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Short-Term Repeated Dose Biochemical Effects of *Catha edulis* (Khat) Crude Extract Administration in Rats

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Abstract: The leaves of khat (*Catha edulis*) are reported to have stimulating and pleasurable effects and are chewed habitually by people of East Africa and Arabian Peninsula. Due to various effects of khat the present study was undertaken to evaluate the short-term repeated dose effects of freeze dried khat leaves crude extract administration to male Sprague-Dawley rats. In this study, the effects of *catha edulis* leaves extract oral administration on plasma concentration of Malonyldialdehyde (MDA), triglycerides, cholesterol, HDL-cholesterol, LDL-cholesterol, uric acid, albumin and testosterone and liver enzymes activities were examined. Four groups of rats were exposed to 0, 500, 1000 and 2000 mg kg^{-1} body weight/day for 6 consecutive weeks. Our results demonstrated that food consumption and body weights changes were non-significantly different relative to the control. There were no significant effects observed on the levels of plasma MDA, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, uric acid, albumin, liver enzymes or Acid Phosphatase (ACP) in the treatment groups relative to the control. Administration of freeze dried crude *catha edulis* leaves extract for 6 weeks was found to increase plasma testosterone levels in the two high doses treatment groups (1000 and 2000 mg kg^{-1} body weight) in more than 2 folds, while it was non-significantly increased in the 500 mg kg^{-1} body weight treatment group, as compared to control. The data indicated that at the doses and time period tested, *catha edulis* freeze dried crude extract could be considered as aphrodisiac. Moreover, it did not produce any significant effect on the normal biological markers of liver toxicity or prostatic adverse effects.

Key words: Khat, *Catha edulis*, lipid peroxidation, MDA, testosterone

INTRODUCTION

The habit of khat chewing represents a major socio-economic problem in the countries of Southern Arabia and the Horn of Africa. The leaves of *catha edulis* (Celastraceae) (khat), a plant growing wild and cultivated in Eastern Africa and Southern Arabia are chewed for their stimulating and sympathomimetic effects (Kalix and Braenden, 1985; Kalix, 1994; Alem *et al*., 1999). A large number of people chew khat leaves because of its pleasurable and stimulating effects. Although, the use of khat has spread Worldwide, it has until recently remained mostly confined to the regions where the plant is grown since only fresh leaves have the potency (of cathinone) to produce the desired effects. The fact that cathinone has a closer structural similarity with amphetamine and both share common pharmacodynamic features, led to the conclusion that cathinone is the most important active ingredient of khat which causes the major pharmacological effects (Hollister, 1995).

The chemical constituents of khat leaves include in addition to cathinone, norpseudoephedrine, meru-cathinone, ethereal oils, sterols, triterpenes, flavonoids, a significant amount of ascorbic acid and tannins (Kalix and Braenden, 1985). It has been reported that the dried khat leaves contain a considerable concentration of tannin ranges 3.5-9.7% in different types of Yemeni khat as stated by Alles *et al*. (1961) and 14.5% mainly condensed tannins as reported by El Sissi and Abdulla (1966) and some of these tannins were found to be of aglycone flavonoid nature, glycosides of kaempferol, quercetin and myricetin.

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The alkaloid fraction of khat is very efficiently extracted by chewing and the major compounds are absorbed in the oral cavity (Toennes *et al*., 2003). The detrimental effects of the active principle of khat on man and animals and the common adverse effects include insomnia, anorexia, irritability, hyperthermia, mydriasis and endocrinological disturbances have been described (Nencini *et al*., 1993; Brenneisen *et al*., 1990). Khat-induced analgesia has also been reported (Connor *et al*., 2000), although it is not known whether the mechanism is central or peripheral. Acute autonomic responses, such as elevated blood pressure and tachycardia, have been reported (Wilder *et al*., 1994). Clinical trials have shown khat to delay gastric emptying period after khat chewing (Heymann *et al*., 1995). The chronic use of khat has also been associated with the development of hypertension (Halbach, 1972). The present study was undertaken to evaluate the short-term repeated dose effects of freeze dried crude extract administration of *catha edulis* leaves on body weight, white blood cells, lipid peroxidation products Malondialdehyde (MDA) measured as plasma TBARS, lipid profiles, liver enzymes, total and prostatic Acid Phosphatase (ACP), uric acid, albumin and testosterone.

MATERIALS AND METHODS

Experimental animals: Thirty six randomly selected Sprague-Dawley male rats weighing 200-250 g and 5-7 weeks old were provided locally from the Animal House of Faculty of Veterinary Medicine and housed at the Animal House, Faculty of Medicine and Health Sciences, University Putra Malaysia. Rats were caged individually and were allowed free access of water and pelleted food *Ad libitum*. They were acclimatized to laboratory conditions for 1 week prior to the experiment and were kept in polypropylene cages with wood shavings as bedding in 12 h light/dark cycle at 27°C. The experimental procedures were carried out in strict compliance with the Animal Ethics Committee's rules and regulation followed in this institute. All groups were received treatments or distilled water in the control, daily for 6 consecutive weeks.

Study design: Rats were divided into 4 groups and exposed by force feeding to 0, 500, 1000 and 2000 mg kg^{-1} body weight/day freeze dried *catha edulis* leaves crude extract for 6 consecutive weeks. Khat leaves were purchased from the khat suppliers in Sana'a, Yemen. After 2 h of leaves collection, the fresh edible parts were washed and freeze dried. The leaves were ground, weighed and soaked in distilled water for 5 h and the filtrate was used for administration into rats. Dose selection was adapted based on the average daily consumption of khat leaves by the khat users in Yemen according to Nencini and Ahmed (1989) and Kalix (1990, 1994). Cage-side clinical observations were performed each morning on all animals and body weights were recorded at the study initiation and weekly.

At the end of the study, food was withheld for 12 h to provide fasting blood samples. Animals were sacrificed under chloroform anesthesia and blood was collected by cardiac puncture procedure. Blood samples were collected into heparinized and plain tubes. Plain tubes were left at room temperature for clot to form and centrifuged for 5 min at 1500 rpm. Heparinized tubes were used for white blood cells count and differential count, while another part was centrifuged immediately. Plasma and serum were separated and stored at -80°C for later analysis. The procedures of this research were conducted in accordance with the European Community guidelines (EEC Directive of 1986; 86/609/EEC) and in adaptation of the Organization for Economic and Co-operation and Development (OECD, 2001) and approved by the Animal Care and Use Committee (ACUC), Faculty of Medical and Health Sciences, University Putra Malaysia.

White blood cells and differential count were done manually. Clinical chemistry parameter evaluated on separated plasma samples was MDA, measured as Thiobarbituric Acid Reactive Substances (TBARS). The parameters evaluated on separated serum samples included total cholesterol, High Density Lipoprotein (HDL) cholesterol, triglycerides, albumin, uric acid, Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Lactate Dehydrogenase (LDH), Gamma Glutamyl Transferase (GGT), Total Acid Phosphatase (ACP), prostatic ACP and testosterone levels.

Determination of MDA: Malondialdehyde (MDA) estimation was based on the reaction of MDA with two molecules of TBA to give a colored complex. MDA was determined in the form of TBARS and estimated according to the procedure of (Yagi, 1998), 0.1 mL of plasma sample was combined with 0.1 of 8.1% SDS (Luka, BioChemika) followed by 2.5 mL TBA buffer (pH: 3.5) containing 1.06% TBA (Sigma), 20% acetic acid (Bendosen) and sodium hydroxide (Amresco). The mixture then boiled at 95°C for 60 min followed by 10 min cooling on ice bath to room temperature. Samples mixed and centrifuged at 3000 rpm for 15 min. A standard curve was prepared by diluting 1 mM Tetraethoxypropane (TEP) (Sigma) in 0.1N HCl. Absorbance of the clear supernatant measured at 532 nm in spectrophotometer (Pharmacia). Readings of MDA was taken from the standard curve.

Clinical chemistry: Serum cholesterol, triglycerides, HDL-cholesterol, uric acid, albumin, AST, ALT, ALP, GGT, total and prostatic ACP levels were measured using the Chemistry Analyzer (Hitachi 902 Automatic Analyzer, Japan) while testosterone levels were estimated using electrochemiluminescence immunoassay kit from Roche, using ElecSys 2010 analyzer (Roche).

Statistical analysis: Statistical tests were performed using SPSS version 14. All data were expressed as the mean±STD. To test for significant differences between groups, we used one-way Analysis of Variance (ANOVA) with subsequent Dunnett's post hoc analysis to detect further differences between groups. Values of $p<0.05$ were considered significant.

RESULTS

The short-term repeated-dose effects of freeze dried crude khat extract administration on weight changes in rats are represented in Fig. 1. At the time of sacrifice, mean body weights among the treatment groups 0, 500, 1000 and 2000 mg kg^{-1} body weight/day were not significantly different, 366, 366, 365 and 368 g, respectively. White blood cells total and differential counts of rats revealed no biologically significant differences between the *catha edulis* crude extract treated and vehicle control treated rats. The values of total and differential white blood cells count studied were within normal limits (Table 1).

Our results as shown in Table 2, demonstrate a non-significant differences in MDA in the three treatment groups, being reduced 23 and 14.3% in the 500 and 1000 mg kg^{-1} body weight respectively, while increased by 3.8% in the 2000 mg kg^{-1} body weight. Similarly, a non-significant reduction, in the 3 treatment groups,

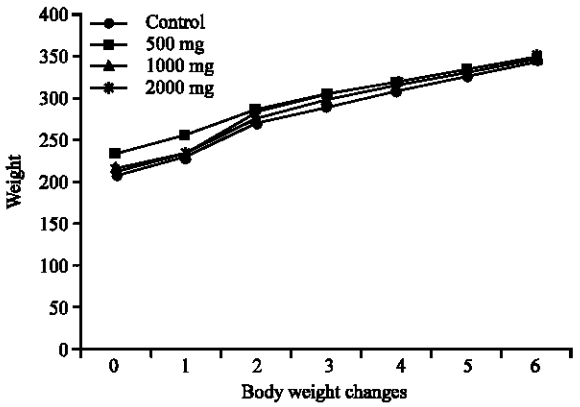

Fig. 1: Weight changes in groups fed *Catha edulis* crude extract for 6 weeks compared to the control group

Table 1: White blood cells differential count in treatment compared to the control group

Group	WBCs×10^3 mm^{-3}	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)
Control	11.5±5	20.7	74.77	3.11	1.44	00.00
500 mg kg^{-1}	12.5±5	25.8	70.20	1.80	2.20	00.00
1000 mg kg^{-1}	7.3±4.8	24.23	70.38	3.38	1.92	0.07
2000 mg kg^{-1}	9.7±3	21.1	74.9 0	2.90	1.10	00.00

Table 2: Plasma levels of MDA, cholesterol, HDL-cholesterol, LDL-cholesterol, Triglyceride and uric acid

		Catha edulis		
	Control group	500 mg kg^{-1} bw	1000 mg kg^{-1} bw	2000 mg kg^{-1} bw
MDA (µmol L^{-1})	2.10±0.65	1.60±0.69	2.18±0.59	1.80±0.49
Cholesterol (mmol L^{-1})	1.32±0.18	1.25±0.18	1.32±0.17	1.22±0.18
Triglycerides (mmol L^{-1})	0.89±0.36	0.89±0.41	0.93±0.29	0.79±0.34
HDL-cholesterol (mmol L^{-1})	0.83±0.11	0.79±0.12	0.82±0.10	0.75±0.12
LDL-chol (mmol L^{-1})	0.32±0.12	0.28±0.09	0.31±0.06	0.31±0.06
Uric acid (mmol L^{-1})	68.0±21.8	75.1±41.6	76.0±56.5	70.2±17.3

Table 3: Plasma levels of MDA, lipid profiles, uric acid, liver enzyme activities, Total and Prostatic ACP and Testosterone and albumin in the 6 weeks treated groups

		Catha edulis		
	Control	500 mg kg^{-1} bw	1000 mg kg^{-1} bw	2000 mg kg^{-1} bw
AST (U L^{-1})	99.2±26.0	95±21.4	81.8±18.7	82.24±14.0
ALT (U L^{-1})	41.6±7.3	38.4±6.4	37.2±5.1	40.3±6.7
LDH (U L^{-1})	363±159	380.4±166	300±21	178.9±85.5
ALP (U L^{-1})	142.6±18	163.14±53	179.7±41.6	182±42.0
GGT (U L^{-1})	0.32±0.12	0.28±0.09	0.31±0.06	0.31±0.06
Albumin (mmol L^{-1})	37.2±1.90	36.6±2.9	38.3±1.90	36.7±2.00
Total ACP (U L^{-1})	18.9±5.5	16.5±4.3	14.4±3.8	18.2±4.2
P-ACP (U L^{-1})	13.9±4.8	11.7±2.9	10.3±3.0	13.2±3.7
Testosterone (ng mL^{-1})	1.18±0.62	1.83±0.93	3.36±1.95*	2.92±1.22*

*$p<0.01$

respectively, of cholesterol (5, 0 and 7.5%), triglyceride (0, 4.5 and 11%), HDL-cholesterol (4.8, 1.2 and 9.6%) and calculated LDL-cholesterol (12.5, 3 and 3%) while uric acid was non-significantly increased (10, 11.7 and 3.2%, respectively) compared to the control group. On the same line Table 3, shows the results of liver enzymes, albumin, prostatic ACP and testosterone. Liver enzymes activities were demonstrated to be non-significantly affected and were mostly reduced in the treatment groups compared to the control group. Since, AST was reduced by 4-17.7%, ALT by 3-10%, GGT by 1-3% and total and prostatic ACP by 3-23.8% in the 3 treatment groups, while LDH was increased in the 500 mg kg^{-1} body weight treatment group and reduced by 17 and 50% in the other 2 groups, respectively, however non-significant. ALP was observed to be non-significantly increased in the treatment groups by 14-27% compared to the control group. In addition albumin was non-significantly affected compared to the control group. Plasma prostatic ACP was found to be non-significantly reduced by 5.3-26% in 3 treatment groups compared to the control. While, the only parameter significantly affected in this study, was plasma testosterone levels in the high concentrations treatment groups. Mean plasma testosterone levels in the 1000 mg kg^{-1} body weight treatment group were found to be significantly higher ($p<0.01$) by 184%, however it was increased by 147% in the 2000 mg kg^{-1} body weight treatment groups with respect to the control group while it was 55% increased in the 500 mg kg^{-1} body weight treatment group, however non-significant.

DISCUSSION

Our data showed plasma levels of MDA to be non-affected after 6 weeks of khat extract administration. These results were found to be in agreement with our previous observation (Al-Zubairi *et al*., 2003) that khat chewing may not provoke lipid peroxidation and hence may have some antioxidative property. This would follow, since khat has been known to contain polyphenolic (proanthocynidines) constituents that have been reported to play a role as antioxidants (Koga *et al*., 1999) and flavonoids that have been suggested to act as antioxidant through free radical scavenging (Tirkey *et al*., 2005). In addition, total cholesterol, triglycerides, HDL-cholesterol and calculated LDL-cholesterol were found to be non-significantly affected in this short-term study. However, these levels were non-significantly increased in the low test concentration groups, while these levels were found to be non-significantly decreased in the high dose treatment group. Low levels were also observed by Ahmed and El-Qirbi (1993), who reported Adrenocorticotrophic Hormone (ACTH), to be increased in rabbits given *Catha edulis* extract and attributed it to the stimulation of β-adrenergic receptors (Tariq *et al*., 1989) and later on supported by the observation of Al-Habori and Al-Mamary (2004). These findings were similar to that observed by Ramadan *et al*. (1979) who reported that total cholesterol, α- and β-lipoproteins were not greatly affected by khat consumption.

The increase of serum uric acid considered to be one of the body's natural responses to scavenge excessive free radicals produced as uric acid is one of the quenchers of free radicals (Davies *et al*., 1986). It's an endogen antioxidant and takes part in the tissues natural defense against oxidative stress. Serum levels of uric acid were non-significantly increased in the treatment groups, less change were also reported by Farag and Qirbi (1991) in khat fed rabbits. These results were in controversy with the results of Al-Qirim *et al*. (2002), who observed that intragastric administration of khat or its alkaloid significantly decreased the circulating activities of free radical metabolizing enzymes and glucose while increased the circulating level of uric acid. While they observed that khat consumption under stressful situation can bring about a derangement in free radical metabolism, for which the alkaloid fraction of khat seems responsible as the flavonoids present in khat are found to enhance free radicals scavenging enzyme activities like glutathione-S-transferase and catalase if given alone, or were capable of preventing the stress induced decrease of enzyme levels. Albumin is another antioxidant substance in the body play a major role in quenching metal ions through their transport in plasma. Albumin results were also observed to be non-significantly affected in this study.

The expression of toxicity of xenobiotics is usually determined biochemically by monitoring of some plasma enzymes and lipids. A rise in AST, ALT, ALP, TG and cholesterol are commonly measured as indices of the damage of the liver cells (Abdel-Baset *et al*., 1997). Acid and alkaline phosphatases have been directly implicated in cellular damage and toxicity (Vinitha *et al*., 1995), particularly in the liver and cardiac tissue. Thus, the changes in activity and concentration of tumor marker enzymes like AST, ALT, ACP and ALP in tissue such as liver could reflect the state of hepatotoxicity (Vinitha *et al*., 1995). Our results showed no significant differences in the activities of serum ALT, AST, ALP, GGT total and prostatic ACP in the treatment groups compared to the control group. This suggest that 6 weeks administration of freeze dried *Catha edulis* crude extract has no hepatotoxic effects in rats. This can be concluded from the results of liver enzymes activities obtained. These results were in agreement with that observed by

Mwenda *et al.* (2006) who concluded that there were no observed histopathological changes in the testis, epididymis, liver, kidney and pituitary gland of the experimental animals fed with crude *Catha edulis* extract. However, these results were in controversy with the results of Al-Habori *et al.* (2002), who observed that exposure of rabbits to *Catha edulis* leaves may lead to toxic hepatocellular jaundice.

The consumption of khat is said to produce an increase in libido but also spermatorrhea and precocious ejaculation (Elmi, 1983) and that its Long-term habitual use may lead to impotency (Halbach, 1972). On the other side, in females it increased the sexual desire and performance (Elmi, 1983). The effect of khat on human reproduction remains an area of considerable interest. Results of total and prostatic ACP generated were found to be non-significantly affected in the treatment groups; however khat chewers claim to have spermatorrhea on khat chewing. Controversy remains regarding the potential effects and mechanisms by which khat may affect reproductive functions. Limited studies that have been done provide conflicting results, with some investigators suggesting that khat increases sexual desire and can be used as an aphrodisiac (Islam *et al.*, 1990). In contrast, alternative findings suggest khat may have the opposite effect and may result in impairment of sexuality (WHO Advisory Group, 1980). Islam *et al.* (1990) reported loss of libido and decreased semen output in people who chew khat. Taha *et al.* (1995) reported no evidence that cathinone could be as an aphrodisiac. Treatment of male mice with khat extract resulted in a reduction in the rate of fertility and in females, khat treatment induced post-implantation loss during the first week of pregnancy (Tariq *et al.*, 1986).

A recent histopathological examination of sections of the male reproductive tract suggested that *Catha edulis* leaves had stimulated spermatogenesis and the cauda epididymides and Leydig cells were unaffected, when compared with equivalent sections from untreated rabbits (Al-Mamary *et al.*, 2002; Al-Habori *et al.*, 2002). The phenylpropanolamines cathine and norephedrine (the immediate metabolites of cathinone), at concentrations similar to those detected in blood samples of individuals who chewed khat leaves for 1 h (Toennes *et al.*, 2003), were demonstrated *in vitro* to directly affect mammalian sperm function, accelerating capacitation and inhibiting spontaneous acrosome reactions (Adeoya and Fraser, 2005). More recently, in a study by Mwenda *et al.* (2006) who used the olive baboon, observed that khat administration causes a significant increase in the mean levels of testosterone while prolactin and cortisol levels were reduced. They concluded that khat may exert a transient effect on male fertility by interfering with the hormonal profile. In addition (Nyongesa *et al.*, 2006) postulated that khat extract at high concentrations may cause reproductive function impairment in the user but at low concentrations it may enhance testosterone production with accompanying effects on reproductive functions in male mice.

Our results were observed to be similar to that reported by a number of previous studies that *Catha edulis* can be used as an aphrodisiac. However, this may be attributed to enhancement of steroidogenesis by cAMP dependent or non-dependent pathway as reported by Nyongesa *et al.* (2006), due to the effects of cathinone contents of khat leaves. This is in contrast to earlier observations in humans (Kalix and Braenden, 1985) and mice (Islam *et al.*, 1990) in which khat consumption (in humans) or treatment with cathinone (in mice) resulted in a decrease in plasma testosterone levels. The results of this oral toxicity study revealed no significant changes when compared to the corresponding control groups supporting the results of Tariq *et al.* (1983) who reported khat extract to have a less pronounced effects on cholesterol, total protein, albumin, uric acid, alanine amino transferase and aspartate amino transferase.

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