Review on Toxicological effect of cathaedulis (khat) on the Histology and Function of liver

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Abstract

Khat (Catha edulis, family: celastraceae) is a plant grown in the east-Africa and the south west of the Arabian Peninsula. The habit of khat chewing has prevailed for centuries in this part of the world. The purpose of this review is to give a comprehensive report of the existing data on the potential adverse effects of khat (Catha edulis) on liver toxicity. We used 64 different published materials for the compilation of this review article. The Google search engine was used for accessing published materials from databases like google scholar, Pubmed and Hinari. Literature surveys and clinical diagnostic studies revealed an association with incidence of liver toxicity such as elevation of serum enzyme, oxidative Stress Parameters and histopathological changes mainly in high dose exposure to khat (Catha edulis) in both human and experimental animal models.

Key words: Liver, Serum enzyme, Oxidative Stress and Histopathological changes

Introduction

Khat (Catha edulis, family: Celastraceae) is a plant grown in in East-Africa and the south west of the Arabian Peninsula, in countries such as Somalia, Kenya, Djibuti, Yemen, or Ethiopia. In those countries the chewing of khat is also 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]. The leaf of this plant is habitually chewed by several millions of people in these countries for its pleasant stimulant effect on physical activity, consciousness, motor and mental functions as well as its anti fatigue action [2]. Like in Yemen, the use of Catha edulis is ever increasing in Ethiopia [3]. Catha edulis previously known to grow mainly in the eastern part of Ethiopia is now widely cultivated in all parts of the country and neighboring regions. It is consumed regularly with the young generations being the primary targets [4, 5]. In Ethiopia, current ways of chewing Catha edulis has changed from the traditional way of consumption, which is highly regulated [6,7], towards the use by adolescents, chewing Catha edulis in tea shops that operate day and night as well as early morning use [8].

The psychostimulant component of khat is cathinone, which is released within 15–45 minutes during chewing [9]. A khat chewing session, however, may last 3 to 7 hours [10]. Khat chewing has a social and cultural tradition, and it may occur while in the company of others or alone [11]. Cathinone, like amphetamine, acts by releasing catecholamines from presynaptic storage sites and subsequently inhibit their uptake, thereby increasing temporal and spatial presence of these neurotransmitters (dopamine [DA], serotonin [5-HT] and noradrenaline [NA]) at the presynaptic receptors [12]. Psychostimulants and other drugs that inhibit uptake of 5-HT into the presynaptic nerve terminals increase serotonergic neurotransmission by enhancing its synaptic concentrations. Chewing the leaves is an effective way of extracting Cathinone: the chemical constituent of khat that produces an amphetamine-like stimulatory effect [13].The medical and socioeconomic impact of Khat use on society has generated a debate as to whether Khat should be considered an illegal drug and banned or tolerated as an innocuous stimulant, similar to caffeine. Toxicological evaluation of Catha edulis leaves has been reported by Al-Habori et al [14]. Moreover, the toxicological potential of Khat has been reported by Carvalho [15]. It has also been reported that Khat induces cytotoxic effects in cells, in the liver and kidney of rabbits [16]. Recently, the effect of Khat extract was reported to be cytotoxic and induced a rapid cell death effect [17]. It also induced apoptosis through a mechanism involving activation of capase-1, capase-3 and capase-8 [18]. It also establishes Khat as an etiological risk factor in chronic liver disease and suggests a potentiating effect of Khat toxicity on chronic hepatitis B and Delta virus mediated liver damage [19]. The studies about cathaedulis (khat) are generally poor or concerning some markers of liver integrity and action of hepatotoxicity controversial. Here, we review different scientific literatures to evaluate the functional and histological effect of cathaedulis (khat) liver and its possible action of toxic city.

Methods

Databases like google scholar, Pubmed, Hinari and Scopus were searched to retrieve the papers for this review. Selected papers date between 1947 and 2014. The search methodology can be summarized as follows: after selecting a set of search terms and generating reliable combinations, we used electronic research databases to search for related articles. A backward/forward search was conducted, and the abstract was analysed to ensure that the papers met the search criteria. Papers that failed to meet any of the search criteria were excluded. The reference lists and bibliographies of all articles were then cross‐checked for additional published and unpublished studies. The following keywords were used separately and combined in all databases and search engines: Khat and oxidative stress; alternation in serum enzyme and hitological alternations. These terms were then used in the online databases, Google scholar, Pubmed, Hinari and Scopus. Of this initial selection, an abstract matching and backward/forward search was conducted to assess whether the topic covered was relevant. Then we select a maximum of 64 papers for each combination of search terms that meet the selection criteria.

Studies were included in this review if they met the following criteria:

- Experimental studies using standard, valid and reliable histological techniques in identifying alternation microscopic structure of the liver and change in biochemical component of the liver.
- Results which show at least one functional change in liver due to khat toxicity.
- Full text articles in English, published between November 1947 and 2014.

The search method applied in this review

Step Search method

1. Generate plausible combinations of terms to be used for, search using the key search terms identified.
2. Search for these terms on google scholar, Pubmed and Hinari and Scopus.
3. Select a base set for the results consisting of the 58 papers
4. Match the abstract and perform a forward and backward search to verify the relevance of the paper for the selected base set.
5. Exclude papers that address none of the topics covered, that only makes a brief reference to the subject at hand or that are not written in English.

Effect of khat exposure on liver

Various studies have reported that Khat becomes a serious public health issue in east Africa and Saudi Arabia due to its widespread use. Many unfavorable side effects have been associated with khat chewing [20, 21]. The WHO (2003, 2006) recorded that Khat consumption has created a major health problems by affecting numerous vital organs of the human body [22]. Luqman and Danowski [23] reported liver cirrhosis among the Yemeni population that might be due to Khat consumption; however these investigators did not report any specific reason. Table-1 summarizes the observations of aluminium induced male reproductive toxicity in various laboratory animals.

Table 1: khat and its toxicity in various experimental animals and peoples

No	Animal model	Route of exposure	Dose	Duration	Observations	Reference
1	white albino rats	Oral administration	500 mg/kg *Catha edulis*	28 days	Significantly elevates the liver enzymes and show marked degenerative changes	[14]
2	male human population	khat chewing	Variable	>5years	The finding indicates that ALT and AST activities were significantly increased in the serum of Khat users..	[25]
3	Yemeni peoples	khat chewing	Variable	>5years	Revealed that elevated liver enzymes mainly ALT and AST.	[26]
4	white rabbits	Gavage	*C. edulis* (10, 20 and 30%)	Six month	Treated animals were increased the plasma ALP	[27]
5	Male rats	Oral gavage	2000, 1000 and 500 mg/kg .	Eight weeks	Serum activity of liver enzymes was significantly altered and liver showed a degenerative vacuolation and coagulative necrosis in zone 3 (pericentral region).	[42]
6	*scuniculus* rrabbits	standard chow	2 gm/ kg fresh khat leaves	7, 14 and 20 days	Destruction of the normal architecture and hepatocytes were showed.	[47]
7	male	force feeding	0, 500, 1000, 2000 mg /Kg *Catha edulis*	6weeks	Liver enzyme activities were demonstrated to be reduced in the treated group.	[63]
8	Thamar city female populations	khat chewing	Variable	>5years	An increase in the activities of ALT and AST of khat chewer group compared to the control group	[64]

Possible mechanism of khat toxicity to liver

Experimental studies suggested that following mechanism might be commit for khat toxicity, liver: alternation of serum biochemistry; serum enzyme; oxidative stress and hitological alternations.

Khat and serum enzyme

Fahaid et al demonstrated that the activities of these enzymes were elevated in the serum of Catha edulis extract treated rats, indicating their leakage into extracellular fluid as a result of toxic damage of hepatic tissue by the extract[24]. Similarly, finding also reported that levels of hepatic enzymes AST, ALT, ALP and GTT are elevated in liver damage due to tissue necrosis or membrane damage serum of Khat users [25, 26, 63, 64]. These findings are consistent with those of Al-Habori et al who reported that long term feeding of khat leaves of New Zealand white rabbits increased liver enzyme levels and concluded that prolonged exposure to Catha edulis leaves may lead to toxic hepatocellular jaundice [27]. Hyperbilirubinemia is often the first and sometimes the only manifestation of liver disease [28]. Oral administration of Catha edulis hydro-ethanol extract in our study significantly increased serum bilirubin, suggesting a direct toxic effect of the extract on liver cells, leading to decreased uptake and conjugation of bilirubin and reduced secretion into bile ducts. In the study of Fahaid et al, there was a significant decrease in serum total protein and albumin of Catha edulis extract treated rats as compared to control rats. This indicates impaired liver function, decreased protein synthesis, either primary as in liver cell damage or secondary to diminished protein intake and reduced absorption of amino acids [29].

Elevation in the serum activity of alkaline phosphatase (ALP) in the HD-group of male SD-rats and HD- and MD-groups of female SD-rats indicates a possible hepatotoxicity [30]. The elevation of several markers would be of a greater diagnostic value than a single one [31]. The lack of specificity of AST, ALP, and GGT cannot authorize any conclusion because such enzymes are ubiquitous in various tissues and serum elevation could represent not only liver, but also heart, bones, and muscle damages [32]. Moreover, the inhibited activity of serum alanine minotransferase (ALT) could indicate normal hepatic function because of its specificity as a marker for hepatocytes integrity [33, 34, 35 36, 37]. Another possibility could be the establishment of a covalent binding between certain components of Khat and ALT [31].

Although serum ALT was reported to be a poor marker in predicting hepatotoxicity in rats [37], the higher serum activity of aspartate aminotransferase in HD-group of males as well as HD- and MD-groups of females than that of normal control rats (NC) suggests leakage into circulation from ruptured cell membranes of hepatocytes upon exposing to injury [32]. Although AST is widely distributed in various organs, its concentration in hepatocytes is still the highest [33]. Pancreatic damage was unlikely, since serum amylase (AM) was on significantly changed despite its lack of specificity [38]. Again, elevations of AST due to straited muscles injury should be associated with parallel elevations in serum creatine kinase (CK) as a marker of skeletal and/or heart muscle injury [32, 33, 39, 41]. However, CK in the tested groups of male and female SD-rats was non significantly different from that of NC. Histopathological examination of biopsies from heart muscles indicated no abnormal findings in both male and female SD-rats. Elevations of GGT in rodents were rarely detected, even if liver was exposed to a known hepatotoxic compound, so this does not exclude hepatotoxicity of khat [31]. Consequently, elevations of serum AST were of hepatic origin rather than cardiac, muscular, or pancreatic origin. In addition, the lower levels of serum albumin (A) of female SD-rats with HD and LD suggested a defect in the hepatic synthesis capacity [38, 40]. However, the elevation of serum activity of ALT in the rabbits in the fore mentioned article was contrasted to the findings of Abdulsamad et al study because ALT was higher in rabbits which may be because the doses given to rabbits were higher and exposure was longer than that in the current study [42]. So, there is too much uncertainty in biological data to draw back any conclusion and only histological findings assess Khat hepatotoxicity in rats.

Khat and oxidative stress

Reactive oxygen species (ROS) are ions or radicals generated through normal cellular metabolic processes. They comprise free radical species like superoxide anion and hydroxyl radical as well as non-radical species like hydrogen peroxide. These molecules are involved in numerous normal cellular processes like gene expression, proliferation and differentiation [61, 62]. Exogenous and endogenous stress may generate excessive amounts of ROS that can damage molecules like nucleic acids, proteins and lipids. In the study of Fahaid et al [24] revealed that TBARS (a marker of redox balance and lipid peroxidation in cells) level increased two folds in the liver and kidney homogenates of Catha edulis extract treated rats. Some constituents of the extract might have been converted to prooxidant metabolites or the extract might have induced decreased synthesis/activity of the antioxidant system in treated rats. In addition, the extract could have increased fatty acyl coenzyme A oxidase activity leading to increased lipid peroxidation. Fahaid et al [24] also reported that the activities of SOD and CAT were decreased in rats treated with Catha edulis suggesting that the extract generated free radicals or directly inhibited synthesis of antioxidant enzymes. This finding is similar to a recent study in which administration of the Catha edulis extract or its alkaloid fraction was shown to alter the activities of the free-radical metabolizing/scavenging enzyme system [43]. GSH is a thiol which plays a central role in coordinating the body's antioxidant defense processes. The role of glutathione as a protective agent against oxidative organ damage has been the subject of extensive studies [44]. The exposed sulfhydryl groups in glutathione bind to a variety of electrophilic radicals and metabolites that may cause cell damage [45]. As expected, Catha edulis treatment markedly depleted hepatic GSH stores in rats. It could be hypothesized that administration of the extract led to a saturation of detoxification pathways in the liver so that intermediate metabolites accumulated and caused liver damage by covalent binding to tissue molecules and proteins such as GSH. Another hypothesis could be that Catha edulis extract contains an oxidizing agent or causes suppression of GSH synthesis leading to increased production of reactive oxygen species and induction of oxidative stress [46].

Khat and Histopathological changes

Wafaa et al [47] demonstrated that histopathological changes induced by khat were fatty degeneration of hepatic cells, focal area of necrosis, the central veins and surrounding sinusoids were congested, dilated and filled with stagnant blood. Accumulations of mononuclear inflammatory cells were found around the central vein and portal tract. The current changes were incompatible with many previous studies [27, 48, 49, 50]. In confirmation of the hepatotoxicity of khat ingestion, a case report described an East African man with a regular khat chewing habit that developed jaundice as a result of acute hepatitis [51]. On examining the histopathology of tissue sections of the liver evidences of a chronic inflammatory state were observed in the tissue sections obtained from animals treated with all levels of Catha edulis leaves used in this study [27]. This is confirmed by the observed moderate infiltration of the portal tract by chronic inflammatory cells at the 10 and 20% levels and

higher infiltration at the higher level of 30% with porto-portal fibrosis. The consequences of which would be spreading fibrosis leading to nodularity of the liver and eventually cirrhosis [27].

Another report also described a patient with impaired liver function attributed to khat chewing [52]. More recently, severe acute liver injury has been attributed to khat chewing in the USA [53]. Simlarlly, histopathological examination of the livers of Catha edulis treated rats revealed marked degenerative changes compared to the control animals, the observed degenerative alterations include disorganization of hepatic cords, cytoplasmic vacuolization of hepatocytes and invasion of infiltrative inflammatory cells. Furthermore, necrotic changes were seen [24]. Comparable finding also revealed liver sections of high dose groups of khat-treated male and female SD-rats showed a degenerative vacuolation and coagulative necrosis in zone 3 (pericentral region) and degenerative changes in persisting parenchyma with congestion and hemorrhage. There were dilatation of sinusoids and mononuclear inflammatory infiltrates and Kupffer cells around the central vein and portal tracts [42]. Additionally, a case report of end stage chronic liver disease related to chronic Khat consumption [54]. The mechanism of khat toxicity of the liver is uncertain. It was reported that, the administration of khat extracts showed a deranged systemic capacity to handle oxidative radicals and induces cytotoxic effects in cells of liver [55]. A vasoconstrictor action of cathinone would also contribute to this liver pathology [56]. On the other hand, there was a suggestion that the sub chronic administration of the Catha edulis crude extract has no hepatotoxicity adverse effects in male rats, but may have antioxidant property due to its phenolic compounds [57]. A rather unusual adverse effect on the liver of chewing khat was a parasitic infection of the liver by Fasciola hepatica as a contaminant of the khat leaves [58]. In contrast, there were no histopathologies changes observed in the liver of the experimental animals fed with Catha edulis extract [14] which supports the safety use of the aqueous extract of P. edulis in pharmacological studies [59]. This controversy with result may be explained by the animal differences, concentrations of khat obtainable and the period of treatment. Since almost all of the investigations of khat effect have been done with whole undifferentiated chewable leaves (smooth crimson and green), the results of such works have been often inconsistent [60].

Conclusion

The results of present review provide evidence for adverse effects khat toxicity in the liver, such as the alternation of serum enzymes, and oxidative stress and hitological alternations. Accordingly, using khat can be expected to affect a broad range of liver toxicity and other health problems.

Abbreviations A: Albumin, ALP: Alkaline Phosphatase, ALT: AlanineAminoTransferase, ANOVA: Analysis of Variance, AST: AspartateAmino Ttransferase, C.edulis: Catha edulis, g/dl: gram per deciliter, g: gram, HD: High dose, hr: hour, LD : Low dose , MD: Medium dose , mg/dl: milligram per deciliter, mg/kg: milligram per kilogram , ml/kg: milliliter per kilogram, NC :Normal control, ^{o}C: degree centigrade, SD: Sprague-Dawley, SPSS : Statistical Package for the Social ScienceTB:Total Bilirubin u/l: unit per litter, wt: weight.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Adhanom Gebreslssie proceeded with the literature review and drafted the paper in addition to this Birhane Alem and Yared godefa providing guidance, critical assessment and peer review of the writing. All authors have given their final approval of this version to be published. All authors read and approved the final manuscript.

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