

# Effects of Khat (*Catha edulis*) chewing on seminal fluid parameters: Findings from a fertility clinic cohort and cessation trial

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**Summary** Background: Khat (*Catha edulis*) chewing is a culturally ingrained practice in Yemen and has been associated with potential impairment of male reproductive function. However, rigorous quantitative assessments of its effects on seminal parameters are limited. This study investigates the relationship between khat consumption and semen characteristics and examines the reversibility of any adverse effects following cessation.

Methods: A prospective two-phase study was conducted at Dr. Najat Al-Malas IVF Center in Sana'a, Yemen (2019-2024). Phase 1 compared semen volume and related parameters across four age-, BMI-, education-, and socioeconomic-matched cohorts: infertile khat chewers (n = 91), infertile non-chewers (n = 60), fertile khat chewers (n = 91), and fertile non-chewers (n = 32). Phase 2 involved a three-month supervised khat cessation intervention among infertile chewers. Semen samples were obtained via standardized collection methods. Associations between khat use and seminal parameters were analyzed using univariate and multivariate regression models.

Results: Khat chewers demonstrated significantly reduced semen volumes compared to non-chewers in all comparisons. Infertile chewers had lower volumes ( $1.94 \pm 0.48$  mL) than fertile chewers ( $2.36 \pm 0.52$  mL;  $P < 0.001$ ,  $d = 0.85$ ) and infertile non-chewers ( $3.07 \pm 0.74$  mL;  $P < 0.001$ ,  $d = 1.72$ ). Pooled analysis indicated that chewers (n = 182) had 29.6% lower semen volumes than non-chewers (n = 92) ( $2.15 \pm 0.89$  mL vs.  $3.04 \pm 0.76$  mL;  $P < 0.001$ ). Notably, cessation of khat chewing led to a 35% increase in volume among infertile chewers (from  $1.94 \pm 0.48$  mL to  $2.62 \pm 0.52$  mL;  $P < 0.001$ ,  $d = 1.21$ ). Hormonal analysis (n = 15) showed increased testosterone and decreased prolactin post-cessation ( $P < 0.05$ ).

Conclusions: Khat chewing is significantly associated with reduced semen volume and impaired seminal fluid parameters in men. Importantly, cessation of khat use leads to a marked improvement in semen volume and favorable hormonal changes, indicating partial reversibility of its adverse effects. These findings highlight khat's detrimental impact on male reproductive health and underscore the potential benefits of quitting khat for fertility restoration.

**KEY WORDS:** *Catha edulis*; Semen volume; Semen parameters; Male infertility; Substance-related disorders; Reproductive health; Yemen.

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## INTRODUCTION

Khat (*Catha edulis* Forsk.), a flowering evergreen shrub of the Celastraceae family, contains psychoactive alkaloids structurally and pharmacologically related to amphetamines (1, 2). This stimulant is culturally entrenched in East Africa and the Arabian Peninsula, particularly Yemen, where it is traditionally consumed during social occasions to enhance alertness and productivity (3, 4). Globally, an estimated 20 million individuals use khat, with Yemen exhibiting particularly high prevalence: approximately 60% of adult males and 35% of females consume 100-200 g of fresh leaves daily (1).

Although the adverse physical and psychological effects of khat are well documented, its impact on male reproductive health remains inadequately characterized (1). A recent narrative review identified significant knowledge gaps concerning khat's reproductive toxicity in humans (5). Emerging meta-analyses suggest associations between khat use and detrimental reproductive outcomes, including reduced semen volume and increased risks of low birth weight and congenital anomalies (6). However, these findings are based on limited primary data, and mechanistic studies are lacking. Moreover, controlled investigations addressing dose-response effects and reversibility are scarce.

Seminal fluid volume is a critical parameter influencing male fertility, providing nutritional and protective functions essential for sperm viability during transit through the female reproductive tract (7). In 2021, the World Health Organization defined hypospermia as ejaculate volumes consistently below 1.4 mL (8). Etiologies of reduced semen volume include psychological factors, collection artifacts, and pathological conditions affecting accessory sex glands or ejaculatory ducts (9).

Khat chewing is widespread among Yemeni men of reproductive age, and accumulating evidence implicates it in male infertility (5, 10). For example, *El-Shoura et al.* reported that khat-dependent individuals exhibited significantly reduced semen volume, sperm motility, and sperm counts compared to non-users (11). These findings align with other studies demonstrating khat's negative effects on sperm quality and testosterone levels (10, 12, 13).

However, most research has been conducted outside

Yemen, where genetic and environmental factors differ. Given Yemen's high khat prevalence and cultural normalization, there is an urgent need for population-specific data. This study aims to evaluate the effects of khat on seminal parameters and hormonal profiles in Yemeni men, providing locally relevant evidence to inform clinical practice and public health strategies. The findings will contribute novel insights into khat's reproductive toxicity and its potential reversibility, with implications for fertility management in endemic regions.

## MATERIALS AND METHODS

### Study design

This study employed a dual-phase approach. The first phase was a prospective cross-sectional study comparing seminal parameters across frequency-matched groups of fertile and infertile men, stratified by khat chewing status. The second phase consisted of a prospective interventional cohort study assessing the impact of khat cessation on infertile khat chewers. The study was conducted at *Dr. Najat Al-Malas IVF and ART Center in Sana'a, Yemen*, over a five-year period from 2019 to 2024.

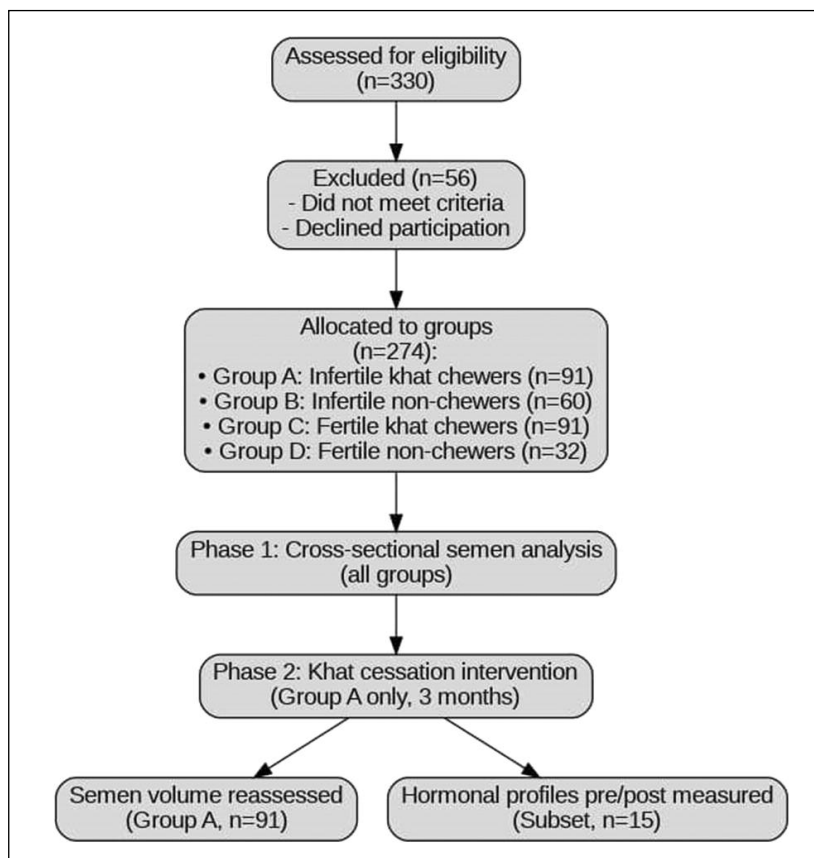
### Participants

A total of 330 Yemeni men aged 20 to 40 years were initially recruited, with 274 completing the study, yielding an 83% retention rate. During the study period, 56 participants were excluded: 52 withdrew prematurely, primarily due to discontinuation of the khat cessation interven-

tion in Group A, and 4 were excluded for protocol violations, specifically unplanned khat cessation during Phase 1. The final analytic sample comprised 274 participants, as detailed in the CONSORT flow diagram (Figure 1). Participants were allocated into four frequency-matched groups to ensure comparability: infertile khat chewers (Group A,  $n = 91$ ), infertile non-chewers (Group B,  $n = 60$ ), fertile khat chewers (Group C,  $n = 91$ ), and fertile non-chewers (Group D,  $n = 32$ ). Matching criteria included age ( $\pm 3$  years), body mass index (BMI,  $\pm 2$  kg/m<sup>2</sup>), educational attainment (primary, secondary, tertiary), and socioeconomic status, assessed via the Hollingshead Index tertiles. This matching strategy was designed to minimize confounding influences related to demographic and lifestyle factors.

### Inclusion criteria

Participants were classified as fertile or infertile based on established definitions. Fertile men (Groups C and D) had documented natural conception of at least one child within the preceding 24 months and were voluntarily recruited as comparative (control) groups. Infertile men (Groups A and B) met the World Health Organization's criteria for infertility, defined as failure to conceive after 12 months of regular unprotected sexual intercourse (14). Regular khat chewers (Groups A and C) were those consuming 100-200 grams of fresh *Catha edulis* leaves daily, with chewing sessions lasting a minimum of three hours, sustained for at least 12 months. Khat use was verified through family interviews and standardized measurement of khat bundle weights.



**Figure 1.**

Participant flowchart depicting recruitment, allocation, and study phases.

Of 330 men assessed for eligibility, 274 were allocated into four frequency-matched groups: infertile khat chewers ( $n = 91$ ), infertile non-chewers ( $n = 60$ ), fertile khat chewers ( $n = 91$ ), and fertile non-chewers ( $n = 32$ ).

Phase 1 involved cross-sectional semen analysis of all groups.

Phase 2 consisted of a three-month supervised khat cessation intervention in Group A, with semen volume reassessment in all participants and hormonal profiling conducted pre- and post-cessation in a subset of 15 individuals.

### Exclusion criteria

All participants underwent thorough andrological evaluations to exclude confounding conditions. Exclusion criteria included tobacco use exceeding five cigarettes per week, positive urine toxicology for recreational drugs, and endocrine disorders such as hypogonadism (serum testosterone < 2.5 ng/mL measured by liquid chromatography tandem mass spectrometry). Men with congenital reproductive tract anomalies (e.g., ejaculatory duct obstruction confirmed by transrectal ultrasound and absent seminal fructose), chronic metabolic diseases (diabetes mellitus with HbA1c > 6.5%, hypertension with blood pressure > 140/90 mmHg), or use of medications affecting semen quality or sexual function (including 5 $\alpha$ -reductase inhibitors,  $\alpha$ / $\beta$ -blockers, antipsychotics) were excluded. Additionally, individuals with active inflammatory conditions (urethritis, prostatitis, and seminal vesiculitis diagnosed by NIH-CPSI score > 14 and positive Meares-Stamey test) were excluded.

### Sample size calculation

Sample size was calculated using a two-sample t-test framework based on prior data indicating a mean semen volume of  $2.5 \pm 1.0$  mL (15). To detect a clinically meaningful difference of 0.6 mL between groups with 90% power at  $\alpha = 0.05$ , 80 participants per group were required. Anticipating a 20% attrition rate, recruitment targets were set at 100 participants per primary comparison group (chewers vs. non-chewers). Post-hoc power analysis of our study confirmed that the final sample size exceeded 90% power to detect observed effect sizes, with Cohen's  $d > 0.8$ .

### Semen collection and analysis

Participants provided semen samples following a standardized abstinence period of four days (range: 2-7 days), maintained consistently across collections. Two collection methods were employed: condom-protected intercourse with immediate post-ejaculatory withdrawal, and masturbation into pre-weighed sterile containers (Sarstedt AG), conducted seven days apart. The mean semen volume from both methods was calculated to enhance measurement reliability. Semen analyses were performed within 60 minutes of collection at 37°C by a technician blinded to participant group allocation, following WHO 2021 guidelines (16). While semen volume was the primary parameter, additional semen quality indices (sperm concentration, total sperm count, progressive motility, morphology) were recorded for exploratory analyses using samples obtained by masturbation only. Hormonal evaluation (total testosterone, follicle-stimulating hormone [FSH], luteinizing hormone [LH], and prolactin) was performed for all patients at baseline and for a subset of Group A participants after the khat cessation period.

### Intervention protocol (Group A)

Group A participants underwent a supervised three-month khat cessation program. Compliance was monitored monthly using validated craving and withdrawal scales (e.g., Khat Withdrawal Scale, reference). Bimonthly random salivary cathinone measurements were performed via high-performance liquid chromatography-mass

spectrometry (HPLC-MS) with a detection threshold of 5 ng/mL to objectively verify abstinence. Missing or inconsistent compliance data were addressed through sensitivity analyses. Post-intervention semen analyses employed identical collection protocols to ensure comparability.

### Outcome measures

The primary outcome comprised comparative analyses of semen parameters among fertile and infertile khat chewers and non-chewers. The secondary outcome focused on evaluating changes in semen parameters before and after khat cessation within infertile khat chewers (Group A).

### Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) and R software, Version 4.0 (R Foundation for Statistical Computing, Vienna, Austria). The distribution of continuous variables was assessed for normality using the Kolmogorov-Smirnov test. For normally distributed data, parametric tests including independent samples t-tests and one-way analysis of variance (ANOVA) with Tukey's post hoc comparisons were employed. When normality assumptions were violated, appropriate non-parametric alternatives were utilized. Within-subject changes following khat cessation were evaluated using paired t-tests. Effect sizes were calculated using Cohen's  $d$  and interpreted according to conventional thresholds: small (0.2), medium (0.5), and large (0.8). To adjust for potential confounding variables such as age, body mass index (BMI), and abstinence duration, multivariate linear regression models were constructed. Correction for multiple comparisons was performed using the Bonferroni method to control the family-wise error rate. Both intention-to-treat and per-protocol analyses were conducted to ensure robustness of findings. Statistical significance was set at a two-tailed  $p$ -value < 0.05.

## RESULTS

### Intergroup comparisons of semen parameters among study participants

Our analysis demonstrated statistically significant differences in seminal volume between khat chewers and non-chewers across all study groups. Infertile khat chewers exhibited significantly lower semen volumes ( $1.94 \pm 0.48$  mL) compared to fertile khat chewers ( $2.36 \pm 0.52$  mL; mean difference -0.42 mL, 95% confidence interval [CI] -0.77 to -0.07;  $P < 0.001$ ; Cohen's  $d = 0.85$ ) and infertile non-chewers ( $3.07 \pm 0.74$  mL; mean difference -1.13 mL, 95% CI -1.55 to -0.71;  $P < 0.001$ ; Cohen's  $d = 1.72$ ). When pooling all khat consumers ( $n = 182$ ), seminal volume was significantly reduced ( $2.15 \pm 0.89$  mL) relative to non-consumers ( $n = 92$ ;  $3.04 \pm 0.76$  mL; mean difference -0.89 mL, 95% CI -1.21 to -0.57;  $P < 0.001$ ; Cohen's  $d = 1.07$ ). Notably, no significant difference was observed between fertile and infertile non-chewers (mean difference 0.07 mL, 95% CI -0.52 to 0.66;  $P = 0.811$ ; Cohen's  $d = 0.04$ ), underscoring khat consumption as the principal factor associated with reduced seminal volume (Table 1).

**Table 1.**

Intergroup comparisons of semen volume among frequency-matched participant groups.

Comparison	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Statistical test	Mean difference (95% CI)	P-value	Effect size (Cohen's d)
Khat chewers (Fertile vs. Infertile)						
Fertile chewers (Group C)	2.36 ± 0.52	-	Independent t-test	0.42 (0.25 to 0.59)	< 0.001	0.85†
Infertile chewers (Group A)	-	1.94 ± 0.48				
Non-chewers (Fertile vs. Infertile)						
Fertile non-chewers (Group D)	3.00 ± 0.78	-	Independent t-test	-0.07 (-0.42 to 0.28)	0.69	0.09
Infertile non-chewers (Group B)	-	3.07 ± 0.74				
All chewers vs. all non-chewers						
Chewers (Groups A + C)	2.15 ± 0.89	-	Independent t-test	-0.89 (-1.12 to -0.66)	< 0.001	1.07†
Non-chewers (Groups B + D)	-	3.04 ± 0.76				
Multi-group comparison (ANOVA)						
Fertile chewers (C) vs. Fertile non-chewers (D)	2.36 ± 0.52	3.00 ± 0.78	One-way ANOVA (Tukey)	-0.64 (-0.98 to -0.30)	< 0.001	0.94†
Infertile chewers (A) vs. Infertile non-chewers (B)	1.94 ± 0.48	3.07 ± 0.74				

† Large effect size ( $d \geq 0.8$ ).  
\*Statistical adjustments for age, BMI, and abstinence duration were performed via multivariate linear regression.  
P-values: \* $P < 0.01$ , \*\* $P < 0.001$ .

### Multivariate linear regression analysis of factors influencing semen volume

Adjusting for age, BMI, and abstinence duration, multivariate linear regression identified khat chewing as the strongest independent predictor of diminished semen volume ( $\beta = -0.92$ , 95% CI -1.15 to -0.69;  $P < 0.001$ ), explaining 28% of the variance (partial  $\eta^2 = 0.28$ ) (Table 2). The regression model exhibited excellent fit ( $R^2 = 0.41$ , adjusted  $R^2 = 0.39$ ) and no multicollinearity issues (variance inflation factors  $< 1.2$ ).

### Effect of Khat cessation on seminal fluid volume and hormonal profile

Following a supervised three-month khat cessation pro-

gram, infertile khat chewers demonstrated a significant 35% increase in seminal volume, rising from  $1.94 \pm 0.48$  mL to  $2.62 \pm 0.52$  mL (mean difference 0.68 mL; 95% CI 0.49-0.87;  $P < 0.001$ ), with a large effect size (Cohen's  $d = 1.21$ ). This improvement surpassed the World Health Organization's minimal clinically important difference for semen volume and restored values comparable to those of untreated fertile individuals ( $p = 0.12$ ), indicating reversibility of khat's detrimental effects on male reproductive function. Additional semen quality parameters – including total sperm count, progressive motility, and normal morphology – also exhibited statistically significant improvements, with effect sizes ranging from medium to large (Table 3 and Figure 2).

Predictor	Unstandardized $\beta$ (95% CI)	Standardized $\beta$	P-value	VIF	Partial $\eta^2$
Khat chewing (Yes vs. No)	-0.92 (-1.15 to -0.69)	-0.53	< 0.001	1.12	0.28
Age (years)	-0.02 (-0.05 to 0.01)	-0.08	0.18	1.08	0.03
BMI (kg/m <sup>2</sup> )	-0.03 (-0.07 to 0.01)	-0.10	0.12	1.05	0.04
Abstinence duration (days)	0.11 (0.06 to 0.16)	0.22	< 0.001	1.04	0.12

Model summary:  $R^2 = 0.41$ , Adjusted  $R^2 = 0.39$ ,  $F(4, 269) = 32.7$ ,  $P < 0.001$ .  
VIF = Variance Inflation Factor (all values  $< 2$  indicate absence of multicollinearity).  
Continuous predictors were centered prior to analysis.

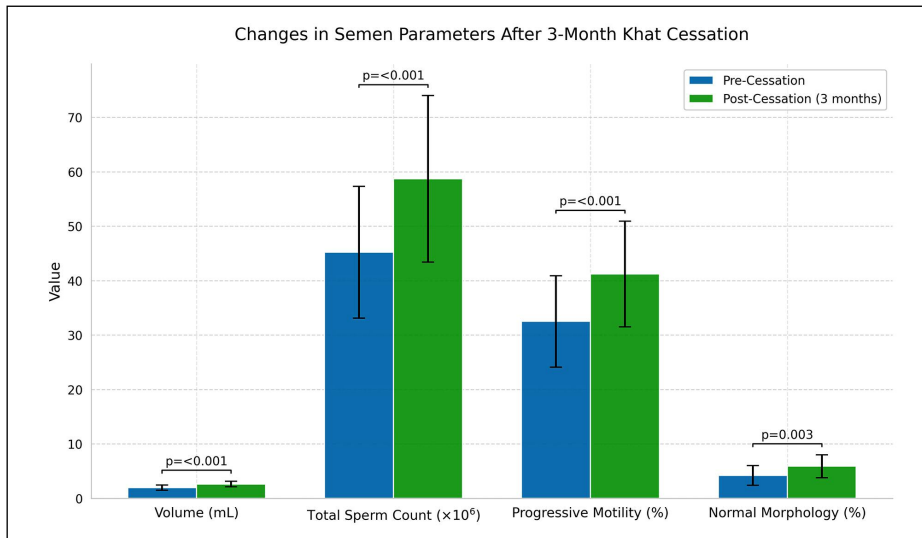
**Table 2.**

Multivariate linear regression analysis of factors affecting semen volume.

Parameter	Pre-cessation (Mean ± SD)	Post-cessation (Mean ± SD)	Mean difference (95% CI)	P-value	Effect size (Cohen's d)
Volume (mL)	1.94 ± 0.48	2.62 ± 0.52	0.68 (0.52 to 0.84)	< 0.001	1.21†
Total Sperm Count ( $\times 10^6$ )	45.2 ± 12.1	58.7 ± 15.3	13.5 (9.8 to 17.2)	< 0.001	0.98†
Progressive Motility (%)	32.5 ± 8.4	41.2 ± 9.7	8.7 (6.2 to 11.2)	< 0.001	0.89†
Normal Morphology (%)	4.2 ± 1.8	5.9 ± 2.1	1.7 (1.1 to 2.3)	0.003	0.72‡

† Large effect size ( $d \geq 0.8$ ).  
‡ Medium-large effect ( $d > 0.5$ ).  
Statistical test: Paired t-test. Terminology reflects alpha-adrenergic mediation of seminal emission.

**Table 3.**Semen parameter changes after 3-month Khat cessation in infertile chewers (Group A,  $n = 91$ ).



**Figure 2.** Changes in semen parameters following three months of khat cessation in infertile khat chewers (Group A). Significant improvements were observed in semen volume, total sperm count, progressive motility, and normal morphology ( $p < 0.05$ ,  $p < 0.01$ ).

Hormone	Pre-cessation (Mean ± SD)	Post-cessation (Mean ± SD)	Mean difference (95% CI)	P-value	Statistical test
Testosterone (ng/dL)	412 ± 98	438 ± 105	26 (12 to 40)	0.012	Paired t-test
FSH (IU/L)	5.2 ± 1.8	5.0 ± 1.6	-0.2 (-0.6 to 0.2)	0.35	Paired t-test
LH (IU/L)	4.8 ± 1.5	4.9 ± 1.4	0.1 (-0.3 to 0.5)	0.62	Paired t-test
Prolactin (ng/mL)	15.3 ± 4.2	14.1 ± 3.9	-1.2 (-2.0 to -0.4)	0.021	Wilcoxon signed-rank test*

*Non-normal distribution (Shapiro-Wilk P < 0.05).  
FSH = Follicle-stimulating hormone; LH = Luteinizing hormone.*

**Table 4.** Hormonal profile changes after Khat cessation (Subset Cohort,  $n = 15$ ).

Hormonal assessment in a subset of 15 participants revealed a significant increase in serum testosterone levels accompanied by a modest but statistically significant decrease in prolactin concentrations. *Follicle-stimulating hormone* (FSH) and *luteinizing hormone* (LH) levels remained unchanged. These findings collectively suggest that khat cessation positively influences both seminal parameters and select hormonal profiles, supporting its beneficial impact on male reproductive health (Table 4).

## DISCUSSION

This study investigated the impact of khat (*Catha edulis*) chewing on male reproductive parameters, with a specific focus on semen volume, and assessed the reversibility of these effects following supervised khat cessation. Our findings indicate that chronic khat chewing is significantly associated with impaired semen quantity and quality, including reductions in semen volume, total sperm count, progressive motility, and normal morphology. Encouragingly, these adverse effects showed substantial improvement after three months of cessation, concurrent with favorable hormonal changes – increased testosterone and decreased prolactin levels.

Chronic khat chewing is increasingly recognized as a contributor to male infertility. Studies consistently associate it with reduced semen volume, sperm concentration, motility, and increased abnormal sperm morphology (6, 11). These alterations often coincide with lower testos-

terone and altered prolactin secretion, potentially disrupting spermatogenesis and sperm function (5). The underlying pathophysiology appears multifactorial. Khat's primary psychoactive alkaloids, cathinone and cathine, act as potent stimulants. This activity may trigger oxidative stress and heighten sympathetic nervous system activity, leading to increased *reactive oxygen species* (ROS) that damage sperm DNA and cellular membranes, compromising viability and motility (17-19). Furthermore, khat's adrenergic effects could impair seminal emission, potentially through receptor desensitization or neurotransmitter depletion, thereby reducing semen volume.

While some animal studies suggest dose-dependent or biphasic effects, the prevailing evidence points to khat disrupting endocrine regulation and inducing oxidative damage within the seminal environment (5, 6, 19, 20). Collectively, these findings suggest khat-related infertility arises from a complex interplay of hormonal changes, oxidative stress, and impaired seminal fluid dynamics.

Khat shares sympathomimetic toxicodynamic pathways with other substances (e.g., indirect sympathomimetic activity, monoamine modulation,  $\alpha$ -adrenergic receptor overstimulation), contributing to reproductive toxicity (17). However, khat's natural alkaloid profile and pharmacokinetics may lead to distinct, potentially biphasic, dose-dependent hormonal effects not always observed with synthetic sympathomimetics (13, 21).

Ejaculation comprises two main phases: emission (sympathetically controlled movement of seminal fluid into the

urethra) and expulsion (muscle contractions propelling fluid outward) (22). Khat may interfere with both phases, particularly emission, by potentially inhibiting acetylcholine release and smooth muscle contraction via pre-junctional  $\alpha_2$  adrenergic and 5-HT<sub>7</sub> receptors (6, 23-25). Our results demonstrate that khat chewing is independently associated with reduced semen volume in both fertile and infertile men. This aligns with the pharmacology of cathinone and cathine, potent norepinephrine releasers and reuptake inhibitors (26, 27). Alpha-adrenergic stimulation is critical during emission for coordinating contractions in the vas deferens, seminal vesicles, and prostate (28, 29). Chronic adrenergic overstimulation from khat may lead to receptor desensitization or neurotransmitter depletion, impairing seminal emission and reducing volume (5, 20, 30). Reduced contractility in accessory sex glands due to  $\alpha$ -adrenergic dysregulation may also decrease seminal fluid volume and alter viscosity, mirroring effects seen with  $\alpha_1$ -blocker medications known to impair fluid release and contribute to infertility (12, 31). These mechanisms suggest the observed reduction in semen volume among khat chewers is more likely due to impaired emission than impaired production.

Our findings of reduced semen parameters among khat chewers align with previous studies. *El-Shoura et al.* reported significantly lower semen volume, sperm motility, and concentration in khat users (11). *Hakim et al.* also found correlations between long-term khat chewing and changes in seminal fluid, including decreased volume, count, and motility, though statistical significance varied (20). Additional studies link khat chewing with reduced libido and possible erectile dysfunction, highlighting the need for further causal research (32, 33).

A key observation is the reversibility of khat's adverse effects on semen parameters following cessation. Infertile chewers who abstained for three months showed substantial improvements in semen volume, total sperm count, progressive motility, and normal morphology. The recovery in volume supports the hypothesis that alpha-adrenergic dysfunction caused by chronic khat chewing is, at least partially, reversible as receptor sensitivity and neurotransmitter balance recover (26, 34). Concurrent improvements in other semen parameters suggest khat's detrimental impact extends to spermatogenesis and sperm maturation, potentially through oxidative stress, impaired testicular vascular function, or hormonal disruption (11, 32, 33). While the cross-sectional design limits definitive causal claims, the pattern of reversibility provides supportive evidence. These findings highlight the potential for recovery of male reproductive function with cessation and underscore its relevance for clinical counseling.

Hormonal profiling in a subset of participants revealed modest increases in total testosterone and decreases in prolactin levels after khat cessation, while FSH and LH levels remained stable. These shifts are consistent with khat's dopaminergic effects, potentially alleviating hyperprolactinemia – a known contributor to hypogonadism and impaired semen quality (3). The stability of gonadotropins suggests that khat's primary impact on fertility may occur peripherally (e.g., testicular and accessory glands) rather than centrally via the hypothalamic-pituitary-gonadal axis. These hormonal changes likely interact with the observed

oxidative stress pathways to impair semen quality (5, 17). Dopaminergic modulation could influence prolactin levels and antioxidant defenses, while adrenergic overdrive directly contributes to the generation of oxidative stress (35).

Animal studies offer further mechanistic insights, though with nuances requiring careful interpretation. *Mohammed et al.* and *Shulman et al.* reported biphasic effects on male rat sexual behavior, with higher doses diminishing performance and lower doses sometimes enhancing motivation, potentially linked to testosterone fluctuations (13, 36). Khat administration has reduced epididymal sperm count without consistently altering endocrine gland function in some models, suggesting direct gonadal toxicity (5). Other studies demonstrate khat or cathinone reducing sperm count and motility, increasing abnormal sperm, and inhibiting spermatogenesis, with variable effects on reproductive hormones depending on dose and species (5, 13, 18, 37, 38). Importantly, the observed biphasic effects in animals underscore the complexity of dose-response relationships, which may also exist in humans but remain inadequately characterized due to variations in chewing habits and alkaloid content (5). Furthermore, the stable levels of gonadotropins observed in our human cohort contrast with some animal data showing LH suppression, highlighting species differences and underscoring the need for targeted human research to understand dose-dependent effects and distinguish between central and peripheral actions.

### **Clinical and public health implications**

Our findings have significant implications for clinical practice and public health, particularly in regions where khat chewing is prevalent. Clinicians should routinely inquire about khat use during infertility evaluations and preconception counseling, given the evidence of its association with impaired semen parameters and the potential for reversibility upon cessation. Men presenting with reduced semen volume, abnormal semen parameters, or hormonal disturbances such as low testosterone or elevated prolactin should be specifically screened for khat consumption. In reproductive counseling, it is essential to inform men planning conception or concerned about fertility of the potential reproductive risks associated with khat chewing. The demonstrated reversibility of semen impairment following cessation offers an encouraging message and a concrete intervention strategy for affected individuals. From a public health perspective, these results underscore the need for targeted educational campaigns that address the reproductive risks of khat alongside its other health consequences. Integration of khat cessation support within existing reproductive health and substance use services could enhance the effectiveness of interventions. Community-based awareness initiatives and the development of practical biomarkers for objective exposure assessment would further strengthen monitoring and prevention efforts. Collectively, these strategies could contribute to improved male reproductive health outcomes in populations with high rates of khat use.

### **Study limitations**

Several limitations warrant consideration. The cross-sectional design of much of the data limits causal inference,

although the observed reversibility provides supportive evidence. Hormonal analyses were constrained by a small sample size, limiting generalizability and emphasizing the need for larger prospective studies. The three-month cessation period may not fully capture the timeline of reproductive recovery; longer-term follow-up is important. The reliance on self-reported khat consumption introduces potential recall bias, and the lack of detailed usage pattern data prevents dose-response analysis. The single-center design and recruitment of fertile controls via volunteer sampling may limit generalizability and introduce selection bias. Despite adjustments for key confounders, residual confounding from unmeasured variables (e.g., diet, concurrent substance use, environmental exposures) cannot be excluded. Finally, the precise mechanisms by which khat influences seminal fluid production, especially autonomic regulation of accessory glands, require further elucidation. Addressing these limitations necessitate multicenter studies employing objective biomarkers, extended longitudinal monitoring, and evaluation of sympathetic nervous system function.

## CONCLUSIONS

This study demonstrates that khat chewing is significantly associated with reduced semen volume in both infertile and fertile men, with khat use emerging as a strong independent predictor of this reduction. Importantly, cessa-

tion of khat consumption leads to a substantial recovery in semen volume, accompanied by favorable hormonal changes, including increased testosterone and decreased prolactin levels. These findings corroborate prior evidence linking khat use to impaired male reproductive parameters and suggest that the adverse effects on seminal fluid volume are at least partially reversible. Given the cultural prevalence of khat chewing in affected regions, these results underscore the need for targeted public health interventions and further research into the mechanisms underlying khat's reproductive toxicity and its potential reversibility.

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## DECLARATIONS

**Ethical approval:** Approval for the study protocol and all related procedures was granted by the Institutional Ethics Committee of Dr. Najat Al-Malas IVF and ART Center in Sana'a, Yemen. The protocol was further approved by the Institutional Review Board of Dr. Najat Al-Malas IVF Center (Reference number 0031MN-2024, dated 21 January 2024). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki, with participants retaining the right to withdraw from the study at any time without penalty. The study protocol was initially established on 1 June 2019 and registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), Japan, under registration number T000009772 (see: [https://center6.umin.ac.jp/cgi-bin/ctr\\_test\\_e/ctr\\_view\\_reg.cgi?recptno=T000009772](https://center6.umin.ac.jp/cgi-bin/ctr_test_e/ctr_view_reg.cgi?recptno=T000009772)).

**Availability of data and material:** All data generated or analyzed during this study are included in this published article.

**Competing interests:** The author declares no conflicts of interest.

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**Authors' contributions:** All authors contributed substantially to the conception, design, data acquisition, analysis, and interpretation of the study; participated in drafting and critically revising the manuscript; approved the final version for publication; agreed on the journal for submission; and accept responsibility for all aspects of the work.

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