1.3-5.9; $P=.01$).

CONCLUSION: In this large cohort of patients with ACS, khat chewing was prevalent and was associated with increased risk of stroke and death. In the context of increasing global migration, a greater awareness of potential widespread practices is essential.

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ACS = acute coronary syndrome; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

Khat (*Catha edulis*) is a leafy green shrub that can grow to tree size (Figure). Users chew this stimulant habitually for its euphoric effects and as a recreational drug that also improves performance.^{1,2(pp79-107),3} Cathinone and cathine are the main ingredients of the plant. These compounds are structurally related to amphetamine, noradrenaline, and ecstasy (3,4-methylenedioxymethamphetamine).^{4,5} The sympathomimetic and central nervous system-stimulating effects produced by khat chewing are mainly due to cathinone.

Khat grows and is widely used in the region extending from Eastern to Southern Africa, as well as on the Arabian Peninsula, mainly in Ethiopia, Somalia, Yemen, Kenya, Malawi, Uganda, Tanzania, the Congo, Zambia, Zimba-

bwe, Madagascar, and South Africa.^{6,7} In these countries, “khat parties” have a long history as part of formal social customs, for example, to encourage discussion of community issues.^{2(pp79-107)} A khat quantity of 100 to 200 g is usually consumed in each session,⁸ which is equivalent to an oral dose of 5 mg of amphetamine.⁹

Khat chewing is currently legal in the United Kingdom; however, cathinone and cathine are controlled drugs. Although khat chewing is illegal in the United States (as well as in Canada, Norway, and Sweden), it could be a hidden medical problem; khat use in the United States is most prevalent among immigrants from Somalia, Ethiopia, and Yemen.¹⁰ The amount of khat seized by federal law enforcement officers has increased dramatically in the past few years^{11,12}; however, studies of the consequences of khat use in these communities are lacking.

The purpose of this article was to assess the prevalence and importance of khat consumption as a risk and prognostic factor among a large cohort of Middle Eastern patients presenting with acute coronary syndrome (ACS).

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PATIENTS AND METHODS

Data were collected from a 6-month prospective, multicenter study of the Gulf Registry of Acute Coronary Events

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FIGURE. Khat (*Catha edulis*), a leafy green shrub that can grow to tree size (left). Person chewing khat (right).

that recruited 8176 consecutive patients with ACS from 6 adjacent Middle Eastern Gulf countries (Bahrain, Kuwait, Qatar, Oman, United Arab Emirates, and Yemen). Patients with the diagnosis of ACS, including unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), were recruited from 64 hospitals. An on-site cardiac catheterization laboratory was available in 30% of hospitals, whereas 31% of hospitals had a laboratory available within 60 minutes. Most hospitals (73%) had an on-site coronary care unit. There were no exclusion criteria, and thus all prospective patients with ACS were enrolled. The study received ethical approval from the institutional ethical bodies in all participating countries. Full details of the methods have been published previously.^{13,14} Diagnosis of the different types of ACS and definitions of data variables were based on the American College of Cardiology clinical data standards.¹⁵ History of khat chewing was recorded at the time of presentation.

All patients provided written informed consent for use of their data, and treating physicians obtained and recorded patient data. Completed data forms were sent to the central data processing center for uniform monitoring and registration. Patients were divided into khat and non-khat chewers.

STATISTICAL ANALYSES

Patients' characteristics are presented as proportions, medians, or mean \pm SD, as appropriate. When possible, rates were used to describe patient populations. The frequencies of categorical variables in the 2 populations (khat chewer and non-khat chewer) were compared using the

χ^2 test. Continuous variables were compared using the 2-tailed *t* test. Variables influencing in-hospital mortality, cardiogenic shock, and stroke were assessed with multiple logistic regressions after adjustment for covariates, including age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking, thrombolytic therapy, and khat use. Odds ratios, 95% confidence intervals, and *P* values are reported for significant predictors. *P* < .05 was considered significant. All *P* values were obtained using 2-tailed tests. All data analyses were performed with the Statistical Package for Social Sciences, version 14 (SPSS Inc, Chicago, IL).

RESULTS

Of the 8176 study patients, 7242 (88.6%) were non-khat chewers, and 934 (11.4%) were khat chewers. Khat chewers were mainly of Yemeni origin, representing 72.2% of the total Yemeni patients studied. Khat chewers were more likely to present with STEMI (74.4%), followed by unstable angina (14.3%) and NSTEMI (11.2%; *P* < .001). In non-khat chewers, presentation with NSTEMI (34.9%) was comparable to that of STEMI (34.6%), both followed by unstable angina (30.5%).

Overall, khat chewers were older and more likely to be men (Table 1). Additionally, they were less likely to have diabetes mellitus, hyperlipidemia, hypertension, renal impairment, and obesity. Subset evaluation of age among Yemeni patients revealed that khat chewers were 3 years younger than non-khat chewers (mean \pm SD age: khat chewers, 57.1 \pm 11.1; non-khat chewers, 60.9 \pm 12.5; *P* < .001). Cigarette

TABLE 1. Clinical Characteristics of Khat and Non-khat Chewers Presenting With Acute Coronary Syndrome^a

	Khat	Non-khat	P value
No. of patients (N=8176)	934 (11.4)	7242 (88.6)	
Age (y)	57±11	56±12	.01
Female sex	134 (14.3)	1849 (25.5)	<.001
Diabetes mellitus	241 (25.8)	3063 (42.3)	<.001
Hypertension	299 (32.0)	3740 (51.6)	<.001
Dyslipidemia	104 (11.1)	2497 (34.5)	<.001
Smoking	565 (60.5)	2416 (33.4)	<.001
Prior aspirin use	297 (31.8)	3029 (41.8)	<.001
Family history of CAD	131 (14.0)	977 (13.5)	.70
Prior CAD	328 (35.1)	3362 (46.4)	<.001
Prior revascularization	75 (8.0)	1193 (16.5)	<.001
Renal impairment ^b	4 (0.4)	77 (1.1)	.09
Presentation >12 h (STEMI + LBBB)	408/682 (59.8)	521/2456 (21.2)	<.001
Heart rate (beats/min)	90±23	85±22	<.001
Blood pressure (mm Hg)			
Systolic	130±32	140±30	<.001
Diastolic	83±20	83±18	.50
Body mass index	26±5	27±5	.001
Killip class >1	275 (29.4)	1519 (21.0)	<.001
GRACE risk score ^c (%)			
Low/moderate	57.8	69.2	<.001
High	42.2	30.8	.05
Laboratory results			
Total cholesterol (mg/dL)	224.4±116.1	174.1±77.4	<.001
Serum triglyceride (mg/dL)	288.7±525.0	210.0±787.5	.003
First blood sugar (mg/dL)	169.2±162.0	189.0±216.0	.005
First serum creatinine (mg/dL)	1.002±0.079	1.055±0.101	.10

^a Values presented as No. (percentage) or mean ± SD, unless indicated otherwise. CAD = coronary artery disease; GRACE = Global Registry of Acute Coronary Events; LBBB = left bundle branch block; STEMI = ST-segment elevation myocardial infarction.

^b Dialysis required.

^c For STEMI, low/moderate-risk score is 49-154; high-risk score, 155-319. For non-ST-segment evaluation for acute coronary syndrome, low/moderate-risk score is 1-140; high-risk score, 141-372.

smoking was more prevalent among khat chewers. Despite the fact that khat chewers had a favorable cardiovascular profile compared with non-khat chewers, their heart rate, Killip class, and Global Registry of Acute Coronary Events risk scores were higher on admission. This may be due in part because khat chewers presented later: 59.8% of khat chewers presented more than 12 hours after onset of symptoms compared with 21.2% of non-khat chewers; hence, they had larger infarcts.

TREATMENT

In-hospital. Overall, use of clopidogrel, unfractionated heparin, and angiotensin-converting enzyme inhibitors was higher among khat chewers vs non-khat chewers (Table 2). Aspirin, low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, and β-blockers were prescribed more frequently to non-khat chewers.

Among patients with STEMI or left bundle branch block myocardial infarction (MI), thrombolytic therapy was the primary reperfusion strategy in our registry, and

TABLE 2. Variability in Presentation, Final Diagnosis, and Hospital Treatment of Khat and Non-khat Chewers^a

	Khat (N=934)	Non-khat (N=7242)	P value
Atypical presentation	66 (7.1)	471 (6.5)	0.5
Final diagnosis			
STEMI + LBBB	695 (74.4)	2507 (34.6)	<.001
NSTEMI	105 (11.2)	2526 (34.9)	<.001
Unstable angina	134 (14.3)	2209 (30.5)	<.001
Coronary angiography	111 (11.9)	866 (12.0)	.90
In-hospital therapy			
Thrombolytic therapy ^b	204/274 (74.5)	1617/1935 (83.6)	.001
Primary PCI ^c	7/274 (2.6)	167/1935 (8.6)	.001
Aspirin	903 (96.7)	7093 (98.0)	.02
Clopidogrel	583 (62.4)	3777 (52.2)	<.001
Unfractionated heparin	813 (87.0)	3061 (42.3)	<.001
LMWH	90 (9.6)	3728 (51.5)	<.001
Glycoprotein IIb/IIIa inhibitors	12 (1.3)	866 (12.0)	<.001
ACE inhibitors	639 (68.4)	4557 (62.9)	.001
ARB	38 (4.1)	357 (4.9)	.30
β-Blockers	557 (59.6)	4758 (65.7)	.001
Therapy at discharge			
Aspirin	825 (88.3)	6835 (94.4)	<.001
Clopidogrel	579 (62.0)	3470 (47.9)	<.001
ACE inhibitors	661 (70.8)	4936 (68.2)	.90
ARB	60 (6.4)	476 (6.6)	.90
β-Blockers	633 (67.8)	5484 (75.7)	<.001
Statins	791 (84.7)	5796 (80.0)	.001

^a Values presented as No. (percentage), unless indicated otherwise. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LBBB = left bundle branch block; LMWH = low-molecular-weight heparin; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

^b Total No. of patients eligible for reperfusion: khat, 682; non-khat, 2456.

^c Total No. of patients eligible for reperfusion: khat, 274; non-khat, 1935.

the overall use of primary percutaneous revascularization therapy was low (<8%). Khat chewers were less likely to receive coronary reperfusion therapy, mainly because more than 50% of these patients presented greater than 12 hours after symptom onset.

IN-HOSPITAL OUTCOME

Khat chewers had significantly higher mortality rates compared with non-khat chewers (8.7 vs 2.9%; *P*<.001)

TABLE 3. In-hospital Outcome and Duration of Hospital Stay for Khat and Non-khat Chewers

Hospital outcome	Khat (N=934)	Non-khat (N=7242)	P value
Recurrent ischemia	76 (8.1)	704 (9.7)	.10
Reinfarction	11 (1.2)	190 (2.6)	.01
Heart failure	156 (16.7)	1168 (16.1)	.60
Cardiogenic shock	95 (10.2)	320 (4.4)	<.001
Major bleeding	6 (0.6)	53 (0.7)	.90
Stroke	17 (1.8)	39 (0.5)	.001
Mortality	81 (8.7)	211 (2.9)	<.001
Hospital stay (d) (mean ± SD)	6.9±4.7	5.3±4.5	<.001

Values presented as No. (percentage), unless indicated otherwise.

(Table 3). They were also more likely to develop cardiogenic shock and stroke, whereas non-khat chewers were more likely to have recurrent MIs. There were no differences between the 2 groups in regard to bleeding and heart failure complications.

MULTIVARIATE ANALYSIS

Multivariate regression showed that age, female sex, diabetes mellitus, and khat use were independent predictors of increased risk of death, whereas thrombolytic therapy, β -blockers, and statin use were associated with reduced mortality (Table 4). Age, female sex, and diabetes mellitus were associated with increased risk for the development of cardiogenic shock, whereas khat use was not associated with increased risk. Finally, age, diabetes mellitus, and khat use were independent predictors of increased risk of stroke.

DISCUSSION

To our knowledge, the current study is the first to provide a detailed description of khat chewers presenting with ACS. The significant delay in patients presenting after symptom onset resulted in less likelihood of receiving reperfusion therapy; this delay may be due in part to the analgesic effect of khat biochemical constituents.¹⁶ Although khat chewers had a lower risk profile, including lower prevalence of diabetes mellitus, hypertension, dyslipidemia, and obesity, and were less likely to be women, they had higher in-hospital complications, including death and stroke, in part because of delay in presentation. The current study highlights the importance of evaluating cardiac patients from certain ethnic and geographic origins in regard to khat chewing.

PREVALENCE OF KHAT CHEWING

In the current study, khat chewers represented 11.4% of the overall ACS population in 6 Arab Middle Eastern countries; they originated exclusively from Yemen. Furthermore, among patients with ACS in Yemen in this registry, 72.2% were khat chewers. This high prevalence of khat chewing among Yemeni patients is comparable to that in previous reports among Yemeni cardiac patients¹⁷⁻¹⁹ as well as in the general Yemeni population.^{2(pp60-78)} These findings suggest that self-reporting of khat chewing is accurate. Recent reports indicate that 80% to 90% of East African men use khat on a daily basis. Alem et al²⁰ reported a 50% prevalence of khat users in Ethiopia, with 17% self-describing daily use. With immigration, khat chewing has spread recently to other continents, including Europe and North America.^{10,21,22} Several tons of khat pass through Heathrow airport (London) every week.¹² Some of this khat is reexported to other European countries. Because of

TABLE 4. **Multivariate Analysis for Predictors of In-hospital Mortality, Cardiogenic Shock, and Stroke in Patients With Acute Coronary Syndrome**

Variables	Odds ratio (95% CI)	P value
Mortality		
Hypertension	1.2 (0.9-1.8)	.20
Dyslipidemia	1.4 (0.9-2.1)	.08
Age	1.1 (1.0-1.07)	<.001
Female sex	1.8 (1.3-.2.7)	<.001
Diabetes mellitus	1.5 (1.1-2.1)	.02
Khat chewing	1.9 (1.3-2.7)	<.001
Smoking	0.9 (0.7-1.4)	.90
Thrombolytic therapy	0.5 (0.3-0.6)	<.001
β -Blockers	0.4 (0.2-0.6)	<.001
Statin therapy	0.4 (0.3-0.6)	<.001
Cardiogenic shock		
Hypertension	1.2 (0.9-1.6)	.20
Dyslipidemia	1.5 (1.1-2.0)	.02
Age	1.0 (1.0-1.1)	<.001
Female sex	2.3 (1.7-3.1)	<.001
Diabetes mellitus	1.5 (1.2-1.9)	.002
Khat chewing	1.1 (0.8-1.5)	.40
Smoking	1.3 (0.9-1.7)	.14
Thrombolytic therapy	0.5 (0.4-0.7)	<.001
Stroke		
Hypertension	1.3 (0.6-2.8)	.40
Dyslipidemia	1.6 (0.7-3.7)	.20
Age	1.0 (1.0-1.08)	.003
Female sex	1.5 (0.7-3.4)	.20
Diabetes mellitus	2.2 (1.1-4.6)	.03
Khat chewing	2.7 (1.3-5.9)	.01
Smoking	0.6 (0.3-1.5)	.20
Thrombolytic therapy	0.8 (0.4-1.7)	.50

CI = confidence interval.

the rapid influx of immigrants from these regions into the United States, certain quantities of khat are believed to be smuggled into this country, although importation is illegal; hence, it is imperative to evaluate khat use among appropriate patients and even advise them against its use. Data on the prevalence of khat chewing in the Western world are limited, and most studies are conducted in the United Kingdom. Griffiths et al²³ reported that 78% of a Somali study population (N=207) in London were using khat. Patel²⁴ reported that 83% of Somali immigrants residing in 4 cities in England used khat during their lifetime and that 34% used khat in the month before interview. Data are lacking on immigrants' use of khat in the United States.

KHAT CHEWING AND CARDIOVASCULAR DISEASE

The pharmacologic effect of khat chewing is mainly due to cathinone. Cathinone is regarded as an indirectly acting sympathomimetic alkaloid that has catecholamine-releasing properties at both central dopaminergic and serotonergic synapses as well as at peripheral noradrenaline storage sites; it operates through the same mechanism as amphetamine.^{4,5} Several studies have reported increases in heart rate and blood pressure in association with khat chewing.²⁵⁻²⁹ In a cross-sectional study of 4001 adults aged

25 to 64 years in Addis Ababa, Ethiopia, Tesfaye et al²⁵ reported a significant association between khat chewing and elevated mean diastolic blood pressure ($P=.02$). The same observation was also noted by Brenneisen et al⁴ and Hassan,²⁵ and this increase correlated with plasma levels of cathinone. Furthermore, Gugelmann et al²⁹ reported positive inotropic and chronotropic actions in isolated atria in response to the administration of cathinone.

To date, 3 preliminary studies and 1 case report have examined whether khat chewing has a role in precipitating MI.^{17-19,30} In a case-control study conducted between 1997 and 1999, Al-Motarreb et al¹⁷ reported that khat chewing was more frequent among patients with MI (100 patients) compared with controls (89% vs 69%), suggesting an increased risk of MI among khat chewers. This increased risk is further supported by the dose-response relationships between MI risk and the quantity of khat chewed, with significant increased risk among moderate (odds ratio, 7.62) and heavy (odds ratio, 22.28) khat chewers compared with non-khat chewers. Moreover, this risk correlated with duration of khat chewing; the risk was increased with more than 4 hours of chewing per episode.

Alkadi et al¹⁹ reported similar observations in 2002; the prevalence of khat chewing among 120 patients with MI in Yemen was 79%, which was significantly higher compared with that in controls (55%; $P<.0001$). Furthermore, they observed that 49.4% of events among khat chewers occurred after completion of khat chewing, whereas 20.7% occurred during khat chewing; on the basis of these 2 observations, the investigators proposed that khat chewing be considered a risk factor for the occurrence of MI. More recently, Saha et al³⁰ described a 33-year-old East African man living in the United Kingdom who presented with acute anterior MI; the patient had no risk factors other than khat chewing and cigarette smoking. After discharge, the patient continued to chew khat, and 27 months later he presented with severe ischemic cardiomyopathy believed to be secondary to khat chewing.

The current study extends these observations in a much larger cohort of patients (934 khat chewers among 8176 consecutive Middle Eastern patients). The high prevalence of khat chewing among patients of Yemeni origin (72.2%) was also observed in the current study. Additionally, 60% of khat chewers were current smokers. This high prevalence of smoking among khat chewers was also observed by Al-Motarreb et al,¹⁷ Griffiths,²¹ and Bawazeer et al.³² Coronary vasospasm is the most likely mechanism by which khat causes MI, with increased myocardial oxygen demand induced by catecholamines and catecholamine-mediated platelet aggregation with subsequent thrombus formation.³² This theory is supported by Al-Motarreb and Broadley³³ and Baker et al,³⁴ who reported cathinone-

induced coronary vasoconstriction in isolated guinea pig hearts. Furthermore, this vasoconstriction occurred via a mechanism other than indirect sympathomimetic activity or α_1 -adrenoreceptors.³⁴ This hypothesis of coronary spasm is further supported by the fact that amphetamine, which is structurally related to cathinone, has been reported by several investigators to cause MI secondary to coronary spasm.³⁵⁻³⁹

PROGNOSTIC IMPACT OF KHAT CHEWING AMONG PATIENTS PRESENTING WITH ACS

To our knowledge, the current study is the first to report in-hospital outcomes of khat chewers presenting with ACS. Khat chewers had significantly higher rates of death, cardiogenic shock, and stroke complications compared with non-khat chewers despite the fact that they had lower cardiovascular risk profiles, including lower prevalence of diabetes and prior cardiovascular disease.

This poorer outcome may be explained in part by the following. First, 59% of khat chewers (compared with 21.1% of non-khat chewers; $P<.001$) presented more than 12 hours after symptom onset. This delay in presentation may be attributed to the cathinone analgesic properties similar to those of amphetamine and cocaine; cathinone reduces responsiveness to painful stimuli. This delay resulted in significantly more khat chewers being ineligible for reperfusion therapy and hence having a larger infarct. In experimental studies, these analgesic properties were blocked by either monoaminergic depletion or by the opiate antagonist naloxone.⁴⁰ Second, because khat chewing increases blood pressure and heart rate, this inotropic and chronotropic effect increases myocardial oxygen consumption, suggesting that the direct result is a larger higher infarct. These 2 factors may explain the poor hemodynamic parameters at presentation among khat chewers observed in our study, with higher Killip class and Global Registry of Acute Coronary Events risk scores. Third, amphetamine and methamphetamine, which are structurally related to cathinone, have been reported to directly induce cardiomyopathy^{41,42}; indeed, additional structural and functional changes of myocytes were related to methamphetamine exposure, as well as clinical manifestations of cardiomyopathy and congestive heart failure.^{43,44} Cathinone may also directly, adversely affect myocytes and contribute to this poor outcome. Finally, and more importantly, could this poor outcome be related to improper management, as in the case of cocaine-induced MI in which using β -blockers may leave the α effect unopposed, causing paradoxically increased blood pressure that may increase myocardial oxygen demand and infarction size? Furthermore, unopposed α blockade can worsen the coronary artery vasospasm. The same mechanism may occur in khat-induced coronary spasm.⁴⁵

Finally, we observed that khat chewing among ACS patients is an independent predictor of stroke; several cases of khat chewing-induced strokes have been published. In 2006, Vanwalleghem et al⁴⁶ described a 44-year-old Somali immigrant who resided in Belgium for years before experiencing 2 consecutive strokes (18 months apart) that were attributed to khat chewing. The patient had no further episodes after abstaining from khat chewing. Moreover, acute cerebral infarctions and stroke-like complications have been reported with khat chewing⁴⁸ and with sympathomimetic drugs like cocaine and amphetamine, which are structurally related to cathinone, the main active substance in khat.^{48,49} Khat chewing may predispose to the development of stroke through cerebral circulation vasospasm.

STUDY LIMITATIONS

Our data were collected from an observational study. However, well-designed observational studies provide valid results. Long-term follow-up is needed in both groups to consolidate our findings.

CONCLUSION

In this large cohort of patients with ACS, khat chewing was prevalent and was associated with increased risk of stroke and death. The study highlights the importance of properly evaluating cardiac patients on the basis of their ethnic and geographic origins. Patients of Eastern African and Yemeni origins should be evaluated and counseled about khat chewing, even when they are living in Western countries. In the context of increasing global migration, a greater awareness of potential widespread practices is essential.

Khat chewing increases the risk of MI through coronary spasm and exacerbates outcome. Further studies are needed to better evaluate the effects of khat.

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