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REVIEW ARTICLE

Khat: Pharmacological and Medical Aspects and its Social Use in Yemen

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Fresh leaves of the khat tree (*Catha edulis Forsk*.) are chewed for their euphoric properties in East Africa and parts of the Middle East, such as The Yemen. This review describes the history, cultivation and constituents of khat, and the social aspects of khat chewing in Yemen. The major pharmacologically active constituent of the fresh leaves is (−)-S-cathinone. The pharmacology of (−)-S-cathinone in the central nervous system and the peripheral effects are described. (−)-S-Cathinone is regarded as an amphetamine-like sympathomimetic amine and this mechanism of action is discussed in relation to the central stimulant actions and the cardiovascular effects of increasing blood pressure and heart rate. The risk factors associated with khat chewing are described, with emphasis on the reported increased incidence of acute myocardial infarction.

Keywords: khat; (−)-S-cathinone; acute myocardial infarction; risk factors.

INTRODUCTION

The chewing of khat (or qat) leaves (*Catha edulis Forsk*.) is widely practised in East Africa and parts of the Middle East, such as The Yemen where it forms a deep-rooted social and cultural function (Drake, 1988). This habit has now spread to ethnic communities in the rest of the World, including Britain such as the Somali Communities in South Wales and London (Griffiths, 1998). The pleasure derived from khat chewing is attributed to the euphoric actions of its content of (−)-S-cathinone, a sympathomimetic amine with properties described as similar to those of amphetamine (Kalix and Braenden, 1985; Kalix, 1988, 1992). Although (−)-S-cathinone is restricted under international convention and in the UK under the Misuse of Drugs Act 1971, khat is not controlled and its possession and use are not restricted in the UK (Griffiths, 1998).

THE ORIGIN OF THE KHAT PLANT

The khat tree was first described by Peter Forskal (1736-1763), a Swedish botanist who had travelled with his friend the geographer Karsten Niebuhr (1736-1815) on an expedition to Egypt and Yemen organized by King Friederick V of Denmark (Raman, 1983). Among the many things collected was khat, which Forskal described as *Catha edulis* in the family Celastraceae. Karsten Niebuhr was the only survivor of the five members of the expedition and in memory of his friend, he called khat *Catha edulis* Forskal; this was published in the botanical papers in 1775 (Raman, 1983).

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Most researchers believe that khat originates from Ethiopia. Although it has grown for centuries in Yemen, there is no certainty of the date for its introduction (Al-Radee, 1992). One opinion is that khat was introduced to Yemen during the Ethiopian occupation of Yemen in 525 AD, when it was limited to the invaders. However, this date is believed by others to be too early as Abu Al-Hasan Al-Hamdani in the 10th century (945 AD) does not mention khat in his botanical treatise on the many plants he described. The view that khat came to Yemen at the beginning of the 13th century is supported by a letter written by a religious scholar, Ahmed Ben Alwan, asking the ruler at that time to legally ban the habit of khat chewing because it prevented Yemenis from performing their prayer, especially the afternoon (*Asr*) and sunset (*Maghreb*) prayer periods.

The first report of khat as a medicine was by the Arabian physician Abu Al-Rihan Bin Ahmed Al-Baironi (973-1051 AD) in his book *Pharmacy and Therapeutic Art* (El-Tahir, 1990). Khat is also mentioned in an Arabic medical book *The Complex Drugs* which was written in 1237 AD. The author, Najeeb Al-Deen Al-Samargandi, described khat as a treatment for depression, because it led to happiness and excitement (Al-Attas, 1981).

The historian Ibn Fadl Allah Al-Amri (1301-1348 AD) mentioned khat in the events of the war between Sabr Al-Deen (the King of Ifat) and the King of Ethiopia (Emdasyoon). In the excitement of his victory, King Sabr Al-Deen swore to demolish the residence of the Ethiopian king (Marade) and to plant khat in its place (Al-Attas, 1981). In view of the above considerations, the consensus of opinion is that khat was probably introduced into Yemen as a social habit in the 13th century.

THE KHAT TREE: CULTIVATION IN YEMEN

The khat tree is a perennial green plant (Fig. 1) which is

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Figure 1. Typical row of khat trees in Yemen

grown by grafting, usually reaching 6–7 m in height. However, under optimal conditions it may grow to 15–20 m in height. It grows at altitudes of 1500–2500 m. In places experiencing severe frost in winter, the aerial parts of the plants are either stunted or killed, and the tree never develops to a height of more than 1.5 m (Raman, 1983). It is allowed to grow for 3–4 years before harvesting the leaves.

The trunk is straight and slender and the bark is thin, smooth and greyish brown in appearance. The plant has a tap-root which grows to a depth of 3 m or more. The khat plant is polymorphic and the branches have either opposite or alternate leaves. The leaves are 2–5 cm wide and 5–10 cm long. The shapes of the leaves range from ovate-lanceolate to elliptical and have serrated edges. Old leaves are leathery in texture, highly polished on their upper surface and deep green in colour. The leaf peduncle is around 3–7 mm long (Raman, 1983). The leaf odour is faintly aromatic and the taste is astringent and slightly sweet (Kalix & Braenden, 1985).

When plants grown under different climatic characteristics were subjected to quantitative analysis, it was found that the chemical profile of khat leaves grown in Yemen was largely determined by the environment in which it grows rather than by the cultivators (Raman, 1983). Therefore the type of khat in Yemen is referred to by its geographic area of cultivation. Thus, there are around 44 types of khat, from 44 different geographic areas of the country. Table 1 shows the types of khat with the concentration of two important constituents, (−)-S-cathinone and tannic acid (Al-Qirbi, 1997). Additional types of khat, such as Rawdhi, Dalee, Yafee, Halemee and Muraisi come from three provinces. The taste of khat leaves varies from one kind to another, and depends on the tannic acid concentration. The potency, determined by the use of khat, depends on the concentration of (−)-S-cathinone (Al-Qirbi, 1997). Khat is not cultivated in the coastal cities that enjoy a hot climate like Aden, Hodieda and Mokalla. These three provinces receive their khat from the surrounding villages and provinces.

Land preparation in Yemen depends on local circumstances and experience. The soil is broken up to a depth of about 40 cm and cleared of stones and small herbs. Small fields in serrate mountains and bigger fields on flatland are prepared in this manner. Khat is propagated from branches arising at ground level in the adult tree. Suckers (3–4) are then planted in each of several holes. The khat tree is planted in rows, with 2–3 m between the plants. Irrigation of the khat field on terraced mountain sides depends on rain water. In the flatlands, water is channelled from an appropriate source either by open shallow trenches or through pipes.

Table 1. Concentrations of cathinone (mg/100 g) and tannic acid (g/mg) in fresh khat leaves obtained from different regions of Yemen

No	Khat type	Cathinone	Tannic acid
1	Nehmi	342.8	9.69
2	Hori	337	9.71
3	Harazi	326.1	9.59
4	Sawti	323.55	9.35
5	Serafi	256.6	7.45
6	Dula'ee (upper)	255.3	7.46
7	Dula'ee (middle)	235.8	7.04
8	Rada'ee	220.6	6.83
9	Ghorbani	206.9	5.94
10	Matari	206.6	6.43
11	Shar'abi	191.3	5.53
12	Shro'ee	187	5.52
13	Habashi	182.9	5.46
14	Bani Heshaish	180.6	5.19
15	Maswani	176.6	5.35
16	Samawee	170.5	4.98
17	Bukhari	170.5	5.17
18	Malahi	169.7	5.21
19	Mabra'ee	169.2	5.09
20	Najri	167.9	4.94
21	Sabri	167.3	4.96
22	Khawlani	164.4	4.8
23	Hajwee	163.4	9.38
24	Shagi	162	0.82
25	Sa'di	158.3	4.91
26	khattabi	158.2	4.79
27	Baladi	148.8	4.56
28	Abbasi	148.5	4.52
29	Harami	148.3	4.61
30	Jayshani	147.3	4.75
31	Mabra'ee	137.7	4.34
32	Sharafi	135.8	4.18
33	Dehla	127.4	4.01
34	Hamdani	123.3	3.72
35	Kotobi	122.2	3.77
36	Wadi Dahr	115.3	3.45
37	Adnani	109.5	6.2
38	Ofashi	109.4	6.86
39	Saifi	77.7	4.84

Cathinone assays were performed spectrophotometrically in the Biochemistry Department, Khat Research Unit, College of Science, Sana'a University, Yemen.

The first harvesting of chewable leaves is usually after the third or fourth year of growth of a new tree, although it requires a further 6–7 years for the tree to attain maturity. A healthy tree will continue to give good harvests for another 50 years. It appears that khat is not damaged to any extent of economic significance by any known pathogens (Raman, 1983). Farmers of the crop consider the presence of a tiny green leaf hopper (*Empoasca* species) to be beneficial because it causes older tips to wilt and die off for the eventual emergence of the new shoots which can be harvested. However, prior to harvesting, the hopper is removed by dusting the plants with very fine dust particles. This appears to be effective by preventing the hopper from attaching itself to the tree. Recently, some farmers have used an insecticide to get

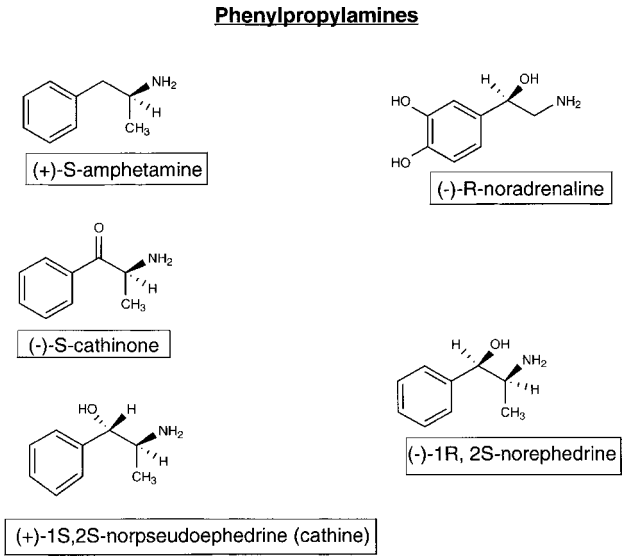

Figure 2. Chemical structures of the phenylpropylamine alkaloids from khat (*Catha edulis* Forsk.), cathinone, norephedrine, norpseudoephedrine (cathine) compared with amphetamine and noradrenaline

rid of the hopper. The compound is mixed with plant juice which is consumed by the hopper. Although the use of the insecticide leads to better branches and leaf growth, there are concerns relating to the safety to humans. Indeed, many consumers look for khat bundles, that have not been treated with the insecticide. As a result, many farmers are returning to the fine dust treatment to achieve customer satisfaction.

CONSTITUENTS OF THE KHAT LEAF

The three main alkaloids present in khat leaves are the cathines, (−)-S-cathinone (S-α-aminopropriophenone), norpseudoephedrine (cathine) and norephedrine (Szendrei, 1975a, 1975b; Schorno and Steinegger, 1979), which are phenylpropylamines structurally related to amphetamine and noradrenaline (Fig. 2). The phenylpropylamine composition varies between the plant region and country of origin. A comparison of khat from Kenya, Madagascar and Ethiopia showed that the highest level of cathinone occurred in khat bundles originating from trees and sold in Nairobi's street market. The highest concentrations of these amines were found in the young shoots already carrying leaves (Brenneisen and Geisshusler, 1985). In addition, there are two further types of alkaloid found in the khat plant. The phenylpentenylamines, merucathine, merucathinone and pseudomerucathine, were isolated from the fresh plant material cultivated in the Meru region of Northern Kenya (Brenneisen *et al.*, 1984; Brenneisen and Geisshusler, 1985, 1987) (Fig. 3). The third type of khat alkaloid are the cathedulines; these are a group of sesquiterpenes which are polyesters of euonyminol (Fig. 3) (Samuelsson, 1992). They are identified as K1, K2, K6 and K15 from Kenyan khat, of which K2 is the most abundant. The equivalent catheduline in khat from Yemen is Y1 (Crombie *et al.*, 1979). The structures shown in Fig. 3 were obtained from Crombie *et al.* (1979). It is unlikely that the cathedulines and phenylpentenylamines have significant biological activity (Kalix *et al.*, 1987). Other constituents present in khat leaves include small amounts of essential oils, sterols and triterpenes, and 5% protein of insignificant nutritional value (Kalix and Braenden, 1985). Ascorbic acid is also present in the leaves (Raman, 1983). Khat also contains tannin (7%–14% by weight in dried leaves) and minute amounts of thiamin, niacin, riboflavin, iron and amino acids (Lugman and Danowski, 1976). Apart from tannin, these substances are unlikely to contribute to the biological effect of khat (Kalix, 1984).

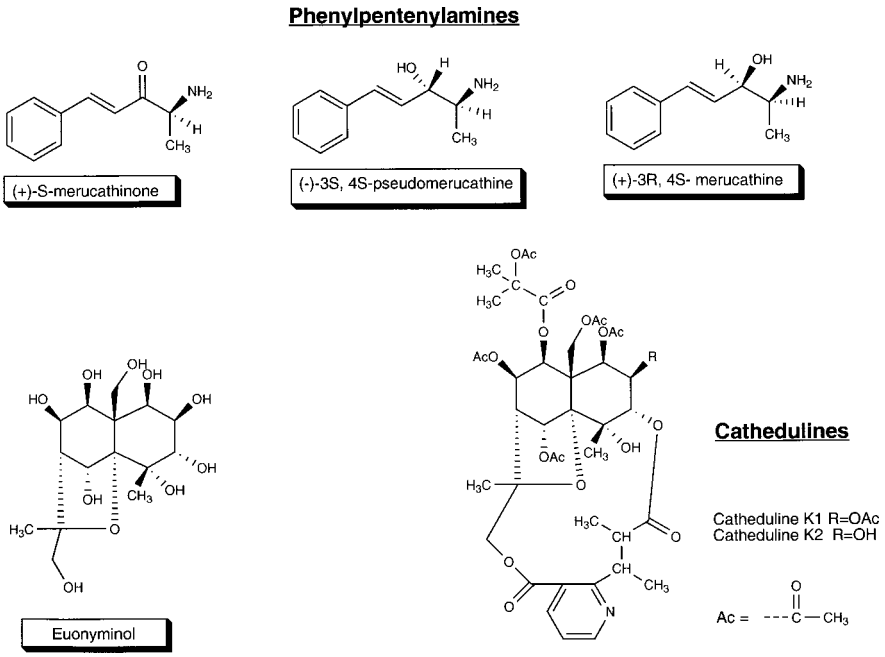

Figure 3. Chemical structures of the phenylpentenylamine and catheduline alkaloids from khat (*Catha edulis* Forsk.)

STABILITY AND PHARMACOKINETICS OF THE KHAT ALKALOIDS

It is only the fresh leaves of the khat trees that are chewed, as this produces maximal central stimulant effect with good leaf taste. As a consequence, khat is almost always used on the same day of harvesting the branches, and preferably within a few hours of picking. Farmers and consumers keep the leaves fresh by wrapping them in plastic foil, wet clothes or shawls, or banana leaves. In addition, they immerse the cut end of the stem in water for one minute or more to prolong freshness. At best, the leaves can remain in an acceptable condition for up to 5 days. However, it is an important commercial fact that the value of the leaves drops dramatically after the first day of harvesting. This reflects the instability of the main active constituents in the isolated leaf, which was appreciated by the consumer a long time before the scientist (Brenneissen and Geisshusler, 1985). (−)-S-Cathinone, the main effective constituent of the khat leaves, is relatively unstable and decomposes into (+)-norpseudoephedrine and norephedrine within a few days of picking or if the leaf is dried. Thus, only freshly picked leaves have the full efficacy. Norpseudoephedrine and norephedrine are slowly absorbed and then excreted mainly in the unchanged form within about 24 h (Brenneisen *et al.*, 1986). The major metabolites of (−)-S-cathinone after ingestion are (−)-R,S-norephedrine and (−)-R,R-norpseudoephedrine (Brenneisen *et al.*, 1986). Controlled studies in human volunteers have shown elevated plasma levels of cathinone (Brenneisen *et al.*, 1990; Widler *et al.*, 1994), the peak occurring at 1.5–3.5 h (Halket *et al.*, 1995).

PHARMACOLOGY OF KHAT

Stages of intoxication associated with khat chewing

The effect of khat chewing varies according to the type of khat and according to the person. As with most drugs taken for pleasure, the response is peculiar to the individual. In general and from the experience of one of the authors (AA-M) as an ex-khat chewer of more than 20 years, the effect of khat on the chewers can be divided into the following stages:

1. The euphoric, cheerful sensation and excitement stage (Brenneisen *et al.*, 1990; Widler *et al.*, 1994) which lasts about 1–2 hours (Kalix & Braenden, 1985). This is clear among the young chewers, and it is repeated at each session.
2. The khat chewers start to discuss serious issues with some emotional irritability and great awareness of the problem (Kalix & Braenden, 1985). They normally start to discuss a general issue then pairs of people talk on personal issues in a low voice and in private.
3. The *Sulaimania hour*; this stage usually starts at the beginning of darkness (around 6.30 pm in summer and 5.30 pm in winter) when the khat chewer does not like to switch on lights but keeps silent, enjoying the view if he is in the *Mandher* or the sound of the water and the green garden if he is in the *Mafraj*. At this stage, his imagination is very active in generating a mood of great excitement. This feeling was the reason for calling this stage *Sulaimania* after the king and prophet Sulaiman. At the beginning of this stage, some chewers like to listen to local music either by a musician invited to sing for them live or recorded on tape.
4. A depressive stage which usually comes at the end of the khat session just before spitting out the khat bolus and continues afterwards. This stage is characterized by exaggerating private problems with great concern and a pessimistic view. The depressive stage depends on the potency of the khat. Some khat chewers promise themselves to stop khat chewing and blame khat for this depressive state.
5. Irritability, anorexia and insomnia. This stage is characterized by an increase in the imaginative sensation of self-confidence, ideas fly around and there is an inability to concentrate on one issue (Kalix & Braenden, 1985). Next morning, lethargy and a sleepy state accompany amnesia of most of the enthusiastic ideas, which had been discussed the night before. By 10 or 11 am in the morning, the khat chewer starts to long for the day's khat session and how to arrange it. This feeling is too strong and overcomes his resistance and pledge of the past night to stop the habit. The time factor in these stages is flexible and depends on the session itself and the people involved. There are large differences between an election campaign, a wedding party or a funeral gathering and the normal daily session.

The main common non-CNS effects are constipation and sometimes heartburn, both of which might be related to the tannin content of the khat leaves. Staring and mydriasis are common after the session.

Withdrawal symptoms associated with khat

Physical symptoms of withdrawal such as those of morphine and alcohol do not occur in khat users. When a chronic khat chewer stops chewing the leaf, he feels hot, especially in his lower extremities, lethargic and gripped with a desire to chew khat in the first two days; the desire to chew khat may last longer. During sleep usually he will have what is called *Razem* (a nightmare). This takes the form of seeing himself facing a dangerous situation unable to shout or move. This *Razem* lasts only for 1–2 nights, after which sleep returns to normal. His sleep is longer and deeper, the appetite is better, he is less constipated and smokes less. He returns to a life where he has more time for other things, like sport, reading and the family.

Risk factors associated with khat

Khat chewing is a major health problem in Yemen. There is great awareness among Yemeni doctors about the role of khat on the general health and its effects on different diseases. Many of them have performed studies based on their clinical observations. Most of this work has been presented at local medical meetings and is as yet unpublished. However, the World Health Organization is aware of the problem and commissioned a report reviewing the risks associated with chronic khat use

(WHO Advisory Group, 1980), some of which are summarized below.

Khat and the urinary bladder. Khat chewing produces a fall in urinary flow rate, an effect that has been shown to be inhibited by the selective α_1-adrenoceptor antagonist, indoramine, and therefore attributed to activation of this receptor subtype (Nasher *et al.*, 1995).

Khat and the gastrointestinal tract. In the gastrointestinal tract, the astringent characteristic of the tannins accounts for periodontal disease, stomatitis, oesophagitis and gastritis (WHO Advisory Group, 1980). Khat chewing has also been reported to be a risk factor for duodenal ulcer formation (Raja'a *et al.*, 2000). Delay to intestinal absorption contributes to some degree to malnutrition. and may lead to liver cirrhosis. Tannins and norpseudoephedrine contribute to constipation, the most common medical complaint of the khat user. In a randomized-controlled trial, Heymann *et al.* (1995) reported a delay in gastric emptying after chewing khat. A generalized brown pigmentation in the oral cavity is related to the habit of chewing the leaves of khat (Ashri and Gazi, 1990).

Khat and the liver. Liver toxicity was evident from raised plasma concentrations of alkaline phosphatase, alanine aminotransferase and total bilirubin, and from histopathological changes to the liver after 3 months of khat ingestion by rabbits (Al-Mamary *et al.*, 2002).

Khat and the reproductive system. Many Yemenis believe khat chewing improves their sexual desire and excitement, but for other people khat chewing causes impotence. It is known to cause spermatorrhoea usually at the first micturation after the session ends. In a comparison between khat-addicted and non-khat addicted subjects, semen volume, sperm count and sperm motility were found to be lower among the addicts. There was also a greater proportion of deformed spermatozoa present among the addicts (El-Shoura *et al.*, 1995). However, in rabbits fed khat for 3 months, there was an increased rate of spermatogenesis (Al-Mamary *et al.*, 2002). This observation contrasts with the findings of Islam *et al.* (1990) that animals receiving the active ingredient, cathinone, displayed degenerative changes in the testicular tissues.

Khat and the respiratory system. Khat increases the desire for active tobacco smoking and is associated with passive smoking. Some people also smoke a common water-pipe. This might increase the chance of spreading tuberculosis. Recently most chewers have preferred cigarette smoking because it does not need preparation and it is easy to smoke anywhere.

Khat and acute myocardial infarction. There is preliminary evidence that khat chewing, like amphetamine and 'ecstasy' (3,4-methylenedioxymethamphetamine, MDMA), may have adverse effects on the heart. In a study of 157 patients admitted with acute myocardial infarction (AMI) to the ICU of Al-Thawra Hospital, Sana'a, Yemen, 124 (79%) were regular khat chewers. While early morning presentation of most AMI patients has been reported worldwide, in this group of patients this trend was reversed. 59% of the khat chewers had onset of symptoms between 2 pm and midnight, which is associated with the period of khat chewing (khat-effective period). Of the non-khat chewers, only 36.4% had onset of symptoms during this afternoon and evening period (Al-Motarreb *et al.*, 1997, 2002). Large intervention studies such as ISIS-2 (1988), confirm earlier suggestions that the time of onset of acute myocardial infarction shows a marked circadian rhythm, with a peak onset in the early hours of the day. Selwyn *et al.* (1991) and Detry and Vincent (1992) reported that major cardiovascular events, such as acute myocardial infarction and sudden death, exhibit diurnal rhythms, with a peak incidence in the early morning after waking and rising. This diurnal rhythm is associated with increased sympathetic outflow and circulating catecholamines producing increases in heart rate, blood pressure (Hassan *et al*., 2000), myocardial contractility and oxygen demand soon after rising. Thus, khat chewing appears to reverse the normal trend of presentation of AMI. It was therefore suggested that the (−)-S-cathinone in khat was responsible for precipitating AMI and that khat chewing may be a risk factor for ischaemic heart disease. Since (−)-S-cathinone is an amphetamine-like substance (Kalix, 1981, 1982) which releases endogenous catechol-amines from peripheral and central neurones, there may be an association with the well-documented relationship between amphetamine misuse and acute myocardial infarction. Acute myocardial infarction has been reported after injecting amphetamine intravenously (Carson *et al.*, 1987; Ragland *et al.*, 1993; Packe *et al.*, 1990). Although coronary angiography was normal in these cases, the potential mechanism for AMI after amphetamine abuse is coronary vasospasm, catecholamine-mediated platelet aggregation and increase in myocardial oxygen demand (Bashour, 1994). 'Ecstasy' (3,4-methylenedioxymethamphetamine, MDMA) is another amphetamine-like substance, abuse of which has also been associated with an increased risk of cardiovascular toxicity, including arrhythmias and hypertension (Henry *et al.*, 1992; Gledhill *et al.*, 1993).

Another cardiovascular complication of khat chewing is a higher incidence of haemorrhoids, 65% of chronic chewers had haemorrhoids compared with only 4% among non-khat chewers (Al-Hadrani, 2000).

MECHANISM OF ACTION OF KHAT

Central actions

(−)-S-Cathinone is the most potent constituent of khat leaves as a stimulant of the central nervous system (Zelger *et al.*, 1980; Glennon *et al.*, 1984). The phenylpentenylamines, such as merucathinone (Fig. 3), which are found in Kenyan khat are unlikely to play a significant role in the stimulating properties of khat (Kalix *et al.*, 1987). When the central stimulant properties of (−)-S-cathinone were compared in rats with (+)-R-cathinone and (+)-norpseudoephedrine, (−)-S-cathinone was found to be the most potent with an ED_{50} value of 0.22 mg/kg, compared with ED_{50} values of 0.72 and 1.61 mg/kg for (−)-S-cathinone and (+)-norpseudoephedrine, respectively (Glennon *et al.*, 1984). The pharmacological profile of (−)-S-cathinone has been shown both *in vivo* and *in vitro* to closely resemble that of amphetamine (Brenneisen *et al.*, 1990), and as such its

mechanism of action has been linked to the release of monoamines (Kalix and Braenden, 1985).

Like amphetamine, the main central effects of (−)-S-cathinone are hyperactivity, euphoria, excitability, restlessness and anorexia (see *Stages of intoxication associated with khat*), actions that have been attributed to the ability of amphetamine and amphetamine-like drugs to stimulate the release of 5-HT (Kalix, 1984), dopamine (Kalix, 1980) and noradrenaline (Kalix and Braenden, 1985). Both (−)-S-cathinone and amphetamine increased levels of dopamine released in the anterior caudate-putamen and nucleus accumbens of the rat measured by *in vitro* microdialysis (Pehek *et al.*, 1990). Indeed, when the behavioural effects of (−)-S-cathinone and amphetamine were investigated in mice (Valterio and Kalix, 1982) and rats (Zelger *et al.*, 1980), pretreatment with dopamine receptor antagonists such as haloperidol, were shown to significantly reduce the increase in alerteness, locomotor activity, grooming, licking and biting induced by (−)-S-cathinone or amphetamine.

Although (−)-S-cathinone has been shown to release [^{3}H]-5-HT from [^{3}H]-5-HT-loaded rat striatal tissue (Kalix, 1984), the relevance of 5-HT pathways to the behavioural actions of (−)-S-cathinone are less defined than those of dopamine, since the 5-HT receptor antagonist BC-105/B does not influence the behavioural actions of (−)-S-cathinone in the rat (Rosecrans *et al.*, 1979). However, selective 5-HT uptake inhibitors such as fluoxetine are clinically used in the treatment of depression, to 'induce a feeling of well being' (Song *et al.*, 1993). As both (−)-S-cathinone and amphetamine have been shown to reduce the uptake of 5-HT in a rat model of psychostimulation (Fleckenstein *et al.*, 1999), a possible involvement of 5-HT in mediating the euphoric actions of cathinone cannot be ruled out.

Given the central stimulant 'rewarding' actions of (−)-S-cathinone, if khat leaves are repeatedly chewed, drug dependence can develop (Eddy *et al.*, 1965). This has been observed in experimental animals, where both cocaine and (−)-S-cathinone exerted similar efficacy in the response rates of monkeys trained to press a lever for a drug reward. In these experiments, the more dependent the monkeys, the faster the response rate of lever pressing (Woolverton and Johanson, 1984).

Drug dependence is often associated with drug tolerance, where repeated consumption leads to progressively smaller 'less intense' responses (Koob, 1992). This is demonstrated in the experiments of Woolverton and Johanson (1984), where as mentioned earlier, the more dependent the subject, the faster the response rate of lever pressing in order to obtain a drug reward. Tolerance to the effects of a drug is believed to be caused by a depletion in the releasable stores of monoamines, an argument that in the case of (−)-S-cathinone is supported by the fact that in rats, chronic administration of (−)-S-cathinone leads to a significant reduction in dopamine concentrations in the caudate, telencephalon and midbrain (Wagner *et al.*, 1982). Among khat chewers, the idea of dependence and tolerance development is reinforced by the need of the user to secure an increasing daily supply of khat, at the expense of food, water and family (see Social aspects of khat chewing), and the presence of withdrawal symptoms if khat chewing is suddenly stopped (see Withdrawal symptoms associated with khat). Psychosis has been attributed to heavy khat chewing (McLaren, 1987; Alem and Shibre, 1997).

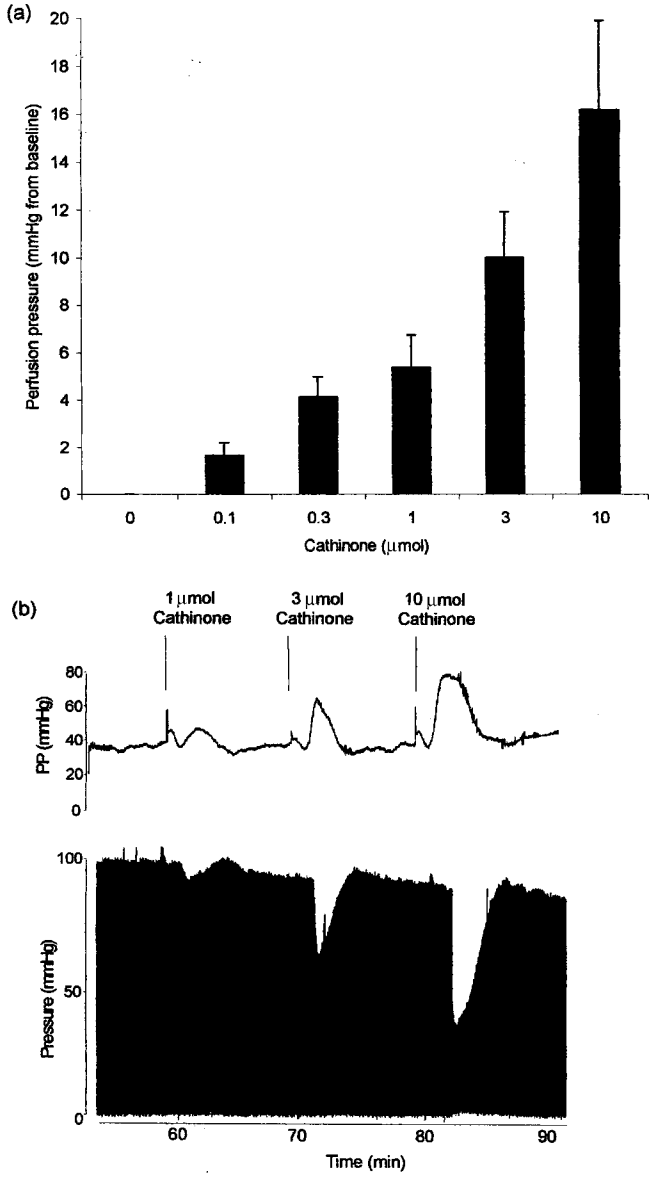

Figure 4. Coronary vasoconstriction in the Langendorff perfused guinea-pig heart in response to bolus injections of cathinone. Hearts were perfused with Krebs-bicarbonate solution via the cut aortic stump delivered at a constant rate of 5–7 ml/min^{-1} by means of a Gilson peristalic pump (Minipuls 2)). The Krebs solution was gassed with 5% CO_2 in oxygen and prewarmed to 37 °C and the hearts were jacketed at 37 °C. Coronary perfusion pressure was monitored by means of a pressure transducer (Druck Ltd, Type PDCR 75) situated between the aortic cannula and the flow inducer. A Condon manometer was also located at this position to accommodate some degree of volume change during drug responses. Cardiac contractions were recorded by insertion of a balloon constructed from polyvinylchloride film (Clingfilm) into the left ventricle and measuring intraventricular pressure with a pressure transducer (DTXPlus, Beckton Dickinson, Temse, Belgium) Recordings were made on a computer using a Powerlab™ data acquisition system (4SP) and software (ADInstruments). (a) Mean increases in perfusion pressure ±SEM ($n = 6$) to increasing doses of cathinone (0.1–10 μM), zero is the vehicle control. (b) Typical responses of coronary perfusion pressure (PP) (upper trace) and left ventricular pressure (lower trace) to cathinone (1, 3 and 10 μM)

Peripheral actions

As well as the central stimulant actions of (−)-S-cathinone (discussed above), the chewing of khat also

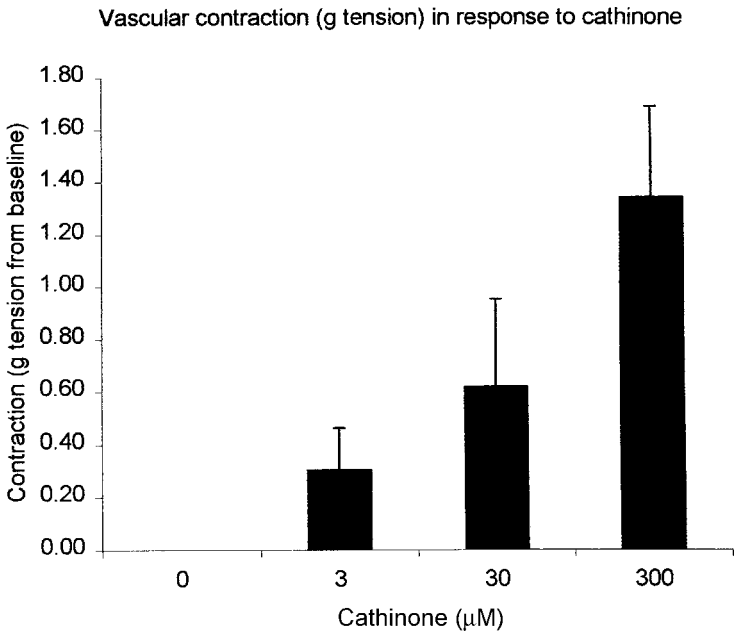

Figure 5. Vasoconstrictor responses of guinea-pig isolated aortic rings in response to bolus injections of cathinone (0–300 μM). Thoracic aorta was cut into rings (0.5 cm) with the endothelium intact. These were mounted between two horizontal wires, the lower was fixed to the tissue holder and the upper was attached via a cotton to an isometric transducer (Dynamometer Type UF1, 55 g sensitivity range) (Pioden Control Ltd). The aorta was immersed in an organ bath (20 mL) containing Krebs-bicarbonate solution gassed with 5% CO_2 in oxygen and maintained at 37 °C. Tension was recorded on a computer using a Powerlab™ data acquisition system (4SP) and software (ADInstruments). Values are mean increases in tension ±SEM ($n = 6$)

leads to several peripheral effects that include the development of a dry mouth, blurred vision and mydriasis (Nencini *et al.*, 1984) and increases in blood pressure and heart rate (Brenneisen *et al.*, 1990; Hassan *et al.*, 2000). These effects are believed to result from the ability of cathinone (like amphetamine) to act as an indirect sympthomimetic agent and to facilitate the release of catecholamines from sympathetic nerve terminals (Kohli and Goldberg, 1982; Kalix, 1983). Indeed, in anaesthetized dogs, the increase in heart rate, blood pressure and cardiac contractile force induced by both (−)-S-cathinone and amphetamine were inhibited by pretreatment with the neuronal uptake inhibitor, methylphenidate (Kohli and Goldberg, 1982). Similarly, pretreatment with cocaine and desipramine inhibited the efflux of [^{3}H]-noradrenaline from [^{3}H]-noradrenaline-loaded rabbit atria in response to (−)-S-cathinone (Kalix, 1983).

Of the peripheral actions of (−)-S-cathinone, the one that is of most concern is the effect on the cardiovascular system (see Khat and acute myocardial infarction). Chronic use of khat has been associated with the development of hypertension (Halbach, 1972) and an increased incidence of acute coronary vasospasm and myocardial infarction (Al-Motarreb *et al.*, 1997). (−)-S-cathinone has been shown to facilitate the electrically induced constriction of isolated rabbit ear and pulmonary arteries (Knoll, 1979), suggesting that the drug is capable of influencing vascular tone and as such may contribute to the development of myocardial ischaemia. Indeed, a direct vasoconstrictor action of (−)-S-cathinone has recently been demonstrated in our laboratories. In these studies, (−)-S-cathinone produced a dose-dependent vasoconstriction in both Langendorff perfused guinea-pig hearts (Fig. 4.) and isolated aortic rings (Fig. 5). The vasoconstriction was not inhibited by cocaine (10 μM), suggesting that the response was not an indirect sympathomimetic action (Al-Motarreb *et al.*, 2000). This contrasts with pharmacology at other sites where, as mentioned previously, (−)-S-cathinone is reported to have indirect actions by releasing noradrenaline (Kalix, 1983).

SOCIAL ASPECTS OF KHAT CHEWING IN YEMEN

Men

It is not common for a naïve person who is just starting to chew khat to feel the euphoric and stimulating effect of khat. It takes time to reach this point. However, continuous khat chewing for long enough will create the 'magic feeling' of khat (Al-Zubairy, 1981). The khat chewers usually try to make themselves thirsty. They do this by different means. They fast from morning just after breakfast to lunchtime, avoiding drinking water and eating fruits and all drinks and food that might reduce their thirst. In addition, they eat foods in the morning and for lunch that increase their need for water such as hot spicy food and salty meat extracts. If the khat chewer is not thirsty yet, they walk for long distances on the flat or climb mountains or they go to the hot Turkish baths. All of these steps increase the desire for water, which makes the khat taste more enjoyable and needed. People usually

provoke thirst in cooler cities like Sana'a and in the mountainous areas. In hot cities like Hodieda and Aden it is not necessary as people are usually thirsty.

Khat chewers devote many hours to 'His Majesty' the khat. In fact, khat is the main ruling factor in Yemeni life (Al-Zubairy, 1981). The impact of khat chewing in the life of Yemen is considerable (Kohli and Goldberg, 1982), much time being occupied in buying the leaves and in the chewing sessions. It affects work time, quality time with the family and influences matters of budget and health. The price of khat varies according to the type; fine quality khat is expensive. For some khat chewers, the daily cost of their habit exceeds expenditure on food for their families.

Figure 6. A typical *Mandher*. A khat session room with many large windows at the top of a multi-storey house

Women

Like men, there has been a long tradition of khat chewing among women who hold their own khat sessions, but less frequently. More recently women have started to chew khat more than before (Kandela, 2000). Women do not practise the fasting regimen, walking or going to the Turkish baths to get thirsty, because they stay at home most of the time, are less habituated and take the habit less seriously. There are two types of session for women (Khalil, 1997); khat sessions associated with social occasions such as a wedding party, a funeral or the celebration of a birth. These sessions are for old and married women. Girls and unmarried young women are not allowed to attend these occasions except for wedding parties. In general such sessions are usually overcrowded with more than 200 women gathered in one place. The second type of khat session for women is held on a regular basis for the sole purpose of chewing the leaves. This type of khat session has appeared only in recent years. Girls and unmarried women attend these sessions in small numbers. Usually they are from the same social level and mostly they are close friends. Just a few years ago, it was unacceptable for girls and unmarried women to either chew khat, smoke a water-pipe or smoke a cigarette. Now such sessions have become accepted to some extent. They are mostly held on a Thursday, although some women have started to chew khat daily just like the men.

Children

Some children start to chew khat as early as 8 years old or less. Usually, their fathers encourage them, on special occasions, such as a wedding party or funeral gathering. Fathers give school-aged children khat leaves to make them more energetic and stimulated, believing that khat chewing increases the ability to study better. Young adolescents have their own khat sessions as they start to form their own friendships.

The location of khat sessions

The room for a khat session occupies the mind of many Yemenis and is seen in the unique architecture of their houses. Thus, the design for a new house will include a large space for khat sessions. Two rooms usually are present in such houses. One named *Mandher* meaning 'viewer' and located at the top of a multi-storey house (Fig. 6). It is usually a small room but with many windows. Here one can see the surrounding vista. This allows the khat chewer to enjoy the view during a session. Another room for khat sessions is called *Mafraj*. This is located at ground floor level with a very large window opening to an area where there is a pool usually surrounded by trees and flowers. The pool contains a big fountain and several other small fountains. Khat chewers derive great excitement and enjoyment from the playing of these fountains. This type of *Mafraj* is present only in Sana'a city and its suburb (Fig. 7). A *Dewan* is a larger room for khat sessions. This is usually located on the ground or first floor. Some houses have a *Dewan* large enough for 200 khat chewers, which is used for wedding parties, funeral gatherings and election campaigns.

Most people chew khat in the afternoon, usually from 3 pm onwards. However, some chew it as early as 12 noon such as labourers, taxi drivers and shopkeepers who have to continue their work in the afternoon. Recently, some khat chewers have been found to prolong their session up to 10 pm. In some villages a few people chew khat in the morning, afternoon and in the evening. In the month of *Ramadan*, the fasting month, the people chew khat in the evening instead of the afternoon. They start their session just after dinner, usually around 8 pm. The session then continues until 12 o'clock midnight. Recently, some khat chewers have been found in session

Figure 7. A typical *Mafraj*. A khat session room located at the first floor with one side of the room opened in the form of a big window. In front of this window a pool with many fountains and a garden

Figure 8. A khat chewer showing the khat leaves being plucked and the large ball of leaves in the cheek

until 3 am. This may be related to the fact that, in Ramadan, Yemenis do not sleep until the dawn prayer (*Fajr*) around 5 am, and then they sleep in the morning.

The custom is for the khat chewers to sit on cotton mattresses surrounding the room on the floor with their left knee flexed and their right leg bent in the upright position. They lean on their left side using their left elbow resting against specially made hard box-shaped movable pillows called *Madka*. Smaller soft pillows are usually put on the top of the hard ones. Each person has his own 'band' of khat branches from which he picks off the soft younger leaves and chews them on one side of the mouth, usually the left side. Some people chew khat on the right side and rarely on both sides (Fig. 8). Only the juice is swallowed and by repeatedly adding leaves to the mouth, the cheek becomes increasingly full and the retained bolus can be seen as a bulge in the cheek. The session continues for 4–6 h and then the spent khat bolus is spat out. Tobacco water pipes (hubble - bubble) stand in the centre of the session room. Each consists of a tobacco bowl, a 3–4 foot high metal pipe, a water filter and a 20-foot flexible tube. The tobacco is ignited with a layer of charcoal and the flexible tube is passed from guest to guest (Lugman and Danowski, 1976). Recently cigarettes have replaced the water pipe, as these do not require so much preparation. Throughout the khat session, cold water is drunk in small amounts. Sometimes the water is mixed with a special water scent. Coca-Cola™, tea and water mixed with honey may replace the traditional cold water (Lugman and Danowski, 1976). However, these drinks were not accepted by the longterm khat chewers because it is claimed that they change the taste of the khat. In addition, most old people and some of the young ones criticize the changes believing that khat sessions have become less formal. These individuals claim that a more formal session enhances the generation of a relaxing atmosphere, especially in the presence of friends.

Perceived advantages of khat chewing

Yemenis consider that khat sessions represent an important social occasion to meet other people and for the exchange of ideas and information. Although friends and the same social classes are usually gathered together, they are open to anybody who wishes to attend, especially sessions attracting large numbers such as wedding parties, funeral gathering and election campaigns. At these gatherings, social class distinctions are forgotten. During a khat session, there is free talk conducted in a friendly atmosphere. This situation strengthens social relationships and leads to the flow of information among society. In addition, for some khat chewers, such as businessmen and government officials, various aspects of their work can be conducted during the session. It is also considered that a khat session allows the solving of social problems. Usually, Sheikhs and social figures intervene to solve peoples' problems at this stage before the courts. Compliment sessions also occur, in which friends express their wishes or congratulations to their friend or relatives. The demand for khat has been of economic benefit to village farmers and their families. Roads have been built to many villages for the first time, electricity supplies to the village, schools, all financed by local cooperation (McKee, 1987). There have also been other beneficial social changes such as building modern houses, digging water wells, buying agricultural machinery and cars. This has narrowed the large differences between city and village, created jobs in the villages and reduced the migration of villagers to the cities and beyond (Muharram, 1997).

Perceived disadvantages of khat chewing

A case advancing the proposition that the social use of khat has more disadvantages than advantages may also be made. The family in particular has been adversely affected. Thus, the relationship of the family members is weakened and the children are the first victims of the khat habit. The father returns home at lunchtime in a hurry, has his lunch, which is the main meal in Yemen and then leaves the house without having enough time to see either his children or wife. Even when the khat session takes place in his home, the situation is the same; he is in a hurry all the time to reach the khat session on time. Therefore children do not see their father in most cases and fathers do not have effective influence on their children.

Recently, khat chewing among women has increased sharply, and this can be observed in their behaviour, hurrying to reach the women's khat session on time. Husbands buy khat branches for their wives as part of their marital duties and to avoid her requesting him to stay home with her and the children in the afternoon rest period. Without a husband's moral and financial support of his wife, khat chewing by women would be much less. In the past, it was unacceptable for women to chew khat or smoke a water-pipe except for those of senior years (Khalil, 1997). The effect of this new practice is that children are left to play in the street with other children or at best children play in their home garden under the eye of a home-help woman who is usually non-Yemeni (Khalil, 1997). At worst, the children play unsupervised in the street. In the evening, the father returns home in a depressed state not wishing to speak to his family and he passes the time alone, sometimes reading the newspaper or watching television. Thus, there is disruption to the traditional pattern of family life and the children are severely disadvantaged. In the present climate of the popularity of the khat session, adults stopping the habit are faced with social isolation and this poses a major problem for a father and mother in setting the correct priorities. The daily chewing of khat consumes a large

fraction of the family budget. The leaves are purchased at the expense of other important items for the family, such as meat and fruit. It is estimated that 15.8% of the average family income is spent on khat (Al-Zubaidi, 1997).

The growing of khat is not as difficult as other crops such as coffee and grapes and it gives a good income for the farmer. This encourages the farmer to replace coffee trees with khat. At one time coffee was one of the main export products of Yemen. *Moka* is the former name of the country's main seaport, and it was applied to Arabic coffee by western traders, a name which is still in current use. The total area planted with khat increased from 79 020 hectares in 1990 to 92 662 hectares in 1995. This represents 48.7% of the area occupied by fruit plants. While coffee represents only 15.3% of the total agriculture products of the country, khat represented 29.8% in 1990, which had increased to 33.4% by 1995 (Al-Zubaidi, 1997).

The National Anti-khat Association

Although the khat chewing habit in Yemen is deeply rooted in society, being a common daily activity, there is an increasing awareness about the magnitude of the habit and its harmful effects on society. Many people believe that the practice should be curbed and on 16 January 1992, an anti-khat association was formed at a meeting of about 70 citizens of good social standing. The main objectives of this association are to draw society's attention to the social, economic and medical effects of the khat chewing habit by using the information media such as television, regular journals, booklets and posters, to create a social climate to discourage khat chewing especially by young people, and to use all possible means towards achieving a khat-free society.

The Yemeni Government policy on khat issues

Since 1972 no official government action has been taken against khat usage. In fact, most of the government officials are known to chew khat and there are no regulations to curb the khat habit. However, some government officials point out that the khat habit is a big social, medical and economic problem, which adversely reduces productivity of the community. It is realised that the problem is so deeply rooted that a solution will be extremely difficult, probably requiring a vigorous effort spanning several generations to get rid of it. However, currently Yemeni society does not consider that the khat habit is a real problem and this contributes to the magnitude of the effort required to redress the issue and this is undoubtedly the reason why to date no action has been taken.

In 1972, a time before the unification of the country, Prime Minister Mohsen Al-Aini's Government in North Yemen passed a resolution to up-root khat trees on land owned by the state and at the same time promulgated the harm of the khat habit. The resolution was backed by large scale mass media campaigns. Unfortunately, such action had very limited response from the public and was a total failure. However, this revealed that the problem was much too deep to be resolved by a simple resolution or legal action.

In the Southern part of Yemen prior to the unification with the North in 1990, there were also serious steps taken to fight khat. The government passed a legal ban on khat in December 1976 prohibiting its sale and purchase. Chewing the leaves was also prohibited under the legal ban except that it was allowed during the weekend. Unfortunately since the unification of Yemen, people throughout the unified hinterland have persisted in the habit.

CONCLUSIONS

The chewing of khat leaves is a well-established social habit in the Yemen and other parts of the Middle East and East Africa. The euphoric effects have been demonstrated to arise from the main constituent, (−)-S-cathinone, and there has been abundant research on the involvement of central neurotransmitters in this action. Cardiovascular actions due to the indirect sympathomimetic activity of (−)-S-cathinone have also been identified. Recent studies suggest that khat chewing may be associated with increased risk of cardiovascular complications. Abuse and overdose of amphetamine and 'ecstasy' (3,4-methylenedioxymethamphetamine, MDMA), to which (−)-S-cathinone is closely related, also cause an increased risk of myocardial infarction and cardiac arrhythmias. With the spread of use of (−)-S-cathinone, as khat, to the UK and USA there must be concerns of increased incidence of cardiac toxicity in these countries arising from its chronic use. Furthermore, a synthetic analogue, methcathinone ('Cat'), has emerged as a recreational drug of abuse (Sparago *et al.*, 1996). It has equivalent psychomotor activity to methamphet-amine and shows 5-HT neurotoxic activity but there is no information on its cardiovascular effects. Thus, while there is growing information on the effects of these agents on the central nervous system, there is a need for definitive studies on their actions on the heart and vasculature.

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