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RESEARCH ARTICLE

Khat extract mediated morphological and histochemical alterations in rat liver

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Abstract

The habit of Khat-chewing has prevailed for centuries among populations in the horn of Africa and the Arabian Peninsula. The biological effects of Khat on liver are inadequately investigated. The aim of this study is to investigate the histological and morphological changes in liver of rats after crude Khat extract treatment. The present study was carried out on 60 male rats for one month. They were divided into two groups (Control and treated groups). Half of each group was sacrificed after two week from the beginning of the experiment. The mean body weight of the Khat treated rats as well as their liver weights showed a significant increment ($P< 0.01$). Hematoxylin and Eosin staining of the liver parenchyma of Khat treated group showed abnormal architecture and widening of the central veins and portal system. The hepatic cells showed the signs of apoptosis and fatty degeneration. Immunohistochemistry by using TACS® 2 TdT DAB apoptosis detection kit indicates many apoptotic liver cells in the Khat treated group compared to the control one. In conclusion, Khat consumption could be associated with hepatic hypertrophy and hepatic disease.

Introduction

Khat (*Catha edulis*) is a plant growing in East Africa and Southern Arabia. The inhabitants of these regions frequently chew Khat because of its psychostimulant properties. Khat chewing efficiently extracts the alkaloid fractions which are absorbed through the oral mucosa and are found to have stimulant and pleasurable effect (Al-Habori, 2005; Toennes et al., 2003). The extract of fresh leaves of Khat contains a number of pharmacologically-active compounds (Kite et al., 2003). Beside cathinone which is the most important active ingredient, with a close similarity to amphetamine, causing the major pharmacological effects, Khat extract contains other alkaloid compounds such as the phenylpentenylamines and cathedulines which could also contribute to pharmacological effect of Khat (Al-Motarreb et al., 2002a; Kalix, 1992). Problems associated with repeated *Catha edulis* consumption have been evident. Literature surveys and clinical diagnostic studies revealed an association with prevalence of psychiatric morbidity (Al-Habori et al., 2002). Repeated intermittent oral administration of *Catha edulis* to laboratory animals leads to development and expression of locomotor sensitization (Calcagnetti and Schechter, 1992). *Catha edulis* also leads to increased incidence of acute coronary vasospasm and myocardial infarction (Al-Motarreb et al., 2002a). *Catha edulis* also accounts for a number of gastrointestinal tract problems, e.g. esophagitis, gastritis, (Gunaid et al., 1995) as well as the development of oral keratotic white lesions and signs of cytotoxic effects at the site of chewing (Hammouda and Halbach, 1972; Soufi et al., 1991).

The effects of Khat on apoptosis are still inadequately investigated and controversial. In spite of the body of knowledge on the adverse systemic effects of Khat, a very little information is known about the biological effects of Khat extract on cells (Carvalho, 2003). Several investigations indicated that repeated Khat consumption induces not only cytotoxic effects in cells (Al-Ahdal et al., 1988; Al-Mamary et al., 2002; Al-Meshal et al., 1991; Dimba et al., 2003), but also it causes formation of micronuclei in human buccal and bladder mucosa in Khat chewers, suggesting genotoxic effects (Kassie et al., 2001). Khat has also a profound effect on cell proliferation, chromosomal and embryonic abnormalities, DNA, RNA and total protein synthesis (Hondat et al., 1984). All morphological and biochemical features of apoptotic cell death have been demonstrated within 8 hours of exposure to Khat extract in cell–line of human leukemia (Kassie et al., 2001), Thus, Khat extract containing the major alkaloid compounds (cathinone and cathine) induces a selective type of cell death. Catha edulis extract causes chronic inflammation with peri-portal fibrosis in liver and acute tubular nephrosis in kidney of laboratory animals (Al-Habori et al., 2002; Al-Mamary et al., 2002) and a chromosomal aberration in the form of gaps, breaks, centrometric attenuations and centric fusion in hepatocytes (Hondat et al., 1984).

The aim of the present work is to study the effects of Khat extract on the liver of rats by using morphological, histological and immunohistochemical methods.

2. MATERIALS and METHODS

2.1. Khat extraction

The procedure for extraction of Khat was the methanolic extraction protocol as previously described by (Dimba et al., 2004; Kimani et al., 2008; Lee, 1995). Fresh Khat bundles were purchased from local Yemeni markets and transferred to the biology department of faculty of medicine for processing. The fresh Khat leaves were separated from the shoots. The fresh leaves were washed thoroughly with distilled water, blotted neatly, then chopped on glass plates and finally crushed. Crushed material was immersed in conical flask containing sufficient amount of methanol (Sigma-Aldrich) and kept on rotary shaker for 18 hours. Filtration of the previous mixture was carried in two steps; firstly using the gauze roll to separate the larger particles and secondly with Whatman No. 1 filter paper. The non-filtered plant material was re-extracted in fresh methanol (Dimba et al., 2004). The filtrate was admixed with the initial filtrate. The resultant filtrate was collected in pre-weighed conical flasks and exposed at 60-65 $^{\circ}$C to evaporate the methanol completely (Kimani et al., 2008), thus leaving semi-solid material (i.e. the extract) which was dried and collected to be kept as a powder in the refrigerator. The fresh solution Khat extract was prepared by dissolving the powder of Khat extract in distilled water, just prior to its oral administration to the rats daily throughout the experiment for 30 days.

2.2. Animal grouping and dosing:

Sixty Sprague-Dawley (SD) male rats weighting 100-150 gm were used throughout the study. The animals were housed in group cages and given free access of food and water. The rats were housed at 24˚C room temperature and 12-h: 12h light and dark cycle. They were acclimatized for one week before starting the experiment.

The rats were divided into two main groups, each consisting of 30 animals:

A) The Khat extract-treated group: The rats were given orally 700 mg/kg body weight Khat extract (Al-Qirim et al., 2002) daily throughout the period of experiment (30 days).

B) The control-untreated group: The rats were given orally normal saline (volume equal to that of the dose of extract in the previous group) daily throughout the period of the experiment.

Half of the animals from the control- and treated- groups were sacrificed after 15 days from the beginning of the experiment and the other animals were sacrificed at the end of the experiment after 30 days. So the entire experiment comprised of four groups of animals: the animals sacrificed after 15 days from the beginning of the experiments were represented as Control I and Treated I groups and the remaining sacrificed after 30 days from the beginning of the experiment were denoted as Control II and Treated II groups. The body weights of the animals were recorded at the beginning and at the end of the experiment just before sacrificing and also the weight of livers after sacrifice. Ratio of the wet weight of the liver relative to the body weight was calculated for each animal.

2.3. Tissue preparation and examination:

2.3.1. Fixation and embedding:

For histological examination, liver tissue pieces of appropriate dimensions were fixed in 10% neutral buffered formalin and processed for embedding in paraffin. Samples for immunohistochemistry were fixed in 4% neutral buffered formalin.

2.3.2. Sectioning, staining and examination:

Paraffin-embedded tissue sections were cut by microtome into 7-5 um thick sections. Sections were stained by routine histological stain (Hematoxylin & Eosin, (Harris, 1900) for general examination and identification of the stages of apoptotic cells morphologically. The sections were examined and photographed on an Olympus microscope with DP72 camera and cell software. Images were imported into adobe Photoshop for labelling.

2.3.3. Immunohistochemistry:

To study the effect of Khat extract on apoptosis; 4% neutral buffered formalin fixed samples were processed and embedded in paraffin. Sections of 5 um thickness were prepared and processed for immunostaining by using TACS® 2 TdT DAB in Situ Apoptosis Detection Kit (Trevigen, USA) according the manufacture instructions. The number of apoptotic cells was estimated by counting the number of apoptotic cells in five microscopic fields in each animals of the control and treated groups. The counting process was performed at high power (X400).

2.3.4. Statistical analysis of the results:

The parameters measured, the body weights, the ratios of the liver weight relative to body weight, numbers of the apoptotic cells are expressed as mean ± SEM for the control-I and -II, Khat-treated-I and -II groups. The one-way analysis of variance (ANOVA) and post hoc by scheffe test were used to statistically analyze and compare the means of control groups with the correspondent Khat extract-treated groups using SPSS version 17. $P < 0.05$ was considered significant (Aaronson et al., 2006; Downing and Hollingsworth, 1991).

3. Results

3.1. Physical parameters

3.1.1. Effect of Khat extract on the body weight (BW) of rats:

There were no significant differences between the mean final body weights between the control-I and Khat-treated-I groups (144.2 $\pm$ 6.95, 151.87 $\pm$ 4.01 gm respectively), and also, between the control-II and Khat-treated-II groups (143.66 ± 6.18, 144.25 ± 4.7 gm, respectively).

The initial body weights of the control I and treated I groups (138.4 ± 6.74, 138.125 ± 2.65 gm, respectively) and also control II and treated II groups (131.16 ± 8.31, 137.37 ± 2.58 gm, respectively) showed no significant differences (Fig. 1).

3.1.2. Effect of Khat extract on the liver weights of rats:

Khat treated-1 rats showed a significant increment in their liver weights (5.79± 0.29 gm /100gm BW) compared to control-1 group (4.48± 0.12 gm /100gm BW). The Khat treated-II rats showed a non-significant difference in their liver weights (5.17± 0.24 gm /100gm BW) compared to the control-II group (4.61± 0.27 gm /100gm BW) (Fig. 2).

3.2. Histological and immunohistochemical observations:

Microscopic examination of liver sections of control rats showed normal architecture of the liver lobules, central veins and hepatic plates (Fig. 3A). Hepatocytes are uniform in structure with intact cytoplasm and prominent one or two nuclei. There were no inflammatory changes or necrotic lesions observed in the liver of those animals (Figs. 4A & 5A).

Livers of Khat-treated rats showed abnormal architecture of the liver lobules, widening of the central veins and hepatic sinusoids with congestion (Fig. 3B-C). Hepatocytes of those rats appeared not uniform in structures. Necrotic changes and fatty degenerations were observed in these cells. In addition, their nuclei showed pyknosis and karyolysis. Disappearance of some cells' nuclei and residues of the nuclei and destroyed cells were also seen (Figs. 4B-C & 5B-C). These changes in the hepatocytes were well marked in the Khat-treated II group.

Immunohistochemical studies were performed by using TACS® 2 TdT DAB for detection of apoptotic cells, showed that the liver of Khat-treated I and II rats had significant increments in the numbers of the apoptotic cells (14.6± 1.37, 16± 1.3, respectively) when compared to the corresponding control I and II groups (2.4± 0.53, 2.62± 0.5, respectively) (Fig. 6). Most of the apoptotic cells were concentrated in the periphery of lobules (Figs. 7A-C).

Figures

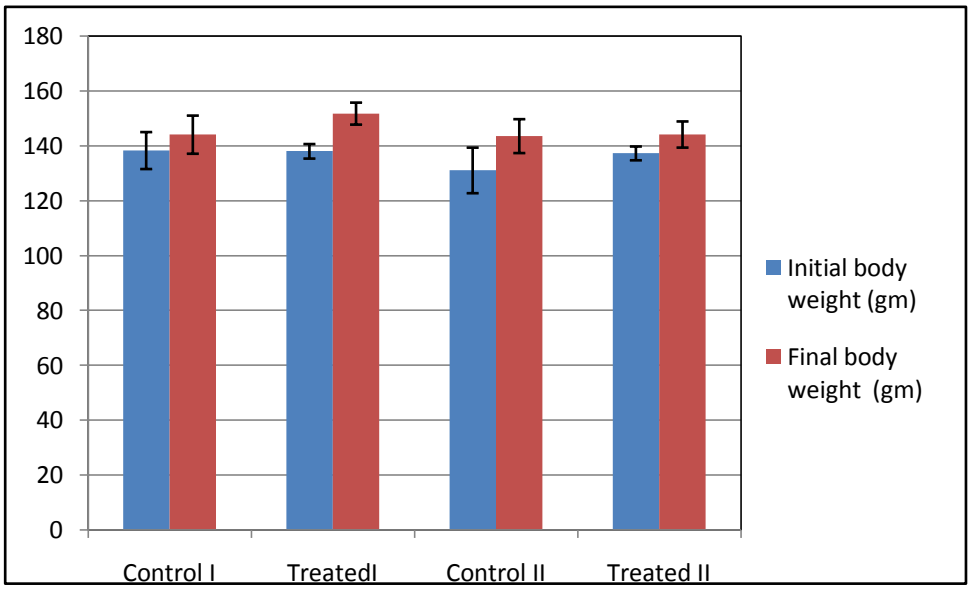

Fig. 1: Histogram showing the initial and final mean body weight (gm) of the control and Khat treated rats groups.

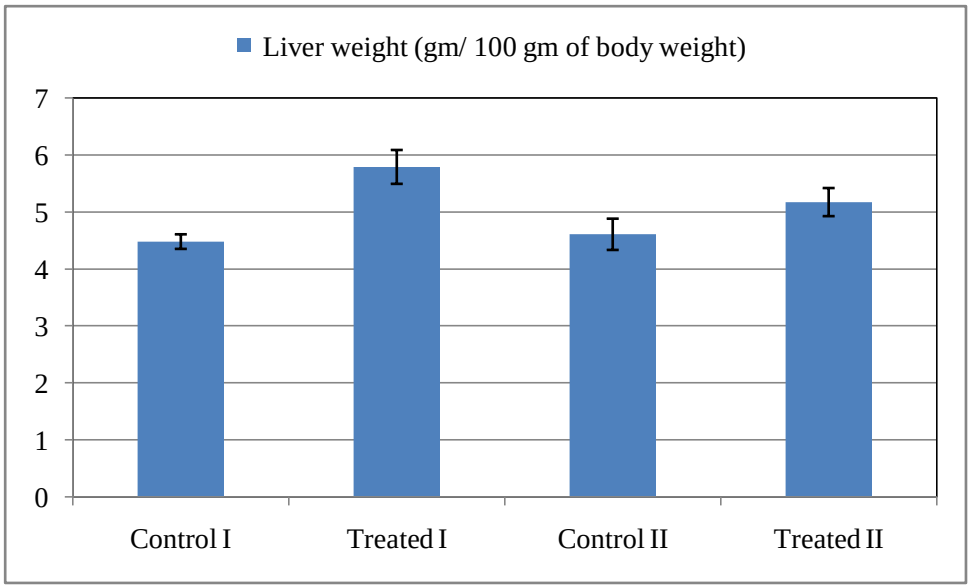

Fig. 2: Administration of Khat led to a significant increment in rat liver weight. Histogram showing the liver weight (gm/100 gm of BW) of the control and Khat treated groups. (*) denotes significant difference at $P < 0.05$).

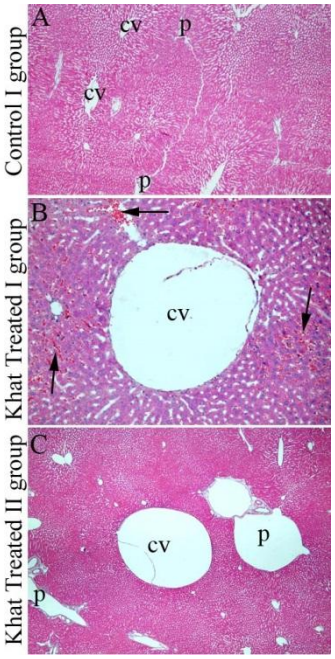

Fig. 3: Khat-treated rats showed abnormal architecture of the liver parenchyma. Khat treated group I& II (B& C) had wide central veins and portal canal compared to the control II (A) and congestion (arrows). cv; central vein, p; portal canal. Haematoxylin and Eosin stain, A&C: X 40; B: X200.

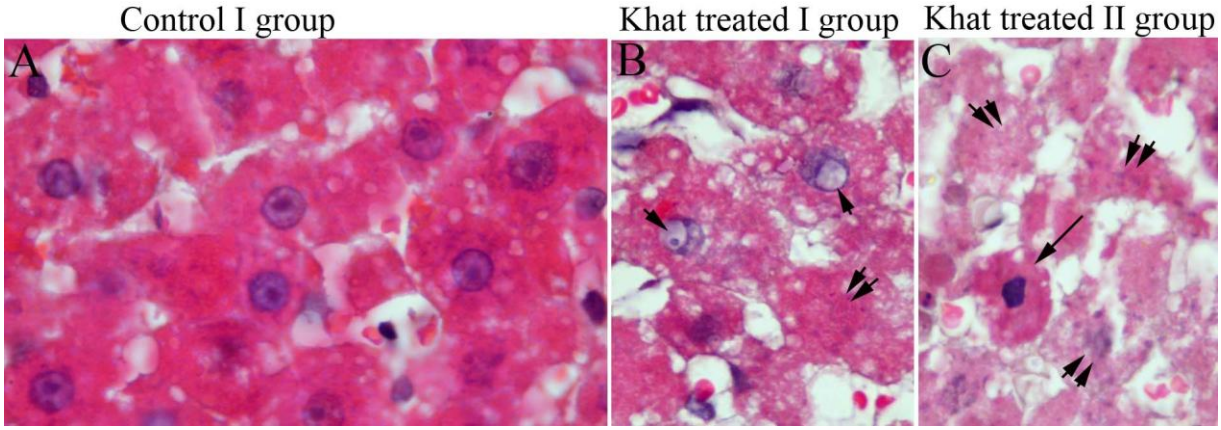

Fig. 4: Liver cells of normal rat group showing normal architecture with prominent nuclei and distinct nucleoli (A). The hepatocytes of Khat treated rat group I (B) and II (C) showed apoptotic changes (arrow); degenerative, necrotic changes and kayolysis (double arrowheads) as well as intranuclear inclusions (arrowheads). Haematoxylin and Eosin stain. X1000.

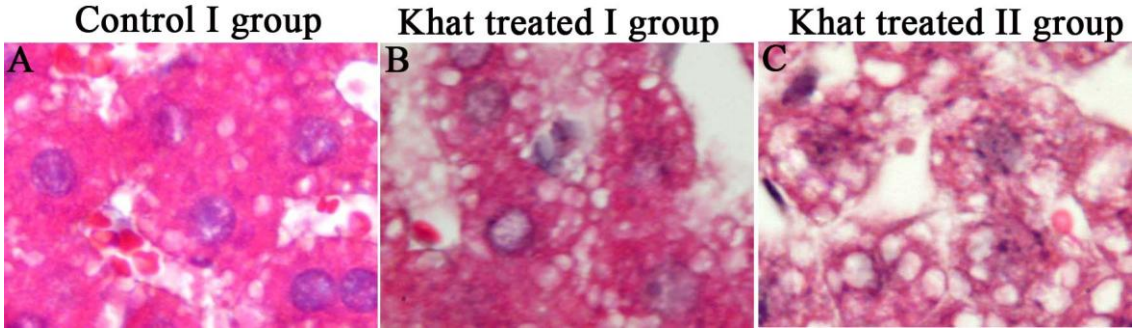

Fig. 5: Photomicrograph showing fatty degeneration in the hepatocytes of the Khat treated group I (B) and II (C) when compared to the control (A). Not that fatty degeneration is well marked in (C). Haematoxylin and Eosin stain, X1000.

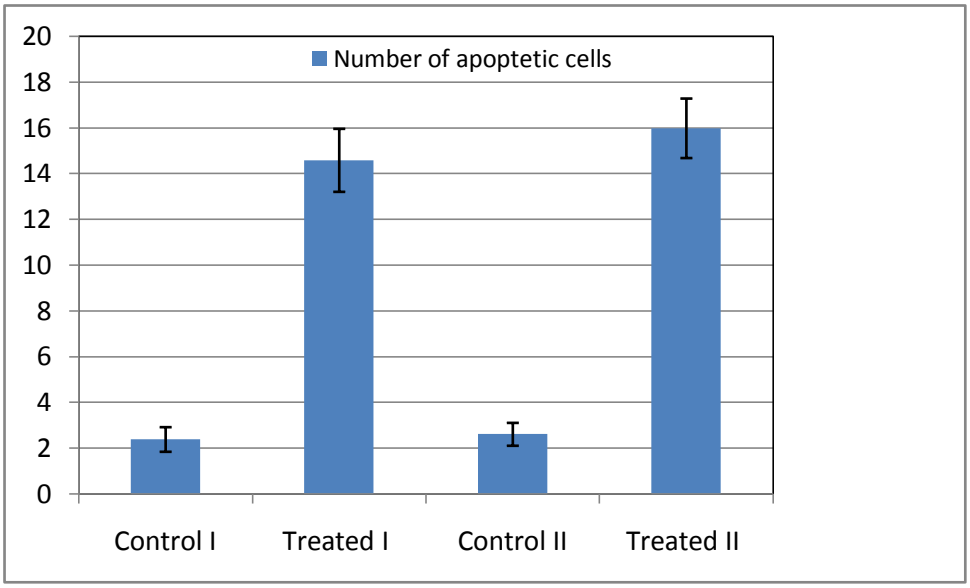

Fig. 6: Histogram showing a significant (P<0.01) increment in the number of apoptotic cells in the Khat treated I& II groups when compared to their control. (*) denotes a significant difference at P < 0.01).

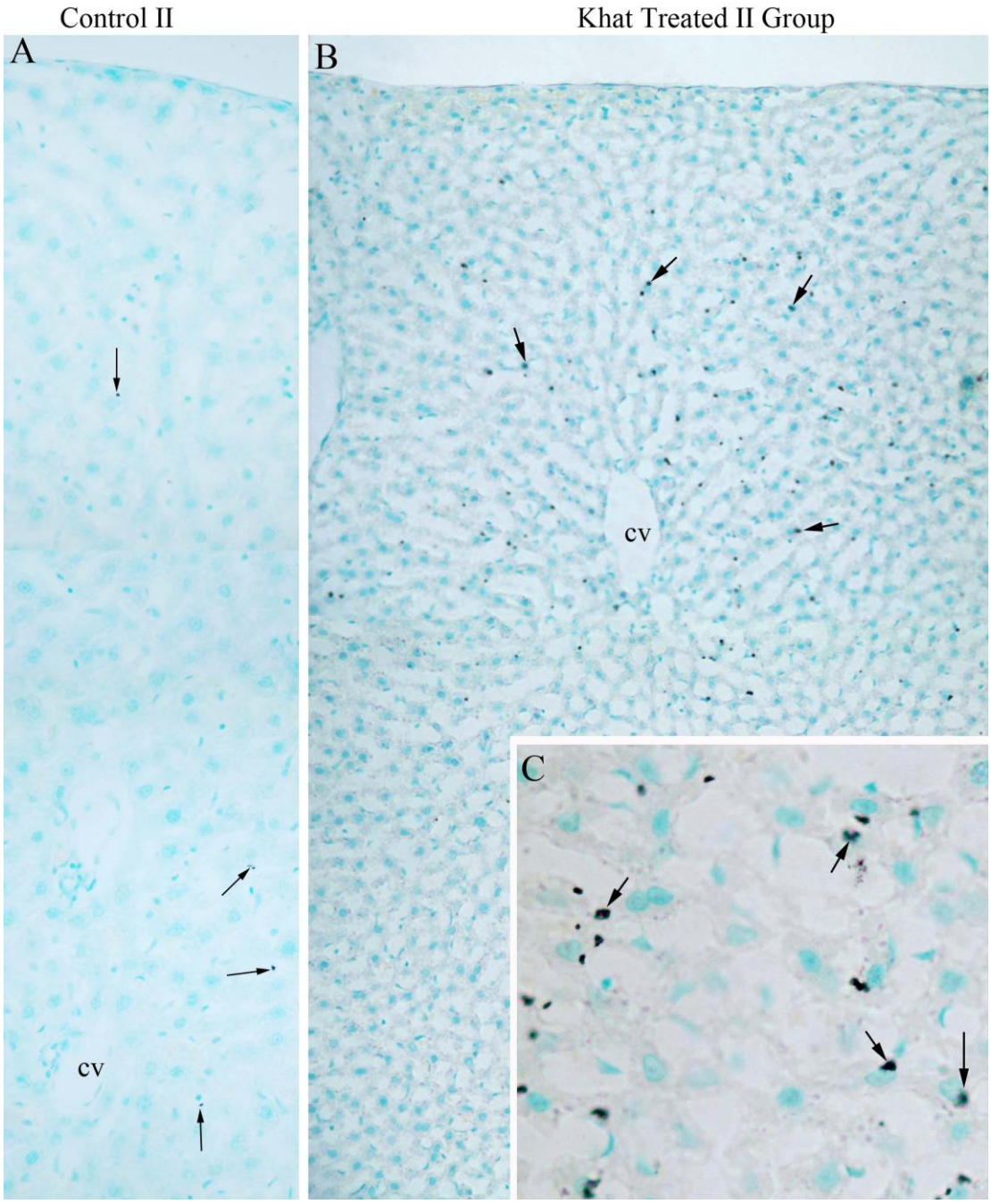

Fig: 7: Photomicrograph showing high number of apoptotic cells in the liver of the Khat treated II group rats (B) when compared to the control II (A). The apoptotic cells appeared more numerous at the periphery of the hepatic lobule (B). C: higher magnification photomicrograph showing the positively stained apoptotic hepatocytes (arrows). cv; central vein. TACS® 2 TdT DAB apoptosis detection kit, A& B X400, C: X 1000.

4. Discussion

The present study showed that administration of methanolic Khat extract (700mg/kg body weight) to rats had no significant effect on their mean body weights. Abnormal architecture of the liver parenchyma, degenerative and necrotic changes in the hepatocytes of the Khat treated group were observed. Moreover, Khat-treated groups showed a significant increment in the number of apoptotic cells in the liver.

In agreement with (Al-Zubairi et al., 2008a) administration of Khat extract had no significant effect on the body weight of rats. On the other hand, (Aziz et al., 2011) reported that subcutaneous injection of Khat extract play an important role in enhancing the anti-obesity effect in SD rats. The inconsistent of these views may be due to the effect of Khat is influenced by the source of Khat ingredients, the way of Khat extraction, the dose level and the mode of administration (Aziz et al., 2011). In Yemen Arab Republic, there are about 44 different types of Khat originating from different geographical areas of the country (Al-Motarreb et al., 2002b; Wabe, 2011).

In accordance with (Alsalahi et al., 2012), Khat-treated rats showed a significant increment in the relative liver weight. Hepatic enlargement represents the inflammatory responses that were associated with histopathological changes in rats after Khat treatment (Alsalahi et al., 2012; Ashafa et al., 2009). (Moore et al., 2006) reported that the increment in organ-body weight ratio is an indication of inflammation while the reduction in the same parameter can be adduced to cellular constriction.

The present results are consistent with many authors (Al-Habori et al., 2002; Al-Motarreb et al., 2010; ALRajhi and Yousef, 2013; Alsalahi et al., 2012; Dimba et al., 2003) who reported that Khat administration led to degenerative and necrotic changes in hepatocytes. In confirmation to the hepatotoxicity of the Khat chewing, a case of acute liver failure secondary to ingestion of Khat leaves was reported (Roelandt et al., 2011). In addition, a case report of end stage of chronic liver disease was associated with Khat consumption (Patanwalaa et al., 2011). In contrast, subchronic administration of crude Khat extract did not produce hepatotoxicity and did not produce any significant effect on the normal biological markers of the liver toxicity in male rats, but may have antioxidant property due to phenolic compounds (Al-Zubairi et al., 2008a ; Al-Zubairi et al., 2008b).

The present study showed that Khat induced apoptosis in hepatocytes detected by using TACS® 2 TdT DAB (a marker for apoptosis). It was reported that Khat extract has cytotoxic effects in cells (Al-Mamary et al., 2002; Al-Meshal et al., 1991; Dimba et al., 2003). Additionally, an organic extract of Khat was found to induce profound morphological effects in HL-60 human acute myeloid leukemia cells (Dimba et al., 2004). The mechanism of the cytotoxic effect of Khat on liver is uncertain. (Dimba et al., 2004) found that cell death by Khat extract was dependent on de novo protein synthesis. Furthermore, the administration of *Catha edulis* extract showed a deranged systemic capacity to handle oxidative radicles and induced cytotoxic effects in cells of liver and kidney, and moreover, it induced cell death in various human leukemia cell lines and in peripheral human blood leukocytes (Al-Habori, 2005; Al-Habori et al., 2002).

In Conclusion:

We found that the Khat had a deleterious effect on liver tissue of rats, such as hepatic enlargement, necrotic and degenerative changes as well as apoptosis in hepatocytes.

These data obtained from this work about the Khat increased our knowledge and improve our understanding for the effect of Khat on liver tissue of Khat-chewer and can be extrapolated to control the Khat-chewing and to promote the community health.

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