Effects of Catha Edulis Abuse on Glucose, Lipid Profiles and Liver Histopathology in Rabbit

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Abstract—The habit of Catha edulis chewing has prevailed for centuries among populations in the horn of Africa and the Arabian peninsula causing many social and economic problems. The present study evaluate the effects of fresh leaves khat on both serum glucose, plasma lipid profile and histopathology of liver. The results showed that feeding with khat leaves reduced total serum cholesterol, HDL-and LDL-cholesterol levels and glucose concentration. After khat withdrawal cholesterol and HDL- cholesterol levels were still significantly decreases whereas serum glucose content was non significant and LDL-cholesterol concentration was significantly increases compared to control group. While, the khat intake had significant elevation on triglycerides serum content and remain elevated after withdrawal from khat. There were histopathology changes confirm the toxic effect of the khat. After khat withdrawal there was normalizing for most of these alteration, confirm diverse and adverse effects of khat.

Index Terms—Catha edulis, glucose, lipid profiles, liver damage

I. INTRODUCTION

Khat chewing is a long standing social-cultural habit in several countries around the Red Sea and in East Africa. People chew the fresh young leaves for their stimulant and pleasurable effects [1] which are mainly attributed to cathinone [2]. Cathinone is the most important active ingredient of khat, causing the major pharmacological effects [3].

In addition to its socio-economic burden, cathinone can cause multiple health problems [4]. The detrimental effects of the active principle of khat in men and animals have been described [5]. Cathinone is similar in structure and pharmacological activity to amphetamine [6], [7]. D-amphetamine is known to exert different forms of hepatotoxicity in-vivo and in-vitro when tested on hepatocytes [8]. khat is expected to cause similar toxic effects on the liver but the available data are few and sporadic. Toxicological evaluation of Catha edulis leaves has been reported by Al-Habori et al [9]. Moreover, the toxicological potential of Khat has been reported by Carvalho [10]. It has also been reported that Khat induces cytotoxic effects in cells, in the liver and kidney of rabbits [11]. Recently, the effect of Khat extract was reported to be cytotoxic and induced a rapid cell death effect [12]. It also induced apoptosis through a mechanism involving activation of capase-1, capase-3 and capase-8 [13]. It also establishes Khat as an etiological risk factor in chronic liver disease and suggests a potentiation effect of Khat toxicity on chronic hepatitis B and Delta virus mediated liver damage [14].

An enormous amount of data has been published on pharmacology and chemistry of khat, but only few reports are available about its effect on blood glucose and lipids [15]. The present study was carried out to evaluate the effect of Catha edulis on glucose and plasma lipid profile as well as the histopathology of tissue sections in liver of the rabbit.

II. MATERIAL AND METHODS

Fresh shrubs of Catha edulis (stem tips and leaves) were obtained regularly from a local supplier. Dose selection (2 gm/ kg) was based on the average amount of khat leaves chewed daily by khat chewers according to Hassan et al. [16].

Experimental animals: Fifteen Oryctolagus cuniculus rabbits (1000-1200 g /w) were housed in individual cages at a 12 hr light/dark cycle and received food and water ad libitum until the beginning of experiment.

Experimental Design: The animals were assigned randomly to 3 groups (5 rabbit each):- Group 1: the control group, the rabbits were fed 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; followed by the standard chow for 7 days.

Biochemical analysis: At the end of day 21, the animals were subjected to overnight fasting, they were sacrificed by decapitation. Blood was collected, sera separated by centrifugation at 3000rpm for 10 minutes. Serum was assayed for glucose (GLUC), triglycerides...
(TGL), cholesterol (CHOL), HDL-, and LDL- cholesterol using enzymatic kits.

Histopathological Studies: 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.

Statistical analysis: The data were analyzed using student’s t-test statistical methods. For the statistical tests a p value of less than 0.01 and 0.05 was taken as significant. All the results were expressed as mean ± standard error of the mean.

III. RESULTS

Biochemical results: Biochemical results of the animal groups are listed in Table I, the results demonstrate a significant reduction in total serum cholesterol (32.74%) HDL-, and LDL- cholesterol levels (71.13%, 28.205% respectively) and the GLUC concentration (37.179%) in khat fed animal as compared with normal control rabbit. In contrast, triglycerides exhibit significant increases (76.045%) relative to the control. In khat-withdrawal rabbits, a significant elevation was recorded in the level of TGL and LDL-cholesterol (24.598%, 33.333% respectively), while a significant decreased in CHOL and HDL-cholesterol serum contents (6.2%, 21.65% respectively) relative to the control. On the other hand, GLUCO serum content exhibits non significant changes as compared with controls. Meanwhile, indeed, after withdrawal of khat feeding, CHOL, HDL-, and LDL-cholesterol levels and the glucose concentration increased significantly (39.474%, 171.429%, 85.714%, 56.46% respectively), while the TG level decreased significantly (29.224%) as respect with khat fed animals.

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>CHOL (mmol/L)</th>
<th>HDL (mmol/L)</th>
<th>LDL (mmol/L)</th>
<th>TGL (mmol/L)</th>
<th>GLUC (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>2.26±0.10</td>
<td>0.97±0.015</td>
<td>0.78±0.02</td>
<td>1.24±0.05</td>
<td>9.36±0.11</td>
</tr>
<tr>
<td>G2</td>
<td>1.52±0.03*</td>
<td>0.28±0.01*</td>
<td>0.56±0.04*</td>
<td>2.19±0.06*</td>
<td>5.88±0.03*</td>
</tr>
<tr>
<td>G3</td>
<td>-2.12±0.15*</td>
<td>-0.76±0.02*</td>
<td>-1.04±0.12*</td>
<td>-1.55±0.1*</td>
<td>-9.2±0.07</td>
</tr>
</tbody>
</table>

Histopathological observations: liver of khat fed rabbit showed destruction of the normal architecture and hepatocytes. The hepatocyte cytoplasm appeared granular or vacuolated with fatty globules (Fig. 2). Mononuclear inflammatory cells were infiltrated surrounding the portal area and within the parenchyma of the liver (Fig. 3 and Fig. 4). Focal necrotic areas were observed containing pyknotic and karyolitic nuclei of hepatocytes (Fig. 3 and Fig. 4). Dilation and congestion of central vein and blood sinusoids were also detected (Fig. 3). 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 binucleated (Fig. 5 and Fig. 6).

Photomicrograph of liver sections of normal, G1& treated groups, G2&G3 (H&E X400) showing:

**Figure 1.** (G1): The portal area including branches of hepatic portal vein (HV) hepatic artery (HA) and bile ductile (BD).

**Figure 2.** (G2): Destruction of the normal pattern of hepatic lobules and fatty changes in the cytoplasm of hepatocytes(arrows) causing increase the size of hepatocytes.
Figure 4. (G2): 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).

Figure 5. (G2): Destruction of the normal pattern of hepatocytes, dilatation and congestion of hepatic sinusoids (arrow).

Figure 6. (G3): Showing portal tract, hepatic portal vein (HV), hepatic artery (HA) and bile ductile restored their normal configurations.

IV. DISCUSSION

Catha edulis (Khat) leaves are used by millions of people as a social habit, and there is little information about its biological activity [10]. Moreover, biological effects of khat are inadequately investigated and controversial [13].

In this work, the rabbits feeding with khat showed a significant reduction (P<0.005) in CHOL, LDH and HDL cholesterol concentration of serum, while a significant elevation (P<0.005) in TGL level compared to the control group. The present findings are consistent with the finding of Al-Habori and Al-Mamary [17], who showed that, feeding rabbits with khat caused a significant reduction in plasma cholesterol throughout the 6-month period. The observed decrease in serum cholesterol concentration in the current work may be attributed to the increase in cAMP concentration that has an inhibitory effect on cholesterol synthesis [18]. The stimulation of [beta]-adrenergic receptors by the amphetamine-like effect of cathinone [19] results in activation of adenyl cyclase and, consequently, increased cAMP. In addition, its stimulatory effect on adrenocorticotropic hormone adrenocorticotropic is reported to be increased in rabbits given C. edulis extract [20]. ACTH is also believed to be mediated by the activation of adenyllyl cyclase, with subsequent increase in cAMP concentration. The observed reciprocal relationship between serum HDL-cholesterol and triglycerides content in khat fed rabbit are in support of recent data demonstrating HDL-cholesterol to vary reciprocally with serum triglycerides concentration and directly with lipoprotein lipase [18]. In contrast, Al-Zubairi et al [21] reported that, there were no significant effects observed on the levels of cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol. From the results obtained it is plausible that khat withdrawal rabbits not showed complete recovery for CHOL, TGL and LDL-cholesterol values, may be the period of withdrawal was not enough for restoring the normal control values.

The significant decrease (P<0.005) in glucose level in khat feeding rabbits was incompatible with many previous studies [17],[22]. The decrease in glucose concentration might be due to the "oxidative stress type" situation [17] produced by khat alone or its alkaloid fraction as flavonoids were recently shown to alter the activities of the free-radical metabolizing/scavenging enzyme system [23]. Glucose is also a scavenger of OH radicals, having a rate constant comparable with mannitol [24]. Moreover, the leaves possess stimulant properties, possibly tannins and the inorganic ions present in khat may contribute to the delayed absorption of glucose there by reducing its level [25]. In addition, the khat-induced delay of gastric emptying [26] may also play a role in reducing the blood sugar after food intake. In the current work, there is a correspondingly positive relationship between the decrease in blood GLUC concentration and the increase in serum TG level, which is associated with increase in insulin level [25]. Since insulin blocks TG degradation, it results in their accumulation. The present results however differ from those reported by Broadley [27] and Bajubair [28], who suggested a significant increase in serum glucose which may be explained by the sympathomimetic actions of cathinone would be expected to raise plasma catecholamine levels. These catecholamines would increase blood glucose levels by activation of glycogenolysis in skeletal muscles and the liver; a β2-adrenoceptor-mediated response. There is also inhibition of insulin release from the pancreatic β-cells via α2-adrenoceptor stimulation which would also elevate blood glucose levels [27]. While some studies show that in healthy non-diabetics, khat does not affect fasting or post-prandial serum glucose levels because of the

Journal of Life Sciences and Technologies Vol. 1, No. 1, March 2013
sympathetic effect of khat induced release of insulin on the rising blood glucose [29].

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. Accumulation of mononuclear inflammatory cells were found around the central vein and portal tract. The current changes were incompatible with many previous studies [6], [9], [11], [22]. In confirmation of the hepatotoxicity of khat ingestion, a case report described an East African man with a regular khat chewing habit who developed jaundice as a result of acute hepatitis [30]. Another report also described a patient with impaired liver function attributed to khat chewing [31]. More recently, severe acute liver injury has been attributed to khat chewing in the USA [32]. Additionally, a case report of end stage chronic liver disease related to chronic Khat consumption [33]. The mechanism of khat toxicity on liver is uncertain. It was reported that administration of khat extracts showed a deranged systemic capacity to handle oxidative radicals and induces cytotoxic effects in cells of liver [34]. A vasoconstrictor action of cathinone would also contribute to this liver pathology [35]. On the other hand, there was suggestion that the sub chronic administration of catha edulis crude extract has no hepatotoxicity adverse effects in male rats, but may have antioxidant property due to its phenolic compounds [36]. 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 [37]. In contrast, there were no histopathology changes observed in the liver of the experimental animals fed with Catha edulis extract[21] which supports the safety use of the aqueous extract of P. edulis in pharmacological studies[38]. 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 were often inconsistent [25].

V. CONCLUSION

The results clearly showed effects of khat on the blood glucose and lipid profiles. There were also histopathology changes confirm the toxic effect of the khat on the liver of the rabbit. Cessation of Khat consumption has been associated with recovery from hypoglycaemic action of khat and histopathology changes of rabbit livers confirm diverse and adverse effects of khat [37]. Meanwhile, incomplete or mild recovery occurred in all serum lipid profiles.

Clearly, our knowledge about the effect of khat chewing on serum glucose and lipids is very sparse and controlled studies are needed to be undertaken. They need confirmation in human and could be helpful to evaluate the risks and/or potential of khat for human health.

REFERENCES


