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Dedication

To the soul of my dear mother Nadia

Acknowledgement

To all medical researchers who are working to promote the life of man, through the gate of knowledge.

Abstract

Khat (Catha edulis) is a plant that is widely grown in the Horn of Africa. People chew the Khat leaves for their stimulating properties. Its tender leaves and early buds are chewed to induce euphoria and stimulation. Khat is an evergreen shrub that can be grown as a bush or small tree. The leaves have a pleasant scent. The taste is astringent with a hint of sweetness. The plant has no seeds and can grow in a variety of climates and soils. The plant contains a vast variety of active compounds, the most important of which are cathinone, Cathine, and norephedrine, which can be classified as sympathomimetics of natural origin. These chemicals are amphetamine analogs, and as such, they have amphetamine-like stimulating effects on the neurological system. There is a significant association between Khat chewing and health risks such as decreased sexual performance, HIV infection, sexual violence, elevated diastolic blood pressure, urinary and digestive system problems, periodontitis, liver damage, psychiatric problems, and ophthalmological problems. The use of Khat is influenced by a number of complex factors. People who are frustrated, poor, or dislocated are more likely to use Khat. Several million people are reported to use Khat on a regular basis for its euphoric and other subjectively explained positive effects. Aside from those nations where Khat is widely used, the habit has a strong socio-cultural legacy. This is especially true in Ethiopia, where chewing Khat is a deeply ingrained socio-cultural habit throughout the country's eastern and south-eastern regions. Although Khat is consumed by people from all walks of life, the overabundance of Khat consumption is associated with youth. Such an alarmingly increasing psychoactive substance has a number of adverse effects. Because the use of Khat is an established cultural custom for many social circumstances in primary cultivation, East Africa, and the Arabian Peninsula, even the government has failed to protect the public from its use. As a result, aggressive measures must be done to raise awareness among the most

common users, such as the poor, taxi and car drivers, school and college students, and the general public. The chewing of Khat leaves has a long religious and sociocultural history. Khat is a commercial crop, and its cultivation provides economic value to the cultures and nations involved. However, there have been allegations of negative economic consequences for those who engage in the Khat chewing practice. The growing global use of Khat, along with the unfavorable public attention it has received, has resulted in the current state of confusion surrounding the originally indigenous habit of Khat chewing. Scientists, primarily from Western Europe, have tended to focus on Khat-related issues, with little regard for the positive function of Khat chewing in society and the globe at large. Furthermore, no investigation has directly linked Khat to organized crime, violence, or antisocial behavior, particularly in nations where Khat is legal.

1. Introduction

Khat is known by many other names, including Khat, qat, chat, qaadka, kus-essalahin miraa, tohai, tschat, Abyssinian tea, African tea, African salad, and brown cows (in tablet form). Khat leaves begin crimson-brown and shiny but eventually turn yellow-green and leathery. The leaves are up to 5 cm wide and 10 cm long, with a strong aromatic scent and astringent and somewhat sweet flavor **[1].** Khat is a flowering evergreen tree and large shrub in the Celastracea family. It is made up of full fresh leaves and buds of a plant called Catha edulis. Ethiopia, Kenya, and Yemen are their native countries **[2].** More than 20 distinct chemicals have been identified from Khat, including Cathinone/aminopropiophenone/, Cathine /nor pseudoephedrine/, and nor ephedrine **[3].** Cathinone is one of Khat psychotropic compounds, according to pharmacologists, and it affects the nervous system "like a mild amphetamine" **[4].** Cathinone is rapidly converted to Cathine (norpseudoephedrine) and norephedrine, which have poor central stimulant effects due to their less lipophilic nature **[5].** Khat is a well-established cultural heritage in numerous social circumstances in primary cultivation, East Africa, and the Arabian Peninsula. Several million people worldwide may chew Khat, with an estimated 10 million chewing Khat leaf everyday **[6].** Long-term heavy chewing has lately been reported to generate a degree of reliance **[7],** despite being mainly seen as a social behavior. Khat is interesting since it is one of the few plants that can be consumed lawfully for their ethnopharmacological effects. Many countries of the world are actively debating the legal status and health impacts of this plant's eating as a result of the expansion of consumption from eastern Africa as a result of migration among East African populations **[8].** Until a few decades ago, Khat chewing was mostly limited to older men or members of Muslim communities who chewed it instead of alcohol for religious reasons, and hence the habit did not cause significant public health or socioeconomic difficulties **[9].** Similarly, Khat use has

been prohibited or even illegal in many European countries and Canada, and it is now categorized as a controlled substance. The Drug Enforcement Agency (DEA) in the United States has declared that the plant itself, Catha edulis, is a Schedule I substance on par with opiates during the period when it contains cathinone, i.e. within the first 48 hours of harvest **[10].** According to research on Khat consumption in the United Kingdom, the context of consumption (i.e. displacement and social marginalization) may have a major impact on the results of Khat intake **[11-13].** However, some Khat supporters claim that because Khat leaf is high in ascorbic acid, the negative side effects of Khat chewing are limited. Of course, ascorbic acid functions as an antidote to the effects of amphetamine by altering catecholaminergic activity or dopamine transmission. **[14,15].** Fresh Khat leaves contain phenylpropylamine alkaloids, the two psychoactive elements of which are the stimulants cathinone (S- (-)--aminopropiophenone) and Cathine (S, S-(+)-norpseudoephedrine). Khat psychotropic chemicals work on two major neurochemical pathways: dopamine and noradrenaline. Cathinone, like amphetamine, is thought to release serotonin in the CNS. Both of these drugs cause dopamine release from CNS dopamine terminals, boosting the activity of dopaminergic pathways. Cathinone is a stronger stimulant than Cathine and is widely regarded as the most essential component. Cathinone, on the other hand, is unstable in the presence of oxygen, oxidizing at ambient temperature and decomposing within a few days of harvesting or drying. After roughly 36 hours, the stored product loses its activity and becomes physiologically inactive. Khat should be collected in the morning and chewed in the afternoon for optimal potency **[16].**Some of the established mental consequences of Khat chewing practices include headaches, dizziness, impaired cognitive performance, fine tremor, sleeplessness, attention, dependency, tolerance, and anxiety **[17].** The main effects of Khat are on the cardiovascular system, the gastrointestinal system, and

the nervous system; much of the concern regarding Khat adverse consequences is due to excessive consumption. A similar conclusion was recently reached: if Khat dependency is weak to moderate, craving and tolerance to Khat effects exist, but there is no obvious withdrawal syndrome. There is no substantial, and even contradictory, evidence linking Khat usage to psychiatric morbidity." Oral administration of Khat was linked to lower levels of blood free radical metabolizing enzymes such as superoxide dismutase (SOD) and catalase (CAT).Furthermore, regular Khat usage has a negative impact on the user's social and economic situation. The daily cost of Khat may reduce the household income available for nutritious food, home improvement, education, or other family necessities, eventually leading to financial difficulties and family breakup. Buying and chewing Khat leaves takes up a lot of time, which affects working hours and time. This leads to absenteeism at work, absence at class, low academic performance, and unemployment. Finally, Khat chewers have a much greater death risk from chronic conditions such as heart disease and stroke than non-Khat chewers **[18].**

2. Khat (Catha edulis)

Catha edulis, a dicotyledonous evergreen shrub in the Celastraceae family, is often known as Khat **[19]** it is widely grown in East Africa and the Arabian Peninsula. Khat is also known as Abyssinian tea, African salad, bushman's tea, Catha, chat, the flower of paradise, gat, herari, jaad, kaad, leaf of Allah, Mirra, qaat, qat, tea of the Arabs, tohai, and tschat **[20]** The botanist Peter Forskal wrote the first scientific paper on Khat in the 18th century **[20].** Many people say that Khat began in Ethiopia and spread to the hillsides of east Africa and Yemen; others claim that it originated in Yemen and spread to Ethiopia and neighboring nations **[22,23]** In any case, the plant has expanded from Ethiopia and Yemen to Kenya, Somalia, Malawi, Uganda, Tanzania, Arabia, Congo, Madagascar, Zimbabwe, Zambia, and South Africa, as well as Afghanistan and Turkestan.Khat is a member of the kingdom Plantae, the class Magnoliopsida, the order Celastrales, the family Celastraceae, the genus Catha, and the species Edulis. Khat (Catha edulis Forsk.) is a shrub with a slender trunk and smooth, thin bark. The lancet-shaped leaves measure between 0.5 and 10 cm long and 0.5 to 5 cm broad. Young leaves are reddish green and eventually, turn yellow-green **(Figure 1).** The leaves are mildly fragrant and have an astringent, slightly sweet flavor. The tap root can develop to depths of 3 meters or more. The shrub can grow taller than 1.5 m in frosty areas, but in areas with more rainfall, such as Ethiopia's highlands and areas near the equator, Khat trees can grow up to 20 m **[22]** Khat can also withstand drought conditions when other crops fail. It grows at elevations ranging from 1.500 to 2.000 meters. Khat is a perennial that is propagated through grafting. Before the leaves are picked, trees are grown for 3-4 years. A healthy tree can produce for up to 50 years. There is no recognized sickness that affects Khat **[22,23].**The chemical profile of Khat leaves is determined by environmental and climatic factors **[22].**Fresh Khat leaves are eaten for their psychostimulant effects. Khat's acute

psychostimulant effects include elevated mood and alertness, euphoria, increased flow of ideas while studying, feelings of optimism, elation, a general sense of well-being, improved concentration, friendliness, contentment, the ability to think more clearly, confidence, and increased vigilance. Cathinone, the main element in Khat, reduces hunger similarly to amphetamine, which is why it is thought to have antiobesity properties. It has been used to avoid weariness and is believed to aid memory and pain relief. Khat was reported to boost motor activity, pleasure, and a sense of excitement and activation in placebo-controlled trials **[24].** Cathinone is released within 15 to 45 minutes of chewing Khat, with peak plasma levels of cathinone obtained 1.5 to 3.5 hours later. Cathinone can be detected in plasma for up to 24 hours after ingestion.

Figure 1. A young Khat shrub.

3. Official and Legal Uncertainty

Emigrants from East Africa and the Arabian Peninsula want to keep their Khat chewing habit alive, and significant quantities of fresh Khat are thus transported into other parts of the world. Every day, between 5 and 10 million people are said to consume Khat. Despite this, Khat is not now under international control, despite the fact that Cathine and cathinone, two chemicals commonly found in Khat, have been under international control since the early 1980s, when all amphetamine-like substances were placed under such supervision **[25].**Cathinone was added to Schedule I of the UN Convention on Psychotropic Substances in 1988, and Cathine was added to Schedule III **[26]** Cathinone is still classified as a Schedule I substance, but Cathine is classified as a Schedule IV substance. However, the legality of Khat use by the general public varies from country to country **[27].**The situation is compounded by the fact that the formal status of Khat as a commodity is unknown. Authorities in the West are unfamiliar with Khat and are unsure how to respond to it: should Khat be classified as a drug, like cannabis, heroin, and cocaine, or should it be classified alongside coffee, cigarettes, and alcohol? Should it be prohibited as a narcotic, or accepted as a culturally significant practice for those involved. Khat trade and consumption are not banned in the United Kingdom, and there have been reports of efforts to cultivate it for personal use **[27].** However, European countries' attitudes toward Khat are not universal. While it is permitted in the United Kingdom and the Netherlands, it is illegal in France, Sweden, and Switzerland. Outside of Europe, it is prohibited in the United States and Canada. Indeed, the case of this plant is confusing, and international law on the subject is ambiguous **[27]**Khat users appear to use very little other drugs or alcohol. Although there is a substantial relationship with tobacco usage, there is little evidence that Khat consumption is a gateway drug to other stimulant drugs.

Khat does not lead to acquisitive criminality in the same manner as cocaine or heroin do, which could be attributed to its low cost and lesser re-enforcing effects. In truth, the Khat industry is a legitimate company. There is no evidence of organized crime or terrorism being involved in the UK trade, probably because of its legality; but, with Khat being outlawed in the US, there is some evidence of organized crime becoming involved in its export to the US **[28].**

Researchers have avoided taking a firm stance in favor of or against Khat. As a result, when reporting on Khat consumption in Rome, Nencini and other 39 tentatively concluded that "the Khat party has thus remained a social event and is one way for the participants to maintain their ethnic identity." According to research conducted in Melbourne and the Netherlands, Khat consumption is strongly viewed as a social event. Using Khat for recreation and relaxation makes individuals feel wonderful, just like going to a pub and having a drink. It is a means for participants in Khat sessions to redefine their identity and reinforce their self-esteem as migrants in a strange society. At the same time, Khat sessions are a vital source of household news and an opportunity to discuss societal information **[29].**

4. Khat History

In Yemen, Khat (qat, kat) is an important cultural phenom. Khat (Qat), an evergreen shrub in the Celastraceae family **[19,30],** was named after botanist Peter Forsskal, who died in Yemen in 1763. Catha is given the Arabic word Khat **[31].** Khat (from the Cathaedulis tree) consumption is widespread in East Africa, Yemen **[32],** and Southern Saudi Arabia **[33].** Khat is grown commercially in Yemen, Ethiopia, Somalia, and Kenya, as well as natively in Turkestan and Afghanistan, Tanzania, Uganda, Zambia, South Africa, and Madagascar **[34-36].** It is also farmed in Israel by Yemeni Jews **[37].** The Khat plant's origins are unknown, and much of what is known about its early history is speculative **[19].** Moreover, the start of qat consumption is modest and uncertain **[31].** According to historical evidence, qat first appeared in the southern Red Sea region (Yemen or Ethiopia) before the mid-fourteenth century **[31].** Rodinson **[38]** believes there is evidence of the drug's introduction into Yemen circa 1300 A.D. According to Schopen **[36],** stimulants were used in Yemen in the early 13th century. According to Kennedy's **[19]** interpretation, the usage of...Khat... may have begun in Yemen as early as the 12th century and expanded to Ethiopia during that time. There are various traditions about the discovery of the Khat plant in both Yemen and Ethiopia. According to Ethiopian and Yemeni tales, a Yemeni goatherd discovered the virtues of Khat after observing the effects of the shrub on his goats. The goat herd tested it himself and discovered that his activity and energy levels soared, allowing him to remain up all night praying. According to Arabic records, Khat was known in Turkestan and Afghanistan as early as the beginning of the 11th century **[19,36].** The plant was first mentioned in Yemeni literature in the mid-sixteenth century. Scholars from Yemen traveled to Mecca at the time to seek the opinion of the renowned holy man Ibn Hajar Al-Haythami on the religious status of Khat. After

consulting with other academics, Al-Haythami concluded that the perspectives were diametrically opposed. Those who opposed Khat stated that it caused bewilderment, intoxication, and sleepiness, as well as a decrease in the desire for cohabitation and food, as well as dehydration and spermatorhea. Those who preferred Khat said that it had stimulating and joyful effects and that by using it, they obtained closer communion with God. He determined that Khat should be regarded as a dubious substance that should be avoided if at all possible, but he did not rule that it should be rendered prohibited (haram) **[31,36,38].** Khat intake was restricted to Sufis and holy men to enhance their spiritual experience, as well as certain members of the upper classes **[19,36,39],** wealthy individuals, and possibly certain farmers who grew it **[19].** Due to the growth of road networks and the availability of air transport during the previous two decades, the habit has spread significantly to Europe and the United States **[40,41].**

4. Chemistry

Khat has around forty different alkaloids, glycosides, tannins, amino acids, vitamins, and minerals. The chemical profile of Khat leaves is determined by environmental and climate factors. Khat has a wide range of chemicals, including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins, and minerals **[42].** The main alkaloids are phenylalkylamines and cathedulins. The cathedulins are polyesters of euonyminol with a polyhydroxylated sesquiterpene backbone. Recently, 62 distinct cathedulins derived from fresh Khat leaves were identified. Cathinone [S-(-)-cathinone] and the two di-astereoisomers Cathine [1S, 2S-(+)-norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R,2S-(-)-norephedrine] are among the Khat phenylalkylamines. These substances have structural similarities to amphetamine and noradrenaline. Only the (-)-enantiomer of cathinone is found in the plant. As a result, S-(-)-cathinone has the same absolute structure as S-(+)-amphetamine **(Figure 2).** Cathinone is primarily found in the young leaves and shoots of plants. Cathinone is converted during maturation to Cathine [(+)-norpseudoephedrine] and (-)-norephedrine **(Figure 3).** The leaves contain [(+)-norpseudoephedrine] and (-)-norephedrine in a 4:1 ratio. The phenylpentenylamines merucathinone, pseudomeruCathine, and meruCathine are also phenylalkylamine alkaloids discovered in Khat leaves. These chemicals appear to contribute less to Khat's stimulating effects **[43].**Cathinone is unstable and decomposes after harvesting, as well as during drying or extraction of the plant material **[43].** Decomposition produces a 'dimer' (3,6-dimethyl-2,5-diphenylpyrazine) as well as possibly smaller fragments. Khat extracts were used to isolate the dimer and phenylpropanedione. Because cathinone is thought to be the main psychoactive component of Khat, fresh leaves are preferable and Khat is wrapped in banana leaves to keep it fresh.

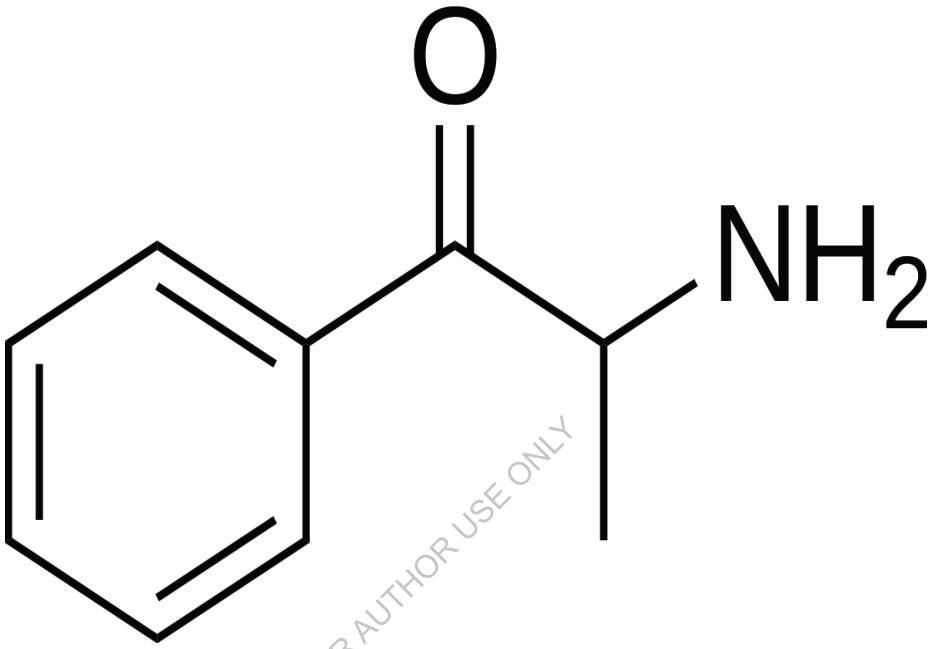

Figure **2. Chemical Structures of Cathinone**

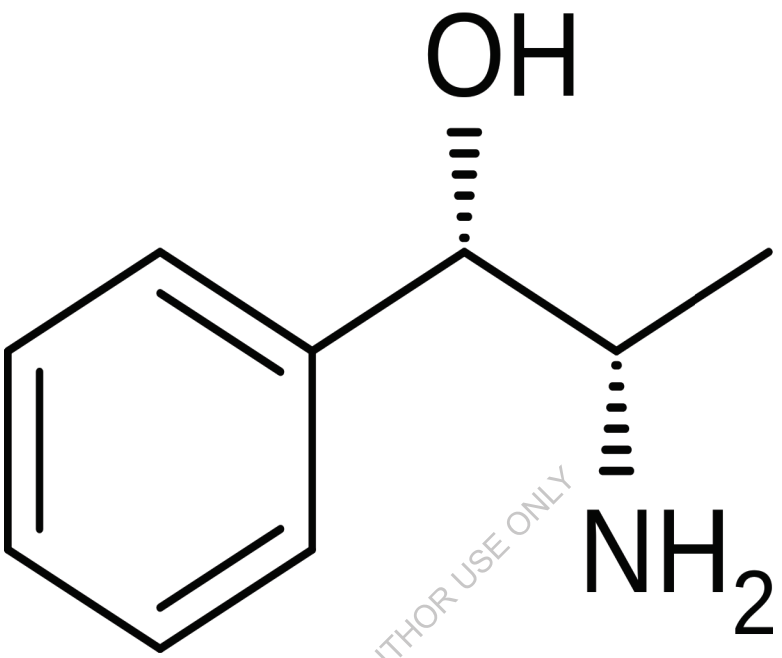

Figure 3. Chemical Structures of Cathine.

6. A Toxicokinetic and Toxicodynamic

6.1 Khat Toxicokinetics

Khat is usually chewed, occasionally steeped as a tea, and never smoked. In a single Khat session, 100-500 g of Khat leaves are chewed over several hours. When chewed, the leaves separate from their branches and are retained in the mouth (chewed sporadically to discharge the active ingredients, or retained in the oral cavity) and later expectorated. Chewing successfully extracts approximately 90% of the alkaloids from the leaves into the saliva. The psychostimulant effects of Khat eating occur 30 minutes later and last for 3 hours. The oral mucosa is important in the absorption of Khat chemicals (60% of total absorbed). Following swallowing, additional absorption takes place in the stomach and small intestine **[44].** The maximal plasma concentration of cathinone is determined by the dose taken and occurs within 1.5-3.5 hours. Cathinone proceeds through phase I metabolism, which is performed by liver microsomal enzymes, creating Cathineand norephedrine by reducing the -keto group to an alcohol. Cytochrome P450 2D6 (CYP2D6) appears to be involved in cathinone-to-Cathine conversion. The metabolism is stereoselective: norephedrine (R, S-(-)-Norephedrine) is the predominant metabolite of S-()-cathinone, whereas Cathine (R, R-(-)-Norpseudoephedrine) is the major metabolite of R-(+)-cathinone. Almost all of the cathinone is swiftly and stereoselectively digested, with only a little quantity, less than 7%, excreted unchanged in the urine **[45,46].**The World Health Organization (1985) **[47]** reported that Khat is rapidly absorbed after mastication and processed in the liver, with only a small fraction remaining in urine. Cathinone's faster and more intense action than Cathine is explained by its increased lipid solubility, which allows for faster access into the central nervous system. The pharmacokinetic parameters of cathinone and other Khat leaf constituents were

determined during an 8-hour period, with peak plasma levels achieved after 1 - 3.5 hours. Similarly, the peak plasma concentrations (tmax) of cathinone, Cathine, and norephedrine have been observed to occur at 2.3, 2.6, and 2.8 hours, respectively. It was observed that after ingestion of 0.8 mg/kg cathinone, the total amount of cathinone absorbed in the body after 9 h was 25 ± 13 µg min/ml. Following administration to humans, S (-)-cathinone is rapidly converted to norephedrine and Cathine . Cathinone was identified in urine samples from four human participants who chewed Khat leaves for 1 hour, spat out the residues, and then had their urine samples tested for the presence of cathinone and its metabolites. Cathinone was detected for up to roughly 26 hours, whereas Cathine and norephedrine were detected for at least 80 hours. Only 7% or less of the absorbed (-)-cathinone is eliminated as norephedrine and Cathine. The amount of norephedrine discharged in urine is substantially more than the amount consumed, implying that (-)-cathinone is also converted to R, S (-)-norephedrine **[44].**

6.2 Khat Toxicodynamic

The main psychoactive and sympathomimetic effects of Khat are caused by cathinone and Cathine. Although both can activate the central nervous system (CNS), cathinone is primarily responsible for all of Khat initial CNS activities. Cathinone is an amphetamine -keto derivative that has amphetamine-like CNS stimulating properties **[48].** Amphetamine derivatives belong to the '-phenylethylamines' class of medicines and are structurally related to catecholamine neurotransmitters, noradrenaline, and dopamine. Amphetamine derivatives sympathomimetic effect is explained by the structural similarity between them and noradrenaline. Furthermore, amphetamine is related to ephedrine in that it shares a metabolite with cathinone, norephedrine. Monoamine reuptake transporters compete with amphetamine derivatives as substrates. Furthermore, amphetamine

operates on the CNS as a monoamine-releasing agent (noradrenaline, dopamine, and serotonin) and causes the peripheral sympathetic nervous system to produce adrenaline **[49].** This mechanism is accompanied by monoamine reuptake inhibition and perhaps monoamine oxidase (MAO) inhibition, which results in increased synaptic monoamine concentrations. Cathinone, like other sympathomimetic and CNS stimulant substances of natural and synthetic origin (e.g., cocaine, amphetamines), exhibits CNS stimulant and sympathomimetic properties **[50].** Cathinone has been shown in preliminary investigations to generate amphetamine-like CNS dopamine release **[51]** and to inhibit MAO, with a preference for MAO-B, the inhibition of which leads to decreased dopamine breakdown and subsequent synaptic buildup **(Figure 4)** depicts the key modes of action. The euphoric impact of Khat is connected with increased activation of dopaminergic pathways in specific parts of the brain **[48].**

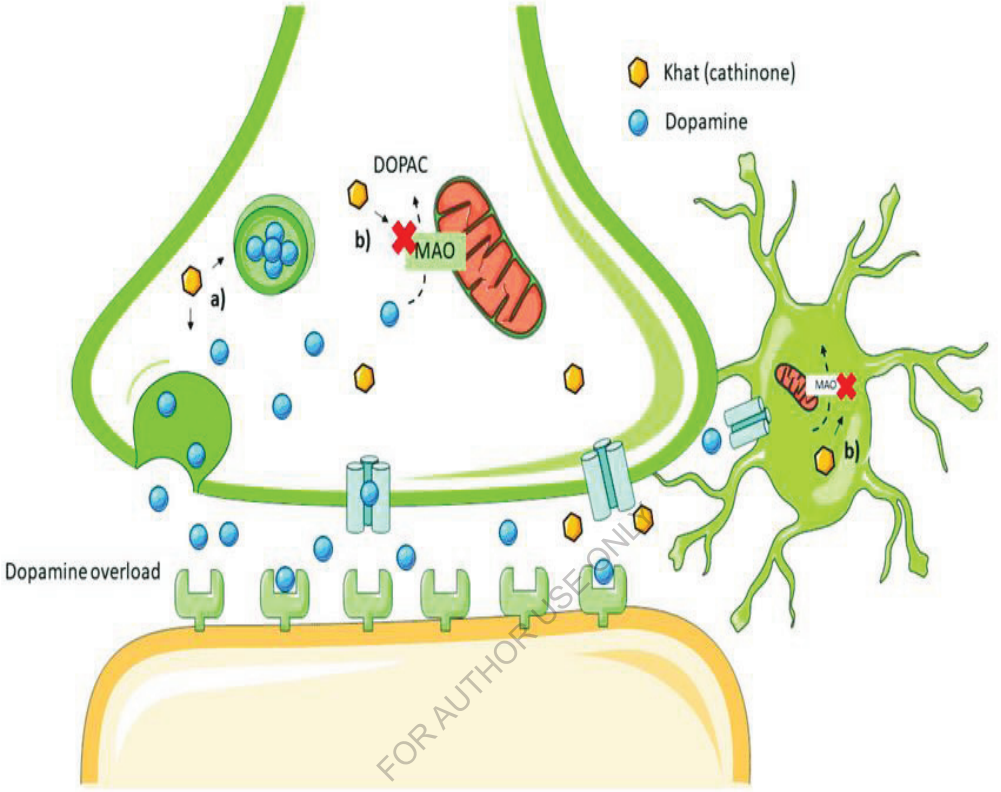

Figure 4. The mechanism of cathinone toxicity on the central nervous system. Induction of dopamine release (a), suppression of MAO in neurons and astrocytes (b).

7. Effects of Khat

Khat has been referred to as a natural amphetamine due to its effects being comparable to those of other recognized psychostimulants such as amphetamine and its congeners. Alles, Fairchild, and Jensen **[52]** and Hughes **[53]** found similar effects to a low dose of amphetamine after self-consuming a bit of Khat. Khat, like amphetamine, has effects on both the peripheral and central neurological systems. The peripheral effects are predominantly sympathomimetic, resulting in a rise in respiration, body temperature, blood pressure, heart rate, and mydriasis. Euphoria, attentiveness, and a sense of well-being are the consequences of the central nervous system. There is also anorexia, sleeplessness, high dosages, hyperactivity, and excessive talking. Manic-like behavior, schizophreniform psychosis, or paranoia can arise as a result of Khat intoxication and are comparable to those seen with amphetamine intoxication. Khat use often begins at a young age and can develop into a compulsive daily habit that lasts a lifetime. There are an estimated 5 to 10 million regular Khat users **[54].** The medical and socioeconomic consequences of Khat usage on society sparks frequent, sometimes intense debate about whether Khat should be deemed a substance of abuse and outlawed, or whether it should be viewed as a harmless stimulant like caffeine that promotes social contact. The energizing and euphoric effects of Khat can provide a powerful enticement for the user to obtain the daily supply and to chew for lengthy periods of time, especially when tolerance develops with continuous usage. This strongly shows that the user is developing psychic or physical reliance or both. According to the World Health Organization, Khat consumption can lead to mild dependence **[55].** Physical reliance is not regarded as a key element because the withdrawal symptoms are modest - lethargy, moderate sadness, nightmares, and little tremor - yet there appears to be a substantial psychic dependency component.

7.1 Active Ingredient of Khat

In 1930, Wolfes **[56]** discovered an alkaloid, or pseudoephedrine (Cathine), in Khat leaves, and this was thought to be the principal active element responsible for Khat effects until the 1960s. However, the amount of Cathine in the leaves was insufficient, accounting for just about 10% of the CNS stimulation observed **[57],** raising the possibility of the presence of another molecule.

The United Nations Narcotics Laboratory launched new research on the elements of Khat leaves. In 1975, fresh and freeze-dried samples from Yemen, Kenya, and Madagascar were investigated, and the existence of cathinone, a keto analog of Cathine, was discovered **[58],** Cathinone was discovered to be a labile chemical found primarily in young fresh leaves, and its concentration fell rapidly when the leaves were removed from the Khat tree. The cathinone level varied (0.9-3.3%) depending on the place of origin, with Kenyan Khat having the highest cathinone content **[59],** Cathinone's chemical structure was shown to be comparable to amphetamine **(Figure 5).** Aside from ketamine and cathedulins, over 20 additional chemicals identified from Khat have been studied, including tannins (7-14%), vitamin C (150 mg/100 mg), and trace quantities of thiamine, niacin, riboflavin, and carotene.

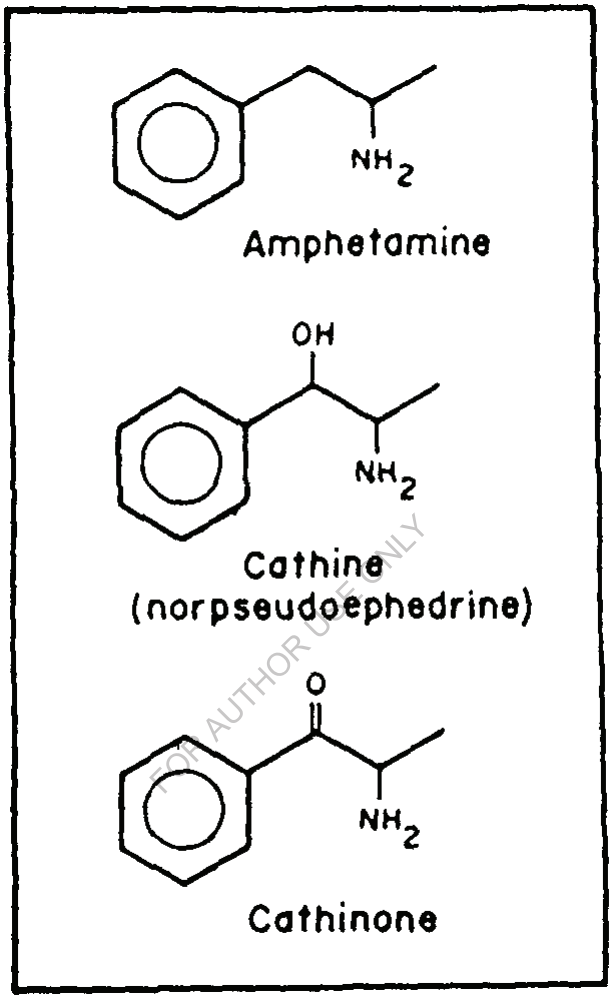

Figure 5. Structure of cathinone, Cathine (norpseudoephedrine), and amphetamine

7.2 Cathinone Effects

Several research was conducted to investigate whether cathinone is responsible for the Khat effects. In six drug-free volunteers, Wilder et al **[60]** investigated the effect of fresh and alkaloid-free leaves. A single dose of Khat resulted in plasma cathinone concentrations reaching 127±53 ng/ml 127±30 minutes after fresh leaf intake. When compared to the effect after administration of alkaloid-free leaves, the Addiction Research Centre Inventory scale, the motor stimulation scale, and the amphetamine-like effect scale were all significant.The stimulatory impact of this Khat dose was comparable to a cathinone dose of 0.5 mg/kg body weight. In another clinical trial, six healthy volunteers were administered cathinone equating to 100 gm of Khat leaves with an average cathinone concentration. The Addiction Research Centre Inventory surveys revealed a strong psychostimulant and euphorogenic effect, as well as an elevation in blood pressure and heart rate. These alterations occurred in tandem with the presence of cathinone (half-life of about 1.5 hours) in blood plasma.These findings backed up the theory that cathinone was the primary active element in Khat and was principally responsible for its psychostimulatory action. Although the effects observed in humans following Khat use appear to be well explained by cathinone action, the possibility that additional alkaloids, particularly Cathine, could contribute to the Khat effect persisted. Cathine has the same sympathomimetic effect as cathinone at the peripheral level. However, as previously stated, Cathine cannot fully account for the CNS stimulatory effect of fresh Khat. First, while having the same Cathine concentration, dry Khat leaves do not have the same stimulatory effectiveness as fresh leaves. Second, Khat users' preference for fresh Khat over old or aged Khat suggested that there was something contained in new leaves that was missing in old or aged Khat. Because the cathinone content of fresh leaves declines rapidly, and based on the user predilection for fresh leaves, it indicates that Khat users are

looking for cathinone effects. Furthermore, cathinone has a higher lipophilicity than Cathine, which would promote its entry into the CNS over Cathine. Thus, it appears that cathinone is primarily responsible for Khat CNS stimulation, whereas cathinone and Cathine both play a role in the peripheral effects.

7.3 Mechanism of Action of Cathinone

A scientific technique to determining whether cathinone is responsible for the Khat effects is to elucidate its mechanism of action and compare it to that of other known psychostimulants such as amphetamine or cocaine. Because cathinone has a similar structure to amphetamine and Khat has an amphetamine-like effect, most studies have focused on whether the two substances' mechanisms of CNS action are similar. Amphetamine's actions are mediated through the release of neurotransmitters at catecholaminergic synapses, particularly dopaminergic and serotonergic synapses. Kalix **[54,61]** discovered that cathinone increased the release of radioactive labels from various rat brain regions prelabeled with 3H-dopamine (nucleus accumbens, striatum, and caudate nucleus). These areas are involved in amphetamine-induced hypermotility, a characteristic seen with cathinone as well. Cathinone, like amphetamine, has been shown to induce the release of radioactive labels from rat striatal tissue prelabeled with 3H-serotonin. Cathinone, on the other hand, is a third less effective than amphetamine in inducing this release **[54].** Cathinone's affinity for serotonin receptors was discovered to be approximately four times that of amphetamine. This data, together with those of Babayai et al **[62],** suggested that stimulation of the serotonin pathways may play a significant role in cathinone activity when compared to amphetamine.

7.4 Behavioural Effects of Cathinone

Cathinone has been found to preserve drug-seeking behavior in amphetamine-addicted rats and monkeys trained to press a lever for cocaine injection **[63].** This suggests that the effects and locations of action of cathinone are comparable to those of amphetamine and cocaine. Similarly, rats injected with cathinone exhibit the same stereotyped behavior and hyperlocomotion as amphetamines.

8. Problems associated with Khat chewing

8.1 Effects of Khat chewing associated with dental problems

There are links between Khatchewing and periodontal damage which again interfere with plaque accumulation and result in subgingival microbial changes consistent with periodontal health **[64].**

Laurent **[65],** Halbach **[66],** and Luqman and Danowski were the first to notice the negative consequences of Khatchewing on oral-dental tissues **[32].** They discovered that long-term Khatchewing produced stomatitis, which was then followed by secondary infection. Mechanical pressure on the cheek and other oral tissues, as well as chemical irritation on the mucosal surfaces, may be to blame. Mouth dryness, the most common symptom after Khatchewing, could be caused by cathinone's sympathomimetic action and/or excessive saliva flow while chewing. Hill and Gibson studied the effects of Khatchewing on oral and dental tissue in Yemeni males aged 35 years and older **[67].** They discovered a low incidence of caries on the Khat-chewing side, but universal attrition, temporomandibular joint pain, and increased periodontal pocket depth on the non-Khat-chewing side. In 50% of the cases, they also found elevated keratosis on the buccal mucosa. In Kenya, Macigo and colleagues discovered that Khatchewing was not connected with leukoplakia when compared to tobacco and alcohol use **[68].** A recent cross-sectional hospital study revealed an increased risk for a variety of oral and perioral diseases **[69].** The study found that Khatchewing produced a variety of diseases in the tooth's supporting tissues, including gingivitis, periodontal pocket formation, gingival recession, tooth mobility, and tooth mortality. Khat chewing induced clicking and pain in the temporomandibular joints, as well as tooth attrition, discoloration, and cervical caries, especially among crystallized sugar users. Khat chewing induced white lesions on the buccal and gingival mucosa due to constant mechanical friction and/or chemical content. Histopathological examination

revealed acanthosis, papillomatosis, ortho- and parakeratosis, and intercellular edema, but no leukoplakia. In terms of saliva and salivary glands, Khatchewing causes mouth dryness, salivary gland hypertrophy, inflammation, and folding of the parotid papilla at the location of Khatchewing. Khat chewing also results in the noticeable facial asymmetry of face tissues.Oral mucosal keratosis affects 50% of Khatchewers **[67].** This pathological change is classified as a pre-cancerous lesion that has the potential to develop into mouth cancer **[70].** The frequency and length of Khatuse elevated the prevalence and severity of this injury. The significance of Khatwas discovered after it was discovered that the majority of oral squamous cell carcinomas in study subjects were found in the buccal mucosa and lateral sides of the tongue, which come into direct contact with Khatduring chewing **[71].** In several cases, the malignant lesion appeared at the same location as the Khatbolus.

8.2 Effects of Khat chewing associated with the digestive system

The presence of tannins in this plant has the greatest impact on the digestive tract. Some of the most common complaints from Khatusers are gastroenteritis and constipation; Khatalso causes a lack of appetite. Tannins and pseudoephedrine are both blamed for malnutrition and constipation. Toxicity was assessed in laboratory animals, and Khatextracts were found to possess mutagenic components. Khat chewing has also been linked to an increased incidence of duodenal ulcers **[72].**Older research on the consequences of chronic Khatchewing on the digestive system was based on clinical observations that Khatchewers frequently complained of symptoms suggestive of stomatitis, oesophagitis, and gastritis. These effects were thought to be induced mostly by the Khat very astringent tannins **[73].** Gastric symptoms were linked to a hypotonic stomach caused by Cathine and its precursor sympathomimetic effect **[73].** Recent evidence suggests that chewing Khatdoes actually delay the stomach emptying of a semi-solid meal, most likely

due to the sympathomimetic activity of cathinone in Khat **[60].** Delayed gastric emptying may raise the risk of gastro-oesophageal reflux, which manifests as heartburn and acid regurgitation, as well as the risk of Barrett esophagus, a precancerous condition. Anorexia often follows a Khat session, and chewers rarely eat another substantial meal on the same day. A new study on the subjective effects of Khatchewing discovered a substantial reduction in hunger after Khatchewing **[74].** This anorectic effect may be ascribed to the combination of direct cerebral and stomach effects of cathinone in fresh Khatleaves **[60],** rather than an influence on ghrelin or peptide YY levels **[75].** Constipation is a common complaint among Khatchewers, which is likely induced by a combination of the astringent characteristics of Khattannins and the sympathomimetic properties of cathinone. Habitual users attempt to mitigate this unpleasant effect through food adaptation, most notably by eating a high-fat meal before the Khatsession to ease intestinal transit. The constipating action of Khatwas suggested by the observation that when Khatwas banned in Aden in 1957, sales of laxatives dropped by 90% but quickly rebounded to pre-ban levels **[66].** Chewing Khatleaves has been proven to considerably slow both the orofacial transit time and the overall gut transit time. These two pathways may contribute to Khatconstipating impact. Furthermore, Khatinterfered with the absorption of some orally administered antibiotics, particularly ampicillin, and tetracycline **[76],** resulting in reduced bioavailability.

8.3 Effects of Khat chewing associated with the central nervous system

The effect that accounts for Khatattracts is central nervous system stimulation, which is thought to be generated by cathinone, an active chemical in Khatleaves. Cathinone has a faster and more intense action than Cathine due to its increased lipid solubility, which allows for easier entry into the central nervous system. Chewing Khat leaves produces a modest degree of happiness and mild excitement, resulting in the development of social engagement and loquacity **[51].** Chewers experience increased alertness and vitality, as well as improved depth of awareness, as they achieve a sense of subjective well-being. These effects peaked 1.5-3.5 hours after starting to chew and were gradually replaced by mild dysphoria, anxiety, reactive depression, sleeplessness, and anorexia **[73].** The psychological effects of Khat chewing are similar to those of amphetamine **[60],** however, environmental conditions have been considered to have a significant influence on the expression of Khat effects. It has been argued that the effects of Khat and amphetamine differ quantitatively rather than qualitatively. It has also been noted that Khat-induced behavioral conditions can be similar to hypomania since it can include hyperactivity and logorrhoea **[66].** Khat-induced psychosis has become more widespread in Europe in recent years **[77].** When consumed in excess or by a predisposed individual, Khat can cause functional psychosis **[66].** Several reports on psychiatric illnesses caused by Khat chewing have been published, including aspects of mania-like psychosis, schizophreniform psychosis, paranoid psychosis, or symptoms of acute schizophrenia-like psychosis. Furthermore, several chronic Khat users reported persistent hypnagogic hallucinations. Khat appears to generate full-blown paranoid psychosis in one case report from the United Kingdom, with the extra complication of a suicide attempt. In Kenya, excessive chewing resulted in psychotic states that were delusional in character and temporary **[78].** However, when reasonable amounts of Khat were eaten, there was no increase in psychiatric morbidity **[78].** Preliminary data on 65 schizophrenic male patients admitted to

psychiatric care in Sana'a due to uncontrollable symptoms were analyzed **[79].** They found that Khat chewing in psychotic patients was linked with mood and behavior disturbances, exacerbation of delusional symptoms, and decreased responsiveness to antipsychotic medication. Previous research has indicated that failing to refrain from Khat usage can extend a psychotic episode, even while on psychiatric medication **[78].** Alem and Shibre recently considered Khat as a substance of abuse, noting that chewing has the potential to exacerbate psychiatric illnesses and forensic occurrences **[80].** Unlike amphetamine, Khat is significantly less prone to cause tolerance. The stimulating central nervous system effects of Khat, in particular, do not appear to be prone to tolerance **[66],** but most chronic Khat chewers have shown some tolerance to sleeplessness **[32]** and anorexia. A World Health Organization (WHO) Expert Group on drug dependence evaluated the topic of Khat dependence and determined that Khat usage may induce a permanent mental dependence rather than physical dependence **[77],** notwithstanding the fact that psychological reliance might emerge. However, psychological withdrawal symptoms from long-term Khat use appear to be restricted to lethargy, mild depression, modest trembling, and recurring disturbing dreams **[66].** The absence of physical withdrawal symptoms suggests that merely rebound phenomena, rather than a particular abstinence syndrome, exist **[32].** However, Khat was recently submitted to a preliminary examination of psychoactive substances by the WHO Expert Committee on Drug Dependence. The Committee noted that Khat is thought to be addictive and suggested that there be enough evidence on it to justify a critical evaluation (a fully documented study) at a future meeting **[81].** Khat use is frequently combined with the use of other narcotics. Concurrent cigarette smoking is a widespread practice that may alter Khat -induced effects **[66].** Insomnia caused by Khat is common, and Khat users attempt to treat it with sedatives or alcohol.

8.3.1 Psychiatric disorders

Youth Khat use can be hazardous, resulting in lower academic performance and an increased risk of psychiatric illnesses such as lethargy, despondency, and insomnia. In some situations, it might develop into a hypomanic state. Toxic psychosis can also occur as a result of its ingestion, and several such cases have been reported. Anxiety, tension, restlessness, hypnologic hallucinations, aggressive conduct, or psychosis are all symptoms of Khat use. A committee of WHO experts also found that Khat intake can cause "moderate but often persistent psychic dependence." However, withdrawal symptoms from long-term Khat use appear to be restricted to lethargy, mild sadness, slight trembling, and recurring disturbing dreams **[66].**

8.3.2 Khat-induced psychosis

Chewing Khat can cause two types of psychotic symptoms. The first is a manic episode with grandiose delusions, while the second is a paranoid or schizophreniform psychosis with persecutory delusions linked with auditory hallucinations, terror, and anxiety, similar to amphetamine psychosis. Both effects are exceptional and are associated with massive amounts of Khat chewing. When the Khat is removed, the symptoms quickly subside **[82].** In reality, Khat withdrawal appears to be an effective treatment for Khat psychosis, and antipsychotics are rarely required for complete recovery. Nonetheless, antipsychotic medication has been used to reduce symptoms in the majority of cases. Khat psychosis, on the other hand, is a rare occurrence, most likely due to the physical limits of the number of Khat leaves that can be chewed **[83].** Khat psychosis is occasionally accompanied by depressive symptoms and aggressive behaviors. It has been suggested that Khat chewing may aggravate symptoms in persons who already have psychiatric illnesses. There was no extra morbidity among moderate users. Chewing more than two bundles each day was linked to an elevated risk of psychological illness **[84].**

8.3.3 Hypnagogic hallucinations

Chronic Khat users have been observed to experience hypnagogic hallucinations **[85].** These are non-Khat-related continuous visual and/or audio dreamlike experiences that accompany daily living. Patients may regard them as normal and, unless specifically questioned, do not normally disclose these hallucinations.

8.3.4 Impairment of cognitive functions

Khat chewing has been linked to impairments in perceptual-visual memory and decision-speed cognitive functioning **[86].** Toennes and Kauert looked at plasma Khat alkaloid levels in 19 people suspected of driving under the influence of narcotics **[87].**Cathinone or Cathine was identified in all cases of blood and urine, although no link between alkaloid concentrations and impaired driving could be found. Nonetheless, the scientists found that prolonged Khat usage could result in a significant worsening of psychophysical capabilities.

8.4 Effects of Khat chewing associated with cardiovascular effects

Khat chewing causes increases in blood pressure and heart rate. Cathinone (0.5 mg base/kg body weight) produces similar effects when cathinone is present in blood plasma **[88].** These effects were inhibited by the beta1-adrenoreceptor blocker atenolol but not by the alpha1-adrenoreceptor blocker indoramin, indicating mediation via beta1-adrenoreceptor activation. Diastolic and systolic blood pressures were raised for around 3 hours after eating. The elevation in blood pressure occurred prior to the rise in alkaloid plasma concentrations, indicating an early research engagement effect. The dose was one-quarter (0.6 g/kg) of a standard Khat session dose, and the chewing time was one hour. As a result, the average oral intake of cathinone was 45 mg. This relatively low dose had no effect on heart rate, pupil size, or responsiveness to light, nor did it cause rotational nystagmus or reaction impairment. All subjects reported feeling alert and 'energetic'. Other psychophysical functions could not be objectively impaired.

Another study found that diastolic and systolic blood pressure, mean arterial blood pressure, and heart rate all increased throughout the three hours of Khat eating and the hour after **[89].**

8.5 Effects of Khat chewing associated with elevated diastolic blood pressure

Khat is primarily consumed while chewing the leaves. The chewer's blood pressure and heart rate immediately rise after eating Khat. Khat is chewed for a variety of purposes. Most chewers utilized Khat to improve their concentration on prayer. Some chewers claimed that consuming Khat increases energy levels and alertness, boosts inventive ability and the capacity to associate ideas, and improves communication ability **[87].**

8.6 Effects of Khat chewing associated with the urinary system

Regular Khat chewing in humans may induce kidney injury, as total serum protein levels were lowered while urea and creatinine levels were considerably elevated **[90].** Khat extract includes an oxidizing chemical that inhibits glutathione (GSH) synthesis, increasing the formation of reactive oxygen species and inducing oxidative stress **[91].** One of the key pathways leading to Khat-induced kidney impairment is oxidative stress. Endogenous antioxidant defense systems fail to limit Khat-induced reactive oxygen species (ROS) generation under active oxidative stress. Some of the Khat-induced ROS formation in the kidney and liver could be attributed to pesticides and herbicides used on Khat, such as DDT, glyphosate, paraquat, and 1, 2-dibromo-3- chloroporopan (DBCP). These cause renal necrosis, which leads to acute and chronic kidney failure. Khat has a negative impact on renal function. This could be explained by a decrease in glomerular filtration rate caused by Khat-induced renal vasoconstriction, which is mediated by an increase in norepinephrine release from presynaptic storage vesicles in

peripheral sympathetic nerve endings, which stimulates α 1 and β1 receptors.Khat reduces average and maximal pee flow rate in healthy males. Cathinone urinary effects are most likely mediated by alpha1-adrenergic receptor activation. This is demonstrated by indoramin, a specific antagonist of alpha1-adrenergic receptors, completely blocking this action **[92].**

8.7 Effects of Khat chewing associated with adrenocortical function

A Khat extract given orally for 30 days reduced adrenal cholesterol, glycogen, and ascorbic acid while increasing adrenal phosphorylase activity, serum-free fatty acids, and urine 17-hydroxycorticosteroids in rabbits **[93].** These findings have been interpreted as Khat increasing adrenocortical activity. This effect was likewise observed following the administration of cathinone and Cathine (6.5 mg/kg) orally.

8.8 Effects of Khat chewing associated with diminished sexual performance

Khat is suspected of having effects on several reproductive health factors, which can lead to decreased sex performance. Khat use has been linked to decreased libido and sexual performance **[94].** Rat testicles, epididymis, and seminal vesicles were shown to be smaller than controls in an animal investigation **[95].**

8.9 Effects of Khat chewing associated with the reproductive system

The 6-week Khat treatment of male mice resulted in a dose-dependent drop in fertility rate in female mice in the first week after the 6-week Khat therapy **[96].** Cathinone treatment resulted in a considerable drop in sperm count and motility, as well as an increase in the number of defective sperm cells **[95].** In cathinone-treated mice, histopathological analysis of the testes revealed interstitial tissue degradation, cellular infiltration, and Sertoli and Leydig cell atrophy. Cathinone also reduced plasma testosterone levels in rats significantly **[98].** In male adult

olive baboons, a crude Khat extract (equal to 250 g leaves and shoots) given orally once a week for two months increased plasma testosterone levels while decreasing plasma prolactin and cortisol levels **[99].** The testosterone findings contradict previous findings in humans and rats **[95].** Biopsies performed one month following the last Khat treatment revealed no histological alterations in the animal's testis, epididymis, liver, kidney, or pituitary gland **[100].** Male infertility can be caused by a variety of circumstances, including age, drugs, genetic factors, and toxicity exposure. Many occurrences of male infertility are attributable to primary testicular abnormalities identified by aberrant sperm parameters **[97].** Another important cause is ED, which is described as the inability to maintain a penile erection for long enough to allow for satisfactory sexual intercourse **[21].** Khat use is one of several potential risk factors for aberrant male reproductive health and SD. There has been little research into the impact of Khat intake on human reproductive health **[95].** The majority of animal research on the link between Khat intake and poor reproductive and sexual health, including ED, has been undertaken.A 1995 study **[138]** in Saudi Arabia investigated sperm characteristics and ultrastructure between Khat addicts and those who are not. Both groups were matched in terms of age, education, and socioeconomic level, and they were free of any medical conditions that could have influenced the results of the sperm study. The Khat-addicted group had significantly lower sperm volume, motility, and count when compared to the non-Khat-addicted group.

In Ethiopia, a 2002 study that looked at the effect of Khat on seminal fluid analysis in assumed infertile couples discovered a link between long-term Khat usage and aberrant seminal fluid profiles **[120].** The study found that Khat users had lower sperm volume, count, and motility when compared to the control group; however, the results were not statistically significant. The study also discovered aberrant sperm morphology alterations in Khat users **[120].** Another study, conducted in

Kenya, looked at articles published between 1961 and 2002 to see if Khat intake affected reproductive function **[95].** The study found that long-term Khat usage was associated with reduced libido and potential ED, emphasizing the need for more research to establish a definitive causal relationship **[95].**

8.10 Khat chewing habit a possible risk behavior for HIV infection

Various Khat kinds are thought to increase sexual arousal in Khat chewers. This was supported by pharmacological testing in male experimental animals given cathinone orally, albeit there is currently no proof that the enhanced sexual activity is accompanied by erectile and ejaculatory reactions **[101].** The overwhelming evidence, however, implies that the habit causes spermatorrhoea, diminished libido, and, eventually, impotence, as found in Somalia and Djibouti, where as many as 60% of male chewers were reported to be impotent **[32,102,103].** Whether Khat chewing causes increased sexual desire, impotence, or spermatorrhoea, the habit is thought to cause difficult relationships between married couples, as well as family disintegration and/or various sexual practices. The chewing of Khat may thus be regarded as one of the dangerous activities that may contribute to the spread of HIV. In this context, a correlation has been established between Khat use and increased HIV/AIDS exposure among Djiboutian prostitutes **[104].** As a result, the Khat chewing habit, like many other drugs of abuse, may constitute dangerous behavior that contributes to the spread of HIV infection **[105].** The use of Khat is influenced by a number of complex factors. People who are frustrated, or poor are more likely to use Khat. Khat is extensively used for social entertainment and as a medication on occasion. Most importantly, Khat is a viable source of money for growers and market participants in Yemen, Ethiopia, and Somalia. Second, in Yemen, Ethiopia, and Somalia, Khat use is generally acceptable, even among

minors, and is firmly linked to cultural and gender identity, as well as local customs.

8.11 Effects of Khat chewing associated with liver injury

A 2010 study presented a series of six patients with persistent Khat use who developed severe acute hepatitis, resulting in death (1 patient) or liver transplantation (5 patients) **[106].** In 2011, research published in the Netherlands documented a 26-year-old East African man who experienced abrupt liver failure due to Khat-induced necrotic hepatitis, necessitating liver transplantation **[107].** Another study found six incidences of liver damage in long-term Khat users who traveled from East Africa to The Netherlands. Four patients arrived with jaundice and hepatitis; one of these, along with two others, had variceal hemorrhage and hepatic encephalopathy; and two had clinical ascites. Three patients died from spontaneous bilateral peritonitis and sepsis, and one patient who received a liver transplant died afterward **[108].**

8.11 Effects of Khat chewing associated with gallbladder

Chewing Khat has no clinically significant effect on the gallbladder **[109].**

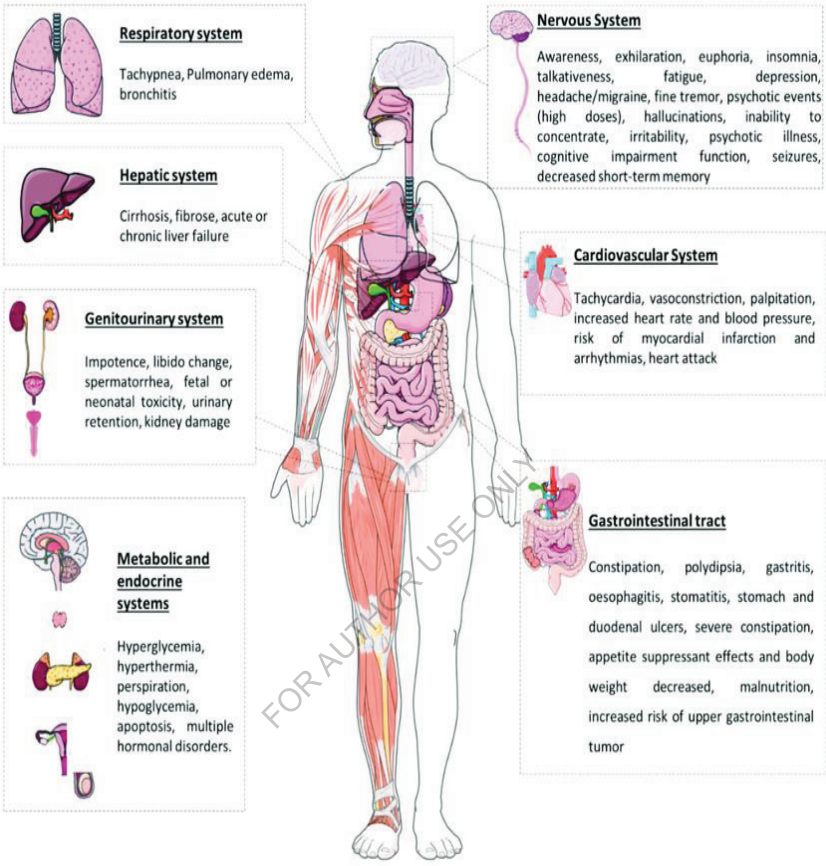

Figure 6. Common adverse effects of Khat abuse [134-137].

8.12 Effects of Khat chewing associated with ophthalmological problems

Khat use causes mydriasis and conjunctival congestion **[110].** Amphetamine, according to one study, lowers intraocular pressure **[111].** A case report described bilateral ocular atrophy in two Khat users who consumed more than usual amounts **[112].**

8.13 Effects of Khat chewing associated with the hematological profile

Certain herbal medicines, pharmaceuticals, and other compounds have been proven to have a negative impact on blood components **[113].** Blood composition changes have been seen in Khat users **[114].** Experiments in rodents and primates have shown that Khat and its components lower red blood cells (RBCs) and so change its indices, resulting in macrocytic anemia **[113].** In contrast, Khat administration in mice resulted in lower levels of RBCs and their indices, which could be a strong indicator of Khat -induced normochromic microcytic anemia. Khat extract induced a statistically significant decrease in total WBC count, while other leukocytes including lymphocytes, monocytes, basophils, and eosinophils also showed significant declines in Khat -treated rats **[113].**

8.14 Effects of Khat Chewing affecting Pregnant / Lactation women

Chronic Khat usage has been linked to negative effects on fetal development, labor outcomes, and postnatal mother and infant health. Despite the numerous detrimental effects of Khat usage during pregnancy and nursing, it is widely used among pregnant women in East African countries. According to one study in Ethiopia, 25% of pregnant women had chewed Khat at least once in their lifetime, with the majority identifying as current Khat users. This study also discovered environmental and social implications for pregnant women's Khat consumption. Female Khat users reported consuming aweza (a hot beverage made by boiling fresh Khat leaves in water) to cause abortions in another study in Ethiopia to investigate the acceptable and harmful uses of Khat **[115].**

An Ethiopian study discovered that Khat consumption may be linked to an increased incidence of anemia in pregnant women. Pregnant women with restrictive dietary habits related to pregnancy (ie, lower meal size or frequency, which may lead to poor iron intake) and those who chewed Khat had a considerably greater prevalence of anemia. The relationship between frequent Khat chewing and an increased risk of anemia could be explained by its appetite suppressant effects as well as its tannin content, which affects non heme iron absorption from the maternal diet. Fetal development risks must be evaluated.

Khat use has also been linked to an increase in the frequency of low-birth-weight newborns, according to research. Khat usage during pregnancy may lower placental blood flow and affect fetal growth; diminished placental blood flow can be assessed by analyzing the mother's urinary (+)-norpseudoephedrine concentrations. Because low birth weight is a risk factor for perinatal and young infant death, Khat chewing during pregnancy may impair normal child development and raise the risk of infant mortality **[116].**

One study in Ethiopia discovered a significant frequency of habitual Khat consumption among pregnant women. Current and previous Khat chewers experienced greater levels of depressive symptoms and psychological discomfort, and social and familial factors appeared to influence Khat use behaviors as well. It's unclear whether chronic Khat usage produces more distress and bad effects during pregnancy, or if those who are susceptible to stress are more likely to use Khat throughout pregnancy. In terms of potential negative effects on pregnancy outcomes, maternal Khat use and psychological distress may share common pathways; both are associated with effects on the hypothalamic-pituitary-adrenocortical (HPA) and cardiovascular systems, which play important roles in pregnancy outcomes, including preterm labor, which leads to infant morbidity and mortality.

Psychoactive medications easily pass the blood-brain barrier and even the placental barrier **[116].** Neonatal psychostimulant exposure is related to morphological and functional alterations in the CNS, resulting in motor dysfunction, cognitive impairment, altered stress response, and learning and memory consequences. Cathine was discovered in the breast milk of a Khat-chewing woman and her infant's urine in one investigation. Women have reported behavioral abnormalities in their infants after consuming Khat. Poor sleeping habits, constant sobbing and shouting, and obvious stomach pain were among the alterations. Low weights in breastfeeding newborns have also been observed, most likely as a result of Khat-related changes in the mother's appetite, resulting in decreased milk production and probable malnourishment of the breastfeeding infant **[115].**

8.15 Effects of Khat chewing associated with the fetus and neonatal health

In terms of reproductive health, epidemiological data from 1181 Yemeni deliveries revealed that the mean birth weight of full-term single infants from moms who chewed Khat routinely or rarely was lower than average **[117].** A study on pregnancy outcomes and Khat found that the children of women who chewed Khat during pregnancy had a considerably higher frequency of low-birth-weight full-term infants than those who did not chew Khat during pregnancy **[118].** Recent evidence suggests that neonates born to mothers who chewed Khat during pregnancy had a significant decrease in all neonatal parameters such as birth weight, length, and head circumference compared to those born to mothers who did not chew Khat during pregnancy **[117].** The intensity of this effect was found to increase with the frequency and duration of Khat chewing during pregnancy. According to the findings of the aforementioned studies, frequent use of Khat during pregnancy may affect intrauterine fetal growth. An animal investigation has demonstrated that Khat can impact intrauterine fetal growth by reducing total fetal

fat and weight and producing some changes in the chemical composition of fetal organs, including the liver, heart, and kidneys **[88].** This effect was ascribed to glucose deprivation and reduction of DNA and protein synthesis in embryonic tissues.

Lactation problems are regularly reported by nursing mothers. Some investigators suggest that this occurrence is related to Khat use since Cathine in Khat inhibits prolactin secretion **[32].** Cathine has been identified in the breast milk of Khat-chewing mothers, and this component has even been detected in the urine of one breastfed infant **[119].**

8.16 Khat and cancer

Because Khat usage is common and typically continues into adulthood, various research on the toxicological implications of regular Khat use has been conducted. Khat frequently affects the oral cavity and digestive tract due to its way of ingestion. Its effect was discovered to be depending on the amount of Khat consumed **[3].** Tumors of the oral cavity (lower maxilla, buccal mucosa, and lateral surface of the tongue) were found in 0.13% of patients seeking treatment at a stomatology clinic in Hodeida, Yemen, over a 2-year period **[71].** The majority of them had been Khat chewers for more than 20 years, and several also chewed Shamma (tobacco powder). A comparable assessment of mouth cancers diagnosed over a 2-year period in Saudi Arabia's Asir region found significant circumstantial evidence associating long-term Khat use with an elevated prevalence of oral malignancies **[121].** Tannins in Khat can thicken the oropharynx and esophagus mucosa and may be carcinogenic. According to a recent study in Yemen, oesophageal and stomach cancer accounted for 6% of all patients who had an upper gastrointestinal endoscopy (183 out of 3064 patients) over a one-year period **[122].** A majority of women with mid-esophageal carcinoma were observed, which had previously only been observed in locations with a high frequency of

oesophageal carcinoma. A high prevalence of Khat chewing and water-pipe smoking (mada'a) was discovered in both men and women, as well as in a group with gastro-oesophageal junction or cardia tumors. This apparent link between Khat and lower esophageal cancer may be due to the Khat-induced delay in stomach emptying, which increases the risk of gastro-oesophageal reflux and Barrett esophagus. The effect of eating Khat on the mucosal histology of the upper gastrointestinal tract in Yemeni patients with dyspepsia was investigated **[123].** Regular daily Khat chewing had no significant effect on the esophagus or stomach, but chewers were more likely to develop duodenal ulcers. This could be related to the high prevalence of smoking in this group.

In a two-year examination of tumors in Saudi Arabia's Asir region, 28 people with head and neck cancer were discovered **[71,124].** Ten of these individuals had a history of Khat chewing. They were all nonsmokers who had been chewing Khat for at least 25 years. Eight of the ten patients had oral cancer. The malignant lesion appeared at the same place where the Khat bolus was held in some cases. There was a strong link between Khat chewing and mouth cancer. Another study conducted in Yemen found that 30 of 36 individuals with squamous cell carcinoma (17 cases in the oral cavity, one in the oropharynx, 15 in the nasopharynx, and 3 in the larynx) had been frequent Khat chewers since infancy **[125].** The writers regarded Khat to be a significant contributor. According to one study, 50% of Khat users develop oral mucosal keratosis. Keratosis of the oral buccal mucosa is a pre-cancerous lesion that can progress to mouth cancer **[126].** Recently observed that 22.4% of Khat chewers exhibited oral keratotic white lesions at the site of Khat chewing, compared to 0.6% of non-chewers also Khat extract, cathinone, and Cathine caused a fast and synchronized cell death with all the morphological and biochemical characteristics of apoptotic cell death **[127].**

8.17 Khat and Genotoxicity and teratogenic

effects Oral Khat extract caused dominant fatal mutations in mice, chromosomal abnormalities in mouse sperm cells **[128],** and teratogenic consequences in rats Using the micronucleus test to evaluate genetic damage, Khat-chewing individuals residing in the Horn of Africa had an 8-fold increase in micronucleated buccal mucosa cells **[129]** Khat use did not result in an increase in micronucleated bladder mucosa cells. 81% of the micronuclei in heavy Khat chewers contained a centromere signal, showing that Khat is aneuploidogenic. It was discovered that the effects of Khat, tobacco, and alcohol were additive. These findings imply that Khat intake, particularly when combined with alcohol and tobacco, may be a risk factor for oral cancer **[129].**

8.18 Khat and diabetes mellitus

Over 20 years ago, a clinical investigation on diabetes patients was undertaken in Yemen **[130].** It was discovered that when the Khat extract was mixed with the glucose used in the glucose tolerance test, there was a significant reduction in blood glucose levels as compared to the non-Khat (control) arm of the trial. This effect was linked to the delayed glucose absorption from the stomach caused by the action of Khat tannins and inorganic ions, particularly magnesium, which has a significant inhibitory influence on gastrointestinal function. It appears that Khat-induced delayed stomach emptying may also have a role in lowering postprandial hyperglycemia in type 2 diabetic patients **[60].** Cathinone, the primary active component of Khat, stimulates dopamine release from central dopaminergic nerve terminals, enhancing the activity of dopaminergic pathways. These catecholamines would raise blood glucose levels by activating glycogenolysis in the skeletal muscles and liver; - an adrenoceptor-mediated reaction. Insulin release from

pancreatic -cells is likewise inhibited by -adrenoceptor stimulation, which raises blood glucose levels, as seen in **(Figure 7)** below **[131].**

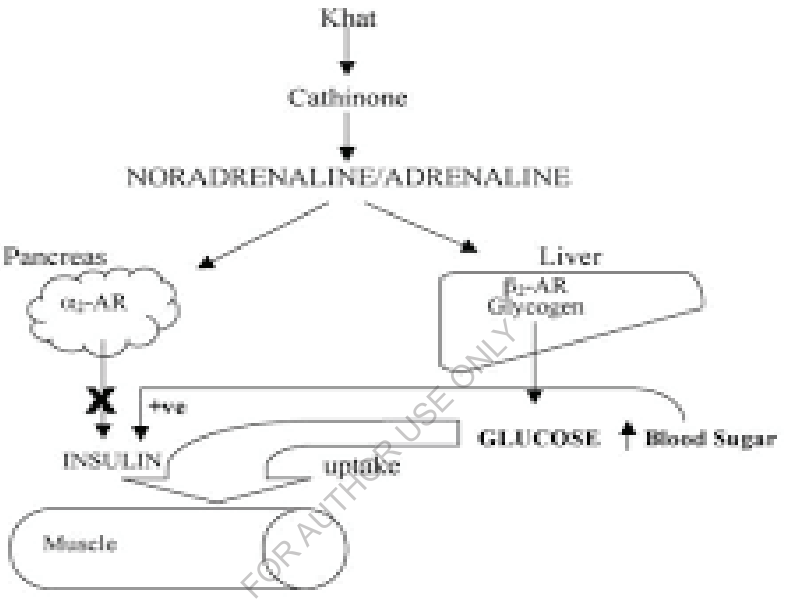

Figure 7. Diagram of the hypothetical effects of Khat and cathinone on blood sugar level adapted from [132].

Chewing DDT sprayed Khat alters glucose metabolism in addition to the cathinone effect on FBS levels. The specific method by which DDT produces hyperglycemia is unknown; nonetheless, DDT decreases pancreatic secretory activity by increasing the activity of gluconeogenic enzymes. Activating glycogen phosphorylase to promote hepatic glycogenolysis. DDT decreases calcium permeability and, as a result, insulin secretion **[133].** Debecho et al., **[131]** discovered that Khat chewing has hypoglycemic potential due to the presence of flavonoids, flavones, flavonols, saponins, and trace elements such as magnesium, chromium, manganese, zinc, iron, vanadium, copper, nickel, lead, and strontium.

Conclusion

Khat (Catha edulis) is a chewable herbal psychostimulant that contains cathinone, Cathine, and norephedrine, the first two of which are principally responsible for the observed psychoactive and sympathetic effects. Cathinone, a component of Khat, is rapidly and stereoselectively converted to Cathine and norephedrine in the digestive tract. Their effects are primarily mediated by the reduction of monoamine release and reuptake, and potentially also in part through inhibition of MAO. These methods of action work together, either additively or synergistically, to increase synaptic monoamine concentrations. They offer happiness and boost energy, alertness, and self-esteem as amphetamine analogs. These positive effects are felt during the initial hours of Khat consumption, while the negative consequences begin at the end of the positive effects and last for many hours. Aside from the acute unpleasant side effects, persistent Khat use results in psychological dependence and withdrawal, as well as severe cardiac, neurological, psychiatric, and gastrointestinal repercussions, among other issues. Cathinone was found to have a deleterious impact on reproductive health (e.g., increased aggressivity and changed sexual behavior), as well as embryotoxic and teratogenic effects (e.g., growth rate retardation). Khat-related cardiovascular toxicity was also discovered. Furthermore, Khat can have a detrimental impact on the renal and immunological systems. Tannin astringency in Khat leaves can induce esophagitis, gastritis, and oral mucosal keratosis, which can progress to oral cancer. Khat users have been known to have liver damage. Khat abuse is associated with a variety of adverse responses, both acute and chronic, and may change the activity of various concurrently used authorized medications. The dangers of Khat usage are one of the most serious global burdens. Because the use of Khat is an established cultural custom for many social circumstances in primary cultivation, East Africa, and the

Arabian Peninsula, even the government has failed to protect the public from its use. At the moment, millions of individuals may be chewing Khat around the world. As a result, aggressive measures must be done to raise awareness among the most common users, such as the poor, taxi and car drivers, school and college students, and the general public.Khat-using communities, as well as health professionals responsible for their care, should be more aware of the physiological and psychological impacts of Khat, as well as the morbidity and mortality concerns connected with its use. There is also a need for international and national data collection on other causes of death related to Khat farming, transit, and trading. Both of these dimensions must be understood.

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