

The Problematic of Medicinal Plant: Negative effect of Catha Edulis (Khat) Abuse and Its Potential Benefits

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Abstract

Catha edulis (khat), belongs to a group of psychotropic plants, which has an amphetamine-like structure and contains many cation and anion. The plant contains hallucinogenic compounds and known for its calming effect thus it's known for its abusive usage. However, khat also provides some medicinal potential. Therefore, a study is conducted to summarize the advantages and disadvantages of khat plant from reported studies. The literature review was written based on various books, journals, and search databases in *Pubmed*, *Medline*, *Cochrane* and *Google Scholar* to show the positive and negative effects of the habit in consuming khat. The results of the scoping review discuss about two distinct effects of khat plant. The positive effects of the composition of khat are anti-inflammatory effect, antidiabetic, anticancer, immunomodulatory and bronchodilators activity. In the contrary, the side effects vary according to how long the plant has been consumed. Oral mucosa and salivary gland disturbances are examples for short time side effects. Meanwhile, local organ disruption to cardiovascular complication such as increased blood pressure to myocardial infarction could occur as long term side effects.

Keywords: Khat, Catha Edulis, Potential benefits, Side effect

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1 Introduction

Catha edulis (khat) is indigenous plant that is widely cultivated across the land of the Republic of Yemen and East Africa. The plant belongs to the family of Cleastracea. This plant can grow in variety of climates and is not affected by the seasons. The native inhabitants have used the plant for many purposes, one of them is as strong stimulant. Not only the leaves, other parts of the plant are considered to share similar potency such as the stem and shoots [1,2]. Khat belongs to one of three types of plants with psychostimulant effects, such as *Ephedra sinica* (ephedrine) and *Erythroxylum coca* (cocaine) which are usually consumed by chewing. The native people in East Africa, especially Ethipoa and Kenya usually chew the young leaves and sometimes keep the chewed reside inside the buccal [2].

Although it is known that khat has a positive effect as a psychostimulan, the use of khat in some countries has been banned. In North America, Kenya, Somalia, Yemen and Saudi Arabia, the import and consumption of khat are prohibited. The prohibition is caused by harmful effects that occur in people who overly consume khat as well as heavy abusers. Currently, the habit of chewing khat still creates some polemics due to its great psychostimulan effect toward addiction system in the brain thus it can damage the entire body system furtherly [3].

The major compounds found in khat are cathinone and cathine. Both are responsible for stimulant action effect and has been utilized for the purpose. Another important compound is phytochemical components such as alkaloids (phenylalkylamines and cathedulins), flavonoids, steroid and triterpenoids, monoterpenes and volatile aromatic compounds, and other miscellaneous compounds like vitamins and amino acids [4]. Cathinone is known for its instability of

chemical feature and usually decompose into cathin dan norephedrine as soon as the plant is harvested. Fresh khat plant could contain 36–343 mg of cathinone but also 83–120 mg of cathine and 8–47 mg of norephedrine per 100 g of leaves. Higher potential could be obtained from drying the leaves. The alkaloids inside of khat leaves are well extracted by saliva during the chewing process. Thus, the psychostimulant effect could be derived from an half of hour to one hour. The first 1.5-3.5 hours after the oral ingestion of khat leaves, it will reach he maximum plasma concentration. The pharmacodynamic of khat share almost similar feature with amphetamine derivate, therefore it manifests mostly in central nervous system (CNS) [5].

The consideration of determining khat plant true benefits still rise controversy in various countries due to unreported studies and ethical concerns. However, this paper aims to compile in scoping method between the positive and negative effects of khat from preclinical to clinical studies.

2 Methods

This literature review was written according to reported studies about khat consumption connected the its positive and negative effects in clinical and molecular aspects. Some included databases are *Pubmed*, *Medline*, *Cochrane* and *Google Scholar* collected from ten years prior. Datas were collected and sorted according to the appropriate topic. The final findings then are resumed and written accordingly.

3 Results and Discussions

Ethnopharmacological studies conclude the purpose of consuming khat since many years ago is to satisfy mood and stabilize work rhythms. However, some countries in South

Africa used this plant to treat influenza, cough, gonorrhoea, asthma, chest pain, and other stomach problems. In 1910, some studies reported from France, the use of khat is to treat nervous disorders, especially in women. Khat is also believed to treat mild symptoms of various diseases such as headaches, colds, myalgia, fever, arthritis, and also depression in Yemen [1].

Initially, khat in the form of dried leaves was served as a brewed drink, yet its psychostimulant effect is known to be weaker than coffee. Long brewing time and grind process of the leaves by overheating technique could reduce the wanted effect. The strategy to elicit maximal potency as hallucinogen become the main goal. The native people started to alter the method of consuming khat leaves as brewed beverage into fully eat the leaves raw. Chewing the khat leaves then becomes the current trend afterwards. The central stimulant effect is obtained from the habit of chewing the fresh leaves of khat which is believed to increase work capacity and overcome fatigue [6].

3.1 The acute effect of khat consumption

Several oral diseases are associated with khat chewing habits. Most of the literature shows an association between white mucosal lesions and other periodontal diseases such as dental caries and attrition, salivary gland diseases, and temporomandibular joint disorders. The studies also reported a positive correlation between khat chewing and the incidence of dental caries events in Kenya and Yemen. In addition, the occurrence of xerostomia is also associated with the habit of chewing khat habits that are derived from the cathinone in khat [7]. Other studies also suggested that the effect of khat overdose is difficult to observe since the chewing process takes longer time to give effects. It's also due to the small composition of cathinone, 1 mg g/leaf [8,9]. There are no evidence reporting deaths due to acute toxicity from khat and consensus said that khat poisoning consumption is a self-limiting disease [10].

3.2 The chronic effect of khat consumption

Many chronic diseases could occur from long term consumption of khat. The notably complication was seen in kidney as various kinds of diseases, specifically chronic liver

disease. In contrary, Coton *et al.* [2011] reported no significant number of cases of liver disease induced by direct consumption of khat in Djibouti. It's showed that people in Djibouti have consumed khat for such a long time yet no reported cases of hepatitis induced of khat consumption ever seen before [11]. Microscopic study has been conducted to evaluate the action of khat metabolites to cells. The in vitro study done by Abid *et al.* [2013] revealed the apoptosis of L02 hepatocyte cells after treated with khat extract showed that khat enables upregulation of Bax protein and downregulation expression of Bcl-2 protein. The rise of the Bax/Bcl-2 ratio is considered to support the massive apoptosis of L02 hepatocyte cells. The downstream pathway of apoptosis process was associated with ROS and MAPK signaling pathways. In addition, khat also triggers the formation of intracellular ROS in the cells which induces activation of JNK pathway thus decrease L02 cell viability and immensely increase cells apoptosis [12].

Some studies showed low evidence of khat consumption to oropharyngeal cancer incidence. This is possibly due to the research design used which is descriptive retrospective method without a control group and does not consider the history of tobacco use. The occurrence of oropharyngeal cancer can be caused by another factor besides khat chewing. Methanol extract in khat can significantly elicit apoptosis of primary human keratinocyte cells and fibroblasts in various concentration and given time. The methanol extract produces reactive oxygen species (ROS) that increase oxidative stress level and decrease the glutathione (GSH) level. It can trigger the death of normal oral mucosal cells. As a result, it will eventually activate the process of carcinogenesis due to mutagenic effects and furtherly leads to oral cancer [13].

Another low evidence levels case using case-control designs of esophageal cancer induced by khat consumption also reports the similar result. One study has investigated the effect of chronic khat consumption by evaluating the psychophysiological and adrenocortical activity through cross-sectional design. The long observation showed a flatter pattern of diurnal adrenocortical activity with weaker stress response including cardiovascular response to acute stress

compared to the non-khat users. However, the correlation with the predisposing factor is still unclear [14]. Increasing systolic, diastolic, and heart rate blood pressure have also been reported as khat effects in cardiovascular system [9]. One of the major compounds found in khat is chatinon. Chatinon shares similar profile with amphetamine and enable the user to gain the hallucinogen effect. Long term consumption can affect the blood pressure and heart rate. Pharmacokinetic studies showed that systolic and diastolic blood pressure will increase after 3 hours of chewing khat. Long-term use of khat causes a tolerance of sympathomimetic effects, nevertheless infrequent consumption leads to slower recovery time of cardiovascular effects. [9,14].

Studies have shown that cardiac complications such as myocardial infarction are correlated to khat consumption. The katin extract is thought to responsible for the side effect. An in vitro study by using heart cells showed how katin decrease Bcl 2 levels and increase Bax levels to eventually trigger H9c2 cell apoptosis. Changes in Bcl-2 are related to the mitochondrial pore stability and activation of caspase [15].

3.3 Anti-inflammatory potential of khat

Phenolic and polyphenolic compounds in khat can inhibit enzyme-mediated hydrolysis and oxidative process and act as an anti-inflammatory. Other potential antioxidant activity observed in khat is the ability to protect healthy cells from lipid peroxidation reactions induced by atherogenesis, thrombosis, and carcinogenesis [16]. A study conducted by Siddig *et al.* [2018] reported that the total phenolic and flavonoid content of khat leaves originating from Saudi Arabia showed a very high hydrophilic antioxidant capacity compared to tea leaves [17,18].

Flavonoid is well known to contain great medicinal benefits although the amount of concentration varies in each plant. Thus, khat plant also provides the similar potency regarding the flavonoid but different soil to climate characteristic affects the percentage. A study in 2015 reported several glycosides flavonoids inside the leaves of khat through air-dried extraction, such as kaempferol, quercetin, and myricetin [19,20]. These secondary metabolites have wide range of anti-

inflammatory effect through many pathways, for example inhibiting ROS generation by donating an electron or hydrogen and scavenges the free radicals. Therefore, it also delivers antioxidant activity [21].

3.4 Anti-diabetic potential of khat

Approximately twenty years prior, a clinical study to evaluate khat extract to treat diabetes patients has been conducted in Yemen. During glucose tolerance test, khat extract mixed with glucose showed a significant decrease in blood glucose levels compared to the non-khat (control) group. This effect is associated with impaired absorption of glucose in the intestines due to the presence of tannin and magnesium in the khat plant which can inhibit gastrointestinal function. In addition, inhibition of gastric emptying by the sympathomimetic effect of the cathinone content of khat also plays a role in reducing postprandial excessive blood sugar levels in patients with type 2 diabetes mellitus. Different results were found in non-diabetic subjects in Somalia that khat did not significantly reduce blood glucose levels in humans [6]. A cross sectional study in 2021 also suggest the ability of khat leaves extract to reduce fasting blood sugar compared to non-treated patients. However, large and multicentered study must be conducted to strengthen the conclusion [22].

Different result is seen from one study applied in animals which compare the cathinone treated group and non-treated group. It reveals cathinone could exacerbate the hyperglycemia in diabetes-induced rats. Further investigation suggests how cathinone slower the stimulation of insulin production from pancreatic β -cells in rats due to its ability to inhibit α -adrenoreceptors on the pancreatic β -cells. However, the final conclusion must not be considered as definite outcome. More studies need to be done to find the underlying mechanism of hyperglycemic activity of cathinone [23].

3.5 Anti-cancer potential of khat

The potential of khat as an anti-cancer was shown in research of methanol extract of khat (200 μ g/mL). It significantly activates apoptosis program of Acute Myeloid Leukemia (MOLM-13) cell line by decrease the expression of anti-apoptotic proteins that trigger the

differentiation of myeloid leukemia cells (Mcl-1) [13,24].

Cytotoxic activity related to abnormal growth cells has also been observed as part of khat's potency. The such ability could be induced through some pathways, such as modifying the apoptotic proteins to increasing ROS production [25]. Mohan, et al. [2016] suggested the khat extract at 86.5 µg/ml could deliver the fifty percent of cell inhibitory activity (IC50) in H9c2 cardiomyoblast cell. Further analysis showed treatment time has significantly relates to increasing rate of caspase-3/7 activity. Caspase 3 (CASP3) is one of the major apoptotic mediator in cancer pathogenesis, especially in promoting cytotoxic activity. Many targeted therapies for cancer have been developed to enhance the CASP3 strength to induce programmed cell death [26].

Another study suggests khat extract has ability to inactivate breast cancer cells. Khat extract can induce the process of apoptosis occurs by activation of the JNK and mitochondrial signaling pathways through Bcl-2 and Bax proteins. Most apoptotic effect possessed by khat is not mediated through classical apoptotic pathway caspase-9. Anti-cancer activity of khat also ROS-mediated, as seen through in vitro study compared to untreated group. As we know that the aging process, mtDNA mutation, and cell death are caused by excessive ROS due to macromolecular oxidation induction. Apoptosis could also be activated by mitochondria-mediated ROS-production. It triggers the release of cytochrome C and proapoptotic proteins which in turn will activate the caspase pathway and apoptosis [27,28].

3.6 Another positive effect of khat

The use of khat as a drug for respiratory diseases by inhibiting the release of acetylcholine and smooth muscle contraction. Effects on fertility due to catin and norephedrine compounds can accelerate sperm capacity and inhibit spontaneous acrosome loss. As an immunomodulator, it was reported that there was an increase in the number of lymphocytes and the percentage of positive CD4 cells in khat users in Somalia. In addition, the cathinone effect can activate IL-2 production, B lymphocyte proliferation, and induction of cytotoxic T lymphocytes [29].

4 Conclusions

Literature studies showed that there are positive and negative effects of consuming khat. Consumption of khat must be regulated with good legitimacy to avoid misuse, which can negatively affect health. Studies on the potential of khat are currently being developed. Khat research related to cancer shows the potential of khat as an anti-cancer has a high confidence rating and has a consistent trend compared to cancer-inducing effects. However, this in vitro study still needs further research supported by in vivo data to validate the results.

5 Declarations

5.1 Author contributions

The first author designed the constructive framework and title for the paper. Second and third author contributed for the material dan data. Fourth author proofread and enriched the overall writings with additional information.

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5.3 Conflict of Interest

The all authors declare no conflict of interest occurred during the writing process of the paper.

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