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Phytochemical and biological activities of Khat (*Catha edulis* Forsk): A review

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Abstract

Catha edulis Forsk (Celastraceae)], is an ancient plant associated with psychological, health and socioeconomic issues on humans. Khat (the flower of paradise) is a plant vastly used on the African continent. Many different compounds are found in khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals. The phenylalkylamines and the cathedulins are the major alkaloids which are structurally related to amphetamine. The major effects of khat include those on the gastro-intestinal system and on the nervous system. Constipation, urine retention and acute cardiovascular effects may be regarded as autonomic (peripheral) nervous system effects; increased alertness, dependence, tolerance and psychiatric symptoms as effects on the central nervous system. The main toxic effects include increased blood pressure, tachycardia, insomnia, anorexia, constipation, general malaise, irritability, migraine and impaired sexual potency in men.

Keywords: Khat (*Catha edulis*), chemical compounds, plants, bioactivities

Introduction

There have been concerns raised about potential individual physiological harms and wider societal harms associated with, or caused by, the use of the naturally-occurring plant stimulant khat. Khat (*Catha edulis*) is a woody plant cultivated predominantly in north east Africa and the Arabian Peninsula. Khat (*Catha edulis*, family: Celastraceae) is a plant grown in East-Africa (mainly in Somalia, Kenya, Djibuti, Yemen and Ethiopia) and the south west of the Arabian Peninsula. In these countries the chewing of khat is very common; it is consumed as qat and kat in Yemen; chat in Ethiopia; miraa, kijiti, gomba, mbachu or veve in Kenya; and as mairungi in Uganda ^[1]. Khat is chewed habitually by users for its euphoric effects and as a recreational drug ^[2, 3]. The psychostimulant component of the khat is cathinone, which is released within 15–45 minutes during chewing ^[4]. Recent reports indicate that 80–90% of East African males and 10–60% of the East African females use khat on a daily basis ^[5]. The main active compounds of khat are cathinone and cathine, although over 40 compounds have been identified in khat extract ^[6]. Cathinone and cathine are scheduled substances under the 1971 UN Convention on Psychotropic Substances. Similar compounds, cathinones, have been manufactured to create novel psychoactive substances, sometimes referred to as ‘legal highs’. Some of these manufactured cathinones have been associated with high levels of harms ^[7]. Various education programs designed to demonstrate the negative effects of the routine social use of this plant could be developed and implemented, in order to create awareness in the khat-chewing community. Such ventures, which could be carried out via appropriate health education and mass media campaigns, could bring an end to the devastating consequences associated with the use of this product, and certainly, a constructive and positive outcome on this khat-chewing population in the future.

Chemical Compounds

Many of Chemical studies are 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 (p)-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. The long-sought phenylalkylamine was finally isolated, characterized as (7)-a-aminopropiophe none and given the name (7)-cathinone ^[8]. Later studies showed that cathinone is present at a high concentration in the young leaves, while being converted

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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 [9]. The reviews by Szendrei [10, 11], provide a comprehensive description of the progress in the understanding of khat chemistry during that period. Many different compounds are found in khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals [12-14]. The phenylalkylamines and the cathedulins are the major alkaloids. The cathedulins are based on a polyhydroxylated sesquiterpene skeleton and are basically polyesters of euonyminol. Recently, 62 different cathedulins from fresh khat leaves were characterized [15]. The khat phenylalkylamines comprise cathinone [S-(–)-cathinone], and the two diastereoisomers cathine [1S, 2S-(+)-norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R, 2S-(–)-norephedrine]. These compounds are structurally related to amphetamine and noradrenaline. The plant contains the (–)-enantiomer of cathinone only. Thus, the naturally occurring S-(–)-cathinone has the same absolute configuration as S-(+)-amphetamine. Cathinone is mainly found in the young leaves and shoots. During maturation, cathinone is metabolized to cathine [(+)-norpseudoephedrine] and (–)-norephedrine the leaves contain [(+)-norpseudoephedrine] and (–)-norephedrine in a ratio of approximately 4:1. Other phenylalkylamine alkaloids found in khat leaves are the phenylpentenylamines merucathinone, pseudomerucathine and merucathine. These compounds seem to contribute less to the stimulant effects of khat [16, 17].

Biological activities

Khat has many different compounds and so khat chewing may have many different effects.

1. Behavioral effects

Rats fed *C. edulis* material (extract or whole) show increased locomotor activity and reduced weight gain [18]. Retardation of growth rate was considered to be due to decreased absorption of food and not due to decreased food consumption. In pregnant rats, khat reduces food consumption and maternal weight gain, and also lowers the food efficiency index. Many reports have since confirmed the enhanced locomotor activity. In addition, khat extracts and (–)-cathinone produce stereotyped behavior, self-administration and anorectic effects in animal species. Qualitatively, this behavior is similar to that evoked by amphetamine [S-(+)-amphetamine] [19].

2. Cardiovascular effects

Khat chewing induces small and transient rises in blood pressure and heart rate. Cathinone (0.5 mg base/kg of body weight) has similar effects coinciding with the presence of cathinone in blood plasma. These effects could be blocked by the beta1-adrenoreceptor blocker atenolol, but not by the alpha1-adrenoreceptor blocker indoramin, indicating mediation through stimulation of beta1-adrenoreceptors [20].

3. Genotoxicity and teratogenic effects

Orally administered khat extract induced dominant lethal mutations in mice, chromosomal aberrations in sperm cells in mice, and teratogenic effects in rats. With the micronucleus test to determine genetic damage, an 8-fold

increase in micronucleated buccal mucosa cells was seen among khat chewing individuals living in the area of the horn of Africa. Khat consumption did not lead to a detectable elevation of micronucleated bladder mucosa cells. Among heavy khat chewers, 81% of the micronuclei had a centromere signal indicating that khat is aneuploidogenic. The effect of khat, tobacco and alcohol was found to be additive. These results suggest that khat consumption, especially when accompanied by alcohol and tobacco, might be a potential cause of oral malignancy [21].

4. Khat-chewing and the digestive system

While chewing khat leaves makes people feel more alert and talkative, it does suppresses appetite. Regular khat chewers go on to develop gingivitis and loose teeth, however, there appears to be no convincing evidence of any association with khat and oral cancer. Among khat users in Yemen there is, however, a higher incidence of esophageal cancer compared with gastric cancer [22].

5. Khat-chewing and the excretory system

Khat affects the urinary system via relaxation of bladder wall muscles and closure of the internal sphincter. Urine retention has been observed, as well significant decreased urinary flow rate [23].

6. Khat-chewing and pregnancy

Khat chewing, which is a wide spread male social habit in countries around the southern shore of the Red Sea and Eastern Africa and is also a common practice in women, even during pregnancy and lactation. According to a recent report, khat chewing during pregnancy results in women giving birth to low weight babies. Khat is also known to be excreted in breast milk, but no studies have been conducted so far on how this affects nursing babies. In pregnant women, khat consumption may have detrimental effects on utero-placental blood flow and as a consequence, impacts fetal growth and development [24].

7. Khat-chewing and neurological disorders

The chemically unstable alkaloid cathinone, S (–) alpha-aminopropiophenone, present in the fresh plant material, is the main psychoactive agent [25]. Numerous laboratory studies have confirmed that cathinone is similar to amphetamine in chemical structure, and affects the central and peripheral nervous systems and behavior. Khat has been associated with numerous somatic and psychiatric health sequelae [26, 27].

Conclusion

The use of khat is interwoven with certain fundamental historic traditional values and religion, which need to be approached cautiously. This present review in an effort put in perspective its cultural legitimacy; to obtain a constructive outcome in the near future.

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