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Khat: A Boon or Bane to Humanity

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Abstract

Khat, an evergreen shrub habitually ingested for its euphoric and stimulatory effects, is grown mainly in eastern Africa and south-western Arabia. Its consumption has, for a long time, been restricted to areas close to the sites of production but, because of recent improvement in efficiency and speed of transportation, khat consumption has spread to far flung lands such as North America, Canada, Australia, United Kingdom and parts of Europe. In regions where it is grown, daily life seems to centre on the crop bringing together farmers, traders, middle men, consumers and transporters. Thousands of dollars change hands daily in market centres where khat business is transacted making it the most lucrative business in these regions. The economies of these regions are therefore driven and sustained by khat trade. Khat contains a psychoactive compound belonging to the phenylpropylamine group of alkaloids called cathinone which has amphetamine-like effects. It causes mild euphoria, wakefulness and a host of other effects on regular consumers. Long distance truck drivers are known to constantly chew khat in order to stay awake. Some chewers, however, derive satisfaction in the ability of khat to promote work endurance while others do it for leisure. Consumers generally prefer young leaves and shoots because they contain a more potent active ingredient cathinone which decays within 48 h to a less potent form called cathine. Despite these positive attributes of khat, it poses serious health risks to consumers arising from the effects of its active ingredient, cathinone,

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on various organ systems. A number of studies have shown that cathinone has serious effects on cardiovascular, oral and digestive, and urogenital systems. Some of these effects are discussed in details in this chapter.

Key words : Khat, Cathinone, Production, Use

Introduction

Plant origin

Khat, (*Catha edulis* Forsk) is a flowering evergreen tree or shrub that belongs to the family *Celestreceae*. It grows wild or cultivated in certain regions of East Africa and southern Arabia. Locally, it is referred to as *miraa* while in Yemen it has several names: *qat, kat, kath, gat, chat, tschat*. The original source of khat seems obscure, as some Arabic sources indicate that it was used in Turkistan and Afghanistan as a medicinal plant at the beginning of the 11th century (Kennedy, 1987), while other reports show that it was prevalent in Ethiopia around the 15th century before its introduction to Yemen in the 16th century following Ethiopian conquest (Getahun & Krikorian, 1973). It then spread to south-west of Arabian Peninsula and around the horn of Africa and East Africa.

Historically, khat has been used for medicinal purposes (Kennedy *et al*., 1983) as well as an aphrodisiac (Margetts, 1967; Krikorian, 1984), although it has also been used as a recreational drug by inhabitants of areas where it is grown (Kennedy, 1987). Fresh leaves and shoots of this plant, which contain the naturally occurring alkaloid cathinone, provide euphoric and psychostimulant effects to the user (Luqman & Danowski, 1976; Baasher, 1980; Brenneisen *et al*., 1990; Kalix, 1992). Since only fresh leaves have the desired effects, the khat use is abundant in areas where it is grown. However, because of the possibilities of modern transportation, khat is now becoming reasonably accessible in many parts of Europe (Motarreb *et al*., 2002). A much larger section of the population in many parts of the world now use khat and it is estimated that, at present, between five and ten million people chew khat each day. Many of them have become compulsive khat users and develop psychic dependence on the drug. Furthermore, with the development of international air travel, khat use has spread to countries far away from the areas of cultivation, in particular through the movement of emigrants (Kalix, 1984). Most researchers have concentrated on medical complications associated with khat. However, other studies have implicated khat to contain medicinal value. The present review highlights its adverse effects in the body alongside its medicinal value.

Geographical distribution

Khat plant is widely distributed in Africa growing in habitats varying from evergreen sub-montane forests to deciduous woodlands. It is an indigenous plant in Ethiopia, Kenya, Somalia, Djibouti, Uganda, Tanzania, Zambia, South Africa and Yemen. In Ethiopia and some parts of East Africa, it is the basis of life style and plays a dominant role in celebrations, marriages, and political meetings (Brooke, 1960). Other areas where khat is known to be grown include Turkistan, Afghanistan and northern Hejaz (Brooke, 1960). In the United States it is now a controlled substance (Dalu, 2000; Al Motarreb *et al*., 2002). Cases of khat-induced psychoses have been reported in the United States and Great Britain (Giannini & Castellani, 1982; Gough & Cookson, 1984).

Fig 1. A farmer in Maua, Meru harvesting khat leaves

Khat grows wild in many mountainous regions of eastern Africa and Arabian Peninsula while being cultivated on commercial scale in Harar district of Ethiopia, Yemen and on the slopes of Mount Kenya. These areas range in altitude between 1680 and 2590 m above sea level (Getahun & Krikorian, 1973). Apart from coffee, khat is the largest cash crop in Yemen and Ethiopia (World Health Organization, 1980). The cultivation and use of khat has profound socio-economic consequences for the countries concerned and has made a considerable impact on the life of individuals.

It is profitable to the huge number of farmers involved in production and marketing of this crop. Taxes collected on khat sales are an important source of revenue to governments where it is grown. In Ethiopia, about 90% of khat produced is exported, thereby contributing significantly to the government revenue (Lemessa, 2001). In Kenya, khat sales fetch at least $ 150 million annually. It is the main source of livelihood to many peasant farmers in Meru District, Kenya. However, khat use may also be damaging to family budgets. Khat chewing is more prevalent in males (Al Motarreb *et al*., 2002), often resulting into family strains through negligence of family duties and dissipation of income. Many of them spend money on khat while neglecting their vital needs, which indicates psychic dependence on the drug (Ahmed & Salib, 1998). It is estimated that about two-thirds of individual income is spent on khat consumption both in Somalia and Yemen, where up to 80% of adult population consume khat. In these two countries, approximately $ 700 million and over $ 57 million respectively are spent on khat imports (Kassie *et al*., 2001).

Chemical constituents of khat: chemical formulae and structure

Studies in an attempt to identify the main ingredient of khat date back to two centuries ago (Flückiger & Gerock, 1887). Some progress was made around 1930 when Wolfes identified the presence of an alkaloid, 1S, 2S-(+)-norpseudoephedrine (NPE) also known as cathine in khat leaves. It was not until 1975 that the keto analogue of cathine was isolated from fresh leaves and shoots (United Nations Nacortic Laboratory, 1975). The name S-(-)-α-aminopropiophenone (cathinone) was suggested as the main psychoactive alkaloid of khat (Szendrei, 1980; Schorno *et al*., 1982; Kalix, 1988, 1990, 1992). Later it became evident that cathinone is a labile compound mainly present in young fresh leaves and reduces by three days after the leaves are removed from khat tree. This is in complete agreement with the fact that khat is usually consumed as fresh and not as dried material (Balint & Balint, 1994). The more rapid and intense activity of cathinone compared to cathine and other khat alkaloids is explained by its higher solubility, facilitating quicker access into the central nervous system (Zelger *et al*., 1980).

The plant only contains the (-)-enantiomer of cathinone but not the (+)-enantiomer (Kalix & Braenden, 1985). Thus, the naturally occurring S-(–)-cathinone has the same absolute configuration as S-(+)-amphetamine. Cathinone is mainly found in young leaves and shoots but during maturation, it is metabolised to cathine [(+)-norpseudoephedrine] and (-)-norephedrine [1R, 2S-(-)-norephedrine]. The contents of [(+)-norpseudoephedrine] and (-)-norephedrine in leaves are in the ratio of approximately 4:1 (Kalix & Braenden, 1985). Cathinone is unstable and undergoes decomposition following harvesting and during drying or extraction of the plant material (Nencini & Ahmed, 1980; World Health Organization, 1980; Kalix & Braenden, 1985; Brenneisen & Geisshüsler, 1985). Decomposition leads to a 'dimer' (3, 6-dimethyl-2, 5-diphenylpyrazine) and possibly other smaller fragments. Both the dimer and phenylpropanedione have been isolated from khat extracts (World Health Organization, 1980). Cathinone is presumably the main psychoactive component of khat, which explains why fresh leaves are preferred and also why they are wrapped in banana leaves (Fig 2).

Most of the pharmacological effects of khat chewing are attributed to cathinone content, which resembles amphetamine in both chemical

Fig 2. Khat leaves and shoots wrapped in banana leaves

structure and biological activity (Zelger *et al.*, 1980). The only difference being the substitution of oxygen double bond on the first carbon of the amphetamine side chain by two hydrogen (Fig 3).

It is, perhaps, worth mentioning that in addition to cathinone and the less psychoactive phenylpropanolamine diasterioisomer cathine and norephedrine, khat also contains cathedulins or khatamines (Baxter *et al.*, 1979). Previous studies revealed the presence of 62 cathedulins in the crude methanolic extracts of fresh khat leaves (Kite *et al.*, 2003). These are pure polyester alkaloids and have until now been isolated only from Kenyan and Ethiopian khat samples. They have been classified on the basis of their relative molecular mass. Medium (750–900 Da) and high

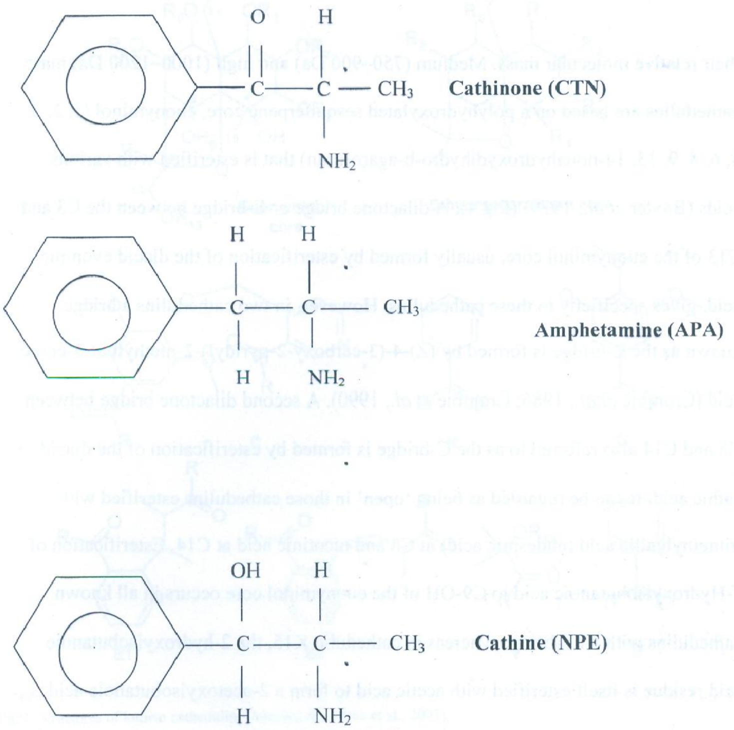

Fig 3. The chemical structure of Cathinone (CTN), Amphetamine (APA) and (+)-norpseudoephedrine (NPE)

(1000–1200 Da) mass cathedulins are based on a polyhydroxylated sesquiterpene core, euonyminol (1, 2, 3, 4, 6, 8, 9, 13, 14-nonahydroxydihydro-b-agarofuran) that is esterified with various acids (Baxter *et al.*, 1979) (Fig 4). A dilactone bridge or E-bridge between the C3 and C13 of the euonyminol core, usually formed by esterification of the diacid evoninic acid, gives specificity to these cathedulins. However, in two cathedulins a bridge known as the E-bridge is formed by (Z)-4-(3-carboxy-2-pyridyl)-2-methylbut-3-enoic acid (Crombie *et al.*, 1986; Crombie *et al.*, 1990). A second dilactone bridge between C8 and C14 also referred to as the C-bridge is formed by esterification of the diacid cathic acid. It can be regarded as being 'open' in those cathedulins esterified with trimethylgallic acid (eudesmic acid) at C8 and nicotinic acid at C14. Esterification of 2-Hydroxyisobutanoic acid to C9-OH of the euonyminol core occurs in all known cathedulins with an E-bridge whereas in cathedulin K15, the 2-hydroxyisobutanoic acid residue is itself esterified with acetic acid to form a 2-acetoxyisobutanoic acid residue (Kite *et al.*, 2003). Three cathedulins so far identified to have lower molecular masses include: cathedulins E2, E8 (Baxter *et al.*, 1979) and cathidine D (Cais *et al.*, 1975). They are esterified with nicotinic acid, benzoic acid and acetic acid and lack the C- and E-bridges.

Apart from cathedulins, new partially pharmacologically active constituents have been identified and their properties published since 1984. They include: (+)-merucathinone, (+)–merucathine and (-)-pseudomerucathinone which occur only in khat found in Meru District of Kenya (Geisshüsler & Brenneisen, 1987; Kalix, 1988). Nearly 20 other compounds have been isolated from khat such as tannins (7 to 14%), vitamin C (15 mg/100 mg) and trace amounts of thiamine, niacin, calcium, riboflavin, carotene and iron (Getahun & Krikorian, 1973), essential amino acids and oils, α and β-sitosterol, friedeline, triterpenoids (Szendrei, 1980).

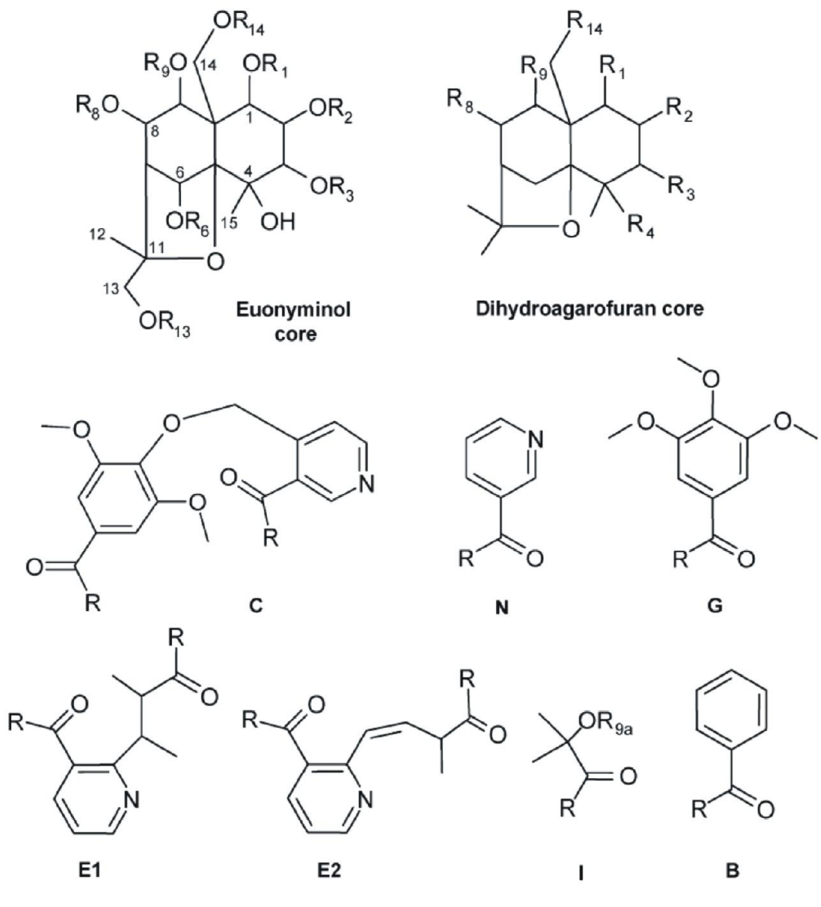

Fig 4. Structures of known cathedulins (adopted from Kite *et al.*, 2003)

According to preliminary investigations, these compounds appear to facilitate the sympathomimetic action of the other components of khat leaves (Balint & Balint, 1994).

The phenylalkylamine content of khat leaves varies within wide limits. Fresh leaves from different origins apparently contained on average 36 mg cathinone, 120 mg cathine, and 8 mg norephedrine per 100 gram of leaves (Geisshüsler & Brenneisen, 1987). A similar analysis from leaves confiscated at Frankfurt airport showed that they contained 114 mg cathinone, 83 mg cathine and 44 mg norephedrine in 100 gram of khat leaves (Toennes *et al*., 2003). Widler *et al*. (1994) found 102 mg cathinone, 86 mg cathine and 47 mg norephedrine in 100 gram of fresh leaves from Kenya confiscated at Geneva Airport. Even more outstanding, Al-Motarreb *et al*. (2002) reported much higher levels, 78–343 mg/100 gram, of cathinone in fresh leaves.

The chemical names, formulae and molecular weight of the phenylalkylamines of khat include: a) cathinone: S-(-)-cathinone; S-(-)-α-aminopropiophenone; (S)-2-amino-1-phenyl-1-propanone; chemical formula-$C_9H_{11}NO$; molecular weight- 149.2; It occurs naturally as S-(-)-cathinone, b) cathine: 1S,2S-(+)-norpseudoephedrine; 1S,2S-(+)-phenylpropanolamine; 2-amino-1-phenyl-1-propanol; chemical formula-$C_9H_{13}NO$; molecular weight- 151.2; occurs naturally as 1S,2S-(+)-norpseudoephedrine and c) norephedrine: 1R, 2S-(-)-norephedrine; 1R, 2S-(-)-phenylpropanolamine; 2-amino-1-phenyl-1-propanol; chemical formula and molecular weight are as for cathine. It occurs naturally as 1R, 2S-(-)-norephedrine.

Mechanism of Action

The mechanism of action of cathinone has been compared to that of other known psychostimulants such as amphetamine and cocaine. Fresh leaves of *Catha edulis*, native to Kenya, Somalia, Yemen, Ethiopia and many other parts of southern Arabia, contain amphetamine-like analogue cathinone, cathine and norephedrine among other alkaloids (Zelger *et al*., 1980). Cathinone has been reported as an indirectly-acting alkaloid having catecholamine-releasing properties at dopaminergic (Pehek *et al*., 1990), serotonergic (Kalix, 1984) as well as peripheral noradrenaline storage sites (Kalix, 1983). It operates through the same mechanism as amphetamine, which explains the observed central nervous system effects in the khat chewer (Kalix, 1992). Thus, for example, drug-conditioned animals do not distinguish between cathinone and amphetamine (Zelger *et al*., 1980). In a separate study, it was demonstrated that cathinone stimulates release of ^3H dopamine from nucleus accumbens, striatum and caudate nucleus of the rat brain and these regions are known to be involved in amphetamine-induced hypermotility; a behaviour also observed with cathinone (Kalix, 1984, 1988). In rats whose nucleus accumbens, striatum and caudate nucleus were radio-labelled with ^{3}H serotonin, cathinone induced its release but the potency was a third-fold less than that of amphetamine in causing the release (Kalix, 1984). The affinity of cathinone for serotonin receptors, however, was found to be four-fold that of amphetamine, suggesting that activation of serotonin pathways probably plays an important role in action of cathinone compared to amphetamine (Glennon & Liebowitz, 1982).

The first report that amphetamine-like compounds redistribute catecholamines from isolated vesicles preceded the demonstration of catecholamine uptake by vesicles.

The findings showed that amphetamines primarily elevate levels of catecholamines via a mechanism that is independent of classical means of transmitter release by secretory vesicle fusion (Sulzer *et al.*, 2005). Earlier studies showed that tyramine, β-phenethylamine, amphetamine, methylamphetamine and ephedrine each induced release of catecholamines, but not ATP, from suspended chromaffin vesicles and that tyramine and β-phenethylamine accumulated into chromaffin vesicles stoichometrically with catecholamine release (Schümann & Weigmann, 1961; Schümann & Phillippu, 1962).

Khat seems to have a similar effect as betel quid (a combination of nut or fruit from *Areca catechu*, leaf from the piper betel and paste of bark from Acacia catechu) in enhancing catecholamine release (Wang & Hwang, 1997; Chu, 2002; Yang *et al.*, 2004) and they both seem to be derivatives of amphetamine. These compounds have been examined for their ability to raise blood pressure, relieve nasal and bronchial congestion resulting from colds and hay fever (Sulzer *et al.*, 2005). Amphetamine derivatives including cathinone have been shown to potentiate the actions of noradrenaline on rat ventricular contraction via prevention of noradrenaline uptake by pre-synaptic nerve terminal and blockade of noradrenaline transporters (Cleary *et al.*, 2002; Cleary & Docherty, 2003). Tariq *et al.* (1989) and Rothman *et al.* (2003) demonstrated the involvement of β-adrenergic receptors in cathinone and amphetamine-induced brown adipose tissue thermogenesis. The studies showed that most of the pharmacological effects are mediated by release of biogenic amines through preferential binding to the norepinephrine transporter, but also partly through binding to dopamine and serotonin receptors. These findings show that action of cathinone and its metabolites involve adrenergic receptors. Earlier studies involving experimental animals showed that cathinone has both positive inotropic and chronotropic effects on the heart, pressor effect on the arteries leading to increased blood pressure and constriction of vas deferens (Knoll, 1979; Kalix & Braenden, 1985). In addition, it produces excitation and hyperactivity (W.H.O, 1980; Kalix & Braenden, 1985), increases metabolic rate and oxygen consumption and, causes hyperthermia as well as analgesia in individual animals via monoaminergic pathways mediating conception (Yanagita, 1979).

Antimicrobial and anticancer activity of khat

Previous studies showed that two compounds isolated from khat (22 β-hydroxytingenone and tingenone) were more potent than streptomycin on mycobacterium species, *Bacillus subtilis*, *Staphylococcus aureus* and *Streptococcus durans*. The compounds, however, were not as effective against *Escherichia coli* and *Candida albicans* (Elhag *et al*., 1999). *In vivo* and *in vitro* studies have demonstrated antimicrobial activity of khat on oral health. Hill and Gibson (1987) published their first report on the effects of khat on dental health among Yemeni khat 'addicts'. It was observed that the chewing side of the dental cavity had low incidence of dental caries while the non-chewing side had a significant number of periodontal pockets, suggesting that khat had a medicinal value on the chewing side of the dental formula. In later studies conducted in Kenya among 131 khat chewers and 199 non-khat chewers, it was shown that khat chewers had low incidence of lingual plague and gingivitis compared to non-khat chewers (Jorgensen & Kaimenyi, 1990). In other studies, prevalence and levels of bacteria associated with periodontal cavities among khat chewers and non-khat chewers as well as their levels both at the chewing and non-chewing sides were analyzed using DNA-DNA checkerboard hybridization. A significant population of *Tanerella forsythia*, a periodontal bacterium, was observed in the subgingival plaque of the khat non-chewing sides, while khat effect on supra-gingival plaque was not pronounced (Al-Hebshi *et al*., 2005a). *In vitro* studies showed inhibition of synthesis of glucans, essential compounds for the attachment of *Staphylococcus mutans,* by aqueous crude khat extracts. In another *in vitro* study, aqueous extracts of khat showed selective antimicrobial activity against *Lactobacillus acidophilus, Porphyromonas gingivalis* and *Tanerella forsythia* while a majority of other cariogenic bacteria were not sensitive to khat extracts. These extracts also potentiated the efficacy of both tetracycline and penicillin G against three resistant strains that were tested (Al-Hebshi *et al*., 2005b).

Previous studies on the effect of khat extracts on human leukemia cell lines and primary peripheral leukocytes showed induction of a synchronised cell death having all the morphological and biochemical characteristics of apoptosis. The cell death was dependent on *de novo* protein synthesis and more potent towards leukemia cell lines than towards peripheral blood leukocytes (Dimba *et al*., 2004). These cytotoxic effects of khat were also observed in earlier studies (Al-Ahdal *et al*., 1988; Al-Meshal *et al*., 1991; Al-Mamary *et al*., 2002; Dimba *et al*., 2003) and in lymphoid tissue, liver and kidney (Al-Meshal *et al*., 1991; Al-Mamary *et al*., 2002).

Rosenzweig and Smith (1966) in their study on effect of chronic khat use on periodontal health attributed the high prevalence of periodontal diseases to khat chewing among Yemenis. Subsequent studies claimed that stomatitis and secondary bacterial infection were common among long-term khat chewers (Halbach, 1972; Luqman & Danowski, 1976). They, however, reported low prevalence of dental caries, but attributed it to factors other than khat chewing.

Use of Khat for Alleviation of Various Ailments

The earliest use of khat as a medicinal plant appears in the New Testament. Its clinical use was reported in the 11th century by Abu Al-Rihan Bin Ahmed Al-Baironi in Pharmacy and Therapeutic Art (Al-Motarreb *et al*., 2002). Specifically, it was used for treatment of various ailments such as headaches, arthritis, fever, cold as well as relieving of symptoms of depression. Today, many khat consumers use it to ward off fatigue and alleviate depression. In Kenya, the use of khat for medicinal purposes has been reported among the Meru tribe for the treatment of erectile dysfunction, malaria, influenza, vomiting and headache. It has also been used for ages to improve performance particularly by students during examinations and enhance alertness by workers on night shifts and long-distance truck drivers. In some cases, it has also been used as a dietary requirement due to its significant amounts of vitamin C, proteins, carotene, calcium, thiamine, riboflavin, niacin and iron. Khat interacts with therapeutic drugs such as phenylpropanolamine to provide synergism in appetite suppression; best prescribed for weight loss. Khat is also used to alleviate pain via its activation of monoaminergic pathways and some opioid systems (Nencini *et al*., 1989). In Ethiopia, processed leaves and roots of khat are used for treatment of cough, influenza, gonorrhoea, asthma, lung congestion and other chest problems (Lemessa, 2001).

Mode of Usage

The mode of use is through chewing fresh leaves and shoots. An average khat chewer consumes between 100 and 200 g of leaves per day. It is also taken as tea and even smoked (Hodgkinson, 1962; Kennedy, 1987). Khat must be chewed while fresh and, usually, it is wrapped in fresh banana leaves immediately after picking to preserve its potency (Elmi, 1983).

Tolerance does not occur due to intrinsic properties together with physical limits on the amount of khat that can be consumed.

Adverse Effects of Khat

Reports concerning long-term khat use among addicts have tended to suggest that it causes various complications ranging from psychotic illness to reproductive disorders. The most affected systems include: nervous, cardiovascular, endocrine, urogenital, digestive and respiratory.

Nervous system effects

Heavy or long-term khat use has been shown to induce manic illness with grandiose delusions and paranoid or schizophreniform psychosis (Pantelis *et al*., 1989a; Dhadphale *et al*., 1981; Pantelis *et al*., 1989b; Gough & Cookson, 1984; McLaren, 1987; Yousef *et al*., 1995; Critchlow & Seifert, 1987). Symptoms rapidly disappear upon khat use withdrawal (Pantelis *et al*., 1989b; Nielen *et al*., 2004; Giannini & Castellani, 1982). In fact, khat withdrawal consistently appears to be an effective treatment of khat psychosis and anti-psychotics are usually not needed for full remission (Pantelis *et al*., 1989a; Jager & Sireling, 1994; Nielin *et al*., 2004). Khat psychosis, however, is uncommon, probably due to the physical limits of the amount of khat leaves that can be chewed (Halbach, 1972; Kalix, 1990; Kalix, 1987). Khat psychosis may be accompanied by depressive symptoms and sometimes by violent reactions (Pantelis *et al*., 1989b). It has been argued that khat chewing might exacerbate symptoms in patients with pre-existing psychiatric disorder (Hassan *et al*., 2002). Dhadphale & Omolo (1988) studied psychiatric morbidity among khat users and found that in moderate users there was no excess morbidity but chewing more than two bundles per day was associated with increased psychiatric morbidity.

Other adverse effects of khat consumption on mental health include impairment of perceptual-visual memory and decision-speed cognitive functions (Khattab & Amer, 1995). Toennes and Kauert (2004) investigated plasma cathinone and cathine concentrations in 19 cases suspected of driving under the influence of drugs. These alkaloids were observed in blood and urine, but there was no correlation between alkaloid concentrations and impaired driving. The authors, however, concluded that chronic khat use might lead to a marked deterioration of psychophysical functions (Toennes & Kauert, 2004). One case history of severe leukoencephalopathy associated with khat misuse has been reported (Morrish *et al*., 1999).

Cardiovascular effects

Previous studies showed that khat chewing is a risk factor for the development of acute myocardial infarction with heavy chewers having a

39-fold increased risk (Motarreb *et al.*, 2005). Two cases of pregnant patients with chest pain, sinus tachycardia and hypertension have been described (Kuczkowski, 2004; Kuczkowski, 2005). Khat chewing has also been reported to be a significant risk factor for acute cerebral infarction (Mujlli *et al.*, 2005). Studies in humans have shown that khat chewing induces mild and transient rise in blood pressure and heart rate (Nencini *et al.*, 1986; Kalix *et al.*, 1991; Kalix, 1992; Hassan *et al.*, 2000; Al Motarreb *et al.*, 2002; Hassan *et al.*, 2005). Furthermore, khat chewing has been implicated in increased incidence of hemorrhoids found in chronic khat chewers (62%) as compared to non-khat users (0.5%) (Hadrani, 2000).

Oral and digestive system effects

Long-term use of khat has also been shown to have various effects on oral mucosa. Oral mucosa keratosis (Hill & Gibson, 1987; Ali *et al.*, 2004) and genotoxic effects on buccal epithelial cells (Kassie *et al.*, 2001) have been observed in long-term khat chewers, suggesting that khat may play a role in oral malignancies. A high frequency of periodontal disease, gastritis (Kennedy *et al.*, 1983) as well as chronic recurrent subluxation and dislocation of the tempro-mandibular joint (Kummoona, 2001) has been reported. Epidemiological studies, however, have yielded conflicting results. Several studies suggested that there were no such detrimental effects of khat chewing on the oral mucosa and instead, pointed out the beneficial effects on the periodontium (Hill & Gibson, 1987; Jorgensen & Kaimenyi, 1990). Another study could not show a significant role of khat chewing and suggested bad oral hygiene as a major factor in periodontal disease (Mengel *et al.*, 1996). No significant association could be found between khat chewing and oral leukoplakia in a Kenyan study (Macigo *et al.*, 1995). In a recent study, the authors concluded that khat chewing does not seem to increase the colonization of gingival plaque and that instead, it might induce a microbial profile compatible with gingival health (Al Hebshi & Skaug, 2005).

Recently, oral keratotic lesions at the site of chewing (Ali *et al.*, 2004) and plasma cell gingivitis (allergic reaction to khat) (Marker & Krogdahl, 2002) have been reported.

The tannins present in khat leaves are held responsible for the gastritis that has been associated with khat chewing (Halbach, 1972; Pantelis *et al.*, 1989b).

Effects on reproductive system

The reproductive dysfunction in both male and female consumers is frequently encountered. In studies on male wistar rats, administration by injection of three doses (5, 10 and 30 mg/kg body weight) of pure cathinone intra-peritoneally was said to cause a significant decrease in sperm count and motility, and an increase in the number of abnormal sperm cells were found (Islam *et al*., 1990). Histopathological examination of the testes revealed degeneration of interstitial tissue, cellular infiltration and atrophy of Sertoli and Leydig cells in cathinone-treated animals. Cathinone also produced a significant decrease in plasma testosterone levels of the rats. Although both enantiomers of cathinone produced deleterious effects on male reproductive system, (–)-cathinone was found to be more toxic (Islam *et al*., 1990). Cathinone also increases the frequency of abnormal sperm in mice treated with different doses 30 and 36 h before sacrificing. It was also observed that an aqueous solution of khat administered orally at doses of 5, 20 or 40 mg/kg body weight respectively to three different groups of male mice for six weeks produced a dose-dependent reduction in fertility with total sterility at a dose of 40 mg/kg body weight (Qureshi *et al*., 1988). The mutagenicity of a methanolic extract of khat on germ cells in male albino mice that were allowed to mate with two different groups of female mice was evaluated by Tariq *et al*. (1990) using a Dominant Lethal Test. It was found that khat extract produced a dose-dependent reduction in the rate of fertility as well as post-implantation loss during the first week following treatment. Other studies on chronic use of khat showed spermatorrhoea in humans (Halbach, 1979; Pantelis *et al*., 1989b). Studies on the effect of khat on hormonal profiles in male rabbits showed that khat lowers plasma LH and testosterone but increases cortisol levels in a dose-dependent manner (Nyongesa *et al*., 2008). The effect of khat on sex steroids and gonadotropin levels indicate both a peripheral and central dysfunction of the hypothalamo-pituitary-gonadal axis. Studies in humans have demonstrated that long-term use of khat decreases sperm count, sperm volume and sperm motility (El Shoura *et al*., 1995; Hakim, 2002). Deformed spermatozoa (65% of total) have been found in Yemenite daily khat users with different patterns including head and flagella malformations in complete spermatozoa, aflagellate heads, headless flagella, and multiple heads and flagella (El Shoura *et al*., 1995). Khat use during pregnancy may have detrimental effects on utero-placental blood flow and as a consequence, on foetal growth and development (Mwenda *et al*., 2003). The use is contraindicated in pregnancy since it causes teratogenic effects and impairment of fetal growth, often resulting into abortions and/or stillbirths (Jansson *et al*., 1988).

National and International Markets

It is estimated that five to ten million people worldwide engage in khat chewing consuming approximately five million portions per day

(Brenneisen *et al.,* 1990; Balint *et al.,* 1991). A large proportion of these chewers are confined to the eastern Africa and south-western Arabia. The Governments in these regions have very little control over the markets leaving its sale and distribution in the hands of a loose outfit comprising of farmers, middlemen or agents, traders, retailers and exporters. Farmers own the fields on which the khat shrubs grow but, due to lack of understanding of the market dynamics, they often leave the middlemen or agents to intercede between them and the market traders. Usually, these are people the farmers have faith and trust in although a number of times they are also exploited by the same people. The middlemen often collect the produce from the farms and ferry them to the markets where they are sold to large scale traders and retailers. A lot of times, the produce is carried away without payments; farmers trusting that they will receive their dues after sales. Immediately after sales, the middlemen deduct their commission and remit the remaining to the farmer. In khat, trade time is of essence because it perishes quickly and the price is determined by the freshness of the produce.

In eastern Africa, the main khat markets are found in Kenya and Ethiopia near the growing zones (Anderson *et al.,* 2007). In Kenya, khat is mainly grown in Nyambene Hills of Meru District, Eastern Province, and the main outlet is Maua Town. It is also grown in small quantities for local consumption in other areas such as Chyulu Hills, Timau, Embu and Taita Hills. Khat from Maua Town is either consumed by the local communities around the growing regions and beyond or exported. Khat for export is often rushed from Maua Town in trucks to Nairobi where the cargo is immediately air-freighted to far flung destinations as Somalia and Europe. Khat trade sustains tens of thousands of people living in the Eastern Province of Kenya where it is estimated to generate approximately $ 150 million annually. Recently, a co-operative society known as *Nyamita* was formed to champion the cause of stakeholders in khat business, mainly in Meru District but, perhaps, aiming to spread its wings to other parts of the country. In Ethiopia where the market is a little more advanced, Mercato market in Addis Ababa provides the largest and most important site of khat trading anywhere in the world where wholesalers, traders, retailers and exporters make it their business to know what is available and their market value (Anderson *et al.,* 2007). In the eastern part of Ethiopia, Awedaye is the most important outlet. In 2004, it was estimated that this market was visited by five thousand farmers, agents, traders and exporters daily making it the second most important khat market after Mercato. Equally important is Harar in the Harerge region where khat growing has become the most dominant venture involving millions of farmers, traders and other service providers

(Gebissa, 1997, 2008). Other markets such as Tula and Teffera operate at night providing a special opportunity to the farmers to sell their produce within the shortest time possible after harvesting, hence, minimizing loses. From Ethiopia, khat is mainly exported to Djibouti although small quantities find their way into Somalia. In Yemen, khat was until 1970s transported using camels and donkeys but today, it has given rise to a rather elaborate national transportation infrastructure (Anderson *et al.,* 2007).

The export market is equally less organized as the local markets. In Kenya, for example, the trade depends on individual contacts between the exporting and importing countries. Thus, an exporter from Kenya transports the cargo directly to an importer in Somalia or even as far as Europe. From Ethiopia, khat is mainly exported to Djibouti although a small proportion also finds its way into Somaliland. Unlike Kenya, exporters and importers from Ethiopia and Djibouti respectively have formed an association with the encouragement from either of the state apparatus to facilitate easy marketing of the produce. Also, individual exporters without state backing have formed their own body to help them export their produce (Anderson *et al.,* 2007). Transportation to importing destinations is usually by air because it takes a shorter time and khat arrives when fresh, hence, avoids wastage. In some cases, khat may be transported through the post office especially to long distant lands. This latter route is the most frequently used when transporting freeze-dried khat. It is the preferred route for exporting khat to North America, Europe as well as Australia.

The price of the commodity varies according to the time of the year; higher during the dry periods and lower in the rainy periods. Obviously this is purely a demand and supply phenomenon where during rainy seasons, fresh leaves are plentiful thereby lowering the price and vice-versa in the dry seasons.

Agro-techniques for Commercial Production

Khat traditionally flourishes in arid and semi-arid environments where temperatures range between 5 and 35 °C with free draining soil and full sunshine (New Agriculturalist, 2007). It does not tolerate frost or watering because this may lead to drying and subsequent falling of leaves. In some instances, for example in Kenya, khat is grown with other cash crops such as coffee to maximize land use.

There are two ways in which new khat plants can be grown; either from cut sprouting shoots (most preferred method), or from seeds. Propagation of newly sprouted shoots is the most commonly practiced method in large khat plantations where the plant is grown for its commercial value rather than home consumption. According to a khat farmer in Meru District of Kenya, Mr. Marete, this method is preferred because the plant establishes quickly and grows faster. The shoot to be propagated should be isolated from among those sprouting from a pre-existing root and, in addition, have tiny roots that are beginning to penetrate the ground. This makes it easier for the plant to establish itself when propagated. The identified shoot with its tiny roots intact is then scooped out together with the mound of soil into which it was growing and transferred to an already prepared hole measuring 0.6m (diameter) by 0.9 m (depth). The newly propagated plant is then watered daily but in a controlled manner taking care not to give excess water for a period of about two months. Over-watering causes moulds and stem rot killing the plant very quickly (New Agriculturalist, 2007). After two months, the new plant can stand on its own and, within no time, becomes leafy and sometimes bends under its own weight. At this point support should be provided to the new plant. Khat can also be grown from seeds but this is not popular with commercial farmers because the growth rate is very slow and requires a little more care than the cut shoots. Where this is the method of choice, the seeds are obtained from mature khat plants just before dispersion still encased in their seed vessels, dried and freed from their pods. The seeds are then broadcasted on a well prepared soil in the nursery and watered regularly. The seeds germinate within a period of about three months. They are ready for transplantation in another period of three months after germination.

Scope for Commercial Production

Khat cultivation has largely been small scale restricted to regions where it is consumed. This restricted growth and consumption has mainly been occasioned by the transient nature of the active stimulant found in khat. Fresh khat leaves and shoots contain a more potent form of active compound, cathinone, which deteriorates rapidly within a period of 48 h to a less potent one or cathine. Chewers, therefore, prefer fresh khat leaves to the old stock. More recently, however, there has been rapid expansion of speedy and efficient transport system all over the world leading to a marked reduction in delivery time and considerable improvement on the quality of khat delivered over long distances. Consequently, khat distribution and consumption has expanded to countries far from the source including Canada, North America, Europe and Australia.

This expanded consumption portfolio has necessitated an accompanying shift in production pattern to meet the increasing demand. Khat production has therefore expanded from the traditional consumer-based regions to new areas to accommodate this surge in consumption. In eastern Ethiopia, for example, khat has become the chief and most profitable cash crop with the acreage under crop doubling from 6.6% in 1975 to 13% in 1983. Similarly, in Kenya khat cultivation has now expanded outside the known growing areas of Meru near Mt. Kenya to new areas such as Embu and Nyeri (New Agriculturalist, 2007). It is envisaged that in a few years to come, this expansion of the consumption base might result into a phenomenal increase in commercialization of khat production in the growing regions in order to meet the increased demand.

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