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# Chewing *Catha Edulis* with Amphetamine-Like Effect Alters Liver and Kidney Functions of Female Chewers

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***ABSTRACT:*** *Chewing the leaves of Khat, a natural stimulant from the Catha Edulis plant, is a social habit in Yemen and East African countries, which spread to countries such as the USA and Western Europe where Yemeni, Somali and other East African communities are living. The present study has been designed to evaluate the functions of liver and kidney among female Khat chewers in Thamar city, Yemen. Population of Thamar city was divided into two groups; those chewing Khat and those non-chewers. Blood of twenty female Khat chewers and twenty controls (non Khat chewers) were drawn and their plasma were isolated. The activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured along with the measuring levels of creatinine, uric acid (UA), urea and total protein. An increase in the activities of ALT and AST were observed in the plasma of female Khat chewers concomitant with increase in the levels of creatinine, UA and urea. However, a reduction in the total protein level was observed in the plasma of female Khat chewers group. It is concluded that chewing Catha edulis with amphetamine like effect might be responsible for the damage in liver and kidney of female Khat chewers.*

***KEY WORDS****: Amphetamine, Cathinone, Khat, Kidney, Liver.*

## I. INTRODUCTION

Chewing the leaves of Khat, a natural stimulant from the *Catha Edulis* plant, is a social habit in Yemen and East African countries, with the easy transportation of Khat and easing of importation restrictions this has helped this habit spread to countries such as the USA and Western Europe where Yemeni, Somali and other East African communities are living [1]. In India too, where those immigrants especially students studying there used to chew this plant which is transported from Ethiopia. Khat contains chemicals with amphetamine like effect, primarily cathinone and to a lesser extent cathine [2]. Cathinone is the most important active ingredient of Khat which causes the major pharmacological effects [3]. In addition, Khat leaves are rich in phenolic compounds including flavonoid glycosides and condensed tannins [4]. Free radicals and oxidants are now seriously implicated in Khat toxicity despite the presence of different antioxidants as chemical components of Khat [5-6], although the decreased activity of antioxidant enzymes due to reactive oxygen species (ROS) and oxidative stress have been reported in rats [5, 7] and human[8-9]. ROS are potentially very damaging to cells, leading to oxidation of essential cellular constituents including proteins, lipids and DNA [10]. The biological effects of oxidative stress depend upon the size of these changes, with a cell being able to overcome small perturbations and regain its original state. However, more severe oxidative stress can cause cell death and even moderate oxidation can trigger apoptosis, while more intense stresses may cause necrosis [11]. These effects of ROS may lead liver and kidney cell to be damaged and their contents will appear in high amounts in the blood [12]. It has been reported that plasma levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were significantly increased in rabbits following Khat administration [13-14]. In other studies on rats, administration of Khat was reported to cause a reduction in the liver enzyme, ALP, and increased activities of acid phosphatase, lactate dehydrogenase (LDH) and increased total bilirubin [15]. Aside from these biochemical changes, other studies have reported histopathological changes in both livers and kidneys of treated rats [5, 13]. Keeping on mind the structural and pharmacological similarities between cathinone and amphetamine it might be expected that the toxic effects could also be similar. The present study has been designed to assess the liver and kidney function tests in the plasma of female Khat chewers of Thamar city, Yemen.

## II. METHODS

### 2.1. Chemicals

All chemicals used were of highest grade commercial products. Kits of the biochemical tests were purchased from Spinreact, Spain.

### 2.2. Study design, population and grouping

Thamar city 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 problems, carcinoma and diabetes. The study was performed in accordance with the Helsinki Declarations and approved by Ethical Committee.

### 2.3 Sample collection

Blood samples of 40 individuals (20 each group) were collected, plasma of all samples were separated and the biochemical analyses were measured.

### 2.4 Biochemical assays

The biochemical tests includes assays of ALT, AST, creatinine, total protein, urea and uric acid were estimated following the instructions of commercial kits provided by Spinreact, Spain.

### 2.5 Statistical analysis

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.

## III. RESULTS

An increase in the activities of ALT and AST of Khat chewer group compared to the control group was seen in the present study (Fig 1 and 2). This increase was 65.5% and 85.678% of ALT and AST respectively. However, creatinine content was significantly increased in chewing Khat group by 41.19% compared to non Khat chewers group as shown in Fig 3.

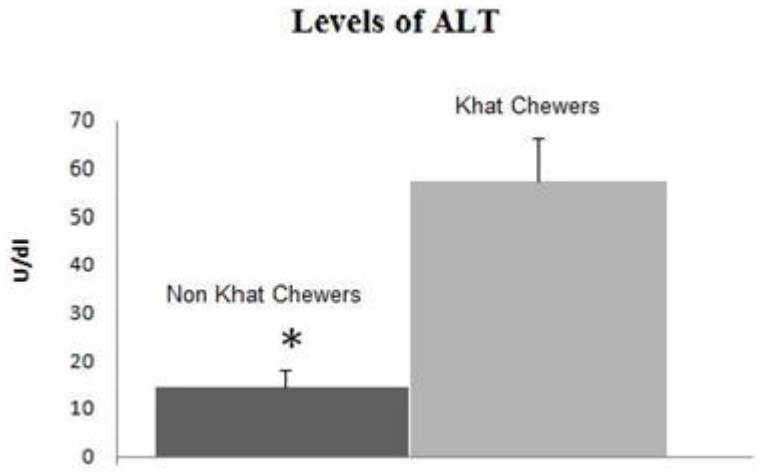


Figure 1: Activity of alanine aminotranferase in the plasma of female non-Khat chewers and Khat chewers. Results are expressed as mean ± S.D.; n= 20. Data were analyzed by student-t- test. *p<0.001 was considered significant from control group.

The total proteins were significantly decreased in Khat chewing group as compared to non Khat chewers group by 7.35% (Fig 4). Urea content was significantly increased in chewing Khat group by 17.39% compared to non Khat chewers group as shown in Fig 5, whereas, uric acid content was significantly increased in chewing Khat group by 44.72% compared to non Khat chewers group (Fig.6).

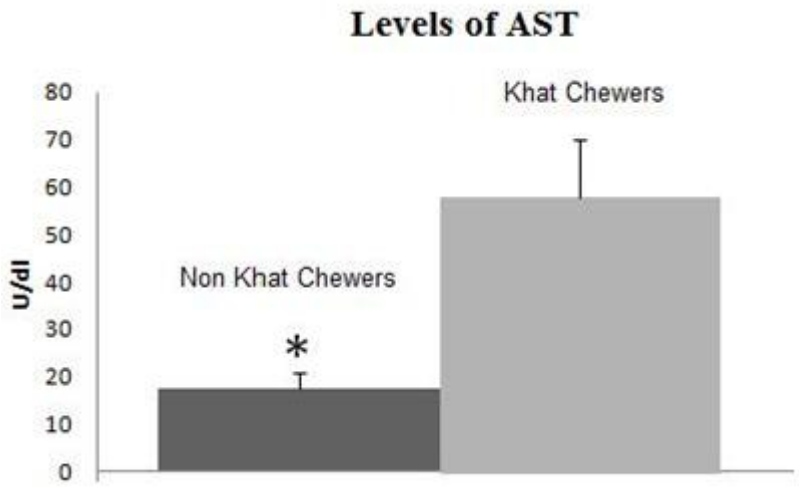


Figure 2: Activity of aspartate aminotranferase in the plasma of female non-Khat chewers and Khat chewers. Results are expressed as mean ± S.D.; n= 20. Data were analyzed by student-t- test. *p<0.001 was considered significant from control group.

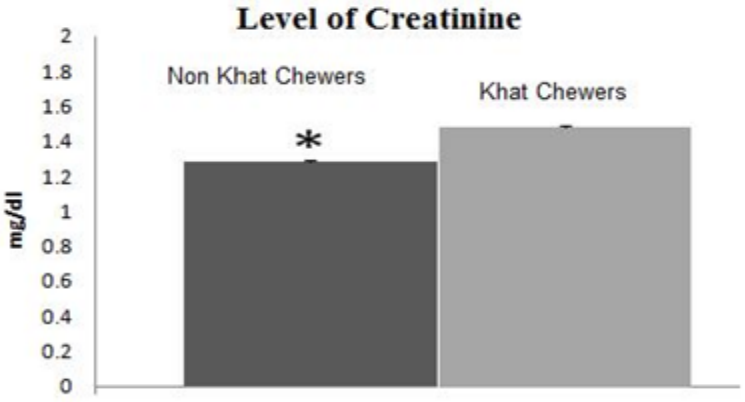


Figure 3: Level of creatinine in the plasma of female non-Khat chewers and Khat chewers. Results are expressed as mean ± S.D.; n= 20. Data were analyzed by student-t- test. *p<0.001 was considered significant from control group.

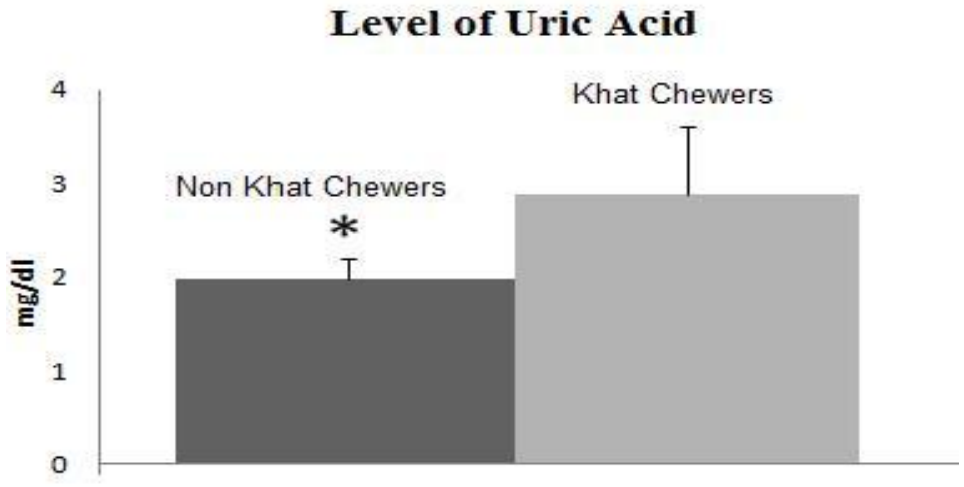


Figure 4: Level of uric acid in the plasma of female non-Khat chewers and Khat chewers. Results are expressed as mean ± S.D.; n= 20. Data were analyzed by student-t- test. *p<0.001 was considered significant from control group.

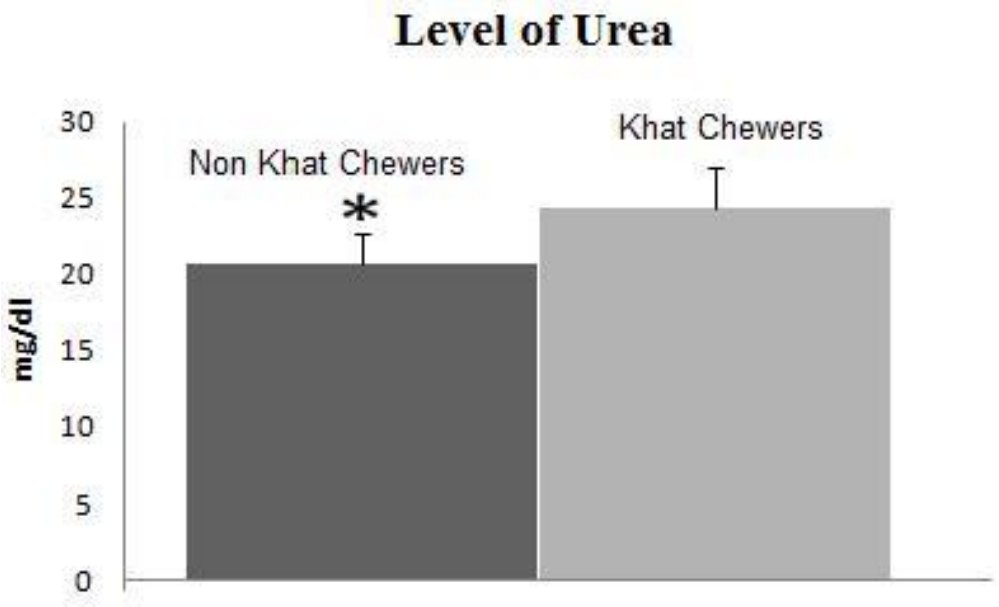


Figure 5: Level of urea in the plasma of female non-Khat chewers and Khat chewers. Results are expressed as mean ± S.D.; n= 20. Data were analyzed by student-t- test. *p<0.001 was considered significant from control group.

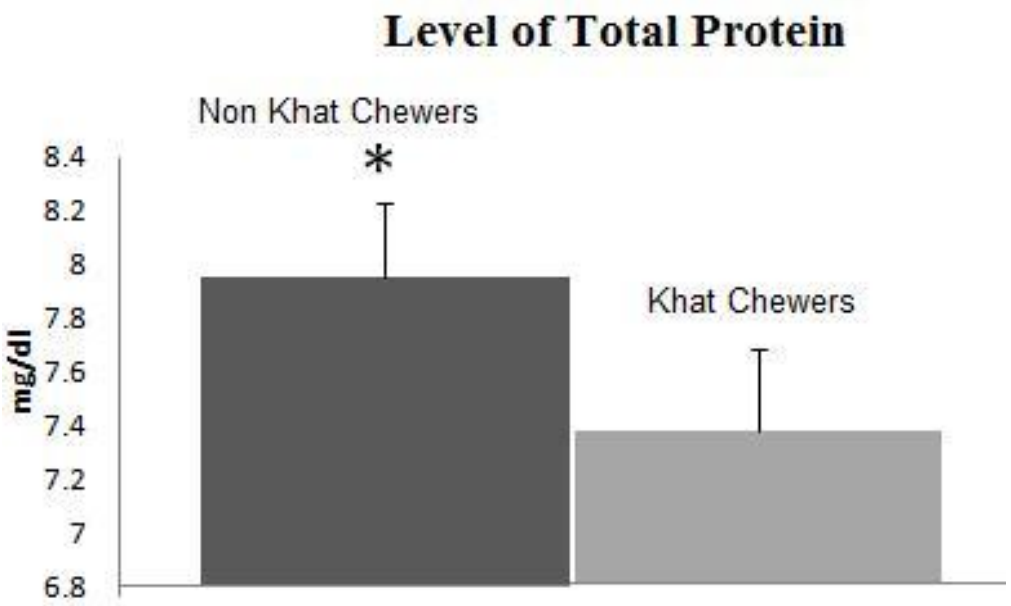


Figure 6: Level of protein in the plasma of female non-Khat chewers and Khat chewers. Results are expressed as mean ± S.D.; n= 20. Data were analyzed by student-t- test. *p<0.001 was considered significant from control group.

## IV. DISCUSSION

The present study investigated the changes in liver and kidney functions as a result of chewing Khat with amphetamine like effect in the plasma of female Khat chewers. We have observed an increase in the levels of ALT, AST, creatinine, urea and uric acid, whereas, the total protein content was decreased in the plasma of female Khat chewers. 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. The effect of Khat extract was reported to be cytotoxic and induced a rapid cell death effect [16]. It also induced apoptosis through a mechanism involving activation of capase-1, capase-3 and capase-8 [17]. Cathinone the main components of Khat leaves has similar structure and pharmacological activity as amphetamine [18]. D-amphetamine is known to exert different forms of

hepatotoxicity in-vivo and in-vitro when tested on hepatocytes [19-20]. It also induced mitochondrial ROS generation [21]. Severe liver disease has been described in human due to Khat chewing [22-24]. Our observations are in agreement with those of Al-Motarreb *et al.,* [13] who reported a significant increase in the level of serum urea, bilirubin , uric acid and creatinine accompanied by significant decrease in serum total protein in rats fed with Khat. Similar findings of those of Al-Habori *et al.,* [14] who reported that long term feeding of Khat leaves to New Zealand white rabbits is responsible for increased liver enzyme levels. It has also been reported that Khat induces cytotoxic effects in cells, in the liver and kidney of rabbits. Liver damage due to tissue necrosis or membrane damage due to oxidative stress will lead to increase the levels of hepatic enzymes ALT and AST in the plasma [25]. 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 [26]. These explain the increase in the levels of ALT and AST in the plasma of female Khat chewers in the present study. Uric acid (UA) is the end product of catabolism of the purine nucleotides in human system [27], its levels in blood and urine serve as valuable indicators for certain clinical conditions. Abnormal levels of UA are related to a number of diseases including kidney diseases [28]. UA is ubiquitous in body fluids and tissues, and its concentration in the plasma is higher than that of most endogenous antioxidants, second only to albumin [29]. In vitro experiments reportedly have shown that UA protects erythrocytes against damage by singlet oxygen, inhibits lipid peroxidation, and protects against free radical-induced damage to DNA [30]. Being an endogenous antioxidant it's able to protect human body from different reactions involving free radicals. The decreased activity of antioxidant enzymes due to ROS and oxidative stress have been reported in rats fed Khat [5, 7] and in the plasma of female Khat chewers [9]. The increase in the plasma UA in the present study is a natural response to production of oxidants by Khat. AlRajhi *et al.,* [31] have reported decreases in total cholesterol, HDL, LDL and glucose levels in serum of rabbits fed leaves of Khat with histopathological changes in liver which confirm the toxic effect of Khat. ROS are potentially very damaging to cells, leading to oxidation of essential cellular constituents including proteins, lipids and DNA [10]. The decrease in total protein of plasma of female chewers in this study is due to increase in ROS produced by Khat, this findings are in agreement with those of Al-Hashem *et al.,* [32] who have reported that there was a significant decrease in serum total protein and albumin of Khat 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. Increased serum urea and creatinine have been linked to kidney disease [32]. Rats treated with Khat extract had significantly increased serum creatinine suggesting impaired renal function due to a reduced ability to excrete these products. These effects could originate from changes in the threshold of tubular re-absorption, renal blood flow and glomerular filtration rate [15, 33]. An increased level of creatinine in the serum of male and female rats fed Khat has been reported by Alsalahi *et al.,* [34]. They also observed histopathological abnormalities confirmed hepatic and renal toxicities of Khat that were related to heavy Khat consumption. They concluded that Khat could be associated with hepatic hypertrophy and hepatotoxicity in male and female rats and nephrotoxicity only in female rats [34].

## V. CONCLUSION

From the data we found that both liver and kidney function tests were affected in the Khat chewing group which was clear by increasing the activities and levels of ALT, AST, creatinine, urea and uric acid, whereas, the protein content was decreased. Thus these changes might be attributed to the generation of ROS due to the presence of cathinone as a main component of *Catha edulis*.

**Conflict of interest**

No financial, personal or other conflict of interest

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## REFERENCES

[1] Manghi RA, Broers B, Khan R, Benguettat D, Khazaal Y, Zullino DF. Khat use: lifestyle or addiction? J Psychoactive Drugs 2009; 41:1-10.

[2] Brenneisen R, Fisch HU, Koelbing U, Geisshusler S, Kalix P. Amphetamine-like effects in humans of the khat alkaloid cathinone. Br J Clin Pharmacol 1990; 30:825-828.

[3] Kalix P. Pharmacological properties of the stimulant khat. Pharmacol Ther 1990; 48:397-416.

[4] Lugman W, Danowski T. The use of Khat in Yemen: social and medical observations. Annals of Internal Medicine 1976; 85:245-249.

[5] Al-Qirim TM, Shahwan M, Zaidi KR, Uddin Q, Banu N. Effect of khat, its constituents and restraint stress on free radical metabolism of rats. J Ethnopharmacol 2002; 83:245-250.

[6] Aleryani SL, Aleryani RA, Al-Akwa AA. Khat a drug of abuse: roles of free radicals and antioxidants. Drug Test Anal 2011; 3:548-551.

[7] Al-Zubairi A, Al-Habori M, Al-Geiry A. Effect of Catha edulis (khat) chewing on plasma lipid peroxidation. J Ethnopharmacol 2003; 87:3-9.
[8] Al-Akwa AA, Shaher M, Al-Akwa S, Aleryani SL. Free radicals are present in human serum of Catha edulis Forsk (Khat) abusers. J Ethnopharmacol 2009; 125:471-473.
[9] Masoud A, Al-Shehari B, Al-Hattar L, Altaezzi M, Al-khadher W, Zindal Y. Alterations in Antioxidant Defense System in the Plasma of Female Khat Chewers of Thamar City, Yemen. Jordan Journal of Biological Sciences 2012; 5:129-134.
[10] Paradies G, Petrosillo G, Pistolese M, Ruggiero FM. Reactive oxygen species affect mitochondrial electron transport complex I activity through oxidative cardiolipin damage. Gene 2002; 286:135-141.
[11] Kumawat M, Sharma TK, Singh I, et al. Antioxidant Enzymes and Lipid Peroxidation in Type 2 Diabetes Mellitus Patients with and without Nephropathy. N Am J Med Sci 2013; 5:213-219.
[12] Al-Motarreb A, Al-Habori M, Broadley KJ. Khat chewing, cardiovascular diseases and other internal medical problems: the current situation and directions for future research. J Ethnopharmacol 2010; 132:540-548.
[13] Al-Motarreb A, Baker K, Broadley KJ. Khat: pharmacological and medical aspects and its social use in Yemen. Phytother Res 2002; 16:403-413.
[14] Al-Habori M, Al-Aghbari A, Al-Mamary M, Baker M. Toxicological evaluation of Catha edulis leaves: a long term feeding experiment in animals. J Ethnopharmacol 2002; 83:209-217.
[15] Carvalho F. The toxicological potential of khat. J Ethnopharmacol 2003; 87:1-2.
[16] Dimba E, Gjertsen BT, Francis GW, Johannessen AC, Vintermyr OK. Catha edulis (Khat) induces cell death by apoptosis in leukemia cell lines. Ann N Y Acad Sci 2003; 1010:384-388.
[17] Dimba EA, Gjertsen BT, Bredholt T, et al. Khat (Catha edulis)-induced apoptosis is inhibited by antagonists of caspase-1 and -8 in human leukaemia cells. Br J Cancer 2004; 91:1726-1734.
[18] Feyissa AM, Kelly JP. A review of the neuropharmacological properties of khat. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32:1147-1166.
[19] Vitcheva V, Kondeva-Burdina M, Mitcheva M. D-amphetamine toxicity in freshly isolated rat hepatocytes: a possible role of CYP3A. Arh Hig Rada Toksikol 2009; 60:139-145.
[20] El-Tawil OS, Abou-Hadeed AH, El-Bab MF, Shalaby AA. d-Amphetamine-induced cytotoxicity and oxidative stress in isolated rat hepatocytes. Pathophysiology 2011; 18:279-285.
[21] Frey BN, Valvassori SS, Gomes KM, et al. Increased oxidative stress in submitochondrial particles after chronic amphetamine exposure. Brain Res 2006; 1097:224-229.
[22] Roelandt P, George C, d'Heygere F, et al. Acute liver failure secondary to khat (Catha edulis)-induced necrotic hepatitis requiring liver transplantation: case report. Transplant Proc 2011; 43:3493-3495.
[23] Chapman MH, Kajihara M, Borges G, et al. Severe, acute liver injury and khat leaves. N Engl J Med 2010; 362:1642-1644.
[24] Peevers CG, Moorghen M, Collins PL, Gordon FH, McCune CA. Liver disease and cirrhosis because of Khat chewing in UK Somali men: a case series. Liver Int 2010; 30:1242-1243.
[25] Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? Mol Med 2009; 15:337-351.
[26] Patanwalaa IM, Burtb AD, Bassendinea MF, M. H. Khat Associated End Stage Chronic Liver Disease: A Case Report. Journal of Medical Cases 2011; 2:104-106.
[27] Huang SH, Shih YC, Wu CY, et al. Detection of serum uric acid using the optical polymeric enzyme biochip system. Biosens Bioelectron 2004; 19:1627-1633.
[28] He JB, Jin GP, Chen QZ, Wang Y. A quercetin-modified biosensor for amperometric determination of uric acid in the presence of ascorbic acid. Anal Chim Acta 2007; 585:337-343.
[29] Becker BF, Reinholz N, Leipert B, Raschke P, Permanetter B, Gerlach E. Role of uric acid as an endogenous radical scavenger and antioxidant. Chest 1991; 100:176S-181S.
[30] Basu J, Mikhail MS, Ahn CW, et al. Plasma uric acid levels in women with cervical intraepithelial neoplasia. Nutr Cancer 2005; 51:25-31.
[31] ALRajhi W, Olfat, Yousef M. Effects of Catha Edulis Abuse on Glucose, Lipid Profiles and Liver Histopathology in Rabbit. Journal of Life Sciences and Technologies 2013; 1:33-37.
[32] Al-Hashem FH, Bin-Jaliah I, Dallak MA, Nwoye LO, Al-Khateeb M. Khat (Catha edulis) Extract Increases Oxidative Stress Parameters and Impairs Renal and Hepatic Functions in Rats. Bahrain Medical Bulletin 2011; 33:1-9.
[33] al-Meshal IA, Qureshi S, Ageel AM, Tariq M. The toxicity of Catha edulis (khat) in mice. J Subst Abuse 1991; 3:107-115.
[34] Alsalahi A, Abdulla MA, Al-Mamary M, et al. Toxicological Features of Catha edulis (Khat) on Livers and Kidneys of Male and Female Sprague-Dawley Rats: A Subchronic Study. Evid Based Complement Alternat Med 2012; 2012:829401.