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Clinical Evaluation of Harmful Effects of Khat Chewing on the Function of the Liver & Its Enzymes Specially (GTP-AST-LPT)

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Abstract

Khat tree have a stimulating effect, and greenery's material has been practiced for many centuries in certain areas of East Africa and Arabian Peninsula and widely consumed among the many segments of society of Yemenis, Ethiopia, The active ingredient of khat responsible for its psycho stimulant effect an alkaloid chemical cathinone, which is structurally and chemically similar to D-amphetamine, hence cathine, milder form of cathinone, highly effective which produces central nervous system stimulation analogous to the effect of amphetamine additionally negative effects of khat include increased blood pressure, tachycardia, insomnia, anorexia, constipation, urine retention, irritability as well many chemical components are use as medicine which spread culturally accepted practice in some countries and is becoming more prevalent and on other hand, these effects results from the fertilizers chemicals. that used for khat tree sprayed, as well pesticides other chemicals and it is not khat impure, in addition to the negative effect, we also intend to explain the positive side of Catha adults, through clinical and practical analysis, among these benefits of it, the positive aspects of, there are more than 12 components it can be used as a medicine for treatments some of diseases such as debates.stress.lethargy, reducing weight, Sexual activity, as well as activity blood circulation contribute to disposal bad cholesterol, excessive weight loss, improve mood little bit and so on

Keywords: Phenylpentenylamines, Phenyl propylamines, Negative & Positive harmful effect Khat chewing, liver enzymes (GTP, AST, LPT) and alkaloid chemical cathinone

Introduction

Khat trees are flowering bushes leafs and twinges native plants, to the East and West Harangue zones of Ethiopia, Arabian Peninsula widely consumed among the many segments of society of Ethiopia, Yemenis, which has been moved, since the entry of Ethiopians to Yemen in the sixth century (575-525 AD), where People chew fresh khat leaves for their stimulant and pleasurable effects which are attributed mainly to cathinone [1, 2].The habit of khat chewing, represents major socio-economic problem in the countries of Southern Arabia and the Horn of Africa Although the use of khat has spread in the world, it has remained most deeply in the source countries because only the fresh twigs and leaves that gives the desired effects.[3], such as motivation, stimulating joy or euphoric effects where, the natural materials located in khat which provide strong inducement for users and to engage in regular sessions [4]. The medical and socio-economic impact of khat use on society has generated a debate to whether khat should be considered an illegal drug and banned or tolerated as an innocuous stimulant, similar to caffeine, while, the khat trees contains the alkaloid cathinone stimulant, cause excitement, loss of appetite, and euphoria.[, 5].

Among communities from the areas where the plant is native, khat chewing has a history as a social custom dating back thousands of years analogous to the use of coca leaves in South America and betel nut in Asia [6] There are many addictive habits that societies take up in the most of the world's population, hence it may be bad and destructive for to the abuser of these substances, includes heroin,, beer alcohol. Cocaine, opium, Cigarettes, different kinds of wines Tobacco and etc. [7]. So these substances are destructive, really devastating for sure and harmful relative, but khat trees has special ability and distinct qualities, which is spreads in African, Arabian Peninsula and Yemen, however the Yemen peoples give this tree special affliction [8]. Therefore, in our research we will brief historically and theoretical description in detail. active substances in the khat trees. Also effected of these substances on the abuser was it a man or a woman its harms and benefit together, also in the lesson will clarify some important and truthful points about chewing of khat, in terms of the if the khat effected on the human body functions, especially liver enzymes specially (GTP, AST, ATP), kidney stones which resulted of abuse khat chewing, similarly, the khat benefits in some disease as positive treatments. Furthered, standpoint, talked about some diseases and their relationship of the habit khat chewing [9], but, some studies have been previous theoretical and practical description of composition, components, where it's exaggerated in terms of the general effected on the body with mechanism affecting some of the function of the parts organs that uncorrected, it was focused only on the harms, and did not comprised even little of the therapeutic benefits of the khat trees [10]. In current and previous studies, will be starting tentatively gradient of Catha trees has been associated with liver and kidney disease. However, evidence of effects of the chewing khat leaves on liver and kidney is often based on limited

numbers of case reports and animal studies [11]. These studies display a habit of Khat leaves chewing interferes with normal body functions, which could lead to serious liver and kidney disorders in humans [12]. On other hand the psych stimulating herbal drug khat is cultivated and used as a recreational drug in East Africa and the Arabian Peninsula, where participants engaged in discussions and keep social contact [13] therefore of what mentioned the fresh stems and leaves are harvested regularly from the trees, and are highly valued for their stimulating properties. Cathinone the major constituent of khat is similar in structure and pharmacological activity to amphetamine which has psychoactive effects produces an initial euphoria that is later followed by depression [14], also who chewing khat may experience irritability and insomnia [15], thus Cathinone and cathine are classified as controlled substances according to the Psychotropic substance [16]. D-amphetamine exerts different forms of hepatotoxicity in-vivo when tested on hepatocytes. Pesticide of khat trees is expected to cause similar toxic effects on the liver [17]. However, Khat leaves contain many chemical compounds such as alkaloids, terpenoids, sterols, glycosides, flavonoids, tannins and some amino acids, including glutamic acid, tryptophan, alanine, glycine and threonine. Some vitamins, including ascorbic acid, thiamine, riboflavin, niacin and carotene, are present in trace quantities. Alkaloids of the phenyl propylamine type of which the main psychoactive constituent is S--α-Amino propiophenone (Cathinone $C_9H_{11}NO$, HCl) [18, 19], where, effects in central and locomotor stimulation via a similar mode of action to amphetamine by inducing dopamine release and inhibiting dopamine reuptake.[20].The regular consumption of Catha adults is associated with a variety of health problems affecting the consumers], reported that consumption has become a common problem that affects the health aspects of life [21].So khat leaves have different degrees of pharmacological action and due to its CNS stimulating phenyl propyl amines, especially to cathinone (α-amino propiophenone, natural amphetamine and too much lesser extent to cathine and nor ephedrine Currently khat is illegal in the USA.Canada, and many European countries [22]. Some studies have been done to investigate the effects of Catha edulis on kidney and liver in humans but, only a few of these studies have been conducted in human and these studies have been carried out in the Middle East countries [23], So we did our research at clinically and practical [24] and find out if the effect of khat chewing or there are is a great exaggeration in the effect khat itself or as a results of other factors, hence it was confirmed that the damage resulted for the materials used for khat improve, growth such as sprayed miscellaneous pesticides and chemical fertilized eta furthermore, Its normal for anything's that if it increases, turns against it. Hence this study evaluated the effect of khat on liver among users in City of Taiz-Yemen [25], also compared the effect of khat chewing between consumers & non-consumers. Where, Khat, back of the stem has been chewed for centuries by the people of various countries such as Yemen, Ethiopia, Eritrea Somalia and Kenya for its stimulant properties [26]. So, khat Trigs & leaves chewing has led to serious liver and kidney disorders as well investigated the biochemical blood constituents' changes among khat chewers in Sana'a city, Yemen and concluded that there was increase in serum urea, creatinine and bilirubin in in khat users. [27, 29], studied the effect Catha adults ingesting, on liver and kidney function in male population of Jazan &

concluded that aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were increased in the serum of users [30] Furthermore, these studies already done have been carried out in the Middle East countries such as Yemen. Additionally, different varieties of khat trees, contain different levels of cathinone which may lead to different effects that need to be investigated [31]. Due to high availability and increase use of Catha edulis use in Taiz Yemen, it is therefore important to determine the effects of Catha edulis on liver functions in adult male consumers and also compared the effect of khat leaves between consumers and non-consumers. [32].

The pharmacology of khat trees

Khat leaves and shoots are contain more than forty complex compounds including the alkaloid stimulants cathinone cathine figure1, where, cathinone is the main active ingredient in fresh khat trees and shoots [34].Cathinone has a closer structural similarity with amphetamine and both share common pharmacodynamic features, that cathinone is the most important active ingredient which causes the major pharmacological effects.[35] where, stored khat leaves lose their stimulatory properties a further it become physiologically inactive after about thirty-six hours as the more powerful cathinone decomposes leaving behind the milder, less active, cathine [36].So chewing khat is an efficient way of extracting cathinone & cathine by the action of enzymes in saliva potential for users to become dependent on khat consume limited by two key characteristics[37]. First it takes a long time for the active ingredients to reach maximal levels in the blood. Second the bulky nature of the herbal material limits the maximum dose that can be received. [38].Central stimulation by Catha edulis is manifested by euphoria, increased alertness, garrulousness, hyperactivity, excitement, aggressiveness, anxiety, elevated blood pressure, and maniac behavior [39] as well the euphoric effect of khat starts after about one hour of chewing, when plasma concentrations of cathinone start to rise, peak plasma levels are obtained within 1.5 hour to 3.5 hour after the onset of chewing [40].

Chemical composition

Khat leaves contains many alkaloids, tannin, amino acids, glycosides, minerals and vitamins], phenylalkylamines are the major alkaloids [41]. The major active ingredients in khat leaves are phenylalkylamine (d-α-amino propiophenone named as cathinone psychostimulant component of khat and cathine nor-pseudo-ephedrine [42], these compounds share similarities with amphetamine, with up to 90% being absorbed during chewing, predominantly via the oral mucosa. Cathinone is found mainly in the young leaves and shoots. During maturation, cathinone is metabolized to cathine, & D-norephedrine [43], phenylalkylamine alkaloids found in khat leaves are the phenylpentenylamines, merucathinone, pseudomerucathine & merucathine. These seem to contribute less to the stimulant effects of Khat leaves on average, 100g fresh khat leaves contain 36-114 mg cathinone, 83-120 mg, cathine and 8-47 mg, nor

ephedrine, Cathinone is labile and is transformed within a few days of harvesting to dimer 3, 6-dimethyl-2, 5-diphenylpyrazine) and it is for this reason that khat needs to be consumed while still fresh [44].

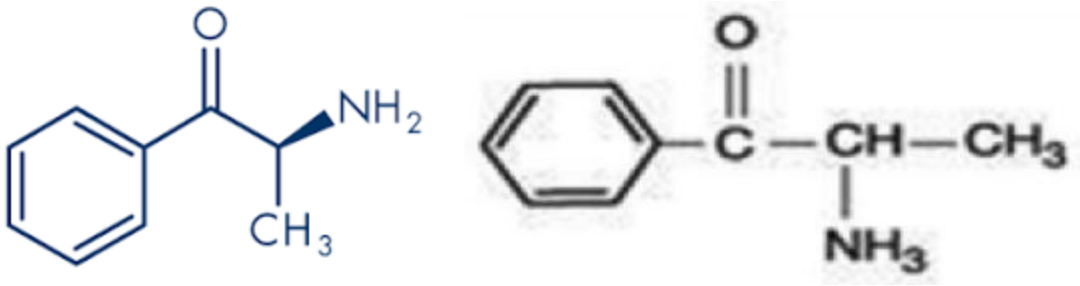

Figure 1: Cathinone chemical structure

Environmental health effects of growing Khat tree

Due to the high economic importance of khat as a cash crop, farmers tend to use pesticides and fertilizers heavily on khat trigs and leaves in order to protect them from pests, to ensure healthy foliage and thus to increase the yield and income A study by. Shows that people who used it which is sprayed with pesticides have the highest health risks due to the combination of the pesticides and other chemical materials sprays used,

Mode of consumption

Khat users prefer the leaves from the tips of the branches and those young shoots. The fresh leaves, twigs, and shoots of the Catha edulis shrub are taken one by one and thoroughly chewed. Catha edulis is chewed differently depending on its type. The juice that comes out of the chewed Catha edulis then swallowed whereas the macerated material is kept for a while in the cheek and later expectorated, In the areas where Catha edulis use originated, groups of people mainly men every day to chewing it. These sessions, in Yemen as literally the council of khat, are informal events [47]. The ingestion of khat produces sympathetic activation characterized by euphoria, increased intellectual efficiency and alertness, anxiety, high blood pressure, and other effects These effects are mainly mediated by phenylalkylamines such as cathinone (the major stimulant) and cathine, although several other stimulant compounds are also found in khat [48].

Social factors leading to the use Khat

Catha chewing is a social occasion among addicts, and is typically done as a group activity until late at night, like coffee, is a stimulant and it is used to improve alertness and performance [49]. Night shift workers such as watchmen and long-distance truck drivers chew it to stay awake and postpone fatigue It is also commonly used for social

recreation. A significant number of students consume Catha edulis to be alert and wakeful at night especially during examination periods; Chewing is done for periods of 3-4 hours, and commonly drink sweet drinks while chewing, to counter the bitter taste of its [50, 51].

Association of Khat chewing with gender and age

Consumption was only limited to older men and members of Muslim communities in the past but today consumption is by all societal groups regardless of age and sex. Khat chewing among women and children has increased and has become socially accepted in Yemen Many studies have demonstrated Catha edulis chewing is associated with age and gender [52].

Effects of the khat chewing on the liver enzymes and function

The liver is a major organ for metabolism of foreign substances and also functionally interposed between the site of absorption and the systemic circulation. These conditions render the liver not only the most important organ for detoxification of foreign substances but also a major target of their toxicity [53] and metabolism is the enzymatic conversion of one chemical compound into another Most drug metabolism occurs in the liver, although some processes occur in the gut wall, lungs and blood plasma [54] Metabolism of cathinone the main constituent of khat, mainly occurs at the first passage in the liver An excess of chemicals hinders the production of bile thus leading to the body's inability to flush out the chemicals through waste. Smooth endoplasmic reticulum of the liver is the principal 'metabolic clearing house' for both endogenous chemicals like cholesterol, steroid hormones, fatty acids and proteins, and exogenous substances like drugs and alcohol [55].The central role played by liver in the clearance and transformation of chemicals exposes it to toxic injury [56] Production of excess reactive oxygen radicals has been hypothesized as mediator of khat induced hepatoxicity Intracellular reactive oxygen radicals generated following exposure to can provoke a series of signaling cascade that promotes liver cells death [57].

Liver toxicity

Hepatotoxicity due to Catha edulis chewing has been evoked in animals and also human. Toxicological effects of Catha edulis leaves have been tested in laboratory animals for a period of six months and the liver biochemical parameters were found to be significantly altered with a profound impact on the alkaline phosphatase (ALP) and alanine aminotransferase (ALT) plasma levels throughout the treatment period [58], thus some workers have demonstrated that the administration of crude extract of Catha edulis to New Zealander white rabbits for three months resulted into hepatocellular jaundice and histopathological abnormalities in the livers of these experimental animals Another report also described a patient with impaired liver function attributed to Catha edulis chewing. Serum alkaline phosphatase was increased, there was unusual liver directed autoimmune activity with positive anti smooth muscle antibody titer (1: 40) and liver biopsy findings showed cirrhosis. [59], more recently, severe acute liver injury has been attributed to Catha edulis chewing in

the United States of America [60]. A case series described jaundice and deranged liver function based on biopsy histology and serum biochemistry in seven United Kingdom (UK) men of Somali origin who were regular Catha edulis chewers. All denied any alcohol consumption and no other etiological factors could be identified [61].

Therapeutic use of Catha edulis

Catha edulis leaves and roots are boiled and the boiled water is drunk so that to treat gonorrhea, to treat influenza, cough and asthma fresh stems are chewed and the juice is swallowed [50]. Endogenous people of East Africa and the Mere people of Kenya chew Catha edulis leaves and the juice is swallowed to treat malaria and also reduce pain associated with arthritis [60] also people in Yemen use khat for treatment of obesity, suppression of appetite and to alleviate their headaches by inhaling the fumes of burning khat leaves in Ethiopia processed (by boiling) Catha edulis leaves and roots are used to treat influenza, cough, gonorrhea, asthma& other chest problems whereby people with these infections drink the boiled water. The roots are used for stomachache and infusions made from them are taken to treat boils [61]

Material and method

Syringe. Tourniquet, Dry cotton, Antiseptic, Tubes without anticoagulation, glass test tube, Centrifuge, D, w, medical plaster, Windrow, Micro pipette

Methods

Four volunteers chewed Catha edulis leaves in an amount equivalent to one quarter of that used in a typical session. blood samples were collected up to 80 hours and the alkaloids were assayed using gas chromatography-mass spectrometry & the detective the level enzyme of GPT by spectrophotometers. data were evaluated using computerized pharmacokinetic compartmental analysis.

Principle of alanine aminotransferase (ALT)

Glutamic pyruvic transaminase (GPT) catalyzes reaction between alpha ketoglutarate and giving glutamate & pyruvic acid in presence of lactate dehydrogenase (LDH), pyruvic acid reacts with NADH giving lactic acid and NAD+. So The absorbance variation is proportional to the ALT activity In the reagent is contained LDH to convert the endogenous pyruvate in to lactate during the preincubation., So there no any change in the concentration of this enzymes with peoples who chewing natural khat free of any insecticide or not sprayed with any insecticide another hand there just a slight change with the peoples groups whose chewing khat sprayed with insecticide and chemical fertilizers.

Results

Through our study we summarized the results n the table 1 and as well clinical blood analyses sample of the targets groups. we found it as follows the first group they were

enjoyed excellent health and them liver function and its enzymes normal. The second group they suffering from some decrease in the Some them liver enzymes slightly.while later group appeared to have major defect in them liver enzymes and other organs function like kidney stones, cystitis.urethritis and etc thus also we took three groups that chewing khat leaves where, one group chewing khat natural, no any sprayed insecticide also no chemical fertilizer and the, second groups that chewing khat randomly as well as insecticide sprayed and chemical fertilized while the third group chewing khat a mixtures of the above two groups with no inters in their food and very larger quantities of khat with many smoking and Pepsi, and some men drinking beer and other stimulate drugs. So, with analysis of blood samples and liver function test resulted appear as follow in the first group, we did not find any effect on each liver enzymes or any defect function on other organs specially heart and liver or others, while in the second groups we found some light changes in concentration of liver enzymes and kidney function.furthermore the table chowed all the analysis blood and liver function test in dials, therefor **t**he result of the study indicates that there is no commonly agreed perceived health impacts among immigrant communities in the new host country, particularly the ten Somalis men who participated in this study differ from one to another in terms of harms related to khat use. In the scientifically oriented communities, harms associated with khat consumption are really contested in the academic literature too [61]. Moreover, despite its popularity in some parts of the globe that we live in, and the potential impact of its consumption on individual and public health, khat use has until now received only marginal attention from the scientific community, for centuries, Catha edulis use was considered to be restricted to some African and Arabian Peninsula countries Paradoxically, recent studies confirm that chewing khat had spread amongst other young immigrant groups then the Somalis and even to young Swedish people [62].Hence the TPB theory explains that some information do not work as it was allocated to do according to TPB human action is guided by three kinds of considerations: behavioral beliefs, normative beliefs and control beliefs. that behavioral intention is the best predictor of behavior, which in turn is determined by attitude toward the behavior and social normative perceptions regarding it [63]. Nonetheless, reliable scientific sources confirm that consumption has negative consequences on the economic development of a country and on the health of the society too. In Kenya, for instance, some authors blamed khat on underdevelopment in ethnic Somali-dominated North Eastern Province of Kenya where there is no war, but many refugees from Somalia [64] Most of the respondents in the study conducted at Sheffield considered khat to be a problem with some negative health and social effects but rationalized usage citing personal pressure, socio-cultural and emotional problems faced as a result of dislocation from country of origin, and need for recreation [65] The TPB highlights that human behavior are governed not only by personal attitudes, but also by societal pressure and a sense of control [66].

Table 1: Summary resulted to the effected khat on the liver function

Natural of khat	Men	Women	N	Std. Deviation	Std Error Mean	ALP level	AST level	GGT level
Without sprayed by insecticide/or chemical fertilized	38.3467 22.4800	38.3467 22.4800	150	26.13452 14.39722	3.01775 1.66245	Normal	Normal	Normal
Sprayed with insecticides & Chemical fertilized	38.3467 22.4800	38.3467 22.4800	150	26.13452 14.39722	3.01775 1.66245	Slightly change	Slightly change	Slightly change
Mixtures & no interest in food	38.3467 22.4800	38.3467 22.4800	150	26.13452 14.39722	3.01775 1.66245	Decrease	Decrease	Decease

Table (1):This table shows the results we have found that first target group they have normal liver function and no any defect in its enzymes level or any other organs decoders, while in the second target group they was some defect in the stilly degrease in the some livers enzymes concentration with suffering kidney stone.as for the third target group they have appeared in them more change in their livers enzymes and big defect for other bodies organs as well stuffing great kidney stones.

Discussion

In this paper researcher tried to examine the impacts of Khat use on various aspects of students. Impacts of use can be categorized as economic, social, psychological, health related impacts and impact on didactic performance of students. As to some of study participants, Khat plays a role in making students awake and stays alerted during long studying hours. It helps students stay focused on what they are doing. In addition, they believed that use makes individuals pleasant and social conformists, also, Khat chewing serves as a way-out from stress, anxiety and personal disturbances. So this needs further investigation by professional researchers interested in the area. Students demand their families to send them some money for different purposes. However, there are cases where regular users secure their daily consumption of at the expense of vital needs, indicating dependence. This uneconomic culture of students has also an impact on their families' economy which was consistent with some other findings. Students who came from areas that condemned khat use for different reason might face isolation and detachment from their friends who are from the same place of origin. In such circumstances, social acceptance and integration of students who use it can be declined. Most of the Study participants added that the increasingly widespread of khat chewing habit increases development of unhealthy risky behaviors among students. In the long run, this led to drug dependence, and addiction which are acute social problems of the youth. Besides, makes students vulnerable to some

psychological diseases and habitual khat use pushes students to develop a positive attitude towards used. Sessions are time consuming let students out of library, reduce study hours and time shall be used for independent learning and doing assignments and also proven by the researcher in which students spent three-five hours on average in a day.

Conclusion

The aim of this study was to evaluate the effects of Khat on liver using biochemical parameters among men chewing adults in Taiz Yemen, & to compare the effects of it on human consumers and non-consumers.

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