Neurobiology of Khat (*Catha edulis* Forsk)

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Abstract Around 20 million individuals in eastern Africa and the Arabian Peninsula chew the fresh leaves and twigs of *Catha edulis* Forsk (khat) for its pyschostimulatory effect, a practice deeply rooted in their traditions and cultures. In 1975, the main active ingredient of khat, cathinone, was identified, and found to be structurally related to and with effects similar to amphetamines and other psychostimulants. Animal studies on the neurobiology of khat are sparse and sporadic, being a neglected area of research in the field of drugs of abuse, and most work has focused on the action of cathinone rather than on khat extracts. Like other psychostimulants, the target of khat and cathinone action on the central nervous system is the dopaminergic system involving the nucleus accumbens. Studies on peripheral tissue also show it effects on the serotoninergic system. In animal self-administration studies, cathinone exhibits an addictive and abuse potential and produces psychomotor sensitization. However, there is little information from either human or animal studies on the short- and long-term effect on brain function of daily or frequent khat use with different patterns of consumption; nor is there information on pre-natal and adolescent exposure to khat or its neurotoxic potential. More research on the effects of khat use is needed as it contains a cocktail of alkaloids which is consumed by the user.

Keywords Drugs of abuse • Cathinone • Psychostimulants • Miraa • Qat • Amphetamine

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1 Introduction

Khat, *Catha edulis* Forsk, is, either daily or frequently, consumed by an estimated 20 million individuals for its pyschostimulatory effect attributed mainly to the presence of cathinone in its fresh leaves and twigs. Cathinone is structurally related to amphetamine and produces many similar effects in humans (see Odenwald 2014) though in some respects khat/cathinone effects may differ from known amphetamines. This chapter starts by a brief review of the history of khat use to show why it has not attracted the international exposure or research importance as other drugs of abuse, followed by a review of studies on its abuse potential, which mainly involve its main active ingredient, cathinone, and then possible mechanisms of action. The literature is sparse and sporadic given that it is a neglected area of research despite its potential adverse impact on the millions of individuals, families, society and economy where khat is grown and consumed routinely.

2 History of Khat Use

This hardy perennial dicotyledonous evergreen shrub is indigenous to and cultivated along eastern Africa, from Madagascar to the Horn of Africa, and the Arabian Peninsula, especially Yemen. Its fresh young leaves and twigs commonly called khat or by local traditional name (Fig. 1) are chewed for their psychostimulant effect by around 20 million inhabitants in these regions (Al-Motarreb et al. 2002; Saha and Dollery 2006; Magdum 2011). Figure 2 shows the distribution of khat use along eastern Africa and Arabian Peninsula with percentage of users and local names. Peter Forsskål, who died in an ill-fated 1761 Danish expedition to the Arabian Peninsula, gave the plant's botanical classification—*Catha edulis* belonging to the Celastraceae family. Carsten Niebuhr, who edited and published Forsskål's botanical collection from this expedition in *Flora-Aegytiaco-Arabia* (1775), named the plant *Catha edulis* Forsk in memory of his friend and colleague. When and

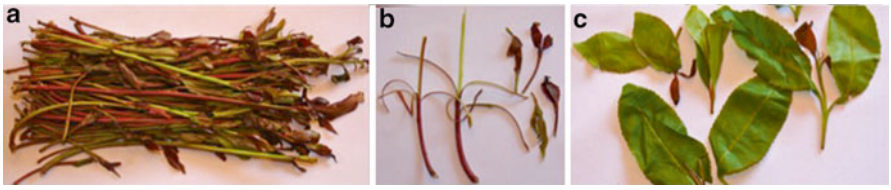

Fig. 1 (**a**) "Kilo" of khat. "Kilo" is not a weight reference but a term used for a bundle. Three to four bundles can be consumed per day or more when there is khat party or binging. (**b**) The leaves and the bark of the twigs are chewed and tucked into the cheek. (**c**) Muguka, leaves from different part of *Catha edulis,* cheaper than miraa and the use of which has increased in recent times

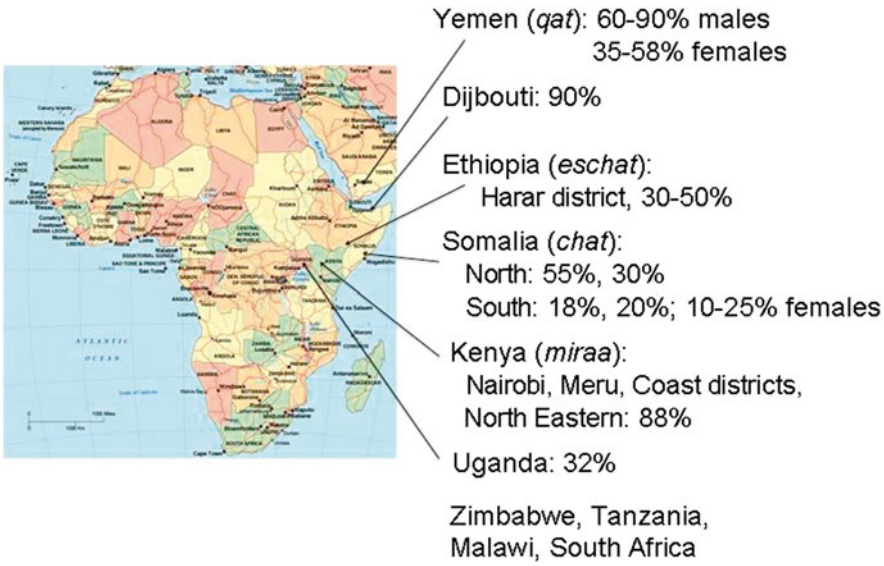

Fig. 2 Major areas of khat use along the eastern Africa and Arabian Peninsula with local names for khat and available estimated percentage of users. (Compiled from various sources)

where the chewing of the young fresh leaves and twigs of *Catha edulis* (khat) started is not known. According to some its use can be traced to the Ancient Egyptians who considered the plant a divine food, which was capable of releasing humanity's divinity for transcendence into "apotheosis" making the person god-like (Giannini et al. 1986). Whether the use originated in Ethiopia or Yemen is a debated issue.

Several early travellers to the Arabian Peninsula commented this habit.

In the 18th century, Neibuhr wrote "…never saw the Arabian use opium like the Turks and Persians. Instead of taking this gratification, they chew kaad [khat]. These are buds of a certain tree, which are brought in small boxes from the hills of Yemen." In early 19th century, Abdullah bin Adbul Kadir (1854), a traveller from Malay, described the prevalence of khat chewing in Al Hudaydah, Yemen: "You observed a new peculiarity in this city—everyone chewed leaves as goats chew the cud. There is a type of leaf, rather wide and about two fingers in length, which is widely sold, as people would consume these leaves just as they are; unlike betel leaves, which need certain condiments to go with them, these leaves were just stuffed fully into the mouth and munched. Thus when people gathered around, the remnants from these leaves would pile up in front of them. When they spat, their saliva was green. I then queried them on this matter: 'What benefits are there to be gained from eating these leaves?' To which they replied, 'None whatsoever, it's just another expense for us as we've grown accustomed to it'. Those who consume these leaves have to eat lots of ghee [clarified butter] and honey, for they would fall ill otherwise. The leaves are known as *Kad* [khat]." These and other observations are similar of the use of coca leaves among the people of western South America.

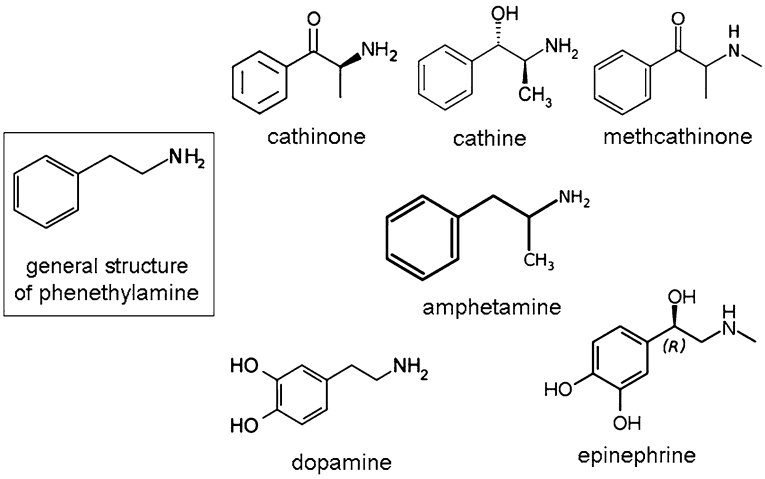

Fig. 3 Phenethylamine group of molecules: note that the addition or substitution on the phenyl ring, ethyl chain or amino group of the molecule produces a large group of psychoactive and bioactive molecules including cathinone and cathine, which are active ingredients found in khat

In 1909, the epidemic of opium use in China resulted in the Shanghai conference, which led to the 1912 International Opium Convention of The Hague, the start of the international regulations in the trafficking, trading and controlling access to drugs of abuse. This convention was subsequently taken up by the League of Nations, and later by the United Nations. In 1935, the matter of khat use and its regulation was first discussed, and debated on and off for a number of years, ultimately cumulating in the resolution that khat use was a regional issue and as confined to a few countries (WHO 1964), possibly not an issue of international regulation, but one that needed to be studied further.

In the deliberations on whether to enter khat on the list of internationally controlled substances, it was recognized that its active ingredient had to be isolated, identified, and its abuse potential studied before a decision could be made. In the 1930s, Wolfes had isolated cathine (d-norpseudoephedrine), but subsequent studies showed that cathine could not fully account for the activity of khat in the user. The United Nations Narcotics Laboratory, after studying fresh khat samples from different sources, isolated 20 components, which included a large group of alkaloids (cathedulins), and in particular, isolated cathinone (alpha-aminopropiophenone), a liable substance, which was a more active ingredient of khat than cathine (UNODC 1980). Once cathinone has been isolated, synthesized and its molecular structure determined (Schorno and Steinegger 1978; Braendan 1979) it was found to be similar to amphetamine, both belonging to the phenethylamine group (Fig. 3). In 1980, the World Health Organisation (WHO) classified khat as a drug of abuse that can produce mild to moderate psychological dependence. Currently, khat and cathinone are on the list of banned or controlled substances in several countries and khat has a higher international profile due to the spread of its use to parts of the world where it was not originally used.

3 Pharmacological Effects on the Dopamine, Serotonin, and Norepinephrine Systems

Two widely used techniques to determine where in the brain a drug could affect neurotransmitter release are *in vitro* tissue and *in vivo* microdialysis methods. Of the number of neurotransmitters systems in the brain, studies on drugs of abuse have highlighted the role of three: dopamine, serotonin, and norepinephrine (noradrenaline). In an *in vitro* study of rabbit striatal and rat nucleus accumbens tissue prelabeled with ^{3}H-dopamine, there was increase in the release of radioactivity on cathinone application (Kalix 1986; Kalix et al. 1987). However, without further analysis, it is not possible to conclude if the increased radioactivity released from these tissues was due only to dopamine or a mixture of dopamine and its metabolites. In *in vivo* microdialysis studies of the anterior caudate-putamen and nucleus accumbens, (−)-cathinone and (+)-amphetamine increased dopamine levels in a dose-dependent manner with amphetamine having a higher effect at the largest doses used, but at lower doses the amphetamine difference was only seen in the nucleus accumbens (Pehek et al. 1990). In synaptosomal preparation, d,l-cathinone like d-amphetamine, released and blocked uptake of ^{3}H-dopamine, and with repeated high doses of d,l-cathinone there was long-lasting dopamine depletion in various rat brain regions and decreased number of dopamine uptake sites similar to amphetamines, but regional brain levels of norepinephrine and serotonin were not altered (Wagner et al. 1982; Fleckenstein et al. 1999). Cathinone also inhibited the firing of dopaminergic neurons (reversible with haloperidol) in the substantia nigra pars compacta, with potency similar to amphetamine (Mereu et al. 1983). These studies, along with the drug discrimination studies (described below), further emphasized the role of dopamine in the action of cathinone, but this is probably only a part of its mechanism. Dopamine systems are involved in motor function through the striatal tissue and "mental" reward system involving the nucleus accumbens. Hence, increase in dopamine could affect both motor and mental function, though cathinone appears to have a less disruptive effect on motor behavior compared to amphetamine.

Like amphetamine, but a third less potent, cathinone induces release of ^{3}H-serotonin (5-HT) from rat striatal preparations (Kalix 1984) and has four times higher affinity for serotonin receptor in an isolated rat stomach fundus preparation (Glennon and Liebowitz 1982). Repeated high doses of cathinone do not alter regional brain levels of serotonin (Wagner et al. 1982). However, high-dose administrations of cathinone to striatal synaptosomes obtained from drug-treated rats rapidly decreased serotonin transporter function, which should result in higher serotonin levels *in vivo* (Fleckenstein et al. 1999). Thus, while, *in vitro* studies show that cathinone causes release of serotonin and has higher binding affinity to peripheral serotonin receptors compared to amphetamine, serotonin is not found to be involved in studies of cathinone's discriminative mechanism (discussed in later section), but this does not rule out serotonin's involvement in other effects of cathinone.

While regional brain levels of norepinephrine (noradrenaline) or serotonin are not altered on a long-term basis by repeated administration of d,l-cathinone

(Wagner et al. 1982), there is increased release of radioactivity from rabbit heart atria pre-labeled with ^{3}H-norepinephrine (Kalix 1983). The effect on rat right ventricle may involve competitive blockade of norepinephrine transporter rather than simple displacement of norepinephrine (Cleary et al. 2002). These changes in peripheral neurotransmitters are not unexpected as khat, cathinone, and cathine produce sympathomimetic effects in the user, but whether the central neural mechanism involve norepinephrine is not known.

4 Experimental Studies on Behavior and Potential for Addiction

4.1 Behavioral Studies

Like amphetamine, cathinone or khat extract produce psychomotor sensitization -hyperlocomotion (Kalix 1980a; Calcagnetti and Schechter 1992a; Banjaw et al. 2005), behavioral sensitization (Banjaw and Schmidt 2005)—as well as pre-pulse inhibition (Banjaw et al. 2005), and increased isolation induced aggression in rats (Banjaw et al. 2006). The psychomotor sensitization reflects nucleus accumbens involvement (Wise and Bozarth 1987) and the psychostimulant-induced activity is blocked by the dopamine release inhibitors CGS 10746B and isradipine (Calcagnetti and Schechter 1992b).

Like other psychostimulants, cathinone produces a hyperthermic response (Kalix 1980b), which is linked to the neurotoxic effect of amphetamines. Treatment of rats with khat extract produces seizures and decreases seizure threshold elicited by pentylenetetrazol (Oyungu et al. 2007, 2009). In addition, cathinone induces head-twitch response (Connor et al. 2002), which is a behavioral proxy for serotonin receptor 5-HT_{2A} activation (Schmid and Bohn 2010). This is one of the serotonin receptors postulated to be involved in the mechanism of activity of hallucinogens (Vollenweider 2001). Taken together, these findings suggest that khat activity could have some other different and subtle effects compared to amphetamines.

4.2 Addictive and Abuse Potentials

4.2.1 Self-administration and Self-reinforcing Experimental Studies

A routinely used experimental approach to assess whether a drug has addictive and abuse potential is to avail the drug to laboratory animals and observe whether they will self-administer the drug. The frequency and amount of the self-administration gives an indicator of the reinforcing property and abuse potential of the drug.

Using a self –administration continuous set-up, Yanagita (1979, 1986) found in rhesus monkeys a spree type usage of cathinone, as seen with cocaine, with spree periods of 6–59 h. Compared to amphetamine and cocaine, both d,l-and l-cathinone maintained significantly higher rates of responding with l-cathinone being more potent (Schuster and Johanson 1979). Woolverton and Johanson (1984) found the reinforcing effects of d,l-cathinone were comparable to cocaine. In mice (Kuz'min and Evartan 1991), comparison of the pattern of intravenous self-administration of morphine, cocaine, amphetamine, cathinone, and ephedrine produced similar bell-shaped concentration curves typical of compounds with addictive potential. Rats also demonstrated cathinone self-administration, which was increased by block of the dopamine D1 receptor with SCH 2390 but not with D2 receptor antagonist, spiperone, suggesting that dopamine D1 receptors are involved in cathinone's reinforcing effects (Gosnell et al. 1996).

4.2.2 Conditioned Place Preference

In conditioned place preference (CPP), an experimental approach to assess the abuse potential of a drug, rats given cathinone either by the intravenous (iv) or intracerebroventricular (ICV) route showed preference for the environment to which they were exposed to with cathinone (Schechter 1991a) and this effect was dose dependent (Schechter and Meehan 1993). Interestingly, no tolerance to CPP was found with repeated cathinone administration unlike that observed in drug discriminative behavior (Schechter and McBurney 1991). CPP was attenuated or blocked by pretreatment with dopamine release inhibitor, CGS 10746B (Schechter 1991a; Calcagnetti and Schechter 1993).

4.2.3 Drug Discrimination Experimental Studies

While self-reinforcing and CPP studies provided evidence that cathinone has addictive and abuse potential, these experimental approaches cannot answer the question of whether (1) the feeling produced in an animal (interoceptive cue) with cathinone is similar to other drugs, especially other psychostimulants, and (2) if mechanism of action of cathinone is similar to that of other known psychostimulants. In the drug discrimination experimental paradigm, the animal is trained to perform a particular task under the influence of a drug and another in the absence of that drug. In a two-lever food-motivated operant task, animals press one lever when in the drug induced mental state (interoceptive cue) and the other when not. The drug used for the training is the training drug, and once the animal has learnt the task it is given other test drugs, and if the animal presses the levers correctly, it is assumed that the interoceptive cue induced in the animal by the test drug is similar to that produced by the training drug.

Table 1 summarizes the drugs that have been found to be able to replace or generalize for the cathinone cue and those that could not. The drugs that can substitute for

Table 1 Drugs that can or cannot substitute for cathinone in the drug discrimination experimental paradigm

Can	Cannot
d-amphetamine[a,b,c]	Apomorphine[a,d,c]
Cocaine[a, e]	Fenfluramine[a]
Pripradol[a]	Fentyamyl[a]
Cathine[a]	Phydroxyamphetamine[a,f]
Methamphetamine[e]	Phenylethylamine[a,d]
Methylphenidate[a]	Deuterated phenylehylamine[e,d,g]
	Chlorodiazepoxide[a]

[a]Goudie et al. (1986)
[b]Rosecrans et al. (1979)
[c]Schechter et al. (1984)
[d]Apomorphine, phenethylamine and deuterated phenethylamine produced 29 % and 60 % generalization (substitution) for the cathinone cue, respectively
[e]Schechter and Gennon (1985)
[f]A polar conger of amphetamine
[g]A long lasting derivative of phenylethylamine which is resistant to metabolism by monoamine oxidase

cathinone are known psychostimulants, and cathinone can also substitute when amphetamine or cocaine is used as the training drug. These results support the view that cathinone is a psychostimulant and represents a "natural" amphetamine (Kalix 1992). When cathinone was used to substitute for amphetamine as the test drug, it was found to be twice as potent as amphetamine (Rosecrans et al. 1979). In rats, injecting cathinone into the nucleus accumbens produced discriminative behavior at a much lower concentration than either by intraperitoneal or ICV route, indicating that one site of action of cathinone in the brain is the nucleus accumbens (Schechter et al. 1992).

In the drug discrimination studies, the time-course for cathinone interoceptive cue behavior in rats was earlier than amphetamine (5 vs. 15–30 min) and effective for about 1 h (Schechter 1989).

Positive results were found in all drug discrimination studies in which the role of dopamine as part of cathinone's mechanism of action was tested, i.e. the dopaminergic system is involved as reported for other psychostimulants. However, depending on the agent used, the assessment of the involvement of the dopaminergic system in cathinone's effect differs. Unlike amphetamine, with haloperidol, a dopamine antagonist, Goudie et al. (1986) found at most 50 % reduction in the cathinone cue, and Rosecrans et al. (1979) found that it did not affect the generalization of amphetamine stimulus to cathinone. Pretreatment with haloperidol failed to alter the stimulant properties of cathinone but did partially antagonize those of amphetamine and cocaine (Huang and Wilson 1986) and attenuated cathinone discrimination (Schechter 1986c). However, co-administration with CGS 1074613, a dopamine release inhibitor, totally antagonized cathinone's generalization to amphetamine (Schechter and Bojaw 1988) and pretreatment blocked cathinone discrimination (Schechter 1992). Use of serotonin antagonist, BC 105/B (Rosecrans et al. 1979), 5-HT receptor blocker, pirenperone (Schechter 1986a), 5-HT_3 receptor antagonist, MDL 72222 (Schechter 1992) or inhibiting serotonin synthesis with p-chlorophenylalanine had no effect on the cathinone

discrimination in rats (Schechter 1991b). Phenoxybenzamine, an alpha-adrenergic antagonist, also had no effect (Rosecrans et al. 1979). Thus, at least from drug discrimination behavior studies, alteration of the dopaminergic neurotransmitter system appears to play a major role in the mechanism of action of cathinone.

5 Tolerance

It is widely assumed khat does not produce tolerance in humans but, as pointed out by Halbach (1979), this could be simply due to self-limiting process of its ingestion. And, in drug discrimination studies with cathinone and cathine development of tolerance is observed. With chronic administration of cathinone over 8 days, tolerance developed as shown by the decrease in the discriminative ability of rats and lasted up to 15 days after cessation of the chronic cathinone treatment (Schechter 1986b). With the same experimental approach, acute tolerance to cathine was found to develop when rats were tested 24 h after cathinone treatment (Schechter 1990a), and this tolerance to cathine was also seen with consecutive administration of cathine, but not with cathinone (Schechter 1990a), and involved the dopaminergic system (Schechter 1990b).

While cathinone shows similarity with amphetamine in its effect and mechanism of action, there are several studies that suggest that cathinone differs in an important aspect from amphetamine that could make it a more desirable drug of use. As Rosecrans et al. (1979) commented, "…dl-cathinone is self-administered at lower doses than d-amphetamine, but was less effective than d-amphetamine in disrupting the operant behavior of primates. Thus, dl-cathinone appears less disruptive to behavior, which might explain why this drug was more potent than d-amphetamine in our discrimination study and in self-administration research. From this, one might also predict that individuals using this drug would be less disrupted and better able to function under its effects. In addition, this drug might produce fewer long term d- amphetamine-like behavioral problems because of its apparent lack of a dopamine agonist action." However, studies show that cathinone increases levels of dopamine, but as pointed out there are at least two functions dopamine is involved in—motor function and reward function. Hence it is possible that cathinone has more effect on the reward function than on the motor function.

6 Possible Differences in the Overall Effect of Khat and Cathinone

Most of the studies on khat focus on the effect of cathinone and not on khat (*Catha edulis*) *per se*. There may be functional differences between cathinone and the cocktail of active substances (cathinone, cathine, norephedrine, cathedulins and other alkaloids) ingested by chewing khat. In post-mortem neurotransmitter analysis done 5 days after 9 consecutive days of S-(−)-cathinone, d-(−)-amphetamine or *Catha edulis* extract treatment in rats, for study of behavioral sensitization, Banjaw and

Schmidt (2005) found only *Catha edulis* extract treated rats had reduced levels of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the anterior caudate-putamen. In a study of isolation induced aggression (Banjaw et al. 2006), compared to cathinone, rats treated with *Catha edulis* extract had higher elevation of dopamine in the nucleus accumbens with both showing similar depletion of serotonin and 5-hydroindoleacetic acid in the anterior and posterior striatum. Hence khat, as a whole, may cause changes that are different compared to cathinone and these changes may also differ depending on the pattern of khat use, i.e., daily, frequently or binging. In addition, khat contains 62 types of cathedulins (Kite et al. 2003) most of which have not been studied for their biological effects. For example, study of cathedulin fractions showed increased release of dopamine from striatal tissue and binding to both D1 and D2 receptors (Houghton et al. 2011).

7 Conclusions and Future Perspectives

Studies on neural basis of the action of khat and its most active ingredient, cathinone, are few and sporadic. Until recently khat was hardly known outside the region of its traditional and culture use. After the isolation of cathinone, its structural determination and effects, it was found to be similar to amphetamine and other psychostimulants. Khat can be considered a natural source of amphetamine, as coca leaves are the natural source of cocaine. While cathinone shows a clear abuse potential, the effects of khat in users are not clear, as the intake is limited due to the method of consumption as well as the different patterns of consumption. Cathinone, like other psychostimulants, acts in part via the dopaminergic system affecting the reward and motor circuitry of the brain. However, cathinone appears to be less disruptive to motor function compared to amphetamine and this property could make it a more desirable drug of use. Analysis by Nutt et al. (2007) put khat dependence and physical harm lower than tobacco, alcohol, and cannabis, but given the paucity of studies, khat may be a more potent natural drug of abuse than the current literature suggests. How much cathinone the khat user consumes is not known, but a number of socioeconomic studies show that regular khat consumption has a negative impact on the user, family, society, and national economy. There are, in addition, several important questions that need urgent study (1) the short- and long-term effects on executive and cognitive brain function with routine khat use, especially as khat use often starts during the adolescent period, (2) as the traditional and culture control have eroded, khat use is also reported to have increased among women, and pre-natal and post-natal exposure to khat needs to assessed, and (3) there is a complete lack of information on its neurotoxic effects in terms of brain regions and neurotransmitter systems. Despite the historical paucity of studies on khat and cathinone, understanding of action of cathinone-like substances will increase in coming years due to increasing recreational use of synthetic cathinones as designer drugs of abuse—mephedrone, methylone, methcathinone, “bath salts”, “plant food”—in high-income countries. However, studies on khat (*Catha edulis* Forsk) itself cannot be neglected as it is khat with its of cocktail of alkaloids that is consumed by a large number of persons.

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