

## REVIEW

# Khat (*Catha edulis*)—an updated review

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### Abstract

*The habit of chewing fresh leaves and twigs of khat (Catha edulis) for their stimulating amphetamine-like effects is highly prevalent in East Africa and southwest on the Arabic peninsula. There is an extensive literature on khat providing information about its history, botany, production, geographical distribution, chemistry and pharmacology, and exploring the social, economic, medical, psychological and oral aspects related to its use. Some of this literature dates as early as the 11th century; however, most of it appeared after the first scientific description of khat by Peter Forskal in 1775. This review provides a panorama of khat and the various aspects of its use. A non-technical description of the plant chemistry and pharmacology is included. The medical, psychological and oral aspects are emphasized, and the current knowledge about the microbiological effects of khat is also presented.*

### Khat at a glance—an introduction

Khat is the name generally used for *Catha edulis*, a dicotyledonous evergreen shrub of the family Celastraceae (Kennedy, 1987a) [also spelled qat, kat, cat or ghat; The Amharas call it 'tchat' and the Gallas 'Jimma'; in Kenya khat is known as 'miraa'; Qat is probably the most correct transliteration of the Arabic word [قَات]. The first scientific description of khat as *Catha edulis* was in *Flora-Aegyptiaco-Arabia* by the Swedish botanist Peter Forskal, who died in Arabia in 1768 (Peters, 1952). Most published work refers to khat as the only representative of the genus *Catha* (Paris & Moyse, 1958; Nordal, 1980); however, Revri (1983) showed that the genus contains another member, *Catha spinosa*, which is found only in Yemen where it exists in the wild state and at lower elevations. The khat tree has a slender bole and white bark (Getahun & Krikorian, 1973). In Yemen, the trees range from 1 to 10 m in height, while in Ethiopian highlands they can reach heights of 18 m; however, they are pruned annually to keep their height to about 5 m (Peters, 1952). Khat cultivars show considerable variations in their general appearance, due probably to cultivation of the plant over centuries under different ecological conditions (Nordal, 1980). A detailed botanical description of the macroscopic and microscopic features of khat leaves, flowers, seeds and fruits is given by Paris & Moyse (1958), Nordal (1980) and Revri (1983).

The major cultivation and production areas of khat are in Ethiopia, particularly in Harar district, and in Yemen (Brooke, 1960). It is also cultivated, to a lesser extent, on the slopes of Mount Kenya and grows wild in many mountainous parts

of eastern Africa including South Africa, Uganda, Tanzania, Rwanda and Zimbabwe (Peters, 1952; Brooke, 1960) (some of these countries are referred to by their older names in the original reports). There are sporadic reports of khat-growing in Turkistan, Afghanistan and northern Hejaz (Brooke, 1960). Khat grows at an altitude of 1670–2590 metres (5500–8500 feet) adapting to a range of soil and climatic conditions. It is cultivated on terraces built on hillsides where the trees grow in rows interspersed occasionally with other crops (Peters, 1952; Brooke, 1960; Getahun and Krikorian, 1973). The khat tree is rarely affected by diseases and can live up to 75–100 years if taken care of properly (Peters, 1952; Brooke, 1960; Kennedy, 1987a).

Khat is a high-cash income crop. It is profitable to the huge number of people involved in its production and marketing including farmers, distributors and merchants. Taxes upon it are an important source of revenue to the governments as well (Getahun & Krikorian, 1973; Kennedy, 1987b; Lemessa, 2001). In Ethiopia, 85–90% of the khat produced is exported (Lemessa, 2001) and thus makes a very significant contribution to the country's foreign exchange earnings. In 1999/2000, khat worth \$55 million was exported to different countries, ranking second in export revenues (Lemessa, 2001). In Yemen, estimates in the early 1980s, i.e. before oil production commenced, attributed 30% of the gross domestic product (GDP) to khat (Kennedy, 1987b). However, as Yemeni khat is not exported, its macroeconomic significance is not pronounced as the case is in Ethiopia. At the family level, khat may be damaging to budgets, especially among the poor.

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In the late 1980s Kennedy (1987b) estimated that 10% of the Yemeni population suffered economic hardship due to khat use; the figure must have increased by now due to economic deterioration since the early 1990s.

There is much speculation about the early history of khat. A theory by Cotterville-Girandet (cited in Kennedy, 1987c) suggests that khat was known to the ancient Egyptians, while more factual Arabic sources indicate that it was known as a medicinal plant as early as the beginning of the 11th century in Turkistan and Afghanistan (Kennedy, 1987c). The most debated historical issue about khat is whether it originated in Yemen and then spread to Ethiopia, or vice versa. The earliest mention of khat in this region is in the chronicle of the Ethiopian king Amda Seyon (1314–1344). Accordingly, most writers believe khat to be of Ethiopian origin (Getahun & Krikorian, 1973). In line with that, Sir Richard Burton, in his *First Footsteps in East Africa*, first published in 1856, describes how khat was introduced to Yemen from Abyssinia (Ethiopia) in the 15th century (Burton, 1966). However, there is some evidence that khat was introduced to Yemen as early as the 13th century (Kennedy, 1987c). The opposite view, that khat is of Yemeni origin, is supported by some Ethiopian legends that were recounted by Gethahun & Krikorian (1973). Based on cytogenetic (hereditary) botanical analysis, Revri (1983) also supports this view. For a comprehensive and attractive account on the history of khat, refer to Kennedy's *The flower of paradise: the institutionalized use of the drug qat in North Yemen* (Kennedy, 1987c).

### Chemistry

During the period from 1887 to 1978, there was a long series of chemical studies focusing on the identification of khat's active principle and the characterization of its alkaloid content. Early attempts attributed the stimulating effects of khat to cathine, a phenylalkylamine-type constituent characterized as (+)-norpseudoephedrine. However, later work provided initial evidence for the presence of another more active phenylalkylamine in the fresh leaves of the plant, possibly a labile precursor of cathine. In 1975, the long-sought phenylalkylamine was finally isolated, characterized as (–)- $\alpha$ -aminopropiophenone and given the name (–)-cathinone (Anonymous, 1975). Later studies showed that cathinone is present at a high concentration in the young leaves, while being converted rapidly in the adult leaves into cathine and, to a lesser extent, into norephedrine: another phenylalkylamine described in khat. Both cathine and cathinone are related structurally to amphetamine (Zelger et al., 1980) (see Fig. 1). The reviews by Szendrei (1980), Kalix & Braenden (1985) and Kennedy (1987a) provide a comprehensive description of the progress in the understanding of khat chemistry during that period.

In parallel, studies also resulted in the characterization of a complex group of alkaloids called cathedulins (Anonymous, 1977a; Baxter et al., 1979). Recently, analysis using liquid chromatography/mass spectrometry revealed the presence of 62 cathedulin alkaloids in the crude methanolic extracts of fresh khat (Kite et al., 2003), supporting earlier beliefs that *Catha edulis* may well be one of the plant species showing the most complicated pattern of alkaloid composition (Anonymous, 1977b). Many other chemical constituents were identified in khat. Tannins were found to be present in considerable quantities that vary among different cultivars (7–14%) (Halbach, 1972). Another constituent also found to be present in significant amounts is vitamin C. Mustard (1952) measured it to be 136 mg/100 g of the leaves and branch tips, and 325 mg/100 g of the leaves only. Other ingredients described in khat include  $\alpha$ - and  $\beta$ -sitosterol and friedeline (Anonymous, 1977b), triterpenoids (Crombie, 1980), essential oils and amino acids (Szendrei, 1980), proteins, carotene, calcium, thiamine, riboflavin, niacin and iron (Getahun & Krikorian, 1973).

### Pharmacology

The pharmacologically active constituents of khat are (–)-cathinone and, to a lesser extent, (+)-norpseudoephedrine. Maximal plasma concentrations of (–)-cathinone, after a single oral dose of khat, are attained in about 2 hours; the terminal elimination half-life is about 4 hours (Widler et al., 1994). The major metabolite of (–)-cathinone is (–)-norephedrine, but small quantities of (–)-norpseudoephedrine also form (Brenneisen et al., 1986); less than 7% of the ingested cathinone appears in unchanged form in the urine (Toennes & Kauert, 2002). In contrast, (+)-norpseudoephedrine is absorbed slowly, has a half-life of 3 hours, and is excreted unchanged (Kalix & Braenden, 1985).

Pharmacology of both khat amines, i.e. (–)-cathinone and (+)-norpseudoephedrine, has been subject to extensive investigation using animals such as rats, monkeys and guinea pigs. A comprehensive review of results from these studies with emphasis on technical aspects is given by Kalix & Braenden (1985). A less technical summary of the pharmacology of khat was prepared by a WHO advisory group (Anonymous, 1980). The pharmacological actions of cathinone are very like those of amphetamine, and thus cathinone is considered a natural amphetamine (Kalix, 1992, 1996).

Most of the somatic effects produced by khat amines are sympathomimetic: positive inotropic and chronotropic cardiac effects, arterial constriction, pressor effects, constriction of vas deferens, mydriasis and increased lipolysis, metabolic rate and oxygen consumption (Anonymous, 1980; Kalix & Braenden, 1985). The sympathomimetic properties are due to peripheral

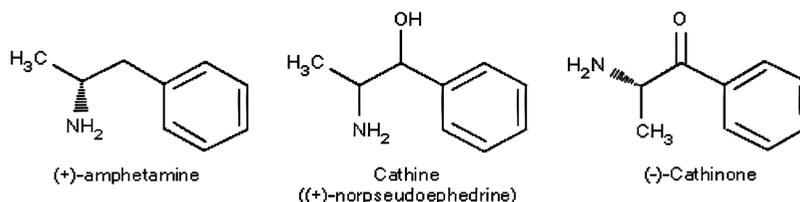


Figure 1. Chemical structures of amphetamine, cathine and cathinone.

noradrenalin-releasing properties of khat amines, which potentiate noradrenogenic transmission; both amines are approximately equipotent in this regard (Kalix, 1983). Recently cathinone was also found to inhibit neural uptake of noradrenalin (Cleary & Docherty, 2003). Other somatic effects produced by cathinone are hyperthermia (Kalix, 1980) and analgesia (Nencini & Ahmed, 1982). The latter was found to be a prolonged effect and involves the activation of monoaminergic pathways and some opioid mechanisms (Nencini et al., 1984a). Hyperthermia may be explained partially by the thyroid-stimulating effect of khat amines (Islam et al., 1990a).

Behavioural effects observed in experimental animals include excitation, increased locomotor activity, stereotyped behaviour, reinforcement and anorexia (Kalix & Braenden, 1985). The anorexic effect is characterized by development of tolerance (Zelger & Carlini, 1980). (+)-Norpseudoephedrine is considerably less potent than (–)-cathinone with respect to these behavioural effects, which are attributed mainly to increased activity of dopaminergic pathways in the central nervous system (CNS) (Kalix, 1983). At cellular levels, mechanisms involved are decreased dopamine uptake by nerve terminals (Wagner et al., 1982), increased dopamine efflux (Kalix, 1981) and inhibition of monoaminooxidase (Nencini et al., 1984b). The involvement of serotonergic pathways has also been suggested (Kalix, 1984a).

The reinforcing properties of (–)-cathinone were studied in animals using different experimental paradigms including self-administration, drug discrimination and conditioned placed preference (CPP). In cocaine-trained monkeys, (–)-cathinone was found to maintain self-administration at rates higher than those generated by cocaine and (+)-amphetamine (Anonymous, 1980). Monkeys were also shown to initiate continuous self-administration of (–)-cathinone with a pattern similar to that of cocaine (Anonymous, 1980). Gosnell et al. (1996) demonstrated cathinone self-administration in rats. In the discriminative paradigm, (–)-cathinone was shown to generalize to racemic cathinone and was employed successfully to train rats to make discriminative responses in a two-lever food-motivated operant task, being more potent than the (+)-isomer and cathine with a median effective dose (ED<sub>50</sub>) of 0.19–0.22 mg/kg (Glennon et al., 1984; Schechter, 1986a). The discriminative properties of (–)-cathinone are mediated probably by activation of dopaminergic neural pathways, as pretreatment with 0.2 mg/kg haloperidol, a dopamine receptor blocking agent, was found to attenuate the (–)-cathinone discrimination (Schechter, 1986b). Schechter (1986c) showed that chronic administration of (–)-cathinone resulted in tolerance to its discriminative properties; the observed tolerance required 15 days for recovery. More recently, (–)-cathinone was reported to produce CPP in rats, especially in those with previous discrimination training (Schechter, 1991). Calcagnetti et al. (1993) showed that CPP could be blocked by a dopamine release inhibitor. Unlike the discriminative properties, CPP was shown not to be affected by chronic administration of cathinone (Schechter & McBurney, 1991).

In humans, the main pharmacological actions of khat are euphoria, hyperactivity, logorrhoea, exaggerated cardiovascular response to physical effort, increased respiratory rate, mydriasis, hyperthermia, anorexia, mouth dryness, sperma-

torrhoea, impotence and insomnia (Kalix & Braenden, 1985). The increase in respiratory rate is in response to hyperthermia, while the dry mouth is due to the sympathomimetic and astringent properties of khat (Kalix & Braenden, 1985).

Although there is much similarity between the effects induced by khat and amphetamine they differ in terms of tolerance, dependence and toxicity. While tolerance to amphetamine can develop rapidly and to a high level, no tolerance to khat has been observed as yet, due probably to the physical limits on the amount of khat that can be chewed (Halbach, 1972; Kalix & Braenden, 1985). Excess intake of amphetamine results in a characteristic toxic psychosis, which is less likely to occur in the excess intake of khat (Halbach, 1972). Dependence produced by khat as well as amphetamine is referred to simply as psychic (Halbach, 1972); however, Kennedy (1987d) argues correctly that the issue in the case of khat is more complex, involving the cultural, social and economic aspects of khat use. Khat does not cause any physical symptoms on withdrawal, but a rebound phenomenon consisting of mild depression, sedation or hypotension can be observed (Halbach, 1972). Heavy chewers may also experience paranoid nightmares, locally called 'razim', the first one or two nights following abstinence (Kennedy, 1987d).

### Khat-chewing habit

#### *History of the habit*

According to a famous legend in Ethiopia, the first human to use khat was a Yemeni herder who noticed the effects of the leaves of the plant on his goats and tried them himself (Getahun & Krikorian, 1973). The legend refers to the mastication of the leaves, which is currently the exclusive method of khat use. However, some early accounts indicate that khat was also used as tea in close connection with the use of coffee (Kennedy, 1987c). In fact, the dry leaves of khat are some times called Abyssinian or Arabian tea (Anonymous, 1949). Following its introduction, the use of khat in Yemen spread slowly until the 16th century, when it became common among esoteric religious groups and the upper classes. Thereafter, its use spread rapidly so that by the beginning of the 19th century it became very extensive and almost universal in some parts of Yemen. By 1900 AD, its trade was well established (Kennedy, 1987c).

#### *Habit description*

Khat is usually chewed at special social gatherings, but is also used frequently during work by labourers, craftsmen, farmers and students to keep alert and reduce physical fatigue (Getahun & Krikorian, 1973; Kennedy, 1987e). The habit has a deep-rooted social and cultural tradition, particularly in Yemen (Kalix & Braenden, 1985).

The social khat session, in Yemen called *majlis al-qat*, is held in the afternoon in a special warm reception room for khat-chewing. Guests sit comfortably and chew the fresh leaves one by one. The juice is swallowed while the residue is retained as a quid against the cheek on one side of the mouth; a quantity of 100–200 g is usually consumed (Kalix, 1996). Initially, the session is lively and as the alerting effects of khat start to work, the session becomes more serious and the

chewers' talk focuses on one subject at a time. The topic may be a current world event, a historical or religious issue, a political situation or a local dispute. After 2–3 hours the session becomes quiet as most of the chewers prefer to be left alone, falling into intense concentration and mental focus. After about 4 hours, people start to depart the session. A detailed description of a typical khat session is provided elsewhere (Luqman & Danowski, 1976; Kalix & Braenden, 1985; Kennedy, 1987e).

Khat-chewing is predominantly a male habit, but women also practice it. The khat session described above is typical for male khat chewers, for whom the chewing is the main event. The female khat sessions, however, are held less frequently and the social gathering itself, in some areas of Yemen called *tafruta*, is more important than chewing; much smaller quantities of khat are chewed and for shorter periods (Kennedy, 1987e). The habit is limited mainly to old and married women, as it is not socially accepted for young unmarried women to chew khat (Al-Motarreb et al., 2002a).

#### *Khat-chewing experience*

The subjective experience associated with khat-chewing is complex. The effects experienced by a chewer can be divided into desirable and non-desirable. The desirable effects are experienced during the first hours of the chewing session, while the non-desirable experiences start near its end and continue for some hours, i.e. negative aftermaths. However, there are also positive aftermaths (Kennedy, 1987f).

The euphoric state associated with relief from fatigue, energy, feelings of elation and enhanced imagination, and the capability to associate ideas, improved communication ability and high confidence is the primary desirable experience (Kalix & Braenden, 1985). This state, referred to in Yemen as *kayf*, is experienced during the first 1–2 hours of the chewing session. The components of *kayf* are contentment, ability to concentrate, flow of ideas, alertness, confidence and friendliness. A later stage in the khat session is an introvert one, in which the chewer detaches somewhat from the surroundings and engages in deep thinking. This phase, sometimes called *sulimania*, is also pleasurable to many and distraction is irritating, although the direction of thought may be pessimistic. However, the state of *kayf* is not always achieved, because of variables such as the quantity and quality of the khat chewed. On some occasions, especially upon excessive use of cheap strong varieties of khat, the chewer experiences a state of confusion or hallucinations instead (Kennedy, 1987f).

Towards the end of the session, a chewer usually starts to experience a depressive stage that continues for 1 or 2 hours. This is the most common negative aftermath experienced by chewers. In addition, some also experience a mild paranoid reaction or even tension and nervousness. Insomnia is another very common side effect, although chronic heavy chewers claim not to be affected. While some chewers have a negative sexual experience (e.g. decreased desire and impotence), others report a positive one with increased desire, prolonged intercourse and a more pleasurable ejaculation. A chewer would not always experience a negative aftermath of khat-chewing; there are also positive aftermaths including an increased desire to work and a feeling of being closer to

Allah. Frequently, a person would experience a mix or alternating periods of negative and positive effects (Kennedy, 1987f).

#### *Prevalence and distribution of the habit*

It is estimated that several million people are habitual khat users, living in geographical areas close to where khat is growing, particularly Yemen, Somalia, Ethiopia, Djibouti and Kenya (Kalix & Braenden, 1985). Because of the availability of road network and air transport and immigration, the habit has spread recently to western countries as far north as Finland (Nencini et al., 1989; Browne, 1991; Tacke et al., 1992).

There are no recent data about the prevalence of the habit in Yemen. The best available figures are probably those made by two Italian doctors, Manciola and Parrinello, who worked in Yemen between 1955 and 1967. Of the 27 410 patients who passed through their clinic, 90.3% of the males and 58.6% of the females over the age of 12 chewed khat, but only 60.3% of the males and 34.9% of the females were classified as 'habitual chewers' (Kalix & Braenden, 1985; Kennedy, 1987c). Kennedy (1987c) estimated that 80–85% of the men and 50–60% of the woman in northern Yemen (at that time known as the Yemen Arab Republic) chewed khat more than once a week.

In Ethiopia khat-chewing is used widely in the Harar district, but is also common in other parts of the country. Data from a survey conducted in 1996 in Addis Ababa and 24 towns across Ethiopia showed that the prevalence of the habit was about 30%, and indicated that khat use had been increasing and that it had become popular among all segments of the population (Selassie & Gebre, 1996). A house-to-house survey in rural areas of Ethiopia gave a similar figure (31.7%) (Belew et al., 2000). However, one recent study with a sample size of 10 468 adults reported a prevalence of 50% (Alem et al., 1999). All reports indicate that the habit was more prevalent among Muslim males. Interestingly, the latter study also reported a strong association between the habit and high educational level.

The prevalence of khat-chewing in Somalia in the early 1980s is given by Elmi (1983), who found that in the south 18.3% were habitual chewers and 20.9% were occasional users, whereas in the north the respective figures were 55% and 29.3%. Of the female population, habitual and occasional chewers collectively were 10.60% and 25.45% in the south and north, respectively. In Djibouti, although khat is not produced locally, it is used daily or occasionally by 90% of the population (Kalix & Braenden, 1985). In Kenya the habit is common in Nairobi and the Meru district, but few statistics about its prevalence are available (Kalix & Braenden, 1985). In a study about drug abuse in outpatients attending rural and urban health centres in Kenya, only alcohol and smoking were found to be highly prevalent (Othieno et al., 2000). In a recent study among children and youth appearing in Nairobi juvenile court, 5.6% reported use of khat (Maru et al., 2003).

#### **Medical and psychological consequences**

Early anecdotal accounts claimed that khat is harmful to health. Since then there has been an increasing number of

reports on this issue, expanding the list of the possible adverse health effects of khat-chewing. Halbach (1972) asserted that khat-chewing causes certain health disturbances including stomatitis, oesophagitis, gastritis, constipation, malnutrition, liver cirrhosis, anorexia, insomnia, spermatorrhoea and impotence. He also alleged that migraine, cerebral haemorrhage, myocardial insufficiency and infarcts and pulmonary oedema had been described after khat intake. Luqman & Danowski (1976) added gastric ulcers, haemorrhoids, urinary bladder hypotonia, poor lactation and schizophrenia to the list, but they mentioned that the effect of khat on sexual behaviour is not definitely negative, as affirmed by Halbach (1972), who was their main reference. However, these reports did not present statistical figures as to the prevalence of the alleged adverse effects of khat-chewing among khat chewers and non-chewers, neither did they cite controlled research to support their conclusions. I quote the following from the article by Luqman & Danowski (1976):

In the absence of more definitive information, one can only cite clinical observations and continue with *hypotheses* concerning clinical disorders in the users of khat.

The most comprehensive controlled study evaluating the adverse effects of khat-chewing on different health aspects is that by Kennedy et al. (1983). The study was conducted on 371 males and 335 females recruited in and around the three major cities of northern Yemen (then known as the Yemen Arab Republic). The participants were categorized as non-, light and heavy chewers and then subjected to a standardized medical history and physical examination, involving each organ system of the body. The physical examination was blinded to the chewing habit of the participants. Ninety-five different diagnoses were made; however, for many of the conditions linked in the literature to khat use, too few cases were diagnosed even to allow appropriate statistical tests to be made. The results showed that gastrointestinal disorders, namely gastritis, constipation and anorexia, were associated significantly with khat-chewing. Emotional problems including insomnia, headaches and emotional instability were also associated significantly with khat use, especially among males. Khat chewers also had a higher prevalence of respiratory problems, namely bronchitis, that the author attributed to smoking accompanying khat-chewing rather than to the habit itself. Female chewers had a higher prevalence of urinary problems. Cardiovascular problems and liver diseases, except for histories of jaundice among females, were not associated with khat use.

There seems to be an agreement among researchers as well as khat users themselves concerning the gastrointestinal problems brought by khat-chewing. These are due probably to the astringency of khat tannins ingested (direct effect) and the sympathomimetic action of khat amines (indirect effect) (Halbach, 1972; Kennedy et al., 1983).

Many studies have been conducted in the last 20 years; each has usually focused on investigating only one of the medical aspects of khat-chewing. The reproductive health aspect of khat-chewing is one such example. A series of studies found that khat may reduce placental perfusion (Jansson et al., 1988a) and result in low birth weight infants (Abdul Ghani et al., 1987; Jansson et al., 1988b; Eriksson et al., 1991).

Islam et al. (1990b, 1994) demonstrated that intravenous cathinone in rats resulted in deleterious effects on the male reproductive system, and that oral doses of methanolic khat extracts, also in rats, had teratogenic effects on fetuses. El-shoura et al. (1995) reported that khat-chewing negatively affected all semen parameters (semen volume, sperm count, sperm motility, motility index and percentage of normal spermatozoa) in humans and resulted in abnormal sperm morphology. On the other hand, a more recent study using rabbits showed that khat stimulated spermatogenesis, and had no deleterious effect on the testis (Al-Mamary et al., 2002). Furthermore, it was shown very recently that cathine and norephedrine, the metabolites of cathinone, accelerated capacitation and inhibited spontaneous acrosome loss, suggesting that they may enhance natural fertility (Adeoya-Osiguwa & Fraser, 2005). In fact, according to the WHO statistical information system, Yemen has the highest fertility and annual population growth rates in the Eastern Mediterranean region.

Association between khat-chewing and myocardial infarction (MI) has also been studied. In a case-control study, Alkadi et al. (2002) found that khat-chewing increased the risk of MI, with an odds ratio of 3. However, as neither selection criteria nor demographic data were described a sound conclusion cannot be made. Al-Motarreb et al. (2002b) reported that khat-chewing resulted in a significant shift in the presentation time of MI; most MI cases in the khat-chewers occurred in the afternoon. They also found that a significant proportion (20%) of the khat-chewers with MI were young (20–39 years); however, without adjustment for the confounding effects of smoking (80% of the khat chewers were also smokers), it is not possible to tell whether this finding was due to either or both habits. Very recently, however, a well-designed case-control study showed, after adjustment for the effect of potential confounders, that khat-chewing was associated with an increase risk of MI in a dose-dependent manner; heavy chewers had a 39-fold increased risk of MI (Al-Motarreb et al., 2005).

The involvement of other organs has also been reported. A few studies showed recently that in rabbits, khat increased plasma levels of hepatic enzymes and indirect bilirubin and induced histopathological changes in the liver as well as in the kidneys, but not in the spleen and testis (Al-Habori et al., 2002; Al-Mamary et al., 2002). One other study reported the high frequency of khat and water-pipe use among cases of oesophageal and gastric carcinomas in Yemen, and ruled out smoking and use of alcohol as risk factors (Gunaid et al., 1995). There are also individual reports relating khat use to haemorrhoids (Al-Hadrani, 2000) and duodenal ulcers (Raja'a et al., 2001).

An aspect of growing khat that can have serious consequences on health is the abuse of pesticides and fertilizers. Unfortunately, except for a recent study showing that people chewing khat contaminated with pesticides reported more subjective adverse effects than did those chewing slightly contaminated or uncontaminated khat (Date et al., 2004), objective information about the adverse acute and long-term effects of these chemicals is lacking.

Recently, the long-term effect of khat on blood constituents in animals was evaluated (Al-Habori & Al-Mamary, 2004). Exposure to khat lowered plasma cholesterol concentrations

by almost 60% during the first 4 months, but the effect became less pronounced by the sixth month. A significant reduction in glucose and triglycerides concentration was also observed by the sixth month. On the other hand, there was a progressive increase in concentrations of uric acid. This study draws a certain amount of attention to the other side of the coin, which is usually ignored, i.e. the possible positive aspects of khat. In line with that, it was found that khat has antimicrobial properties against a number of bacterial species; results showed that two compounds isolated from khat were more potent than streptomycin on mycobacterium species (Elhag et al., 1999). Furthermore, recent studies have demonstrated cytotoxicity of isolated compounds and crude extracts from khat against a number of cancer cell lines, particularly against leukaemia cell lines (Elhag et al., 1999; Dimba et al., 2003). In Ethiopia, processed leaves and roots of khat are used to treat influenza, cough, gonorrhoea, asthma and other chest problems (Lemessa, 2001).

The most common psychic fluctuation as a result of khat-chewing is the mild depressive, or sometimes paranoid, reaction that starts towards the end of the khat-chewing session and continues for a few hours. Occasionally, a chewer may experience a state of temporary confusion or hallucination. Kennedy claims that he did not encounter a single permanent psychic condition that can be attributed to khat-chewing (Kennedy, 1987f). As mentioned above, toxic psychosis due to the excess intake of khat is very rare (Halbach, 1972). However, khat-chewing has been alleged repeatedly as being a cause of psychosis. The majority of publications related to this topic are case reports and letters (Dhadphale et al., 1981; Giannini & Castellani, 1982; Anonymous, 1984; Kalix, 1984b; Critchlow & Seifert, 1987; McLaren, 1987; Maitai & Dhadphale, 1988; Pantelis et al., 1989; Jager & Sireling, 1994; Yousef et al., 1995; Alem & Shibre, 1997; Mion et al., 1997). A number of these describes the psychic condition caused by khat as paranoid (Critchlow & Seifert, 1987; Maitai & Dhadphale, 1988; Pantelis et al., 1989; Jager & Sireling, 1994; Yousef et al., 1995). Schizophreniform (Anonymous, 1984) and manic- or hypomanic-like (Giannini & Castellani, 1982; Pantelis et al., 1989) psychoses were also reported. Because many of the cases reported were Somali refugees, it may be that khat induces psychosis in predisposed individuals. Results from a few cross-sectional studies comparing khat chewers with a control group of non-chewers are contradictory. While one study shows a significant association of psychic symptoms with khat use, particularly among heavy chewers (Odenwald et al., 2005), other studies refute such an association (Litman et al., 1986; Numan, 2004); the latter showed a negative association between khat use and phobia (Numan, 2004).

### Oral consequences

The teeth are much affected becoming permanently discolored and loose, for the gums become flaccid [opinion of an early visitor (Bury, 1915) to Yemen as quoted by Kennedy (1987g)].

The fact that khat leaves are chewed daily for several hours brings many questions to mind as to the possible dental and oral effects of this habit. Until the late 1980s, however, there

had been no single published, peer-reviewed article that focused primarily on this topic and up-to-date studies with such a focus are unfortunately sparse.

In their 1966 study about the periodontal condition of several ethnic groups in Israel, Rosenzweig & Smith (1966) proposed that the exceptionally high rate of periodontal diseases found in Yemeni males could be explained by the probability that many of the Yemeni males had chewed khat before immigration to Israel. Halbach (1972) claimed that stomatitis is common among chronic khat chewers. Luqman & Danowski (1976) maintained that khat-chewing causes stomatitis followed by secondary infection. They also reported a low prevalence of dental carie, but attributed it to factors other than khat-chewing. However, there were no data presented or controlled studies cited to support such generalizations. Kennedy and his team (1983) diagnosed few cases of stomatitis among the khat chewers they examined. Stomatitis as a result of khat-chewing was not mentioned later in the literature.

The first published report on the oral and dental effect of khat-chewing was in 1987 by Hill & Gibson (1987). The study was conducted on 121 Yemeni males, of whom 115 were khat chewers. The prevalence of dental caries was low (less than 2% of all teeth were carious). The non-chewing sides showed significantly deeper periodontal pockets than did the chewing sides, suggesting that khat had a beneficial effect on the chewing side (or a detrimental effect on the contralateral side). Forty per cent of the chewer subjects experienced mild temporomandibular pain on the side of chewing. Examination of the mucosa revealed some degree of keratosis in less than 50% of the subjects with no indication of malignancy or dysplasia. No stomatitis was evident.

In a study conducted in Kenya, Jorgensen & Kaimenyi (1990) found that there were generally no significant differences in the periodontal health of 131 miraa (khat) chewers and 199 miraa non-chewers. The miraa chewers rather showed significantly lower lingual plaque and gingivitis scores than did the miraa non-chewers. They thus concluded that there was no evidence that miraa chewing is detrimental to periodontal health. In contrast, Mengel et al. (1996), in a larger-scale investigation involving 1001 Yemeni, found that the community periodontal index of treatment needs, the clinical loss of attachment and the calculus index were significantly higher in the khat chewers. The differences were substantial for the 12–24-year age group, while insignificant for those in the 35–44-year group. On the other hand, the study showed that the khat-chewing sides had less clinical loss of attachment than did the non-chewing sides, which is consistent with findings from the study of Hill & Gibson (1987).

Mucosal changes due to khat use have also been investigated. Oral keratosis is common among khat chewers. Hill & Gibson (1987) found that 50% of the khat chewers had some degree of keratosis, while a very recent study showed that 22.4% of the khat chewers had keratotic white lesions, the majority of which was mild (Ali et al., 2004). Neither study suspected dysplasia or malignancy, nor did they make histopathological examination. In a case-control study, khat-chewing was not among the habits that showed significant association with oral leucoplakia (Macigo et al., 1995). However, a recent report demonstrated that khat-chewing had genotoxic effects on buccal epithelial cells in a dose-dependent manner, suggesting that khat may play a role in oral malignancies (Kassie et al., 2001).

Soufi et al. (1991), in a study involving 28 cases of head and neck cancer, found that all eight cases of oral cancer were non-smoker chronic khat chewers; most of them reported khat-chewing on the same side affected by cancer. However, most lesions occurred in the anterior two-thirds of the tongue and floor of the mouth, which are usually not in contact with the khat bolus. No information about snuff use was provided. Awange & Onyango (1993) reported a case of oral verrucous carcinoma with history of tobacco-chewing, snuff-dipping and mirra (khat)-chewing, making it difficult to assess the role of the latter. More recently, a study showed that all 17 cases of head and neck squamous cell carcinoma diagnosed during a 1-year period at the clinics of Saudi Hospital in Hajja, Yemen reported chronic khat use (Nasr & Khatri, 2000). However, 10 of them were also snuff-dippers and five others were smokers, rendering any conclusions imprecise. It therefore seems that urgent, larger-scale controlled studies are needed to assess the extent of association between khat-chewing and oral cancer.

### Microbiological aspects

Very few studies evaluated the microbiological effects of khat. Until recently, the only published such study was the one by Elhag et al. (1999) who showed that two compounds isolated from khat (22  $\beta$ -hydroxytingenone and tingenone) possessed potent antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus durans* and *Mycobacterium* species but not against *Escherichia coli* and *Candida albicans*.

The effect of khat on oral microbiota has recently been assessed. In one of these studies, the prevalence and levels of selected periodontal bacteria in the supra- and subgingival dental plaque of young khat chewers and non-khat chewers as well as of khat-chewing sides and non-chewing sides were compared using DNA–DNA checkerboard hybridization. *Veillonella parvula*, *S. intermedius* and *Eikenella corrodens*, which are known to be compatible with periodontal health, were found to be significantly more prevalent or/and at significantly higher levels in the subgingival plaque of the khat chewers than the khat non-chewers, and of the khat-chewing sides compared to the khat non-chewing sides. The periodontal pathogen *Tanerella forsythia* occurred at significantly higher levels in the subgingival plaque of the khat non-chewing sides. The effect of khat-chewing on the supra-gingival plaque was not pronounced, and the microbial profile induced was, as in subgingival plaque, not incompatible with periodontal health (Al-hebshi & Skaug, 2005).

In an *in vitro* study, aqueous crude khat extracts were shown to interfere with formation of adherent biofilms by *S. mutans* (the principal cariogenic bacteria in humans), and to inhibit synthesis of water-soluble and water-insoluble glucans, which are important for *S. mutans* attachment, in a dose-dependent manner. However, the extracts did not show any antibacterial activity against the bacterium and rather favoured its growth (Al-hebshi et al., 2005a).

In another *in vitro* investigation involving 36 oral strains, aqueous crude khat extracts were found to possess selective antibacterial properties *in vitro*. While the majority of periodontal disease-associated bacteria, particularly *Porphyromonas gingivalis* and *T. forsythia*, were sensitive to the extracts, only a few periodontal health-associated bacteria were susceptible

even at the highest concentration tested. *Lactobacillus acidophilus* showed a marked growth reduction in presence of the extracts; however, none of the other cariogenic bacteria were sensitive. In addition to their selective antibacterial properties, the extracts were also shown to possess antibiotic resistance-modifying properties; they resulted in two- to fourfold potentiation of tetracycline and penicillin-G against the three resistant strains tested (Al-hebshi et al., 2005b).

### Conclusions

- The cultivation and use of khat in Yemen and East Africa is a many-centuries-old tradition with pronounced social and economical dimensions.
- The sympathomimetic and CNS-stimulating effects produced by khat-chewing are due mainly to cathinone, the 'natural amphetamine' present in fresh khat. Compared to amphetamine, however, khat seems to have less potential of inducing tolerance or toxic psychosis.
- Experiments in animal models indicate that cathinone has strong reinforcement properties.
- Khat has been reported to result in gastrointestinal and urinary problems, adverse reproductive effects, increased risk of myocardial infarction, liver and kidney toxicity, esophageal and gastric carcinomas, haemorrhoids and low birth weight infants. However, for many of these, scientific evidence is inadequate.
- Current information suggests that khat may be anticariogenic and that it has little or no impact on the periodontium.
- Frictional keratosis is the most common oral effect of khat-chewing. However, evidence that khat-chewing is a risk factor of oral cancer is weak and needs further investigation.
- The recently reported antibacterial and cytotoxic properties of khat extracts indicate the presence of khat components with potential therapeutic use.

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