AnnalsofClinicalandMedical Case Reports

ResearchArticle ISSN2639-8109Volume7

CathaEdulisForskandItsAdverseEffectsOnHealth:CurrentandOngoing Factuality

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Received: 08 Oct 2021
Accepted: 28 Oct 2021
Published:04Nov2021
JShort Name:ACMCR

Citation:

Bereda G, Catha Edulis Forsk and Its Adverse Effects On Health: Current and Ongoing Factuality. Ann Clin Med Case Rep. 2021; V7(13): 1-10

1. Abstract

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 psy- cho active substances, which produce euphoria and stimulation. Khat is an evergreen shrub, which is cultivated as a bush or small tree. The leaves have an aromatic odour. The taste is astringent andslightlysweet.Theplantisseedlessandhardy,growingin a variety of climates and soils. Khat contains more than forty al- kaloids, glycosides, tannins, amino acids, vitamins, and minerals. The euphoric effects of khat start after about 1 hour of chewing. The major effects include those on the gastro-intestinal system andonthenervoussystem.Constipation,urineretentionandacute cardiovascular effects may be regarded as autonomic (peripheral) nervoussystemeffects;increasedalertness,dependence,tolerance andpsychiatricsymptomsaseffectsonthecentralnervoussystem.

2. Keywords:

AdverseEffects;CathaEdulis;Forsk; Health

3. Introduction

Khat is an herbal product consisting of the leaves and shoots of theshrubCathaedulisForsk,amember(genera)oftheevergreen celastracae (moonseed or spindle-tree) family or tribe [1].

Khat (*Catha edulis*) also known as Abyssinian tea, Africa salad, Bushman's tea, Gat, Kat, Miraa, Tohai and Chat is a flowering shrub, native to the region extending from Eastern to SouthAfrica,aswellthe ArabianPeninsula[2-4].Khat"snaturalrangeextends throughout EastAfrica from Ethiopia, Eritrea and Somalia, throughtoSouthAfrica;itisalsofoundinRwanda,Zaire,Malawi andZimbabwe[5,6].Freshleavesofkhatcontainthealkaloidsofthephenylpropylaminetypeofwhichthetwopsychoactiveconstituents are the stimulants cathinone (S-(-)-α-aminopropiophenone) andcathine(S,S-(+)-norpseudoephedrine)[7].Khatisconsidered a "natural amphetamine" containing amphetamine-like stimulant substancessuchascathinoneandcathine[8].Thecentralstimulant effects of khat are similar to those of amphetamine.The reason is that the main active ingredient in khat is psychoactive alkaloids called cathinone, an amphetamine-like substance [9] (Figure 1).

Thepsychoactiveeffectsofkhataremainlyattributedtocathinone, a potent alkaloid which has a close structural resemblance to amphetamine [10]. The short-lived efficacy of khat leaves is caused by the rapid degradation of (-)-S-cathinone into (+) - norpseudoephedrine and norephedrine within a few days of harvest [11]. Its taste varies from one kind to another and depends on the tannic acid content. Khat leaves have an astringent taste and have an aromaticodour.Theyoungleavesareslightlysweet[12](Figure2).

InEthiopia,khatiscommonlyusedforsocialrecreationandas a recreational drug, the leaves and stem are chewed by people in East Africa and the Arabian countries to elevate mood (as a euphoriant) [113, 14]. Occupational groups such as motor vehicle drivers,truckdrivers,whochewkhatduringlongdistancedriving, tokeepawake,alsousedunderavarietyofotherconditions[15]. A significant number of students chew khat to be alert especial-ly during examination periods [16]. There is also specific usageofkhatbythespecialsectionsofthecommunity:craftsmenand

farmersusekhattoreducephysicalfatigueandtraditionalhealers tohealailments[17].Khatischeweddailybyahighproportionof adult population for its Central Nervous System stimulant effect. Furthermore, it is widely masticated among youth Ethiopians, especiallyhighschool,collegeanduniversitystudents[18].Recent- ly, khat use became popular among other groups of people, and theyusedittoincreaseconcentrationandperformanceduringtrading,farming,academicactivities,andforsocializationandleisure activities [19, 20]. Factional khat use could also include chewing khattocopewithtraumaticexperienceselderMuslimmenincertainethnicgroupsorregionschewedkhatforconcentrationduring studying religious writings and to stay alert during night prayer [21,22].Thekhatchewersexperienceasenseofincreased energy levels,increasedalertnessandabilitytoconcentrate,improvement in self-esteem and an increase in libido, enhanced imaginative ability, improvement in the ability to communicate, capacity to associateideas,andsubjectiveimprovementinworkperformance [23,24].Thechewerfillshisorhermouthwithleavesandstalks, and then chews slowly and intermittently to release the active componentsinthejuice,whichisthenswallowedwithsaliva[25, 26]. The plant material is chewed into a ball, which is kept for a while in the cheek, causing a characteristic bulg [27] (Figure 3).

Widespread use of khat, especially its concurrent use with tobacco,remainsapublichealthchallengeinmanycountriesincluding Asia, Europe, Australia, and the United States [28]

Figure1: Leafofkhat

Figure2: Bundleof khat.Theusual lengthof a bundleis30–40 cm

Figure3: Exemplaryof Khatchewed intoa ball

Chemistry

Many different compounds are found in khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals. The phenylalkylamines and the cathedulins are the major alkaloids [29]. The cathedulins are based on a poly-hydroxylated sesquiterpene skeleton and are basically polyestersof euonyminol. Recently, 62 different cathedulinsfrom fresh khat leaves were characterized [30]. The khat phenylalkylamines comprise cathinone [S-(–)-cathinone], and the two diastereoisomers cathine [1S, 2S-(+)-norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R, 2S-(–)-norephedrine]. These compoundsare structurally relatedto amphetamine and noradrenaline. The plant contains the (–)-enantiomer of cathinone only;the (+)-enantiomer is not found [Cathinone is found mainly inthe young leaves and shoots [31, 32]. During maturation, cathi- none is metabolized to cathine, and (-)-norephedrine. The leaves contain these two substances in a ratio of approximately 4:1[33]. Chemical Names of cathinone is S-(–)-cathinone; S-(–)-α-aminopropiophenone; (S)-2-amino-1-phenyl-1-propanone; cathine is 1S,2S-(+)-norpseudoephedrine;1S,2S-(+)-phenylpropanolamine; 2-amino-1-phenyl-1-propanol; norephedrine is1R, 2S-(–)-norephedrine;1R,2S-(–)-phenylpropanolamine;2-amino-1-phe-nyl-1-propanol (Figure 4).

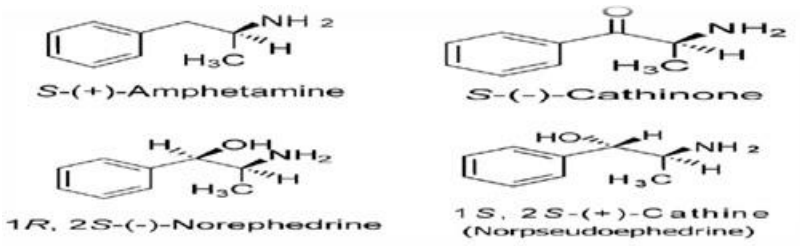

Figure4: Chemical structureof the phenylpropylaminealkaloid from khatcathinone, norephedrine, norpseudoephedrine (cathine)

Pharmacology

The psychotropic effects of khat are caused by the amphetamine-like compounds [34].

MOA

The constituents of khat have been shown to exert their effectsontwomainneurochemicalpathways:dopamineandnoradrenalin [35].Ithasalsobeenpostulatedthat,likeamphetamine,cathinone releases serotonin in the central nervous system [36]. Both cathinone and amphetamine induce release of dopamine from central nervoussystemdopamineterminalsandthusincreasetheactivity of the dopaminergic pathways [37]. Cathinone has a releasing effect on noradrenalin storage sites, which supports the conclusion thatcathinonefacilitatesnoradrenalintransmission.Cathinoneand cathine cause inhibition of noradrenalin uptake [38, 39].

Pharmacokinetics

The euphoric effects of khat start after about 1 hour of chewing [40]. Blood levels of cathinone start to rise within 1 hour andpeak plasma levels are obtained 1.5 – 3.5 hours after the onset of chewing[41].Metabolismofcathinoneisrapid,occurringmainly duringfirstpassagethroughtheliver.Onlyasmallfraction(about 2%) appears unchanged in the urine. Most cathinone is metabolisedtonorephedrineandisexcretedinthisform[42-44].Therate of inactivation is about the same as the rate of absorption, which limits the cathinone blood levels attainable by chewing. Cathine has a slower onset of action, with a serum half-life in humans of about3hours.Itisexcretedunchangedintheurinewithinabout 24 hours [45, 46]. When taking khat, large amounts of non-alcoholic drinks are consumed. There is pharmacological synergism withdrinkscontainingMethylxanthines(e.g.teaandcola),which therefore enhances the effects of khat [47, 48].

AdverseEffectsofKhaton Health

With the migration of khat users from Africa and Arabia, sever-al health problems have been disseminated to different countries around the globe [49]. Khat use affects cardiovascular, digestive, respiratory, endocrine, and genito-urinary systems. In addition, it affectsthenervoussystemandcaninduceparanoidpsychosisand hypomanic illness with grandiose delusions [50, 51]. Apart from thevarioushealthissuescaused,theimpactofkhatcultivationon the national economy is huge. For instance, almost half a household'sincomegoestowardspayingforthekhatrequirementofthe head of the family who often chew it for four to five hours a day. Thisnegativelyaffectstheirworkinghoursandthefamilyincome [52, 53]

CentralNervousSystem

Khat is a stimulant with effects similar to amphetamine, because the main active ingredient in khat is cathinone, an amphetamine like substance [54]. Cathinone is more lipids soluble than cathine anditcaneasilycrossthebrainbloodbarrierandenterinthecen- tral nervous system that is responsible for adverse effect on the body.Italsoexertspronouncedbehavioraleffectsofeuphoria,hyperactivity, and restlessness, like ecstasy (MDMA-3, 4-methylenedioxy-N-methylamphetamine) and amphetamine [55]

MOA:Stimulanteffectsof cathinone

Khat-InducedPsychosis

Khatchewingcaninducetwokindsofpsychoticreactions.First,a manic illness with grandiose delusions and second, a paranoid or schizophreniformpsychosiswithpersecutorydelusionsassociated with mainly auditory hallucinations, fear and anxiety, resembling amphetamine psychosis [56, 57]

SchizophreniformPsychosis

Thepatientstypicallypresentwithparanoiddelusions,fear,ahos- tile perception of the environment, auditory hallucinations (frequently of a persecutory or threatening type), ideas of reference, thoughtalienationandatendencytoisolatethemselves,oralternatively displaying aggressive behaviour towards others [58].

Manic Psychosis

The patient presented with hyperactivity, shouting, pressure of speech, grandiose delusions with flight of ideas and tangential thoughtprocesses,andalabilemoodvaryingfromeuphoriatoanger.Thepatienthadusedkhatforthefirsttime,chewingabout24 leaves (this is equivalent to a single dose of khat) [59].

Hypnagogic Hallucinations

Hypnagogichallucinationshavebeenreportedinchronickhatusers.These consist of continuous visual and/or auditory dreamlike experiences that accompany daily life and are not related to khat sessions.Patientsmayconsiderthemasnormalanddonotusually report these hallucinations unless specifically asked about [60].

Impairment of Cognitive Functions

Adverse effects of khat chewing include impairment of perceptual-visual memory and decision-speed cognitive functions [61]

CardiovascularComplications

Thephenylpropylamine-typealkaloidcathinoneisthemajorcomponent responsible for the effects of khat on the heart and blood vessels[62]**.**Khathasdirecteffectsonthecardiovascularsystem duetotheindirectsympathomimeticactivityofcathinone,causing clear increases in heart rate and blood pressure in humans [63].

MOA:Indirectsympathomimeticactivityofcathinone/cathinone was an indirectly acting sympathomimetic drug having catecholamine-releasing properties at dopaminergic and serotonergic synapses, and at peripheral noradrenaline storage sites [64]

Anothercardiovascularcomplicationofkhatchewingisthehigher incidenceofhemorrhoidsandhemorrhoidectomyfoundinchronic khat chewers (62% and 45%) as compared to non-khat users (4% and0.5%)khatishepatotoxicwithincreasesinliverenzymesand therehasbeenhistopathologicalevidenceofacutehepato-cellular degeneration [65]

CoronaryVessels,Myocardium,andHeartFailure

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)[66,67].Amphetaminealsoshowsvasoconstrictive action by stimulating the release of noradrenaline from sympathetic nerves and may participate inAMI [68]. 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 forAMI, amphetamine abuse may lead to chronic cardiomyopathy, pulmonary heart disease, necrotizingvasculitis,andintracranialhemorrhage[69].Cathinonealso plays a role in the development of congenital heart disease [70]

MOA:increasedreleaseofcatecholaminenstriggeredbythecathinone content of khat, leading to hypertension and acute myocardialinfarction(Increasedthrombogenecity)/Coronaryvasospasm, induced by the cathinone in khat, *causing vasoconstriction may occlude coronary arteries sufficiently to precipitate myocardial infarction* [71] (Figure 5).

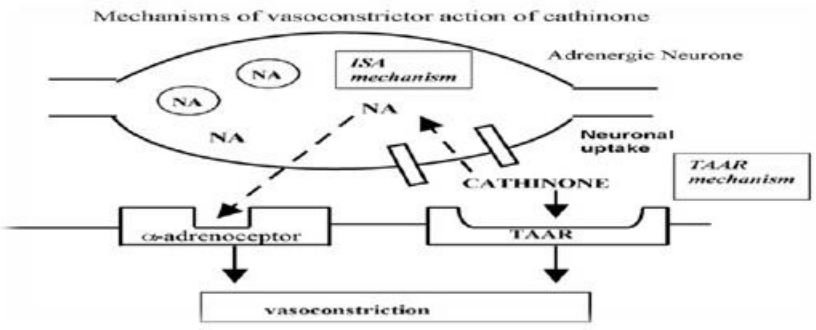

Figure5: Schematicexemplifyofmechanismsofvasoconstrictoractionofcathinone

4. MetabolicandEndocrine Effects

Hyperthermia(IncreasedBodyTemperature)

Theeffectof(–)-cathinoneonbodytemperaturesharesaphenomenon with the effect of (+)-amphetamine and 3, 4-methylenedioxymethamphetamine(MDMA,XTC):hyperthermiaatroom temperatures and above, but hypothermia in animals kept below room temperature [72, 73]

KhatandTypeIIDiabetesMellitus

MOA:Cathinonewouldbeexpectedtoraiseplasmacatechol- amine levels.

Thesympathomimeticactionsofcathinonewouldbeexpected to raise plasma catecholamine levels. There is also inhibition of insulin release from the pancreatic β-cells which would also elevatebloodglucoselevel[74].Usingkhatseemstolowerappetite, causing people to skip meals. When eating becomes less routine, peoplewithdiabetesmaystopfollowingtheirrecommendeddiet. This could lead to higher blood sugar levels [75].

5. GastrointestinalSystem

OralandGastro-Intestinal Problems

MOA:Astringent characteristic of the tannins

In the gastrointestinal tract, the astringent characteristic of the tannins account for periodontal disease, oesophagitis, stomatitis, gastritis and duodenal ulcer formation. Tannins and norpseudoephedrine contribute to constipation, the most common medical complaint of the khat user [76]. The sympathomimetic action of cathinone in khat may cause the observed delay in gastric emptying [77]. Gastrointestinal adverse effects of khat chewing include anorexia, constipation and stomatitis.Anorexia leads to malnutrition and increased susceptibility to infectious diseases, especially tuberculosis[78].Intheoralcavity,khathasbeenassociatedwith histopathologicalchangeslikehyperkeratosis,epithelialhyperplasia and milder dysplasia [79]

Oral keratotic lesions at the site of chewing and plasma cell gingivitis (allergic reaction to khat) have been reported. The tannins presentinkhatleavesareheldresponsibleforthegastritisthathas been observed [79, 80]

EffectofKhat onHumanAppetiteandBodyWeight

MOA:Decreaseshungerandincreasesfullness

Cathinoneaffectappetitecentrally,byactinginthehypothalamus. Apartfromitscentraleffect,itenhancessympathomimeticactivity leadingtoadelayingastricemptying[81].Ahighplasmalevelof theanorectichormone,leptin,hasbeenfound4hourafteraheavy khatchewingsession(400g).Thishormonemaycontributetothe decreased appetite and body weight [82]

6. Cancer

Keratosisoftheoralbuccalmucosaisconsideredasapre-cancer- ous lesion that may develop into oral cancer [83]. In human leukaemia cell lines and in human peripheral blood leucocytes, khat extract, cathinone and cathine produced a rapid and synchronized cell death with all the morphological and biochemical features of apoptotic cell death [84]. Buccal epithelial cells experience genotoxic effects in a dose-related way in khat-chewers; this suggests that oral malignancies can be contributed to by khat [85]

7. ReproductiveSystem

Inchronicchewers,spermcount,spermvolumeandspermmotil- ity were decreased and cause impotence [86].

MOA: Impotence in males Causes spermatorrhoea and deformed spermatozoa

Increasesexualdesireinfemales Increasesvaginalsecretionsand up-regulatesestradiollevel

Khatextractenhancedsexualmotivation,increasedvaginalsecretions and up-regulated estradiol level in female [87, 88]. In pregnant women, khat consumption may have detrimental effects on uteri-placentalbloodflowandasaconsequence,onfoetalgrowth anddevelopment.Khatisgenotoxic,havingteratogeniceffectson the foetus if regularly consumed by pregnant mothers [89]. Neonateshavelowbirthweights–ariskfactorforperinatalandyoung infant death [90]. Currently chewing lactating women have been foundtoexcretenorpseudoephedrineintheirbreastmilk,andtrac- es were found in the urine of a breast-fed infant [91]

8. GenotoxicityandTeratogenicEffects

Deaths and haemiplegia (paralysis of half of the body) becauseof meningeal haemorrhages are reported. The causal mechanism is ruptures of aneurisms following circulatory “coups de fouet” (rupture of the planteris muscle accompanied by sharp disabling pain)engenderedbytheuseofkhatsameMOAincerebralhaemorrhage, cardiac arrest and pulmonary oedema [92]

9. Hepatobiliary System

Effectof khat onliver

MOA: Causes acute hepatocellular degenerative and regenerative activities

Long term chewing of khat leaves can produce repeated episodes of hepatitis and leads to fibrosis and cirrhosis probably through directtoxiceffectfromreactivekhatmetabolites,immune-allergic or idiosyncratic causes. Long term users usually develop complications of cirrhosis or acute or chronic liver failure [93]

10. Renal System

Effectof khat onkidney

MOA: Causes kidney tissue lesions, acute cellular swelling and acute tubular nephrosis

Kidney tissue showed some lesions and the degree of the lesion increasedasthedoseofkhatleavesincreasedincluding:thepresenceoffatdropletsparticularlyseenintheuppercorticaltubules; acutecellularswelling;hyalinetubulesandacutetubularnephrosis [94]. Khat induces a fall in average and maximum urine flow rate inhealthymen.Theurinaryeffectsareprobablymediatedthrough stimulation of alpha1-adrenergic receptors by cathinone. This is indicated by the complete blockage of this effect by indoramin, a selective antagonist of alpha -adrenergic receptors [95]

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11. Others

DecreasedProductivity

Khat chewing leads to loss of work hours decreased economic production, malnutrition and diversion of money in order to buy further khat. Consequently, working hours and possibly productivity can decrease when khat is not used, because of anergia and reduced motivation [96].

FamilyandMarital Problems

Manymensecuretheirdailyportionofkhatattheexpenseofvital needs,indicatingdependence.Familylifeisharmedbecauseof neglect,dissipationoffamilyincomeandinappropriatebehaviour. Khat is quoted as a factor in one in two divorces in Djibouti.Acquisition of funds to pay for khat may lead to criminal behaviour and even prostitution [97, 98] (Table 1).

Table1: Thephysicaladverseeffectsofkhatanditsmechanism

System	Adverse effects	Mechanism
Gastrointestinal system	Drymouth,polydipsia,dentalcaries,periodontaldisease, chronic gastritis, gastriculcer,constipation,paralytic ileus, anorexia, weight loss, increased risk of upper gastrointestinal malignancy, loss appetite	Astringent characteristic of the tannins Decreaseshungerandincreasesfullness
Genitourinary system	spermatorrhoea,spermatozoamalformations,impotence, libido changein males, changes in sex drive, and inability to get an erection	Causesspermatorrhoeaanddeformedspermatozoa
	urinary retention, Increase sexual desire in females	Increasesvaginalsecretionsandup-regulatesestradiollevel
Ocular effects	blurred vision, mydriasis	
Centralnervoussystem	Alertness,dependence,tolerance,andanxiety,sleepdisturbance (insomnia),dizziness,impairedcognitivefunctioning,fine tremor,headaches	Stimulanteffectsof cathinone
Cardiovascular system	Tachycardia, arrhythmias, palpitations, hypertension, vasoconstriction, ischaemia,infarction,pulmonaryoedema,stroke(cerebral haemorrhage).Exacerbationofpre-existingcardiacconditions	Indirect sympathomimetic activity of cathinone
Metabolic and endocrine effects	Hyperthermia, perspiration, hyperglycaemia	Cathinonewouldbeexpectedtoraiseplasmacatecholamine levels
Obstetric effects	lowbirth weight,stillbirths, impaired lactation	Cathinonecanpassplacentalbarrierandaccumulateinfetus blood serum level owing to it is lipid soluble.
Respiratory system	Bronchitis, tachypnoea, dyspnoea, tuberculosis	
Hepatobiliary system	fibrosis,cirrhosis,hepatoxicity	Causesacutehepatocellulardegenerativeandregenerative activities
Psychiatric effects	lethargy,irritability,anorexia,psychotic reactions,depressive reactions, hypnagogic hallucinations	
Renal system	Kidney damage	Causeskidneytissuelesions,acutecellularswellingand acute tubular nephrosis

UsesofKhat

Besidesitstremendousadversehealtheffects,khatmayhavesome medicalusesthatarespeciallyperceivedbykhatchewers.Leaves ofkhathavebeenusedintraditionalmedicineforthetreatmentof depression, fatigue, obesity and gastric ulcers. In folk medicine, khat is claimed to suppress cough, asthma, epidemic influenza, stomach ashes, diarrhea and malaria. It can also relieve pain [99-101].

12. Conclusion

Khat (catha edulis) is a natural stimulant from the Catha edulis plant,foundinthefloweringevergreentreeorlargeshrubofCelastracea family, which grows mainly in Ethiopia, Kenya, andYemen and at high altitude areas in South Africa and Madagascar. Freshleavescontainbothingredients;thoseleftunrefrigeratedbeyond 48 hours would contain only cathine, which explains users' preference for fresh leaves. Khat loses its potency after 48 hours. The psychoactive effects of khat are mainly attributed to cathinone,apotentalkaloidwhichhasaclosestructuralresemblanceto amphetamine.Bloodlevelsofcathinonestarttorisewithin1hour andpeakplasmalevelsareobtained1.5–3.5hoursaftertheonset of chewing. Metabolism of cathinone is rapid, occurring mainly during first passage through the liver. Medical problems associated with khat intoxication include psychiatric manifestations such as deterioration of psychophysical function and schizophreniform psychoses. Khat chewing is also associated with a wide range of health problems including ischaemic heart disease, gastritis, liver toxicity, oral cancer, hypertension, spermatorrhoea and haemorrhoids.

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