International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

KHAT (A NATURAL AMPHETAMINE) AND ITS HEALTH EFFECT: REVIEW

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ABSTRACT

Chewing Catha edulis (Khat, Qat) is a socio-cultural activity commonly practice in Eastern Africa and Southern Arabia, mainly in Yemen. People chew Khat for several hours to get a stimulating and euphoric effect. Khat is a type of evergreen shrub that can be grown as a small tree or a bush. The plants have a pleasant fragrance. The flavor is mildly sweet and astringent. Khat contains various compounds, including Alkaloids, glycosides, terpenoids, tannins, sterols, flavonoids, amino acids, minerals, and vitamins. However, the significant alkaloids that are structurally similar to amphetamine are Phenylalkylamines and Cathedulins.

The impact of Khat on the neurological and gastrointestinal systems are significant effects. Tachycardia, high blood pressure, and hemorrhoids are acute cardiovascular effects. Irritability, General malaise, and decreased sexual potency in the male are the critical toxic effects.

PubMed, Cochrane, Medline, and Google were used to search for literature on various aspects of Khat and its general health effects. Using the words ' Qat,' 'khat,' 'kat,' cathaedulis,' and 'cathinone,' find all related articles written. Only articles involving Khat with human health hazards and animal studies that have been reported in English were included.

Keywords: Khat, Catha edulis, Legality, Human, Animal, Health Effect.

INTRODUCTION

Khat (Qat, Catha edulis) referred to young fresh leaves, original to East Africa, Ethiopia, and Yemen. The khat plant has an aromatic smell and a soft sweetness. It contains an amphetamine-like psychoactive agent in its tender leaves（Figure1）. About 20 million users worldwide intake it regularly for its psychostimulant effects [1-3].

Figure 1: Fresh Khat leaves [1]

Peter Forsska l gave C. edulis its scientific name, and Carsten Niebuhr renamed it C. edulis Forsk in honor of his friend Peter Forsska l. In different countries, Khat was known by various names: gat, Qat, gaat, jaad, chat, Jimma, miraa, and veve. However, Khat, qaad, tchat, Salahin, Tochat, and Tchaad are common names still in use [4]. Regular khat users identify the leaves by their type, flavor, potency, and the kind of Khat they consume may represent their social and economic status: White leaves are rare and costly than red leaves. In Ethiopia, Harai is the best, and Giza is the most popular in Kenya [5].

Khat is consumed by chewing the fresh leaves and twigs, known as quid, placed in one or both cheeks. The residue is spat out after the exudate has been swallowed. Often sweet drinks are taken to counteract the quid's astringency [6]. A regular session could be taken over 3–4 hours. In Scotland, "Herbal Ecstasy" khat was consumed as a beverage [7]. The Khat's leaves could also be dried as a powder to produce an Arabian tea or African tea or taken as a paste mixed honey [8]. Khat is consumed differently, from those who chew it as a morning pick-me-up, identical to coffee, to study, shift staff, and truck drivers who chew it during the day to avoid exhaustion and sleep [9].

Distribution and Prevalence:

According to a poetic reference, the ancient Egyptians believed C. edulis is the holiest herb, a "divine food" as royal honey by bees, release humankind's latent divinity. The Egyptians didn't take Khat to get high but instead

invoke the metamorphic method that led to a theurgic transformation of human existence into personification. Allowing a mere mortal to be elevated to the status of God [4]. According to historical records, Khat was used as early as the 13th century in ancient Ethiopia (Abyssinia), and in the 15th-century, Khat was imported to Yemen [8]. Khat is widely cultivated at high elevations from Yemen to Madagascar. In khat plantations, particularly in Ethiopia's Harar district, Yemen's Jebel Sabr Mountains, and Kenya's Nyambene district, commercial processing is carried out on a wide scale. It is also grown in South Africa, Uganda, Tanzania, Rwanda, Zimbabwe, and Indonesia to a lesser degree [10]. Khat farming has replaced other commercial crops, like coffee, in many countries and contributes significantly to national economies and individuals [11].

In Africa and Arabia, the practice of Khat was both theologically and legally acceptable [8]. In many countries, unlike Coca, Khat is not controlled by the government [12]. Khat was marketed to various countries for $55 million [13]. Khat leaves are smuggled into Europe and U.S.A, selling for $300–500 per kilogram [14]. Ethiopia exports 85–90 % of its Khat, contributing significantly to its export earnings [15]. It's challenging to get reliable data for the global khat trade's value, but seizures of Khat can give an idea of its magnitude [16]. According to the United Nations Office for Drugs and Crime, Khat is the most frequently seized plant-based material over 2009 and 2010; many countries, including Suadi Arabia, Ireland, and Norway, observed considerable increases in khat seizures [17]. However, most khat users in Western societies are immigrants from the Middle East or East Africa, while the general public in Western countries is unfamiliar with its use [8].

The exact number of Khat chewers worldwide is unidentified. However, an estimate of 20 million daily users is now likely to be an underestimate [1-3]. The age to begin chewing Khat has dropped to as early as 12 years and, while Khat was consumed generally by men, it is now being chewed by women [15, 18], including breastfeeding and pregnant [19-21]. Among tribal, cultural, or civic groups, khat use could be highly prevalent.

Illegality of Khat:

In 2005, the World Health Organization sent a survey to 67 countries to assess the severity of the problem globally. Only 9 countries reported awareness of Khat abuse, with Kenya having the highest prevalence (20%). Twenty-five reported there had been no abuse while the rest unaware of the problem [12, 22]. The problem was convenient for some countries: Cathinone, the key active component in Khat, was an addictive drug, and its natural origin should be controlled [23].

The Health Organization lists Khat as a substance of abuse, and it is illegal in the U.S.A, Europe, and Canada [24]. Though, it is legal in Yemen, Ethiopia, and Somalia [25].

Pharmacology and effect of Khat on health:

The phytochemistry of C. edulis Forsk has been examined in-depth, and the results have been fascinating. It contains over 40 alkaloids, tannins, glycosides, amino acids, minerals, and vitamins [26]. However, two phenylalkylamines named cathine and cathinone, identical to amphetamine, are responsible for the stimulating effect [27]. The United Nations Drugs Laboratory identified and isolated cathinone in 1975, and Schorno and Steinegger determined its configuration in 1978 [28]. Halket et al. measured the level of cathinone in the blood after khat consumption (0.8 mg/kg). 1.5–3.5 hours after khat consumption, the average peak of the cathinone level was

83 ng/mL [29]. Toennes et al. examined cathinone and its metabolites norephedrine and cathine in four volunteers' plasma over 54 hours after consuming fresh Khat for 1 hour. Cathinone, cathine, and norephedrine reach their maximum plasma concentrations after 2.3 hours, 2.6 hours, and 2.8 hours, respectively. Cathinone had a half-life of 1.50.8 hours and cathine had a half-life of 5.23.4 hours. Khat has effects (0.8 mg/kg) similar to cathinone (0.5 mg/kg). After the first use of Khat, the maximum cathinone plasma concentration is reached in 127 minutes, with a half-life of 260 minutes [30]. During chewing, 90% of the Khat's active compound is released. Cathinone is absorbed mainly through the oral tissue (60% of absorption), with the remainder absorbed through the G.I.T. [31]. Furthermore, the efficiency of cathinone varies by place of origin [32]. Chappell and Lee found that the dried plant maintained some alkaloids and cathinone remained stable for three years [33]. Khat was traditionally bundled in banana leaves to maintain it moist, which may have required cathinone reductase to convert cathinone to the less potent stimulant cathine [33, 34]. Tannins, also found in Khat, are a category of polyphenolic biomolecules that build complexes with a range of macromolecules, practically proteins, and have an adverse influence on the tissues they come into contact with [34, 35]. Khat also contains 62 different cathedulins, most of which have still not been tested for their biological impacts [36].

Medical harms of khat use:

Since Khat contains different compounds, Khat consumption may have a range of effects. The effects on the gastrointestinal and nervous systems are the most important. Autonomic nervous system effects including urine retention, constipation, and acute cardiovascular effects; C.N.S. impacts including alertness, dependency, resistance, psychiatric and mental symptoms [34]. Furthermore, it has the potential to trigger paranoid Psychosis and hypomanic disease with grandiose delusions [37]. Tachycardia, high blood pressure, anorexia, insomnia, constipation, irritability, general malaise, migraine, and decreased sexual potency in men are the main toxic effects [34].

Systems affected	Adverse effects
Central nervous system And the psychiatric effect	Euphoria, excitement, lethargy, irritability, alertness, talkativeness, insomnia, a sleepy state the following day, depression, headache/migraine, inability to concentrate, fine tremor, anorexia, Hypnagogic hallucinations, impaired cognitive functioning,
Gastrointestinal and hepatic system	Constipation, weight loss, polydipsia, Gastrointestinal disorders, stomach/duodenal ulcers, paralytic ileus, increased risk of upper gastrointestinal tumors, liver fibrosis, and cirrhosis.
Cardiovascular system	Tachycardia, vasoconstriction, palpitation, Increased cardiovascular disorders, high blood pressure, myocardial
Genitourinary system	urinary retention, libido change (mainly in the male), Impotence, Impaired sexual function in males, spermatorrhea, spermatozoa malformation, and reduce account
Neonatal development	Stillbirths, low birth weight, impairment of lactation.
Ocular effects	Mydriasis, blurred vision.
Respiratory system	Tachypnea, bronchitis, Pulmonary edema.
Oro-dental effects	Oro-dental lesions (dry mouth, periodontal diseases, caries), temporomandibular joint dislocation, oral mucosal keratosis,

Table 1: Commonly reported effects of khat chewing

Impairment of cognitive functions:

Human researches on the cognitive impacts of khat use are limited. The C.N.S. impacts are identical to those of amphetamine [34, 38, 39]. Nonetheless, Colzato et al. compared khat chewers to non-khat chewers and found that long-term khat chewing could cause cognitive impairment. Chewing Khat has negative effects such as impaired decision-speed cognitive functions and perceptual-visual memory [34, 40]. Hoffman and al'Absi recorded the detrimental effects on cognitive performance in long-term khat users performing the forward and backward digit range test for memory recall and the Digit Symbol Substitution Study for data processing speed. [41]. In Toennes et al.'s study, 17 participants registered subjective feelings of alertness and being 'energetic.' No significant negative effects have been documented [30].

Since Khat has amphetamine-like actions, Bongarda et al. used a mental arithmetic test to study its emotional regulation. They discovered that regular khat users scored significantly greater trait anger scores than non-khat users or occasional [42]. Khat parties, on the other hand, can include approximately 20 members. The number could be much higher during ceremonial or traditional events, but there have been no indications of regular harmful physical or verbal confrontations during these gatherings [34]. In a Yemen research with young chewers, functional attitude disturbances had documented while chewing Khat. The anxiety and depression effects were just temporary and faded the day after [43]. At the end of the khat chewing session or during khat withdrawal, mild depress reactions were registered, and a sleepy state and lethargy the day after [34, 44]. Insomnia and anorexia were induced by Khat using, resulting in a late wake-up and reduced work activity the day after [45]. Chewing Khat

causes a sense of elation and euphoria and also increased arousal and alertness. This is accompanied by a period of loquacity, vivid discussions, and often an exciting mood [34, 46].

Hypnagogic hallucinations:

Hypnagogic hallucinations were documented in long-term khat chewers [34, 47]. These consist of persistent auditory or visual dreamlike encounters unrelated to khat chewing [34, 46].

Khat-induced psychosis:

Due to the presence of cathinone, the primary substance responsible for its psychostimulatory symptoms, which is similar in structure to amphetamine and has the same effects, Khat was dubbed a "natural amphetamine." [48]. Chewing Khat can cause two different forms of psychotic disorders. A manic illness is characterized by grandiose delusions, while a psychotic or schizophreniform psychosis is characterized by persecutory delusions, paranoia, auditory hallucinations, and terror, which is identical to amphetamine psychosis [34, 46, 49]. Both disorders s are unusual and are correlated to consuming large quantities of Khat [11, 16]. Much reversible khat-induced Psychosis has been recorded, similarly to those registered with amphetamine [50-54]. In Somalia, A study comprising 8723 members of armed organizations showed a relation between khat chewing, posttraumatic stress disorder, and anxiety, with those struggling with PTSD consuming more Khat trying to forget the war memories [55]. However, it was unclear whether people predisposed or vulnerable to Psychosis were more likely to develop mental illness following khat consumption [56]. In general, khat withdrawal tends to be a successful treatment for khat psychosis. However, antipsychotics are rarely required for complete remission [34, 57, 58]. Khat psychosis, on the other hand, is a rare phenomenon due to the physical limits of the quantity of Khat that may be chewed [16, 39, 59]. Khat psychosis is occasionally linked to aggressive reactions and depression symptoms [34]. Dhadphale and Omolo investigated the mental health of khat chewers. Among moderate chewers, there has been no excess morbidity. Over two bundles chewed a day are linked to a higher risk of mental illness. Case studies show that high doses of Khat induce adverse effects [34, 60].

Neurological complications:

There has been one case of extreme leukoencephalopathy associated with khat chewing [61]. Findings on M.R.I. and electroencephalography showed progressive leukoencephalopathy. However, no correlation to khat chewing has been confirmed. Like amphetamine, Cathinone has sympathomimetic effects and C.N.S. stimulatory, including high heart rate, blood pressure, hyperthermia, and mydriasis. Cathinone, like amphetamine, can cause dopamine release in the C.N.S. [34].

Urinary bladder Effects:

In healthy men, Khat lowers the average maximum urine output [45]. Its activation of alpha1-adrenergic receptors most probably mediates a Cathinone's urinary system effects. The reality proves that indoramin completely blocks this effect [62].

Cardiovascular effects:

Cardiovascular risks attributed to cathinone abuse are identical to those associated with amphetamine

abuse [63]. Furthermore, people who abuse Khat have higher heart rates and blood pressure [8]. Another research found that after three hours of khat consumption, heart rate, mean arterial, systolic, and diastolic blood pressure were elevated [64]. Based on research involving 934 khat chewers, the researcher recorded that khat consumption is correlated with a high risk of death and stroke [65, 66]. Acute myocardial infarction has been documented to occur more frequently after midnight, during khat sessions [63]. Acute myocardial infarction has been attributed to the intake of Khat [6, 67, 68]. The researchers found that khat consumption is an independent dose-related risk factor for acute myocardial infarction, with heavy users having a 39-fold greater risk [69].

Another possible cardiovascular consequence of Khat using is a higher rate of hemorrhoids and hemorrhoidectomy reported in long-term khat users than non-khat users [70].

Oral and gastrointestinal Effects:

Khat appears to affect the oral tissue and gastrointestinal tract as a consequence of its consumption process [34]. A Periodontal disorder, persistent chronic subluxation, dislocation of the temporomandibular joint, and gastritis have been recorded as causes of the widely experienced constipation [71]. The tannins in Khat are considered to be the trigger of gastritis [72]. And also the progression of the oro-dental conditions [73-75]. The intensity and nature of the oro-dental impact-induced are expected to differ based on the quantity of Khat and the frequency of chewing. Xerostomia, caries, bruxism, occlusal wear, periodontal diseases, oral ulcers, difficulty in swallowing, oral cancer, and keratosis are also oro-dental effects of khat consumption that have been recorded (Figure 2) [73, 76-78].

Nevertheless, several research have revealed that khat chewing has no adverse implications on the periodontium and may even be beneficial [79-81]. Another study found no evidence of a significant impact on khat consumption and pointed to inadequate oral hygiene as an essential periodontal disease factor [82]. In a Kenyan study, there has been no significant association between khat consumption and oral leukoplakia [83]. In another research, the researchers noted that khat consumption does not show increased gingival plaque colonization, rather than induces a microbial profile that is still safe for gums [84]. One of the advantages of khat consumption could be the mechanical elimination of dental plaque [85, 86].

According to Ali et al., 22.4% of khat users reported white oral leukokeratosis lesions on the khat chewing side, compared to only 0.6% of non-chewers [87]. Other studies have documented an allergic reaction to Khat (plasma cell gingivitis) [88, 89]. Chronic khat chewing can cause constant microtrauma (mechanical) to periodontal structures due to frictional forces and the impaction of hardened bullous (pieces of Khat) through khat chewing [86]. Pocketing depth, attachment loss, and gingival recession are unsurprising outcomes. Furthermore, other behaviors linked with Khat consumption, as drinking energy or sweetened drinks or using a toothpick, can exacerbate periodontal disease [86]. In addition, Pesticides in khat leaves may cause cytotoxicity in the periodontal site, either by accelerating the onset of coexisting periodontal problems or by impairing fibroblast reattachment [75, 90].

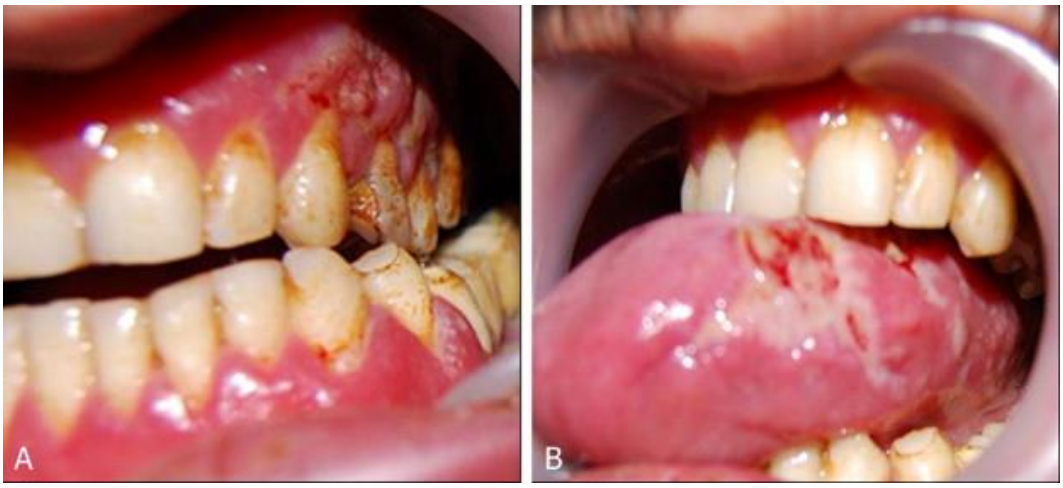

Figure 2: (A) Areas of erosions; gingival recession (B) The lateral side of the tongue showing slight swelling and fibrin-covered ulceration.

Cancer:

In a two-year survey of cancers in Saudi Arabia's Asir area, 28 cases with head and neck tumors were reported. Ten of them were regular khat chewers. They were all non-smoking who had been using Khat for at least 25 years. Oral cancers were found in eight of the ten patients. In certain cases, the tumor developed at the same position as the khat bolus. The researchers realized that there had been a close connection between chewing Khat and oral tumor [91]. In Yemen, frequent khat users accounted for 30 of 36 cases of squamous cell carcinoma (S.C.C.) (17 patients in the oral cavity, 15 in the nasopharynx, three in the larynx, and one in the oropharynx) [92]. The authors found Khat to be a significant contributor. Oral mucosal keratosis affects 50% of khat users, according to estimates [93]. Oral mucosa Keratosis is a precancerous condition that could progress to the oral tumor [92]. With increased frequency and length of khat use, the incidence and severity of these lesions increased [94]. Khat extract, cathine, and cathinone mediated rapid and coordinated cell death in peripheral blood leucocytes and leukemia cell lines, with all of the morphological and biochemical features of cell apoptosis [95]. Researchers discovered an 8-fold rise in micronucleated buccal tissue cells among khat users in the Horn of Africa using the micronucleus test to assess genetic damage [96]. It has been reported that khat use, particularly when coupled with alcohol and tobacco, may be a risk factor for oral cancer [96].

Reproductive System:

There aren't many reports on the impact of Khat on the reproductive system. However, the evidence suggests that long-term consumption can cause spermatorrhea and reduce sexual function and impotence [97, 98]. However, Many Yemeni chewers believe that chewing Khat increases excitement and sexual desire [16]. Volume, sperm motility, and count were reduced in long-term khat chewers [97-99]. In Yemeni daily khat chewers, deformed spermatozoa have been documented [99].

Neonatal Development Effects:

Psychoactive substances cross the blood-brain barrier and also the placental barrier [100]. Neonatal

psychostimulant exposure is attributed to morphological and functional abnormalities in the C.N.S., which result in cognitive decline, motor dysfunction, impaired stress responses, and memory and learning effects [101]. It has been found that khat chewing during pregnancy reduces placental blood circulation and fetal development. The mean birth weight of safe single, full-term, newborn birth after uncomplicated deliveries and pregnancies was significantly lower in mothers who consumed Khat on an irregular or regular basis [102]. In more prominent research of 1141 successive deliveries in Yemen, it has been recorded that mothers who consumed Khat regularly had a slightly higher rate of low-birth-weight infants, however no variations in the rate of congenital anomalies or stillbirth [4]. Since low birth weight is a known risk factor for prenatal and early infant mortality, chewing Khat during gestation could increase infant mortality and harm normal child development [103]. Besides that, restrictive dietary habits and anemia are more common among khat chewers, both of which could harm fetal growth [104].

Animal study:

khat reduced plasma cholesterol, triglycerides, and glucose in white rabbits while increasing plasma alanine aminotransferase and alkaline phosphatase [105]. Khat has been correlated with hepatic toxicity and hypertrophy in both S.D. rat's gender and nephrotoxicity in female S.D. rats [106]. The spleen was unaffected, and the cauda epididymis and testes histoarchitecture were normal, with higher spermatogenesis. The quantity of Khat ingested by the rabbits can't be measured depending on the information provided. According to the researchers, the animals' behavior and actions were judged to be normal in general [107]. In rats, Khat extract was given orally caused teratogenic effects, dominant lethal mutations, and chromosomal abnormalities in sperm cells [108]. Bedada and Engidawork examined the offspring of rats exposed to Khat through pregnancy to seek whether it had any behavioral or cognitive effects. And they reported that rats exposed to Khat showed emotional and motor in-coordination impairment at the maximum khat amount consumed and also poor Y-maze performance [109]. Jansson et al. fed pigs Khat during gestation for 180 minutes to see how it affected placental blood circulation and as a result, A drop in birth weight has been noted, but not in gestational period or litter size. Furthermore, kidney and liver function investigations were abnormal, contributing to the findings or influencing C.N.S. growth or results. [110]. Dose-dependent teratogenic toxicity and embryotoxic were discovered in Wistar rats that were ingested Khat orally [108].

Dependence and Withdrawal:

Although it is well known that long-term consumption of Khat can lead to degradation of general health, it is still unknown whether it causes physical dependence and true addiction [39]. Even though Khat is an amphetamine, it differs from other prototypical amphetamines, including Methamphetamines, in many ways. Khat has a different tolerance, toxicity, and dependency characteristics [12, 38]. Khat has identified the drug that causes the least physical harm among abuse materials in a study of counselor addiction and psychiatrists' experts. However, compared to anabolic steroids and alkyl nitrites, it was shown to cause more dependency [12]. Widler et al. found a substantial impact in the addiction potential, amphetamine-like effects, motor arousal, and relaxation euphoria categories in drug-naive participants provided Khat to ingest using Addiction Research Center Inventory (ARCI) and visual analog scale in the stimulation and Khat energized class "Natural Amphetamine." [38].

Khat's major psychoactive ingredient is cathinone which induces increased dopamine and other neurotransmitter synaptic concentrations [111]. Khat's euphoric effects are attributed to the activation of dopaminergic receptors in specific brain regions. [23, 111]. The cathinone derived from consuming khat leaves is small and quickly degraded, so the effect is only temporary. Consequently, Khat normally induces mild psychological dependence but no strong physical dependence or addiction under normal circumstances [59, 112].

Furthermore, most khat chewers have shown symptoms of psychological dependency rather than physical dependence or addiction. However, If there is an underlying mental disorder or susceptibility, a physical dependence can be a major factor [112, 113]. Male khat users displayed more addiction symptoms than female khat users, and there was an important association with both khat addiction in women and age [114]. Among 204 of khat chewers surveyed, third had symptoms similar to dependency clinical picture, and 38% recorded daily khat consumption despite negative health effects, while 17% recorded withdrawal symptoms, according to the drug dependence syndrome (DSM-IV), (sleep pattern disruption depression and increase in appetite) [115]. Despite this, Khat is listed as having the minimum dependency hazard among 19 different illegal and legal drugs of abuse, including amphetamines, cocaine, tobacco, and alcohol [116].

Another research, also using the DSM-IV instrument, reported tolerance (66.7%), withdrawal (94.0%), desire to avoid or minimize (78.8%), more used than expected (72.7%), decreased social life (97.0%). Continued use amid health problems in Khat used subjects (93.9 %) [115].

Withdrawal symptoms can contribute to regular khat consumption. Withdrawal symptoms, mild depression, Frequent lethargy, slight tremor, social isolation, and nightmares are all common side effects of stopping khat use after a long period of use [117]. Nerveless, there is no hard evidence that khat chewing indicates tolerance.

CONCLUSIONS

Culture, religion, society, beliefs, individual psychology, neurobiology, genetics, and cognition influenced how humans interacted with substances. Several studies showed that khat chewing is a harmful habit on health. Alkaloids, flavonoids, terpenoids, glycosides, sterols, tannins, minerals, amino acids, and vitamins are all contained in Khat; however, the phenylalkylaminesand and cathedulins have the most pharmacological and toxic effects. Khat affects the gastrointestinal and central nervous systems and the cardiovascular, respiratory, genito-urinary, and endocrine systems. The central nervous system effects are identical to those of amphetamine, with certain quantitative variations. Tachycardia, high blood pressure, anorexia, constipation, insomnia, and general malaise are the common toxic effects. Periodontitis, oral leukoplakia, and oral cancer are among the oral diseases linked to qat chewing. However, there is a shortage of exact data on the correlation between qat consumption. And oral cancer development. However, there is no previous data related to Khat chewing with skin lesions. Despite the above observations suggesting the need for further research and documentation on oral cancer and skin lesions such as aging, acne. etc., areas of knowledge.

In conclusion, raising public awareness about the adverse effects of khat-chewing is essential, especially in Africa and Yemen, where Khat is a major social problem. This can be achieved using paper communication and

digital media in combination with effective communication techniques. Raising awareness can also be done by health care providers and public health programs.

Declarations:

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests: The authors declare that they have no competing interests

Funding: ₀ ₀ ₀ ₀ ₀ ₀

Authors' contributions: ₀ ₀ ₀ ₀ ₀ ₀ ₀ ₀

Acknowledgements:

This study was supported in part by the National Natural Science Foundation of China [grant number 81860553and 81860553], the Project for Innovation Team of Department of Science and Technology of Yunnan Province, China [grant number 2018HC005], the "Ten-thousand Talents Program" of Yunnan Province, China, the Medical Leadership Foundation of Health and Family Planning Commission of Yunnan Province, China [grant number L-201613], and the Joint Special Fund of Science and Technology Department of Yunnan Province - Kunming Medical University [grant number 2017FE467(-005)].

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