CHEMICAL PHARMACOLOGY OF KHAT LEAVES

INTRODUCTION:
Khat or qat (Catha edulis) is an evergreen shrub belonging to the family celastraceae. It grows in Yemen and Southern Arabia as well as in certain East African countries such as Ethiopia, Somalia, Djibouti and Kenya. The use of khat has traditionally been confined to the regions where khat is grown because the shoots must be used fresh for the desired effects. In recent years, however, the economic importance and consumption of khat leaves have increased dramatically. This change is due to improved road and air transport, which has allowed a much wider distribution. The cathinone content of the leaves was estimated to be approx. 0.9 mg/g fresh leaves weight by gas chromatography/mass spectrometry (CC/MS) using amphetamine as the internal standard. The difference between khat and other stimulant agents is related to the special way in which khat is consumed.

Young, fresh khat leaves are chewed and held in the lower buckle pouch unilaterally in a bolus for 3 hr or longer. In Italy, as of January 10, 1988, such alkaloids have been considered illegal drugs, but it must be mentioned that only cathines reported 1990 Law which principally governs the control of drugs of abuse. Maximum amount of cathine allowed for individual use (this concept is called 'medium daily dose') was established in March 7 1990, and corresponds to 0.06 g. Above this amount its possession is considered. General plant of khat is shown in fig.1.

CHEMICAL CONSTITUENTS OF KHAT:
There are three main alkaloids present in khat leaves S-(−) –cathinone (s-aminopropriophenone), norepseudephedrine (cathine) and norephedrine. Different types of alkaloids present in khat are shown in fig.4. There are also small amounts of ethereal oil, sterols and triterpenes, together with 5% protein which has insignificant nutritional value. Structures of cathinone and amphetamine are shown in fig.2.

ABSTRACT
The leaves of khat (Catha edulis Forsk, belonging to the celastraceous family), are chewed as a social habit for the central stimulant action due to presence of cathinone as a main constituent. Khat leaves contain high proportions of alkaloids, vitamins, proteins and tannins in small amounts. Norephedrine & norpseudo ephedrine are responsible for its stimulant activity, which are metabolic products of cathinone. These are identified by analytical methods like gas chromatography. Khat leaves shows adverse effects on health mainly on heart, liver and CNS. It increases blood pressure which coincides with rising of cathinone levels in plasma and we observe the positive inotropic and chronotropic actions on heart by the cathinone which indirectly acts as a sympathomimetic amine. Sometimes it also shows negative inotropic action due to impaired coronary perfusion. It elevates the blood glucose levels by glycogenolysis in liver and skeletal muscles; a beta-2 adrenoceptor shows mediated response. khat/cathinone induces the release of dopamine from presynaptic storage sites and chronic administration of either the whole extract or cathinone (100 mg/kg) results in a significant depletion of dopamine in several brain areas, particularly on the nigrostriatal dopamine terminal projections. This is similar to the neurotoxic effect of chronic amphetamine. Secondary metabolites phenolic, flavonoid, and tannins like shows anti oxidant activity.

Keywords: khat, cathinone, nor ephedrine.
Ascorbic acid is also present in the leaves. Khat leaves also contain tannin (7–14% by weight in dried leaves) and minute amount of thiamin, niacin, riboflavin, iron and amino acids. Apart from tannin, these substances are unlikely to contribute to the biological effect of khat. S(-)-cathinone is relatively unstable and decomposes within a few days of picking or if the leaf is dried into (+)-norpseudoephedrine and norephedrine. These are shown in fig.3. Chemical Thus, only freshly picked leaves have the full efficacy. It also contain small amount of fluoride. Norpseudoephedrine and norephedrine are slowly absorbed and then excreted.

**Chemistry of Khat:**

Khat consumers' preference for fresh drug material is due to the presence of cathinone that is considered the main CNS-active component of the Khat leaves. This compound was isolated and identified in 1975 by a group of researchers of the United Nations Narcotics Laboratory working on a project initiated in the early seventies. Cathinone, being a ketoamine base, is extremely unstable and, in particular, it can be transformed into (+) - norpseudoephedrine and (-) - norephedrine by enzymatic reduction. It can also be oxidized to give 1-phenyl-1,2-propandione, while the cathinone as 3,6-dimethyl-2,5-diphenylpyrazine are purely artifacts of the isolation. In addition to the known phenylpropylamines cathinone, norephedrine and norpseudoephedrine (cathine), the presence of other amines such as merucathine, pseudomerucathine and merucathinone have been identified. Pharmacological studies are still being conducted on these compounds, but it is presently believed that the stimulating effect of the plant is principally due to cathine and cathinone. Chemical decomposition of cathinone is shown in fig.5. Due to the presence of secondary metabolites phenolic, flavonoid, and tannins like shows antioxidative activity.
PHARMACOLOGICAL ACTIONS OF KHAT:

1. CARDIOVASCULAR EFFECTS OF KHAT:

In general regular khat chewing causes increasing of mean diastolic blood pressure it also co inside with elevated plasma levels of cathinone. It has positive inotropic and chronotropic actions in atria. Cathinone indirectly act as sympathomimetic amine. Cathinone also causes constriction of the coronary vasculature. It is occurred by cathinone metabolite called norpseudoephedrine. There was also negative inotropy due to impaired coronary perfusion. Mechanism of vasoconstrictor action is shown in fig.6.

3,6-DIMETYL-2,5-DIPHENYL PYRAZINE

Figure 5: Chemical decomposition of Cathinone

Cathinone can act as an indirectly acting sympathomimetic amine (ISA mechanism) through uptake into sympathetic neurones and release of noradrenaline (NA) onto α-adrenoceptors. It can also act via a sympathomimetic-independent mechanism probably directly on trace amine-associated receptors. Another vascular complication of chronic khat chewing is a significantly much higher incident of haemorrhoids. It has a clear evidence that 62% of khat chewers had haemorrhoids, of which 45.4% of the group under haemorrhoidectomy, compared with only 4% of non-chewers displaying.

2. EFFECT OF KHAT ON DIABETES MELLITUS TYPE 2:

The sympathomimetic actions of cathinone would be expected to raise plasma catecholamine levels. These catecholamines would increase blood glucose levels by activation of glycogenolysis in skeletal muscles and the liver; a beta2-adrenoceptor-mediated response. There is also inhibition of insulin release from the pancreatic β-cells, via beta2-adrenoceptor stimulation which would also elevate blood glucose level and serum glucose levels after 2 hours of khat chewing. Khat action on liver and glucose levels is shown in fig. 7.

Figure 6: Cathinone acts via a sympathomimetic-independent mechanism directly on trace amine-associated receptors.

Figure 7: Action of cathinone on blood sugar level
Increase in catecholamine levels leads to increase in Glycogenolysis which eventually elevates blood glucose levels. Raised glucose levels will result in compensatory increases in insulin release. This study also showed that chewing of khat caused a significant reduction in plasma cholesterol throughout the 6-month period. This of course would be a favourable consequence of khat chewing in the context of cardiovascular risk. Clearly, our knowledge about the effects of cathinone and khat chewing on plasma glucose and insulin levels is very sparse and controlled studies need to be undertaken.

3. EFFECT OF KHAT ON CNS:

There have been reports (albeit few) of severe and disabling neurological illness associated with khat chewing. Recently reported such a case in a 58 year old Somali man living in UK who presented with leukoencephalopathy associated with khat misuse. In addition, the CNS stimulating effect of khat has shown to reach the level of acute and chronic toxicity as evidenced by growing reports of psychiatric morbidity associated with khat use. Upto date effect of khat on neuroprotective factors like BDNF, lipid peroxidase is not clear. khat/cathinone induces the release of dopamine from presynaptic storage sites and chronic administration of either the whole extract or cathinone (100 mg/kg) results in a significant depletion of dopamine in several brain areas, particularly on the nigrostriatal dopamine terminal projections. This is similar to the neurotoxic effect of chronic amphetamine administration on the dopaminergic innervations of caudate, inducing their degeneration.

4. ANTIOXIDANT ACTIVITY:

Total phenolic, flavonoid, and tannin contents of 21 Ethiopian khat (Catha edulis Forsk) leaves and their related antioxidant activities were determined in the extracts of the young leaves, matured leaves, and tips of tender stem near the young shoots. A simplified, rapid, and robust method was also optimized for the analysis of total tannins using ovalbumin as a precipitating agent and Folin Denis reagent as the quantification technique. Among the solvents tested, aqueous mixtures of 70 and 80% acetone and 80% methanol provided higher phenolic compounds extraction efficiency than the corresponding pure solvents and other binary mixtures. Total tannin content ranged between 70.2–153 mg tannic acid equivalent/g and 49.4–103 mg tannic acid equivalent/g of the dried young leaves and tips of tender stems, respectively. Similarly, total flavonoids concentration as catechin equivalent varied between 26 to 75 and 26 to 56 mg catechin equivalent/g of dried young leaves and tips of tender stems, respectively. Khat cultivars were found to pose a substantial antioxidative activity (as ascorbic acid equivalent) ranging between 173–290 and 118–211 mg ascorbic acid equivalent/g of dried young leaves and tips of tender stems near the young shoot, respectively. Matured leaves of khat accumulated a significantly lower concentration of secondary metabolites compared to the corresponding young leaves. This study reveals that khat leaves and tender stems accumulated a substantial amount of secondary metabolites, particularly tannins.

CONCLUSION:

The leaves of the tree Catha edulis, known as khat, have for centuries been chewed for psychostimulant and socializing effects by people living in east African and Arabian Peninsula. Traditionally khat chewing has been viewed as an aid to relieving fatigue and has some place in self-medication of depression. While the psychological effects of chronic khat use have been the subject of much debate on its influence of social structure, there is now mounting cause for concern over the health effects on a wide range of peripheral organs. It also have anti oxidant activity. This review has identified a wide range of adverse effects on the cardiovascular, hepatic system, central nervous system.

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