

ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE
DEPARTMENT OF ANATOMY



PROJECT PAPER ON: THE TOXICOLOGICAL EFFECT OF *CATHA EDULIS* FORSK (KHAT) ON THE HISTOLOGY AND FUNCTION OF LIVER.

A PROJECT PAPER SUBMITTED TO ADDIS ABABA UNIVERSITY, POST GRADUAT STUDIES, SCHOOL OF MEDICINE, DEPARTMENT OF ANATOMY IN PARTIAL FULFILMENT FOR THE DEGREE OF MASTERS OF SCIENECE IN ANATOMY.

BY: ADHANOM GEBRESLASSIE

July, 2014

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Summary

In this project paper databases such as Pubmed, Medline, Hinary and Google search, were systematically searched for literature on the different aspects of *Catha edulis* (Khat) to synthesis, review, and present various research publication on the toxicological effect of khat consumption on the histology and function of liver. *Catha edulis* (Khat) is a large green shrub that grows at high altitude in the region extending from eastern to Southern Africa, as well as on the Arabian Peninsula; mainly in Ethiopia, Somalia, Kenya, Malawi, Uganda, Tanzania, Congo, Zambia, Zimbabwe, Afghanistan, Yemen and Madagascar. It is known by a variety of names such as, “chat” in Ethiopia, “qat” in Yemen, “mirra” in Kenya and “Khat” in English. The euphoric effects have been demonstrated to arise from the main constituent, (-)-S cathinone. Most of the findings revealed that there is significant result on toxicological effect of Khat consumption on histology and function of liver. This happens as the exposure of *Catha edulis* in treated liver animal goes from acute to chronic administration starting from the dose of 10% of extracted *Catha edulis*. In general the project paper showed that Khat treated animals including khat users have elevated activities of hepatic enzymes like Alkaline phosphatase (ALP), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and bilirubin were as albumin level was decreased as compare to the control group. In addition to this the histo-pathological pictures of the khat treated liver also showed that degenerative alterations include disorganization of hepatic cords, cytoplasmic vacuolization of hepatocytes and invasion of infiltrative inflammatory cells. These result together indicating leakage into extracellular fluid as a result of toxic damage of hepatic tissue by the extract and so it leads to death of the experimental animals including Khat user.

Keywords: ALP, ALT, AST, Albumin, Bilirubin, *Catha edulis*, , Cathinone, Khat, Kupffer cells

Abbreviations

A.....	Albumin
ALP.....	Alkaline Phosphatase
ALT.....	Alanine Amino Transferase
ANOVA.....	Analysis of Variance
AST.....	Aspartate Amino Ttransferase
<i>C.edulis</i>	<i>Catha edulis</i>
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
°C.....	degree centigrade
SD.....	Sprague-Dawley
SPSS.....	Statistical Package for the Social Science
TB.....	Total Bilirubin
u/l.....	unit per litter
wt.....	weight

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1. Introduction

1.1 General Overview of *Catha edulis* Forsk (khat)

Catha edulis(khat) is a large green shrub that grows at high altitude in the region extending from eastern to Southern Africa, as well as on the Arabian Peninsula; mainly in Ethiopia, Somalia, Kenya, Malawi, Uganda, Tanzania, Congo, Zambia, Zimbabwe, Afghanistan, Yemen and Madagascar (John *et al.*, 2009 and Ezekiel *et al.*, 2010). It is known by a variety of names such as, “chat” in Ethiopia, “qat” in Yemen, “mirra” in Kenya and “khat” in English. People chew fresh young khat leaves for their stimulant and pleasurable effects which are attributed mainly to cathinone (Al-Motarreb *et al.*, 2002 and Belewe *et al.*, 2000). The habit of khat chewing represents a major socio-economic problem in the countries of Southern Arabia and the Horn of Africa (Belewe *et al.*, 2000). Although the use of khat has spread worldwide, it has remained most deeply rooted in the source countries because only the fresh leaves have the potency to produce the desired effects. It is estimated that there are five to ten million regular khat users, worldwide (Kalix, 1984).

The stimulating and euphoric effects of khat provide a strong inducement for the user to obtain daily supplies and to engage in regular khat chewing sessions, especially as tolerance develops with regular use. This strongly suggests development of psychic or physical dependence or both in the user (Al-Habori *et al.*, 2002).

Today in Ethiopia, khat is consumed by all societal groups regardless of age, sex, affluence, class, education and occupation (Ayana and Mekonen, 2004). Chewing the leaves is an effective way of extracting Cathinone: the chemical constituent of khat that produces an amphetamine-like stimulatory effect (Toennes *et al.*, 2003 and Widler *et al.*, 1994).

The medical and socio-economic 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. Khat use has been reported to affect the cardiovascular, digestive, respiratory, endocrine, hepatobiliary and genito-urinary systems (Kalix, 1984).

The significance increase in the activity of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and significance decrease in albumin level in Khat extract treated group indicate a liver damage due to necrosis or membrane damage resulting in the leakage in to the extracellular fluid as a result of toxic action on hepatic tissue (Murry *et al.*, 2008). This project paper shows the toxic effects of Khat leaves, both in short and long-term on different animal livers including Khat users, as evidenced by significant change in plasma levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In addition to this it also assess the histo-pathological changes of livers of the studied animals and Khat users.

1.2. Botany of *Catha edulis* (khat)

Khat is a herbal product consisting of the leaves and shoots of the shrub *Catha edulis*, a member (*genera*) of the evergreen *clastraceae* (moonseed or spindle-tree) family or tribe (Simmons *et al.*, 2008). Under natural conditions, khat grows in and on the margins of dry evergreen forest and mist forest. It grows naturally at elevations of 1,500-2,000m but is found at altitudes of 1,200–2,500m. It is best cultivated at high elevations, with high rainfall in acidic, well-drained clay soils; but can survive long periods of drought. Khat's natural range extends throughout East Africa from Ethiopia, Eritrea and Somalia, through to South Africa; it is also found in Rwanda, Zaire, Malawi and Zimbabwe. *Catha edulis* also found sporadically in Afghanistan, Israel, Saudi Arabia, Syria and Turkistan (Brooke, 1960; Balint and Balint, 1994). In Arabia, it is found principally in the Yemen. Khat grows in clumps, in beds or rows; often mixed in or interspersed with other crops, such as coffee and conifers, when cultivated. The primary areas for cultivation remain Eastern Africa – mainly Ethiopia, Kenya and to a lesser extent the Comoros, Madagascar and Tanzania - and the Arabian Peninsula, especially Yemen.

1.3. Habit of chewing *Catha edulis* (khat)

1.3.1. History of the habit

According to a famous legend in Ethiopia, the first human to use Khat was a Yemeni herder who noticed the effects of the leaves of the plant on his goats and tried them himself (Getahun and Krikorian, 1973). The legend refers to the mastication of the leaves, which is currently the exclusive method of khat use. However, some early accounts indicate that khat was also used as tea in close connection with the use of coffee (Kennedy, 1987a). Following its introduction, the use of khat in Yemen spread slowly until the 16th century, when it became common among esoteric religious groups and the upper classes. Thereafter, its use spread rapidly so that by the beginning of the 19th century it became very extensive and almost universal in some parts of Yemen.

1.3.2. Habit description

Khat is usually chewed at special social gatherings, but is also used frequently during work by laborers, craftsmen, farmers and students to keep alert and reduce physical fatigue (Getahun and Krikorian, 1973; Kennedy, 1987b). The habit has a deep-rooted social and cultural tradition, particularly in Yemen (Kalix and Braenden, 1985). The social Khat session, in Yemen called majlis al-qat, is held in the afternoon in a special warm reception room for Khat-chewing. Guests sit comfortably and chew the fresh leaves one by one. The juice is swallowed while the residue is retained as a quid against the cheek on one side of the mouth; a quantity of 100 – 200 g is usually consumed (Kalix, 1996). Initially, the session is lively and as the alerting effects of Khat start to work, the session becomes more serious and the chewers' talk focuses on one subject at a time. The topic may be a current world event, a historical or religious issue, a political situation or a local dispute. After 2 – 3 hours the session becomes quiet as most of the chewers prefer to be left alone, falling into intense concentration and mental focus. After about 4 hours, people start to depart the session. A detailed description of a typical khat session is provided elsewhere (Luqman and Danowski, 1976; Kalix and Braenden, 1985; Kennedy, 1987b).

1.4. Chemistry of *Catha edulis* (Khat)

Fresh leaves of khat contain the alkaloids of the phenyl propyl amine type of which the two psychoactive constituents are the stimulants cathinone (S-(-)- α -aminopropiophenone) and cathine (S, S-(+)-norpseudoephedrine).

The psychoactive substances in Khat act on two main neurochemical pathways – dopamine and noradrenalin. It has been suggested that cathinone, like amphetamine, releases serotonin in the CNS. Both these substances induce the release of dopamine from CNS dopamine terminals thereby increasing the activity of dopaminergic pathways (Kalix and Braenden, 1985).

Cathinone is a four times powerful stimulant than cathine and is generally regarded as the most important element. However, cathinone is unstable in the presence of oxygen, oxidizing at room temperature, and decomposes within a few days of harvesting or if dried (Griffiths *et al.*, 1997). The stored product loses activity rapidly, becoming physiologically inactive after about 36 hours. For maximum potency, khat must be picked in the morning and chewed that afternoon (Baron, 1999).

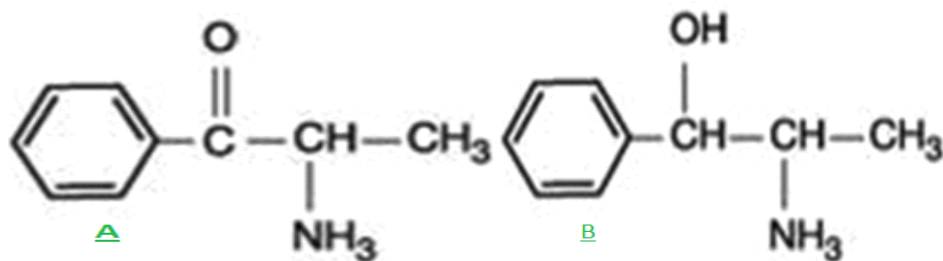


Figure 1. Chemical structure of Cathinone (A) and Cathine (B)

1.5. Pharmacology and Pharmacokinetics of *Catha edulis* (Khat)

1.5.1. Pharmacology of *Catha edulis* (Khat)

Khat leaf contains three alkaloids namely, cathine, cathinone and norephedrine as well as sugar, tannins and vitamin C (Kalix, 1984). Cathinone and cathine are believed to be responsible for most of the pharmacological actions of khat. Cathinone, the active ingredient of khat, has similar structure and action with that of amphetamine. It is believed to contribute for the major

pharmacological effects such as euphoria, alertness and anorexia. On the basis of such similar effects of cathinone and amphetamine, WHO in 1980 classified cathinone as a drug of abuse that can produce mild to moderate psychic dependence.

1.5.2. Pharmacokinetics of *Catha edulis* (khat)

Little was known about the pharmacokinetics of khat (WHO, 1980). However, recently since khat chewing becomes more common in western countries due to migration of people from endemic khat chewing countries like Somalia, Ethiopia and access of air transport of khat, the pharmacokinetics of khat has obtained due attention (Rousseau *et al.*, 1998). Its pharmacokinetics depends on the type of khat ingested. Khat with young leaves contain high concentration of cathinone that can be absorbed, distributed, bio-transformed and excreted within a short time (Al-Motarreb *et al.*, 2002).

1.6. Stages of intoxication associated with chewing *Catha edulis* (Khat)

The effect of Khat chewing varies according to the type of Khat and according to the person. As with most drugs taken for pleasure, the response is peculiar to the individual. In general the effect of Khat on the chewers can be divided into the following stages:

1. The euphoric, cheerful sensation and excitement stage (Brenneisen *et al.*, 1990 and Widler *et al.*, 1994) which lasts about 1–2 hours (Kalix and Braenden, 1985). This is clear among the young chewers, and it is repeated at each session.
2. The Khat chewers start to discuss serious issues with some emotional irritability and great awareness of the problem (Kalix and Braenden, 1985). They normally start to discuss a general issue then pairs of people talk on personal issues in a low voice and in private.
3. The *Sulaimania hour*; this stage usually starts at the beginning of darkness (around 6.30 pm summer and 5.30 pm in winter) when the Khat chewer does not like to switch on lights but keeps silent, enjoying the view if he is in the *Mandheror* the sound of the water and the green garden if he is in the *Mafraj*. At this stage, his imagination is very active in generating a mood of great excitement. This feeling was the reason for calling this stage *Sulaimania* after the king and prophet Sulaiman. At the beginning of this stag some chewers like to listen to local music either by a musician invited to sing for them live or recorded on tape.

4. A depressive stage which usually comes at the end of the Khat session just before spitting out the Khat bolus and continues afterwards. This stage is characterized by exaggerating private problems with great concern and a pessimistic view. The depressive stage depends on the potency of the Khat. Some Khat chewers promise themselves to stop Khat chewing and blame Khat for this depressive state.
5. Irritability, anorexia and insomnia. This stage is characterized by an increase in the imaginative sensation of self-confidence, ideas fly around and there is an inability to concentrate on one issue (Kalix and Braenden, 1985). Next morning, lethargy and a sleepy state accompany amnesia of most of the enthusiastic ideas, which had been discussed the night before. By 10 or 11 am in the morning, the Khat chewer starts to long for the day's khat session and how to arrange it. This feeling is too strong and overcomes his resistance and pledge of the past night to stop the habit. The time factor in these stages is flexible and depends on the session itself and the people involved. There are large differences between an election campaign, a wedding party or a funeral gatheng and the normal daily session.

1.7. Medical and psychological consequences of chewing *Catha edulis* (khat)

Early subjective accounts claimed that khat is harmful to health. Since then there has been an increasing number of reports on this issue, expanding the list of the possible adverse health effects of khat-chewing. Halbach (1972) asserted that Khat-chewing causes certain health disturbances including stomatitis, oesophagitis, gastritis, constipation, malnutrition, liver cirrhosis, anorexia, insomnia, spermatorrhoea and impotence. He also alleged that migraine, cerebral haemorrhage, myocardial insufficiency and infarcts and pulmonary oedema had been described after Khat intake. Luqman and Danowski (1976) added gastric ulcers, haemorrhoids, urinary bladder hypotonia, poor lactation and schizophrenia to the list, but they mentioned that the effect of khat on sexual behavior is not definitely negative, as affirmed by Halbach (1972), who was their main reference.

In general the medical effect of consumption of *Catha edulis* (Khat) can be categorized as acute effects and long-term effects (Cox and Rampes, 2003)

❖ Acute effects include:

Relief of fatigue, increased alertness, reduced sleepiness, mild euphoria and excitement, improved ability to communicate, loquacity, tachycardia, hypertension, moderate hyperthermia,

mydriasis, blurred vision, anorexia, dry mouth, constipation (supposedly due to tannins, but amphetamines may also cause constipation), psychotic reactions at high doses, irritability and depressive reactions at the end of a Khat session and also lethargy and sleepy state (next morning)

❖ **Long-term effects include:**

Malnutrition, psychotic and depressive reactions after chronic use, irritative disorders of the upper gastro-intestinal tract (gastritis, enteritis), cardiovascular disorders, hemorrhoids, impaired male sexual function, spermatorrhoea, impotence, periodontal disease and mucosal lesions (keratosis).

Table 1. Reported and suggested adverse effects of khat in man (Cox and Rampes, 2003)

System	Adverse effects
Cardiovascular system	tachycardia, palpitations, hypertension, arrhythmias, vasoconstriction, myocard infarction, cerebral hemorrhage, pulmonary edema
Respiratory system	tachypnoea, bronchitis
Gastrointestinal system	dry mouth, polydipsia, dental caries, periodontal disease, chronic gastritis, constipation, hemorrhoids, paralytic ileus, weight loss, duodenal ulcer, upper gastro-intestinal malignancy
Hepatobiliary system	fibrosis, cirrhosis
Genitourinary system	urinary retention, spermatorrhoea, spermatozoa malformations, impotence, libido change
Obstetric effects	low birth weight, stillbirths, impaired lactation
Metabolic and endocrine effects	hyperthermia, perspiration, hyperglycaemia
Ocular effects	blurred vision, mydriasis
Central nervous system	dizziness, impaired cognitive functioning, fine tremor, insomnia, headaches
Psychiatric effects	lethargy, irritability, anorexia, psychotic reactions, depressive reactions, hypnagogic hallucinations

2. Review and analysis of published research on toxicological effect of *Catha edulis* Forsk (khat) on the histology and function of liver

In this part of my project paper research publications on toxicological effect of *catha edulis* (Khat) on the histology and function of liver are reviewed, analyzed and presented as follows:

In a study undertaken by Fahaid *et al.* (2011) it was reported that *Catha edulis* (Khat) extract increased oxidative stress parameters and impaired hepatic functions in rats. In this study twenty white albino rats aged between 14 and 16 weeks and weighing between 180-200 gm were used. The rats were fed standard rat pellets and allowed free access to water. They were housed in plastic cages (5 rats/cage) at a controlled ambient temperature of $22 \pm 2^{\circ}\text{C}$ and $50 \pm 10\%$ relative humidity, with 12 hour light/12 hour dark cycles.

The rats were assigned randomly to two groups of ten each. The animals were identified with differently colored tail marks and housed in different segments of the cage, according to their group. The experimental group received single doses (500 mg/kg body weight) of *Catha edulis* extract daily while the control group received equivalent amounts of normal saline daily. At the end of day 28, the rats were subjected to overnight fasting and then blood samples were collected directly from tail veins. Routine histological examination of liver was performed. Tissue fixation was carried out with 10% neutral buffered formaldehyde solution (pH 7.0). Liver enzymes AST, ALT and ALP were assayed.

The result as shown in table 2 revealed that administration of *Catha edulis* extract to rats for a period of 28 days resulted in statistically significant increases in the activities of ALT, AST and ALP in treated rats compared to the control group. In addition, the extract caused significant increases in the level of bilirubin accompanied by significant decreases in serum albumin levels.

Table 2. Levels of Hepatic Enzymes, Albumin and Bilirubin in the Serum of Control and *Catha edulis* treated Rats.

Parameter	Control group	CE-treated group
ALT (u/l)	31.8 ± 1.30	65.2 ± 3.19
AST (u/l)	73.6 ± 1.34	123 ± 3.51
ALP (u/l)	75.3 ± 2.17	117 ± 2.55
Albumin (g/dl)	3.66 ± 0.219	1.16 ± 0.114
Bilirubin (mg/dl)	0.38 ± 0.030	0.76 ± 0.08

- ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphatase
- Values were expressed as mean ± SEM.
- Values are statistically significant at $P < 0.05$

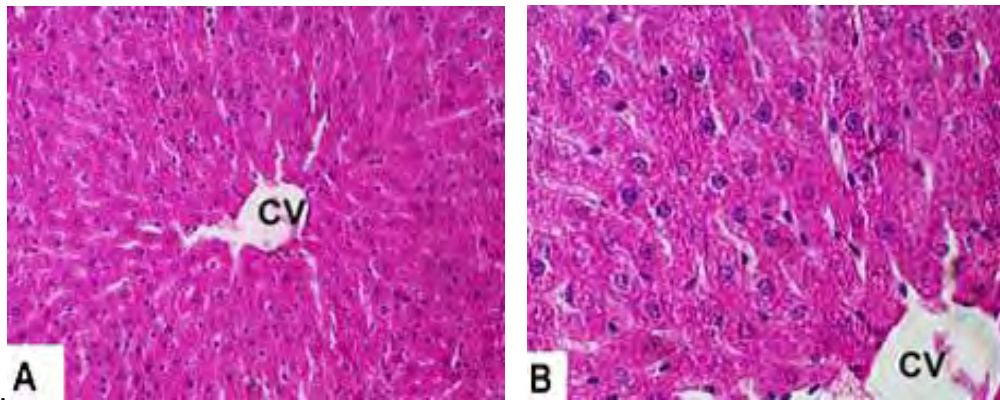


Figure 2. Liver of Normal Rats

A: Liver of normal control rat 20x

B: Liver of normal control rat 40x

Histo-pathological examination of the livers of *Catha edulis* treated rats revealed marked degenerative changes as compared to the control animals (fig. 4).

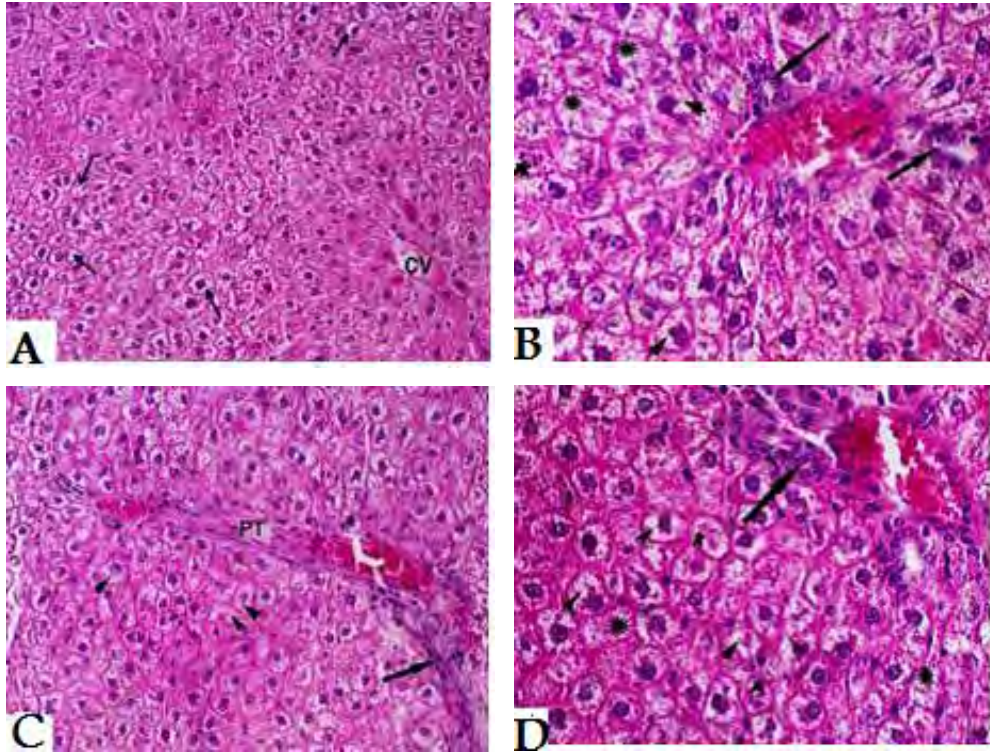


Figure 3. Liver of khat treated Rats

- A:** Liver of Khat-treated rat, showing central veins and disorganized hepatic cords with most hepatocytes having cytoplasmic vacuolization (arrows), 20x
- B:** Liver of Khat-treated rat showing infiltrative inflammatory cells (arrow) and hepatocytes with apparent cytoplasmic vacuolar degeneration (arrowheads) as well as necrotic changes, 40x
- C:** Liver of Khat-treated rat, showing a portal tract, inflammatory Infiltration (arrow) and vacuolized hepatocytes (arrowheads), 20x
- D:** Liver of Khat-treated rat showing more infiltrative inflammatory cells and more hepatocytes with cytoplasmic vacuola degeneration (arrowheads) as well as necrotic alterations, 40x H & E stain.

In general degenerative alterations include disorganization of hepatic cords, cytoplasmic vacuolization of hepatocytes and invasion of infiltrative inflammatory cells as well as necrotic changes were seen in the treated groups.

In another research, Abdulsamad *et al.* (2012) investigated the toxicological effect of *Catha edulis* (Khat) on livers of male and female sprague-dawley rats. In this study forty-eight healthy male and female Sprague-Dawley rats weighing 100–120 g were used. They were randomly grouped into four groups ($n = 6$) designated as high dose (HD), medium dose (MD), low dose (LD), and normal control (NC). Rats were given a single daily dose of crude extract of Khat suspended in pure distilled water according to the body weight of each rat. Rout of administration was by oral gavage. Treated rat were received 2000 mg/kg (HD), 1000 mg/kg (MD) and 500 mg/kg (LD). Normal control (NC) rat werereceived 10 ml/kg of distilled water.

After autopsy, livers were washed in normal saline, blotted with filter paper, and visualized for any surface visible lesions immediately after harvesting and weighed. Then, organs were put in neutral phosphate buffer solution. After that, biopsies were obtained, fixed in 10% neutral formalin, processed, dehydrated, and embedded in paraffin wax. The 5 μ m sections in thickness were stained according to the usual hematoxylin-eosin procedure to be microscopically examined (20x magnification).

The results were computed statistically with SPSS software package version 17 using one-way analysis of variance (ANOVA) for mean difference between groups. Males and females were analyzed separately ($n = 6$) and P value was set at $P < 0.05$. Then post hoc Dunnett test (two-sided) was followed for comparing the tested groups to the single normal control at $P < 0.05$ and $P \leq 0.01$.

Serum activity of alkaline phosphatase (ALP) and alanine aminotransferase (ALT) and AST in treated male SD-rats was significantly increased ($P < 0.05$) as compare to control groups. The mean ALP and AST of HD-treated groups were also significantly increased ($P < 0.05$) to that of MD, LD and NC. However, the mean ALT HD-treated groups indicated a non-significant ($P \geq 0.05$) as compared to NC. In addition, serum total bilirubin (TB) of treated male and female SD

rats was significantly increased ($P < 0.05$) as compared to control groups but the serum albumin (A) of treated male and female SD-rats was non-significantly ($P \geq 0.05$) as compared to NC (Table 3).

Serum activity of ALP, ALT and AST of treated female SD-rats was significantly increased ($P < 0.05$) as compared to control groups. The mean values of ALP and AST HD and MD were also significantly increased ($P < 0.05$) as compared to LD and NC. However, mean values of ALT HD, MD, and LD were not significant ($P \geq 0.05$) as compared to NC (Table 3).

Table 3. Liver function test of male and female SD rats.

Dose(mg/kg)	ALP(u/l)		ALT(u/l)		A(u/l)		TB(u/l)	
	Male	Female	Male	Female	Male	Female	Male	Female
NC (10mL/kg)	155.50 ± 6.22	100.83 ± 13.10	35.33 ± 2.51	39.67 ± 2.47	12.33 ± 1.75	15.67 ± 0.49	1.5	1.0
LD (500 mg/kg)	147.67 ± 22.31	107.67 ± 3.68	28.33 ± 3.44	25.33 ± 2.14	11.50 ± 2.74	12.50 ± 0.56b*	2.0*	2.5
MD (1000 mg/kg)	146.00 ± 16.42	149.67 ± 18.70*	27.17 ± 3.11	30.50 ± 1.52	9.50 ± 2.43	13.67 ± 0.71	2.0*	2.5
HD (2000 mg/kg)	225.67 ± 19.71*	158.67 ± 10.15*	38.17 ± 1.56	31.50 ± 1.5	14.00 ± 1.41	12.50 ± 0.72b*	3.0*	3.0

- A: albumin; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphatase TB: total Bilirubin, HD: high dose; MD: medium dose; LD: low dose; NC: normal control
- Values were expressed as mean ± SEM.
- Values are statistically significant at $P < 0.05$
- (*) denoted a significant difference $P < 0.05$
- (b*) denoted a significant difference at $P \leq 0.01$.

Microscopic examination of liver sections of normal controls of both male and female SD-rats showed uniform hepatocytes, intact cytoplasm, prominent nuclei of cells, and uncongested central vein. In addition, no necrotic lesions, fatty changes, or inflammatory signs were observed in those animals. Similarly, liver sections of LD and MD-groups of male and those of female SD

rats in LD-groups showed normal hepatocytes architecture, preserved-cytoplasm without any apparent necrotic lesions. However, liver sections of HD-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. Such changes were minimally apparent in liver sections of MD-group of female SD-rats (Figure 5c).

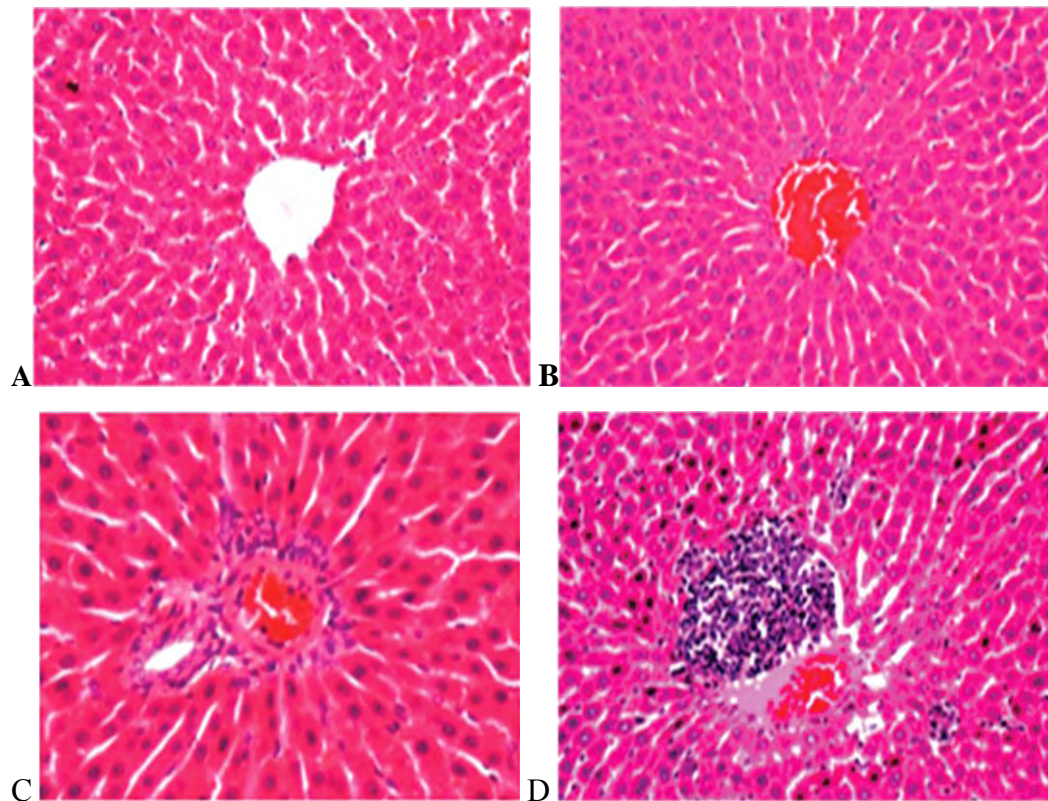


Figure 4. **Effect of Khat on histological sections of liver of male and female rats.**

- (A) Normal control of males with normal liver parenchyma
- (B) Low dose of males with normal liver parenchyma
- (C) Medium dose of males with normal liver parenchyma
- (D) High dose of males with moderate necrotic lesions around the central vein

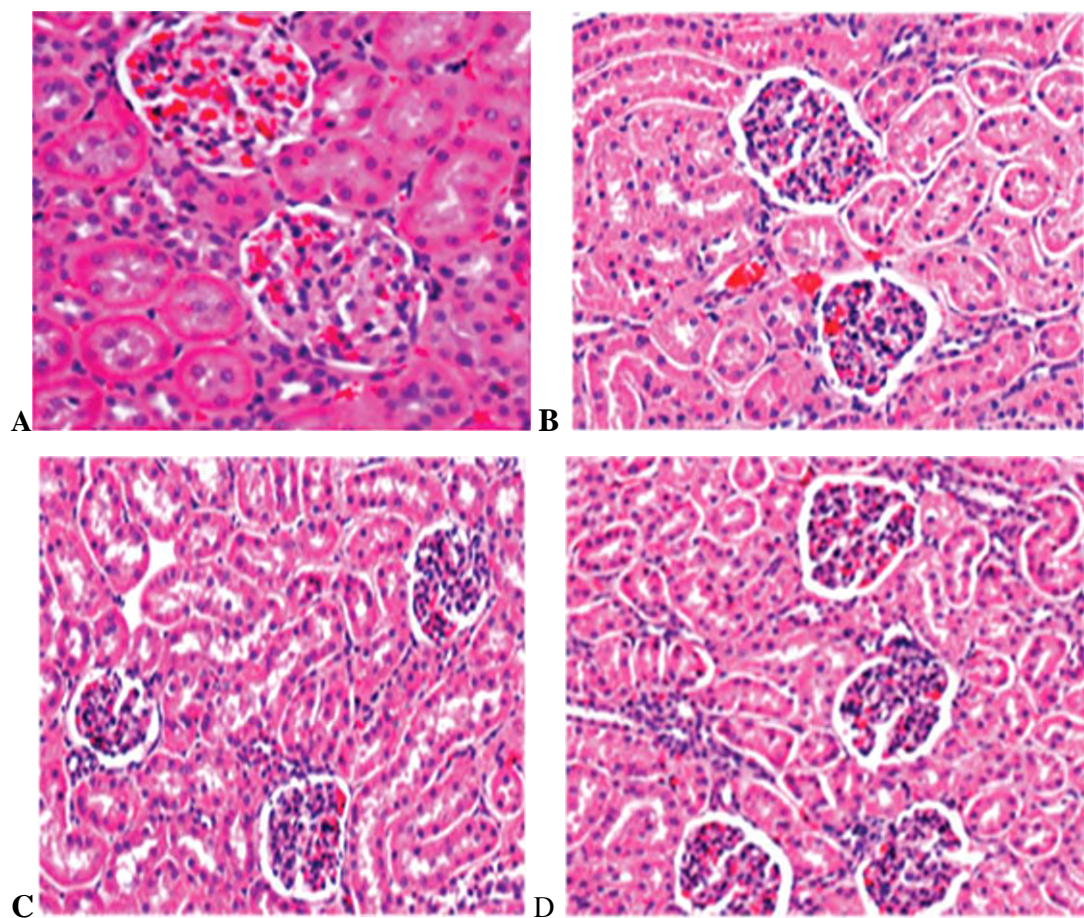


Figure 5. **Effect of Khat on histological sections of liver of male and female rats.**

- (A) Normal control of females with normal liver parenchyma
- (B) Low dose of females with normal liver parenchyma
- (C) Medium dose of females with slight necrotic lesion around the central hepatic vein
- (D) High dose of females with a moderate necrotic lesion around the central hepatic vein

Adal *et al.* (2008) conducted another research on the effect of short term repeated dose biochemical of *Catha edulis* (khat) extract administration in rat. Thirty six randomly selected Sprague- Dawley male rat weighing 200-250g and 5-7 week old were used in this study. SD rats were divided in to four group and exposed by force feeding to 0, 500, 1000, and 2000 mg Kg⁻¹ body weight/dayfreeze dried *Catha edulis* (Khat) leaves for 6 consecutive weeks. After 6 week treatment rats was scarified. Blood sample were collected for determination of albumin, AST, ALT, ALP level measure using the chemistry analyzer (Hitachi 902 automatic analyzer, Japan) . The results were computed statistically with SPSS software package version 17 using one-way analysis of variance (ANOVA) for mean difference between groups and *P* value was set on *P* <0.05. The values were expressed as mean ± SEM.

Liver enzyme activity were demonstrated to be non-significantly affected and were more reduced in the treated group. ALP was observed to be non-significantly increased by 14- 27% as compare to control group, AST, was reduced by 4-17% and ALT by 3-10% in the tree treatment group. In addition to this albumin was non significantly affected compare to control group (Table 4).

Table 5. Plasma level of liver enzyme activity and albumin 6 week treated groups.

Parametrtrs	Control	<i>Catha edulis</i>		
		500 mg /Kg	1000 mg/Kg	2000 mg /Kg
AST (u/l)	99.2± 26.0	95± 21.4	818± 18.7	82.24± 14.0
ALT (u/l)	41.6± 17.3	38.4± 6.4	37.2± 5.1	40.3± 6.7
ALP (u/l)	142.6± 18	163.14± 53	179.7± 41.6	182± 42.0
Bilirubin (mg/dl)	37.2±1.90	36.6±2.9	38.3±1.9	36.7±2.00

- ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphatase
- Values were expressed as mean ± SEM.
- Values are statistically significant at *P*<0.0

Study conducted by Molham *et al.* (2002) evaluated the toxicological effect of *Catha edulis* (khat) leaves by way of long term feeding in experiment animals. In this study twenty four white rabbits (800-1000 g) were caged individually. Rabbits were randomly allocated to one of four groups (six rabbits per group) which were given one of four diets, the control diet or one of three diets containing different proportions of *C. edulis* leaves (10, 20 and 30%) for 6 months. At the end of each month, food was withheld for 16 h to provide fasting blood samples; feeding was then resumed. The blood was withdrawn from the marginal ear vein into heparin-containing tubes. Samples were immediately centrifuged for 5 minute at 2500g and the separated plasma was stored at 20 °C. Plasma was assayed for Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and total bilirubin using Enzymatic kits.

The animals from each treatment were sacrificed at the end of the experiment period (6 months). After sacrificing the animals, the liver was removed from viscera and small pieces of each of these organs were fixed in 10% neutral formalin for histo-pathological studies. Tissues were processed by conventional technique; the paraffin embedded sections of 5 mm thickness were prepared and stained with hematoxylin and eosin for microscopic examination. The data were analyzed as complete randomized design using a one-way analysis of variance (Petersen,1985).

The finding demonstrated a trend of continued supplementation with *C. edulis* leaves at all levels tested did not alter the food intake of animals. However, the activity and behavior of the animals were affected on going through the fourth to sixth months of treatment.

Addition of 10% *C. edulis* leaves to increase plasma concentration of ALP by 22-25% in the fourth to sixth month of treatment; this shows it is not statistically significant as level of *C. edulis* leaves is low when compared with the corresponding control. In contrast, plasma concentration of ALT was significantly increased by 50-/85% throughout the treatment period. Similarly, plasma concentration of AST was significantly increased by approximately 52/- 55%. in addition to this the total bilirubin were also significantly increased by 56-62% during the treatment period (4-6) months (Table 5).

Table 6. Effect of 10% *C. edulis* on liver plasma enzymes (IU) and total bilirubin (mg/dl)

Parameters	Four month		fifth month		Six month	
	Control (Mean± S.D.)	Treatment (Mean± S.D.)	Control (Mean± S.D.)	Treatment (Mean± S.D.)	Control (Mean± S.D.)	Treatment (Mean± S.D.)
AST	34.35± 5.21	53.3± 95.79	33.63± 4.73	51.25± 4.79	26.18± 3.17	40.06± 3.94
ALT	46.88± 2.44	70.22± 5.98	43.32± 4.53	70.68± 7.65b	39.74± 4.86	73.36± 8.57
ALP	50.95± 8.99	63.62± 8.58	52.13± 3.63	58.70± 6.36	49.39± 5.68	60.15± 7.05
Bilirubin (total)	0.221±0.04	0.353±0.09	0.227±0.04	0.368± 0.08	0.243± 0.03	0.37±0.04

- ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphatase
- Values were expressed as mean ± SEM.
- Values are statistically significant at $P < 0.05$.

The addition of 20% *C. edulis* leaves to the animals diet (Table 5) were increased the plasma ALP by 97% in the fourth month and by 38-51% in the fifth and sixth months of treatment. The effect 20% *C. edulis* leaves on plasma ALT was similar to that of the lower dose of 10% *C. edulis* treatment where the 20% *C. edulis* significantly increased it by 46-93% throughout the period of treatment. The 20% *C. edulis* also increased the plasma concentration of AST by 59-69% (Table 6). The effect on total bilirubin was slightly greater (65-72%) than that observed with the lower dose of 10% *C. edulis*.

Table 7. Effect of 20% *C. edulis* on liver plasma enzymes (IU) and total bilirubin (mg/dl)

Parameters	Four month		fifth month		Six month	
	Control (Mean±S.D)	Treatment (Mean± S.D)	Control (Mean±S.D)	Treatment (Mean± S.D)	control (Mean±S.D)	Treatment (Mean±S.D)
AST	34.35± 5.21	57.82± 6.69	33.63± 4.73	53.41± 4.09	26.18± 3.17	42.13± 6.18
ALT	46.88± 2.44	71.81± 4.25	43.32± 4.53	74.19± 6.43	39.74± 4.86	76.61± 5.62
ALP	50.95± 8.99	100.17± 12.5	52.13± 3.63	73.91± 8.00	49.39± 5.68	74.54±10.73
Bilirubin(total)	0.221± 0.04	0.381± 0.06	0.227± 0.04	0.389± 0.06	0.243± 0.03	0.402± 0.05

- ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphatase
- Values were expressed as mean ± SEM.
- Values are statistically significant at $P<0.05$

Addition of 30% *C. edulis* were increased the plasma concentration of ALP further by 107% in the fourth month of treatment and by 200% in the fifth and sixth months. The concentration of ALT increased by 58-96%, in a similar pattern to that observed with the 20% *C. edulis* level. The 30% *C. edulis* leaves were observed to further increase the plasma AST by 86-119% (Table 7). In addition to this the total bilirubin was further increased by 91-94%.

Table 8. Effect of 30% *C. edulis* on liver plasma enzymes (IU) and total bilirubin (mg/dl)

Parameters	Four month		fifth month		Six month	
	Control (Mean±S.D)	Treatment (Mean±S.D)	Control (Mean±S.D)	Treatment (Mean± S.D)	Control (Mean±S.D)	Treatment (Mean±S.D)
AST	34.35± 5.21	63.95± 9.15	33.63±4.73	65.37± 8.15	26.18± 3.17	57.4± 7.77
ALT	46.88± 2.44	74.50± 4.86	43.32±4.53	78.55± 5.15	39.74± 4.86	77.76±5.24
ALP	50.95± 8.99	105.54± 13.58	52.13±3.63	156.44±19.48	49.39± 5.68	148.51±1770
Bilirubin (total)	0.221± 0.04	0.428± 0.06	0.227±0.04	0.434± 0.06	0.243± 0.03	0.464±0.04

- ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphatase
- Values were expressed as mean ± SEM.
- Values are statistically significant at $P<0.05$

In another research, conducted by Wafaa *et al.* (2012) evaluated the effects of *Catha edulis* (khat) on the histopathology liver in experimental animal. In this study fifteen *Oryctolagus scuniculus* rabbits (1000-1200 g / wt) were housed in individual cages at a 12 hr light/dark cycle and received food and water ad libitum until the beginning of experiment. The animals were assigned randomly to 3 groups (5 rabbit each):- Group 1: the control group, the rabbits were feed with standard feed and water ad libitum. Group 2: khat group, they were given standard food containing 2 gm/ kg fresh khat leaves for 21 days. Group 3: khat withdrawal group, the experimental animals were given standard food containing 2 gm/ kg fresh khat leaves for 14 days and followed by the standard chow for 7 days.

Samples of livers were quickly removed for routine histological examination. Tissue fixation was carried out with 10% neutral buffered formaldehyde solution (pH 7.0), dehydrated in

alcohol, cleared in terpineol and embedded in paraffin wax. Sections were stained with hematoxylin and eosin, microscopically examined and photomicrographs were made.

Histo-pathological observations on the liver of khat treated rabbit showed destruction of the normal architecture and hepatocytes. The hepatocyte cytoplasm appeared granular or vacuolated with fatty globules (Fig. 6A). Mononuclear inflammatory cells were infiltrated surrounding the portal area and within the parenchyma of the liver (Fig.7A and Fig.7B). Focal necrotic areas were observed containing pyknotic and karyolytic nuclei of hepatocytes (Fig.7A and Fig.7B).. Dilation and congestion of central vein and blood sinusoids were also detected (Fig. 7A). After withdrawal the hepatic cords were well organized and the cytoplasmic vacuoles disappeared. Most cells exhibited normal size. The portal tract with no inflammatory changes but still some congested blood sinusoids and many hepatocytes were bi-nucleated (Fig. 7C and Fig.7D).

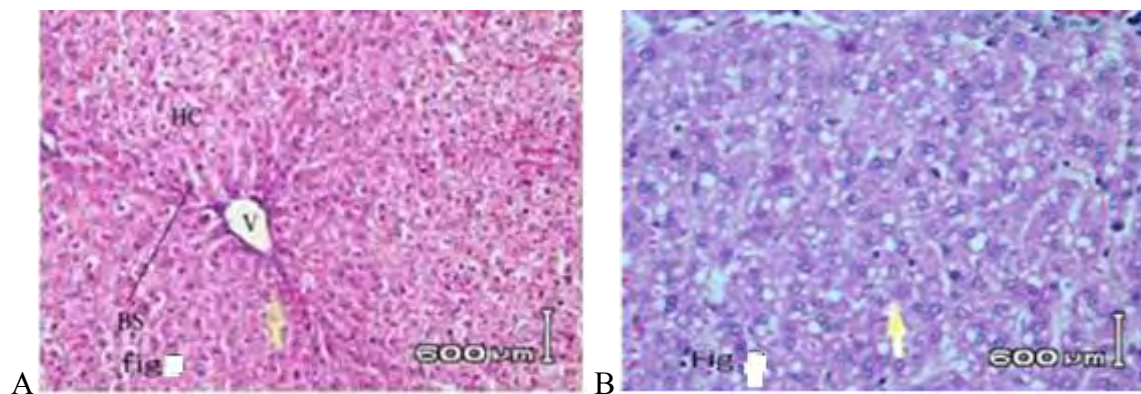


Figure 6. **Effect of Khat on histological sections of liver of rabbit**

- A. The portal area including branches of hepatic portal vein (HV) ,hepatic artery (HA) and bile ductile (BD).
- B. Destruction of the normal pattern of hepatic lobules and fatty changes in the cytoplasm of hepatocytes(arrows) causing increase the size of hepatocytes

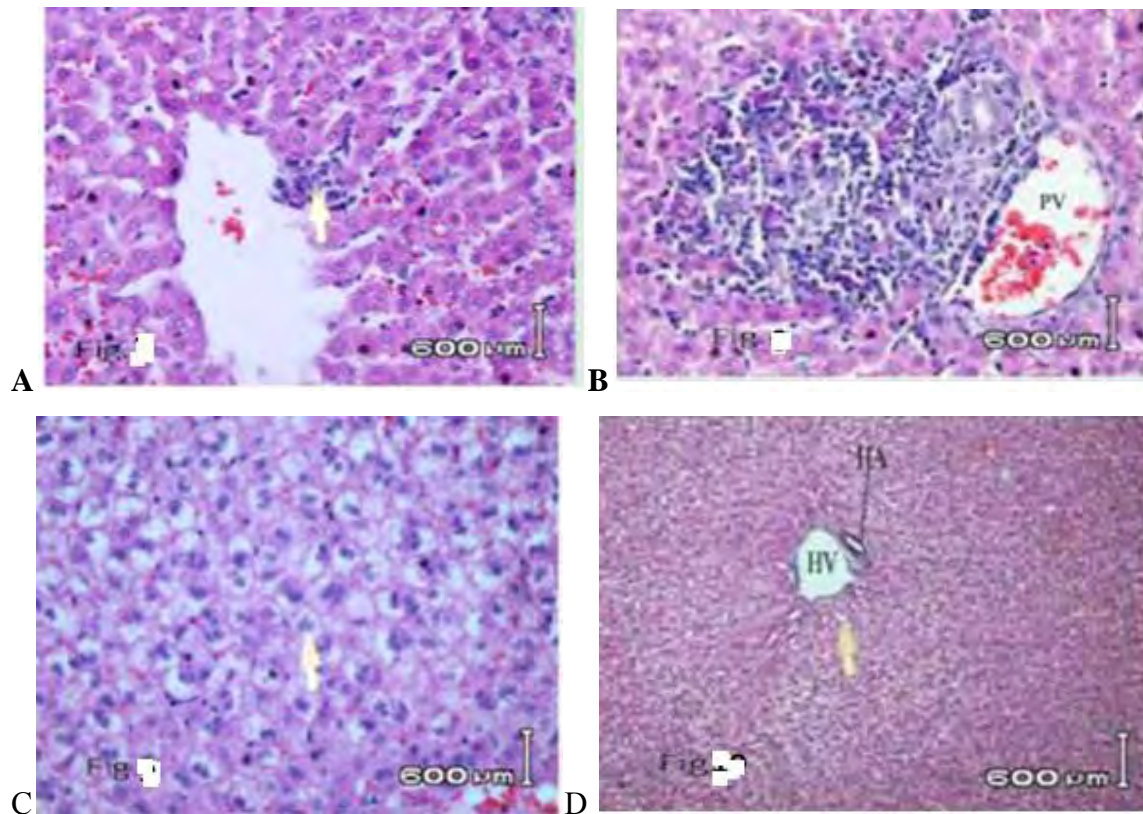


Figure 7. **Effect of Khat on histological sections of liver of rabbit**

- A. Dilated both central vein and blood sinusoids. The blood sinusoids congested with stagnant blood cells. Accumulation of inflammatory cells near the central vein (arrow).
- B. Accumulation of mono inflammatory cells around the area of the portal tract and necrotic cells in the interface . Also, congested portal vein(PV) with stagnant blood cells are detected (arrow).
- C. Destruction of the normal pattern of hepatocytes , dilatation and congestion of hepatic sinusoids (arrow)
- D. Showing portal tract, hepatic portal vein (HV), hepatic artery (HA) and bile ductile restored their normal configurations.

In a study conducted by Shabbiralem *et al.* (2014) it was reported that consumption of *Catha edulis* (khat) affects the functions of liver in male human population. The study was conducted on the Khat consumer humans in Jazan region of Saudi Arabia. Patients attended the primary health centre at the first visit for the symptoms of liver problem and gave history of Khat chewing were recruited for this study. The selection of participants was based on the following inclusion and exclusion criteria: All participants were male khat chewer, at the age above 20 years. Patients with history of drinking alcohol, hepatitis B virus and hepatitis C virus infection, hepatologic genetic disorders, liver problem due to hepatotoxicity by certain drugs were excluded from this study. A total of 100 participants were included in this study. Fifty out of 100 participants were used as a case (khat users). All the participants were interviewed by doctor and questionnaire was completed to cover the personal history of khat chewing (amount of Khat per day, number of hours per day, number of days per week and number of years), smoking (cigarette and water pipe), hypertension, diabetes and any family history of liver problem. Those healthy participants who have no exposure of khat chewing (non-khat users) and smoking in their life time and have no family history of liver problem were used as a control. Written consent was taken from all the participants after explanation of the aim of the study.

The concentration of various biochemical parameters was examined in serum samples collected from khat users and non-users. The biochemical parameters included alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB) and albumin (A) and were analyzed in 10 μ l aliquots of serum by auto-analyzer (Human Star 80, Human Diagnostic Worldwide, GmbH, Germany). Data were statistically described as mean \pm SEM. The chi square test was used to compare the results. A probability value (*p*-value) less than 0.05 was considered statistically significant. The results were computed statistically with SPSS (Statistical Package for the Social Science).

The finding indicates that ALT and AST activities were significantly increased in the serum of Khat users (Table 8). The elevated level of total bilirubin and ALP activity was also noticed in the serum of these khat-users. However, the serum concentration of serum albumin was significantly decreased compared to non-khat users.

Table 9. Biochemical Parameters for Liver Function in khat User and Non-User

Parameter	Khat User	Non- User	p Value
ALT (u/l)	43.09 ± 0.91	39.90 ± 0.56	0.73
AST (u/l)	39.37 ± 1.45	35.02 ± 0.67	0.044
Albumin (g/dl)	4.18 ± 0.21	4.28 ± 0.12	0.94
Bilirubin (mg/dl)	0.98 ± 0.02	0.95 ± 0.02	0.02*

- ALT: Alanin aminotransferase, AST: Aspartate aminotransferase,
- Values were expressed as mean ± SEM.
- The symbol (*) indicated as significant difference at $p > 0.05$

Anwar *et al.* (2014) reported that chewing *Catha edulis* (khat) alters the liver function. In this study Thamar city female populations were divided into two groups each having n=20: **1.**Khat Chewers group: local females with habit of chewing khat. **2.** Non-khat Chewers (control) group: local females never chew khat. Those included in the present study fulfill the following criteria: healthy, non-diabetic volunteers and aged between 20 and 30 years those excluded are suffering from hepatitis, kidney, carcinoma and diabetes. The study was performed in accordance with the Helsinki Declarations and approved by Ethical Committee. Blood samples of 40 individuals (20 each group) were collected, plasma of all samples were separated and the biochemical analyses were measured. The biochemical tests include assays of ALT and AST were estimated following the instructions of commercial kits provided by Spinreact, Spain. Data were expressed as mean ± S.D. and were analysed by student t-test. Differences between groups were considered significant when $P < 0.05$. All analyses were performed using the sigma-stat software.

An increase in the activities of ALT and AST of khat chewer group compared to the control group was seen in the study (Fig 8 and 9). This increase was 65.5% and 85.678% of ALT and AST respectively.

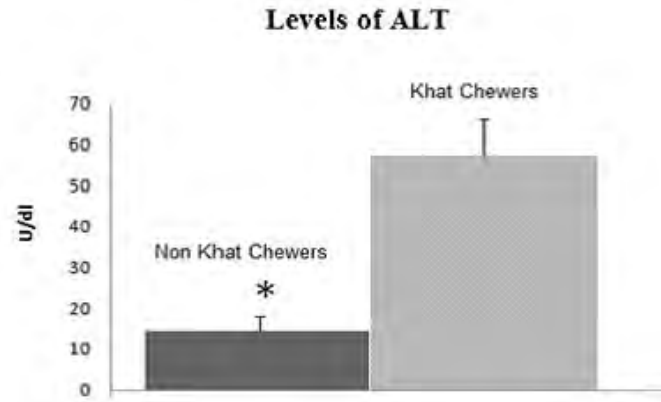


Figure 8. Activity of Alanine aminotranferase in the plasma of female non-Khat chewe and Khat chewers

- Results were expressed as mean \pm S.D.; n= 20.
- Data were analyzed by student-t- test.
- *p<0.001 was considered significant from control group.

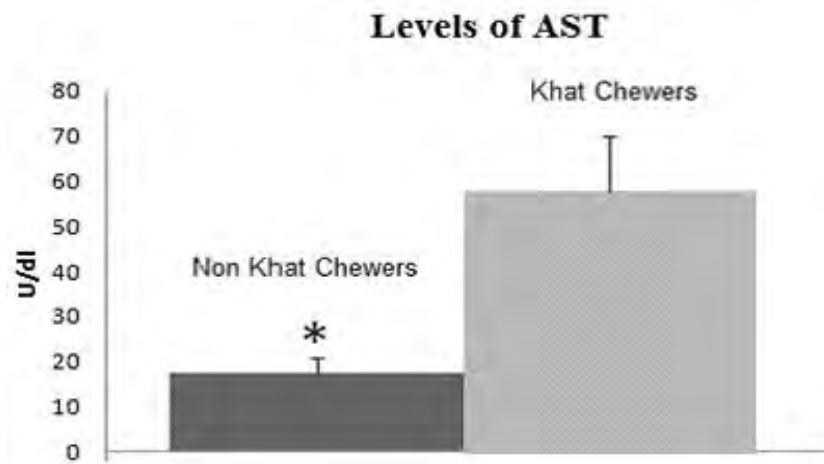


Figure 9. Activity of aspartate aminotranferase in the plasma of female non-Khat chewers and Khat chewers.

- Results were expressed as mean \pm S.D
- Data were analyzed by student-t- test.
- *p<0.001 was considered significant from control group.

In another research performed by Mona *et al.* (2012) investigated on the effect of Khat on liver. A total of 214 Khat users of Yemeni peoples were included in this study. The participants were divided in to two groups according to the presence or absence of hepatic insult either detected by elevated liver enzyme and/or abnormal ultra-sonography. Full medical history and clinical examination were done. Group I include 144 patients with either elevated liver enzyme and/or abnormal hepatic finding in liver ultrasound examination. Group II included 70 patients with normal liver enzyme and normal liver scan. Blood sample were obtained from each participants after fasting period of 10-12 hours for measuring liver enzyme AST and ALT in addition to this patients were tasted for serum albumin and bilirubin.

Statistical calculation were done using computer programs Microsoft Excell version 7 and SPSS version and data were statically described in term of mean \pm standard division a probability value (p- value) less than 0.05 was considered statistically significant.

Result of the study showed that from a total of 144 patients (group one) 127(88%) of them had elevated liver enzymes mainly ALT and AST. But only 17 patient (12%) had normal liver enzyme. In addition, the total blilirubin was significantly increased and albumin were significantly decreased as compare to group two who had normal liver enzyme and normal liver scan(Table 9). Liver ultrasound of group one also showed that 43 patient (30%) with bright liver, 30 patient (21%) with peri portal fibrosis, 12 patient (8%) with hepatomegally picture of fatty infiltration and four patient (3%) with liver cirrhosis. From a total of 144 patients (group one) only 55 patients (38%) had normal liver ultrasound.

10. Biochemical Parameters for Liver Function in group I and Group II

Parameter	group I and Group II	group I and Group II
ALT (u/l)	59.93 \pm 35.7	22.3 \pm 5.97
AST (u/l)	34.7 \pm 30.53	21.59 \pm 4.97
Albumin (g/dl)	12.9 \pm 0.85	12.17 \pm 0.7
Bilirubin (mg/dl)	0.93 \pm 0.32	0.89 \pm 0.35

- ALT: Alanin aminotransferase, AST: Aspartate aminotransferase
- Values were expressed as mean \pm SEM.

3. Discussion

A large number of people chew Khat leaves because of its pleasurable and stimulating effects. Free radicals and oxidants are now seriously implicated in Khat toxicity despite the presence of different antioxidants as chemical components of Khat. Several studies were undertaken to show the short and long term toxicological effect of *Catha edulis* (Khat) on the histology and function of liver.

The studies investigated by Fahaid *et al.* (2011) and Abdulsamad *et al.* (2012) in rat species administered 500mg/kg in similar duration (28day) showed that activities of hepatic enzymes Alkaline phosphatase (ALP), Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were elevated in the serum of *Catha edulis* extract treated rats and decrease in albumin level. These findings were consistent with findings of Al-Habori *et al.* (2002) and Molham *et al.* (2002) who reported for dose of 2mg/kg in long term feeding of khat leaves in rabbits (for 6 week and 6 month respectively) shows a significant increase in plasma levels of Alkaline phosphatase (ALP), Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) with all levels of *C. edulis* leaves tested and throughout the treatment period. These findings were also in agreement with the finding Shabbiralem *et al.*(2014) who confirmed that ALT, AST, ALP and total bilirubin activities were significantly increased and serum concentration of albumin was significantly decreased in the serum in long term Khat users as compared to non-khat users. The finding demonstrated by Anwar *et al.* (2014) on chewing *Catha edulis* (khat) and liver functions of female chewers were also in line with the above findings, the finding shows that an increase in the levels of ALT, AST, whereas, the total protein content was decreased in the plasma of female khat chewers. Al-Hashem *et al.* (2011) have earlier described that administration of hydro-ethanol khat extract to rats for 28 day resulted in a statistically significant increase in the serum activities of ALT, AST and ALP in khat fed rats as compared to control. A number of earlier studies were also described that Khat consumption resulted in to severe acute liver injury and acute hepatitis (Brostoff *et al.*, 2006; Saha and Dollery, 2006; Chapman *et al.*, 2010). In addition to this these findings are in line to the finding obtained by Mona *et al.* (2012) whose showed that groups with liver damage who consistently chew khat had elevated liver enzymes mainly ALT, and AST and the total blilirubin was significantly increased and albumin is significantly decreased as compare to groups of patient with normal liver and who do not chew

khat. These findings are also most likely seems to the study reported since 2010 by Chapman *et al.* on his observation of six patient who use Khat regularly present over a five year period with sever acute hepatitis all had similar histo-pathological finding characterized by multilobular necrosis; and he conclude that Khat chewing leads to chronic liver disease. All the above finding were consistent it might be because the experimental species including khat users were exposed for too much dose or it might be because the treated species liver could be susceptible for the toxicity of the alkaloid of Khat or it is due to the method of administration that is force feeding mode of administration.

Unlike the above finding the research conducted by Adal *et al.* (2008) and Mwenda *et al.* (2006) administration of 500, 1000 and 1500mg/kg *Catha edulis* (khat) extract for 6 week there is no significant difference of ALT, AST, ALP, bilirubin and other hepato toxic effect in the treated group as compare to control group. This suggests that 6 week administration of extract *Catha edulis* has no hepato toxic effect in rat. However, the elevation of serum activity of ALT, AST and ALP effect in liver of rabbits and humans in the aforementioned article was contrasting to the findings of Adal *et al.* (2008) and Mwenda *et al.* (2006) may be because the doses given to rabbits and human were small and exposure was for short time.

The result on histo-pathological examination of the livers of *Catha edulis* treated rats for 28 day investigated by Al-Hashem *et al.* (2011) and Abdulsamad *et al.* (2012) revealed marked degenerative changes as compared to the control group. There were dilatation of sinusoids and Kupffer cells around the central vein and portal tracts. The finding of Abdulsamad *et al.* (2012) also observed hepatic enlargement developed seems to be due to exposure to Khat. These finding were consistent with the research investigated by Molham *et al.* (2002) and Wafaa *et al.* (2012) on rabbit treated for 6 month and 21 day respectively in the dose of 2mg/kg.

4. Conclusion

At present several millions of people were chewing Khat worldwide. The stimulatory effect of Khat have been demonstrated to arise from the main constituent, (-)-S cathinone. This project paper reported the toxicological effects of khat consumption on the histology and function of liver from research articles. Most of the research articles reviewed here, indicate that chronic consumption of Khat is toxic to the function and histology of liver. Howe ever, some experiment on the toxic effect of Khat did not demonstrate significant adverse effect on the function and histology of liver. Those contradictory results may have been the result of differences in dose administrated, duration of exposure, type of species as well as mode of administration. Therefore further articles related to toxic effect of Khat liver should be published and documented well to concise the difference of results on the function and histology of liver.

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