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Original Article

Teratogenic effects of *Khat* (*Catha edulis*) in New Zealand rabbit

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ABSTRACT

Objective: The present study was carried out to evaluate morphometric and histopathological abnormalities during organogenesis in liver, kidney, brain, spinal cord, heart, Lung, digestive tract and spleen in rabbit feti in response to oral administration of *Khat* prepared from leaves of khat tree (*Catha edulis*).
Materials and methods: The current work was carried out with apparently healthy adult New Zealand rabbits (n=27; 3 males and 24 females) weighing 2.5±0.5 Kg. The female rabbits were divided into four equal groups. Three goups (low, medium and high dose groups) were treated with *Khat*. The groups were given 3 mL, 6 mL and 12 mL extract/Kg bwt once daily from day 8 to 18 of gestation, respectively. The control group was given distilled water only. All females were slaughtered on day 28 of gestation. Visceral organ were subjected for histopathological examinations.
Results: *Khat* was found to be associated with hepatotoxicity and nephrotoxicity in rabbits. The kidney of feti of treated dams showed subcapsular hemorrhages along with mild vacuolar degeneration of some renal tubular epithelium. Glomeruli were atrophied, and moderate degenerative changes were observed in renal tubular epithelium and hemorrhages between renal tubules. The liver of the feti showed vacuolar degeneration, necrotic hepatitis, congestion of central veins and hepatic sinusoids, pyknotic clumped nuclei, hemorrhages, edema with atrophy of some hepatocytes, and hyperplasia of Megakaryocytic cells. The *Khat* also harmed the brain causing hemorrhage, edema, degenerative changes, swelling and necrotic changes of some nerve cells as well as supporting cells. The spinal cord was affected showing degeneration of nerve fibers in white matter and some neurons in grey matter. The heart of treated feti showed congestion of epicardial blood vessels and diffuse degeneration of heart muscles. Lung and alimentary tract only showed congestion of blood vessels.
Conclusion: Prenatal exposure of *Khat* in rabbit induces harmful effects in defferent visceral organs including liver, kidney, brain, spinal cord, spleen, intestine, heart and lung.

KEYWORDS

Embryo; Khat; Pathology; Rabbit

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INTRODUCTION

Leaves (young and tender) and shoots of the khat tree (*Catha edulis*) are referred to *Khat*. *Khat* has been chewed for their stimulant and pleasurable effects for centuries by people particularly in the countries around the Red Sea and in East Africa (Motarreb et al., 2002). Khat contains mainly cathinone (Kalix, 1990), which is the most important active ingredient in it that implies major pharmacological effects (Hollister, 1995).

Several works have been carried out considering toxicological and pharmacological effects of *Khat* (Abdul Ghani et al., 1987; Al-Habori et al., 2002; Carvalho, 2003). It has also been reported that *Khat* induces cytotoxic effects in cells of liver and kidney of rabbits (Mamary et al., 2002). The current study aimed to investigate the adverse effect of *Khat* on visceral organ of rabbit feti of orally *Khat* treated dams during the period of organogenesis.

MATERIALS AND METHODS

Experimental animals and ethical approval: The present work was done on 27 adult, apparently healthy sexually mature New Zealand rabbits of both sexes (3 males and 24 females) of average body weight of (2.5±0.5 Kg) obtained from - Abu Sawyer Farm, Ismailia, Egypt. The research protocol of this study was approved by the scientific research ethics committe of Suez Canal University, Egypt (approval no. 201401).

Place: The animals were raised in steel cages, thoroughly cleaned with water and soap then, disinfected by phenol and left for two days then washed with water. The room was cleaned with iodine. Light was left for 12 h during night. The room was air conditioned.

Feeding: The pelleted food (New Tanpool Feed, Tanpool factory for rabbits feed, Al-mohnds, Egypt) and *Khat* were tested whether free from any mycotoxins at the Central Laboratory of Residue Analysis of Pesticides and Heavy metals in Food, Agricultural Research Center, Ministry of Agricultural, EGYPT. Food and water were provided to the animals *ad libitum*.

Acclimatization: In the first two weeks, the animals were administered feed and water ad lib plus vitamin E and selenium in water at 1 gm/L because it is immunostimulant and antistress.

Mating: The females were moved to the cages of males at evening with observation of mating. Specific grunting sound of male in addition to turning on one side after mating indicates successful mating then the females were separated next day morning and consider this is the pregnancy day zero (Wangikar et al., 2005).

Plant material: Fresh khat leaves were harvested during September 2014 from private farm Dhamar, Wedy Alher, Republic of Yemen. The plants were cut into pieces and grinded after drying. *Khat* was tested in Agricultural Research Center, Ministry of Agricultural, Egypt to assure that it is free of residue of pesticides and heavy metals.

Preparation of *Khat* extract: One hundred grams of dried khat leaves were soaked in 500 mL of distilled water for 24 h then heated for 30 min at 60°C in a water bath. The contents were filtered by a piece of cloth to give about 300 mL extract. The extract was kept in refrigerator untill used (Al-Qirim et al., 2002). Dosage was adopted based on the average daily consumption of khat leaves *i.e.*, 2 gm/Kg body weight (bwt) in human (Wafaa and Olfat, 2013). One gram khat gave off 3 mL *Khat* extract. So, we used three doses 3, 6 and 12 mL extract/Kg bwt.

Method of administration: The present study used the oral route of administration of *Khat* to pregnant rabbits to ensure the administration of the definite amount of *Khat* extract to the animals (Wafaa and Olfat, 2013).

Experimental grouping: The female animals were grouped into four categories each of 6 females; the control group was given distilled water only. The low, medium and high dose groups were given 3 mL, 6 mL and 12 mL extract/Kg bwt once daily from day 8 to 18 of gestation, respectively. All females were slaughtered on day 28 of gestation.

Observation: On day 28 of gestation, the female rabbits were anesthetized by intramuscular injection of a mixture of 30 mg xylazine (Rompun®, Butler, Columbus, OH, USA) and 1 mg acepromazine maléate (TechAmerica, Elwood, KS, USA) (Carney and Foote, 1990). Then the animals were slaughtered and laparatomy was performed to observe the fetal swellings. The uterus was excised for the removal of the feti to take the visceral organs (liver, kidney, brain, spinal cord, heart, Lung, digestive tract and spleen). These organs were examined grossly and the morphometric measurements were taken to observe any gross abnormality.

Histopathological sections: The remaining fetuses were fixed in 10% neutral buffered formalin for a week

and subjected for preparing paraffin blocks to histological examination. For light microscopy, serial sections were taken (liver, kidney, and brain) of both control and experimental fetuses. Cross sections of 4-6 mm in thickness were obtained, stained with harries Hematoxylin & Eosin (H&E), as outlined by Bancroft and Stevens (1996).

RESULTS

Macroscopic findings of the viscera: The mean weight of different fetal organs (kidney, liver, brain, heart and GIT) (**Figure 1-5**) in the treated dams (at 0.1 gm/Kg bwt, 2 gm/Kg bwt, 42 gm/Kg bwt) were significantly decreased as compared to those of control on day 28 (**Table 1-5**).

Microscopic findings of the viscera:

Kidneys: Kidneys in control group had normal histo-lgical picture. The *Khat* treated groups showed variable degrees of pathological lesions. Lesions were mild subcapsular hemorrhages along with mild vacuolar degeneration of some renal tubular epithelium in rabbits that were treated with low dose of *Khat* extract (**Figure 6**).

Table 1. Comparison of the kidney weight of feti of control and *Khat* treated dams.

(I) Group	(J) Group	Mean Difference (I-J)
Control	Low dose	.17846*
	Medium dose	.26588*
	High dose	.30738*
Low dose	Control	-.17846-*
	Medium dose	.08742
	High dose	.12892*
Medium dose	Control	-.26588-*
	Low dose	-.08742-
	High dose	.04150
High dose	Control	-.30738-*
	Low dose	-.12892-*
	Medium dose	-.04150-

Table 2. Comparison of the liver weight of feti of control and *Khat* treated dams.

(I) Group	(J) Group	Mean Difference (I-J)
Control	Low dose	1.37328*
	Medium dose	1.71378*
	High dose	2.19294*
Low dose	Control	-1.37328-*
	Medium dose	.34050
	High dose	.81967
Medium dose	Control	-1.71378-*
	Low dose	-.34050-
	High dose	.47917
High dose	Control	-2.19294-*
	Low dose	-.81967-
	Medium dose	-.47917-

Treat with medium dose, kidneys showed severe subcapsular hemorrhage which was extended to cortex. Glomeruli were atrophied, and moderate degenerative changes were observed in renal tubular epithelium (**Figure 6-7**). Kidneys that received the higher dose of *Khat* showed multifocal hemorrhages between renal tubules showing moderate to severe degenerative changes (**Figure 7**).

Table 3. Comparison of the brain *weight* of feti of control and *Khat* treated dams.

(I) Group	(J) Group	Mean Difference (I-J)
Control	Low dose	.15678*
	Medium dose	.29045*
	High dose	.48078*
Low dose	Control	-.15678-*
	Medium dose	.13367*
	High dose	.32400*
Medium dose	Control	-.29045-*
	Low dose	-.13367-*
	High dose	.19033*
High dose	Control	-.48078-*
	Low dose	-.32400-*
	Medium dose	-.19033-*

Table 4. Comparison of the heart weight of feti of control and *Khat* treated dams.

(I) group	(J) group	Mean Difference (I-J)
Control	Low dose	.04968*
	Medium dose	.13552*
	High dose	.22952*
Low dose	Control	-.04968-*
	Medium dose	.08583*
	High dose	.17983*
Medium dose	Control	-.13552-*
	Low dose	-.08583-*
	High dose	.09400*
High dose	Control	-.22952-*
	Low dose	-.17983-*
	Medium dose	-.09400-*

Table 5. Comparison of the GIT weight of feti of control and *Khat* treated dams.

(I) group	(J) group	Mean Difference (I-J)
Control	Low dose	1.02445*
	Medium dose	1.23512*
	High dose	1.51062*
Low dose	Control	-1.02445-*
	Medium dose	.21067
	High dose	.48617*
Medium dose	Control	-1.23512-*
	Low dose	-.21067-
	High dose	.27550*
High dose	Control	-1.51062-*
	Low dose	-.48617-*
	Medium dose	-.27550-*

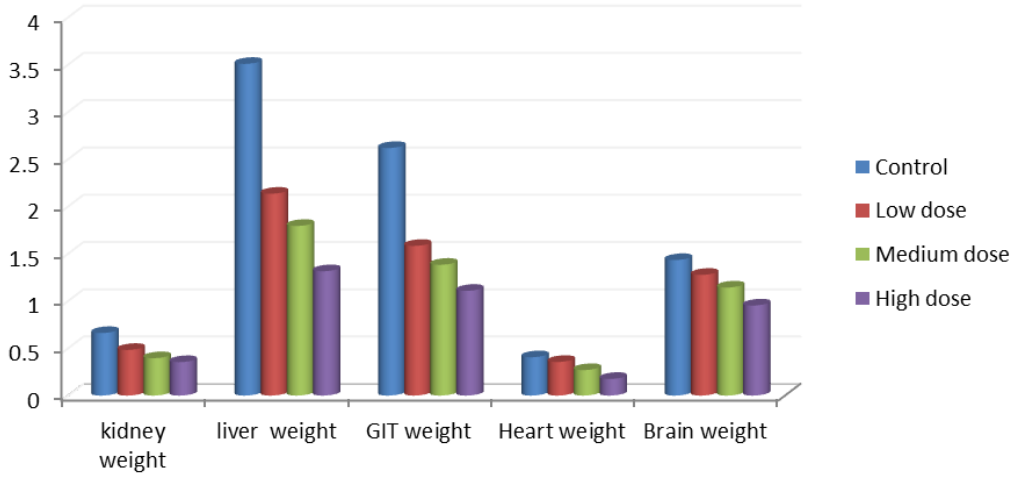

Figure 1. A graph showing the weight of kidney, liver, GIT, heart and brain of feti of control and *Khat* treated dams.

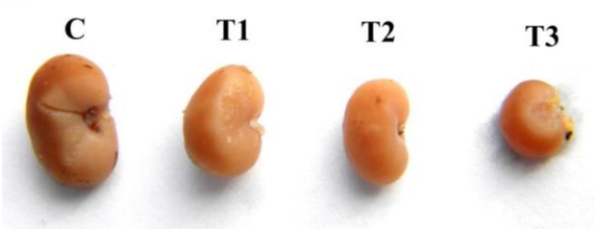

Figure 2. Kidney of feti at 28 day of gestation of control (C) and *Khat* treated dams: low dose (T1), medium dose (T2) and high dose (T3).

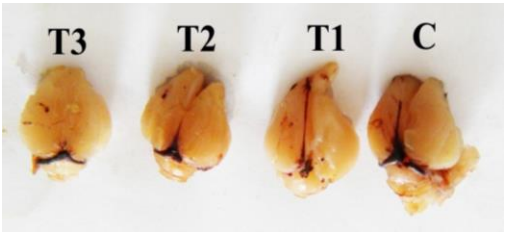

Figure 4. Brain of feti at 28 day of gestation of control (C) and *Khat* treated dams: low dose (T1), medium dose (T2) and high dose (T3).

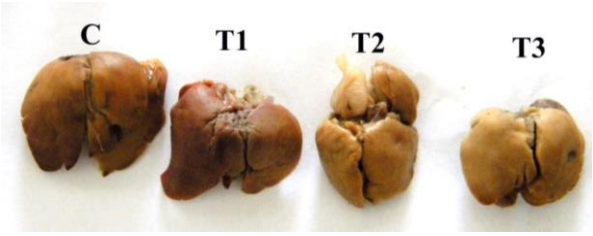

Figure 3. Liver of feti at day 28 of gestation of control (C) and *Khat* treated dams: low dose (T1), medium dose (T2) and high dose (T3).

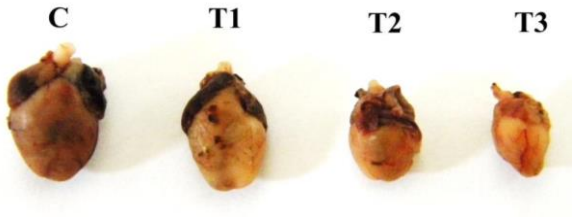

Figure 5. Heart feti at day 28 of gestation of control (C) and *Khat* treated dams: low dose (T1), medium dose (T2) and high dose (T3).

Liver: The liver of control groups showed had normal histolgical picture. Livers treated with low dose of khat showed mild degrees of vacuolar degenerative and individual to minimal necrotic hepatic cells, mild focal congestion of central veins and hepatic sinusoids (**Figure 8**). Discrete foci of hemorrhages were also observed between hepatic cells. The livers received moderate dose of khat showed focal mild to moderate vacuolation of hepatocytes along with multiple foci of necrotic cells recognized by pyknotic clumped nuclei (**Figure 8-9**). Moderate congestion of central veins and hepatic sinusoids. Focal hemorrhages were also observed. The livers treated with high dose of khat showed multifocal severe necrosis of hepatocytes, congestion of blood vessels and severe hemorrhages, edema with atrophy of some hepatocytes (**Figure 8-9**). In addition to the previous lesions, liver showed a dose related hyperplasia of Megakaryocytic cells (**Figure 9**).

Brain: Both meanings and brain of control group showed normal histological structure. Congestion of both meningeal and brain blood vessels was observed and there was dose dependent ranged from mild, medium to severe (**Figure 10**). Hemorrhage and edema

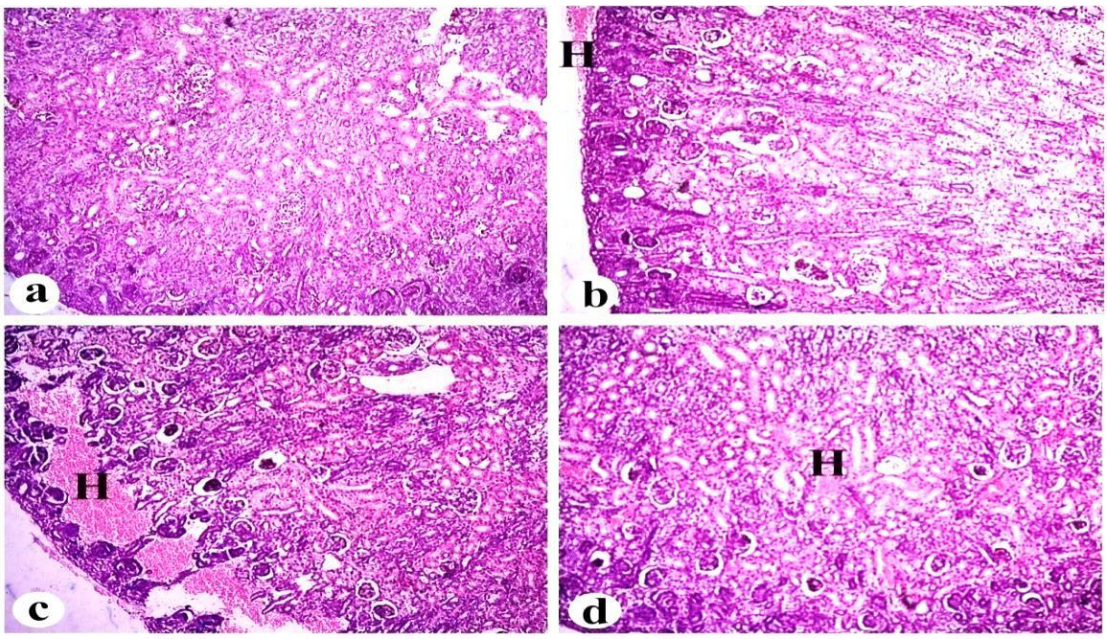

Figure 6. Kidney of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing congested glomerulus (G) with wide urinary spaces around the capillary tuft, distorted Bowman's capsule ,congestion of the intertubular blood capillaries and hemorrhage (H) .). (a) Control H&E. X 100. (H&E. X40).

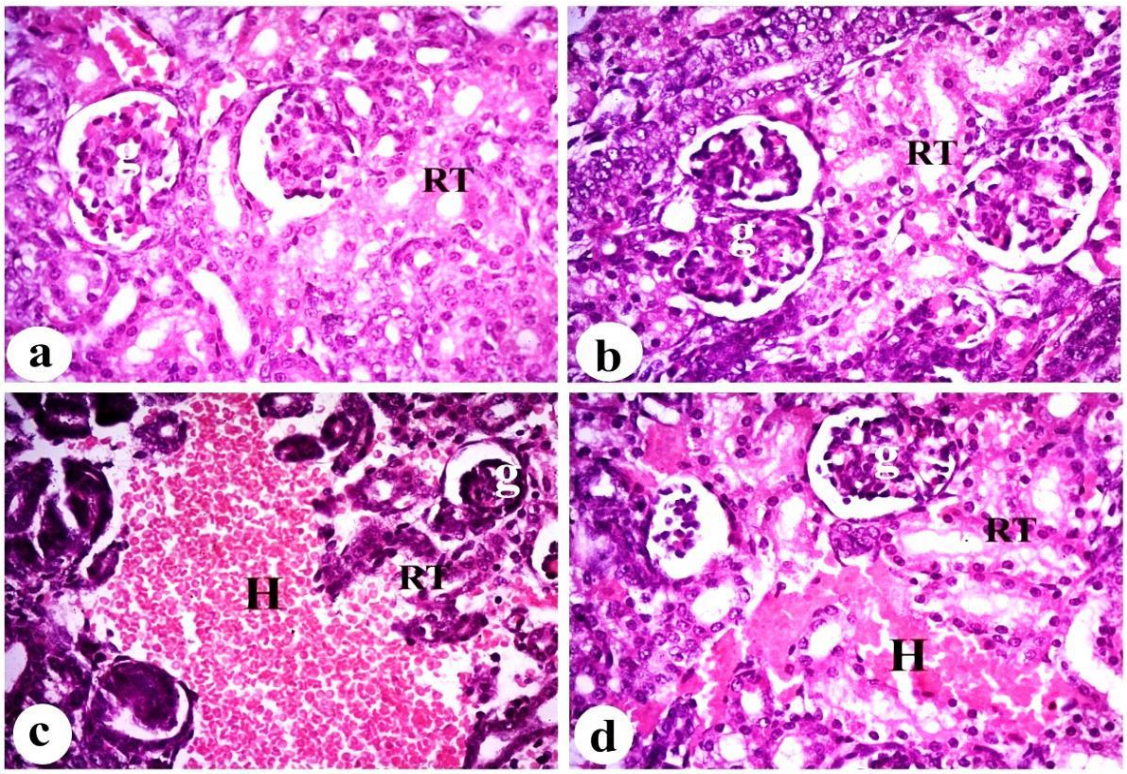

Figure 7. Kidney of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing vacuolar changes of renal tubular epithelium (RT), congested, atrophied glomeruli (g) and intertubular hemorrhages (H). H&E. X 100.

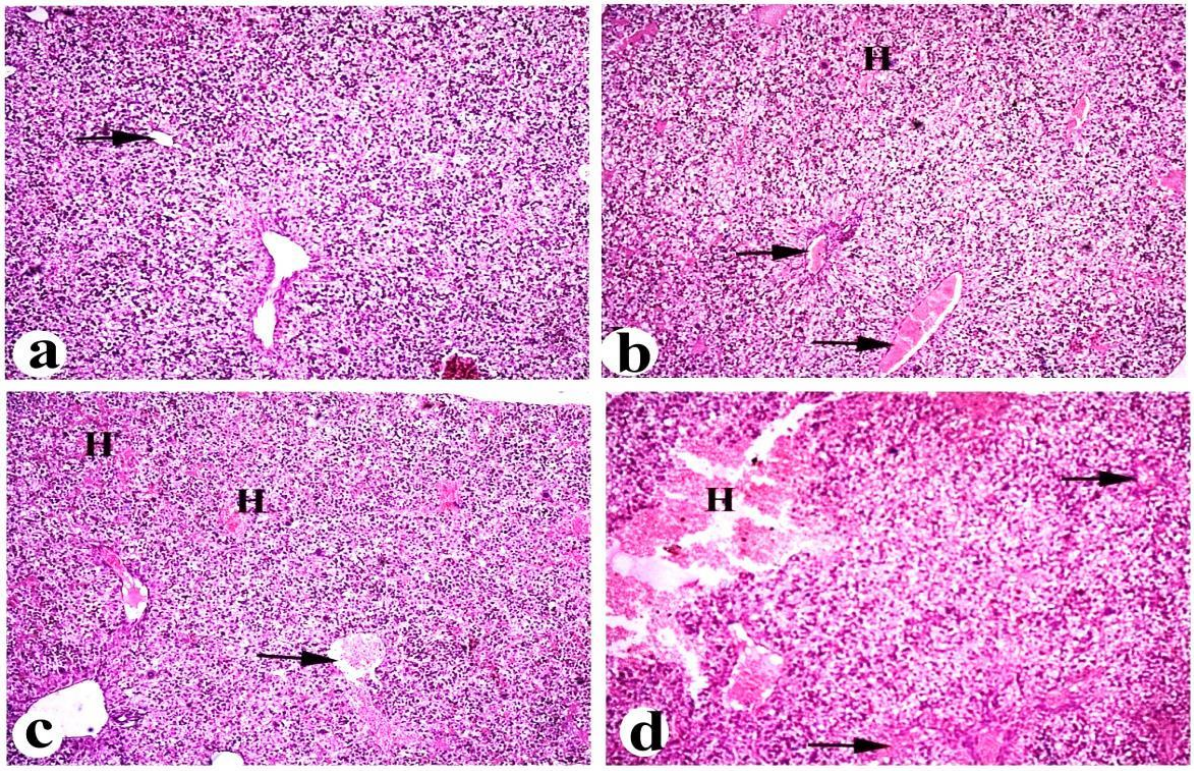

Figure 8. Liver of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing variable degrees of congested central veins (arrows) and hemorrhages between hepatic cords (H). H&E. X 100.

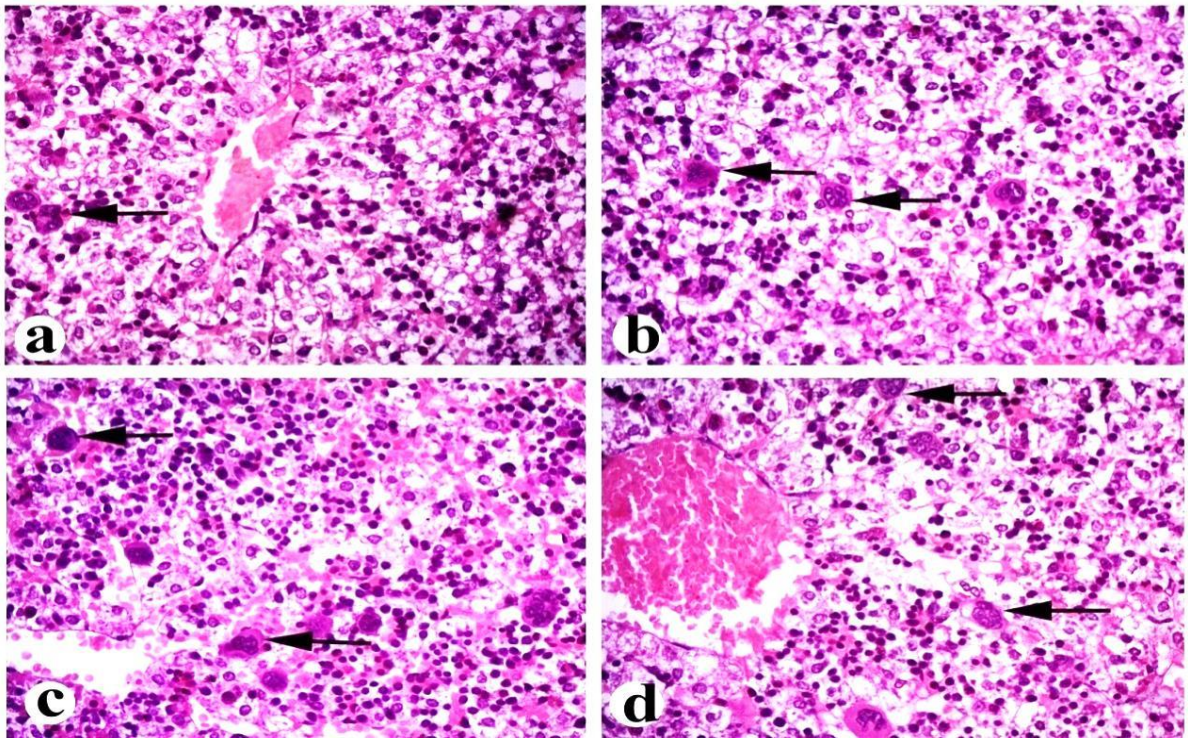

Figure 9. Liver of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing increased number of megakaryocytic cells.). H&E. X 400.

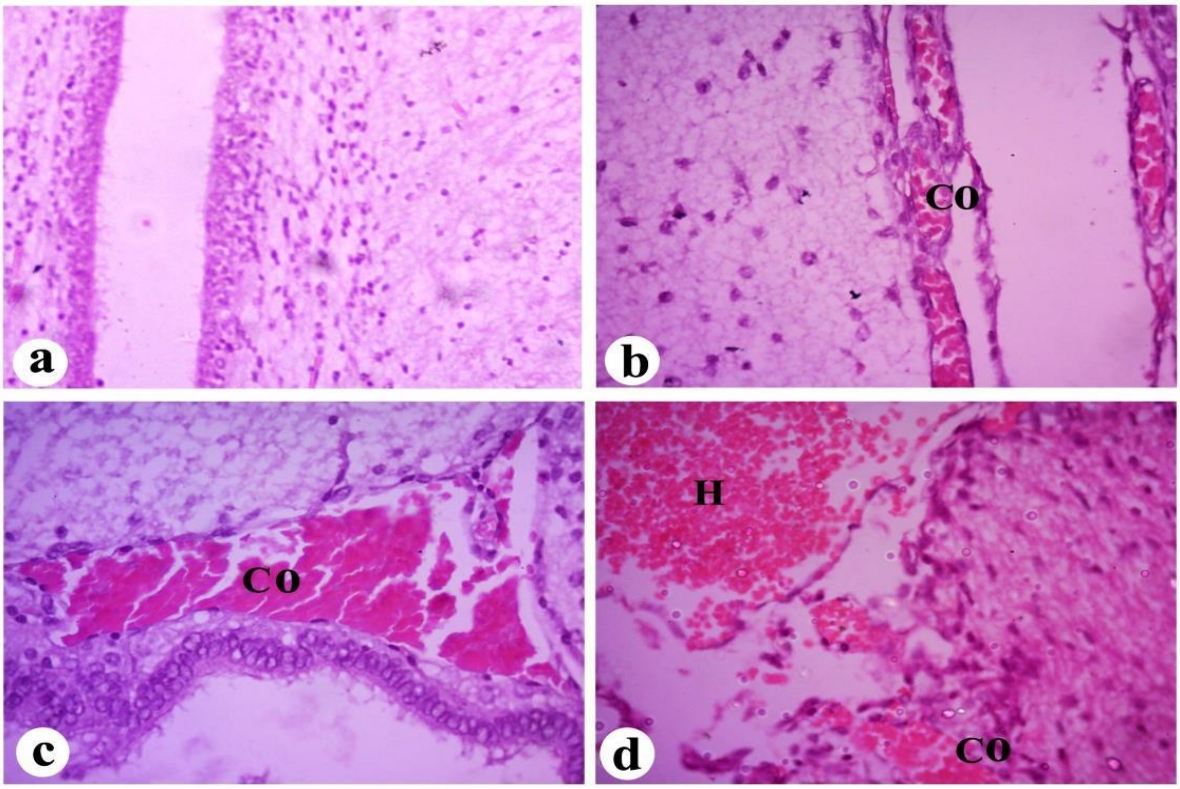

Figure 10. Brain of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing various degrees of congestion (C) and hemorrhages (H). H&E. X 100.

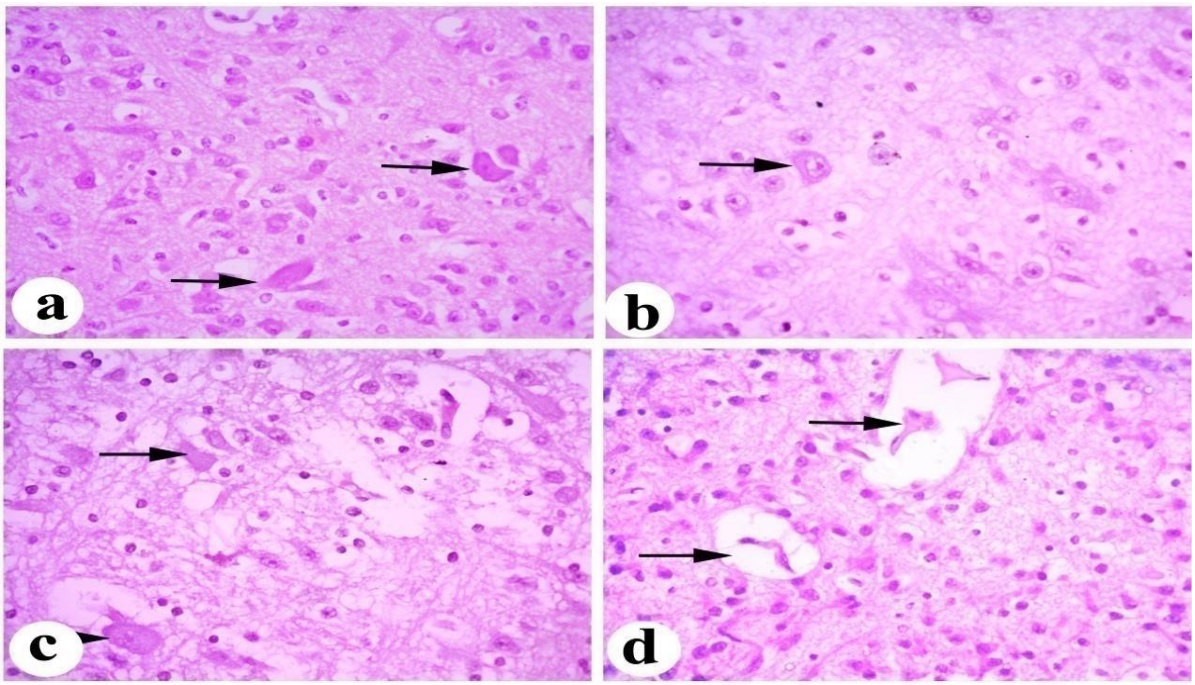

Figure 11. Brain of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing various degrees of degenerated neurons (arrows). H&E. X 400.

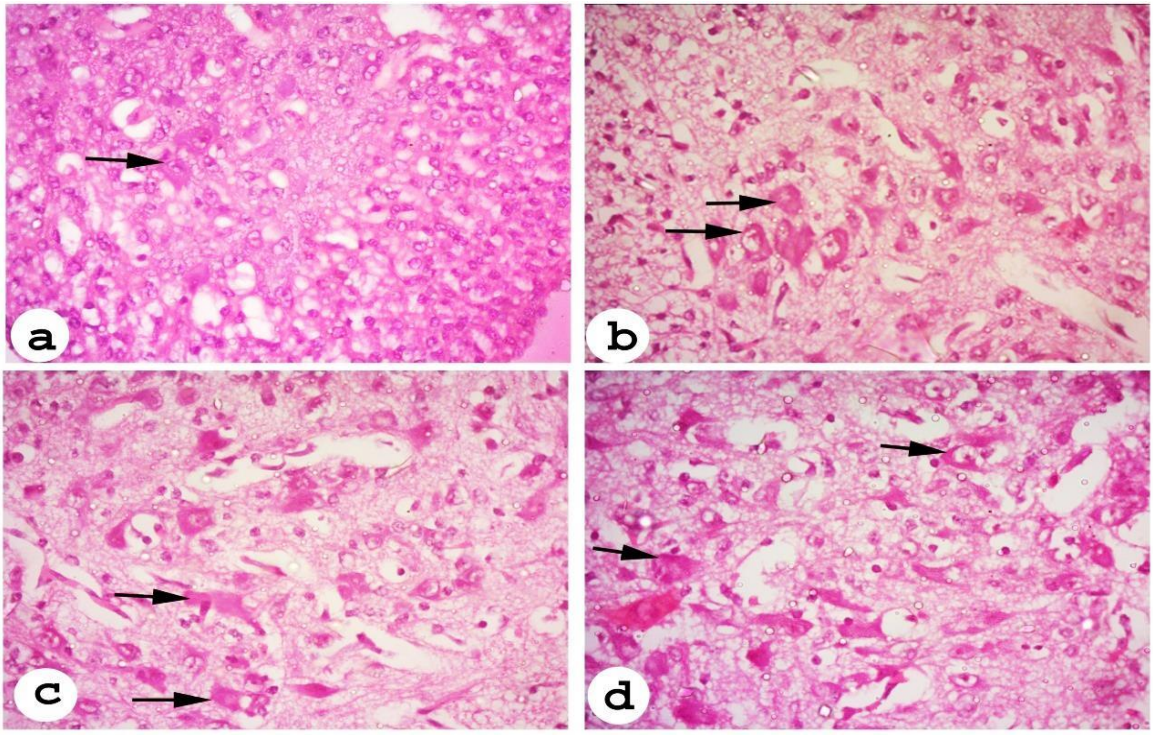

Figure 12. Spinal cord of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing various degrees of degenerated neurons (arrows). H&E. X 400.

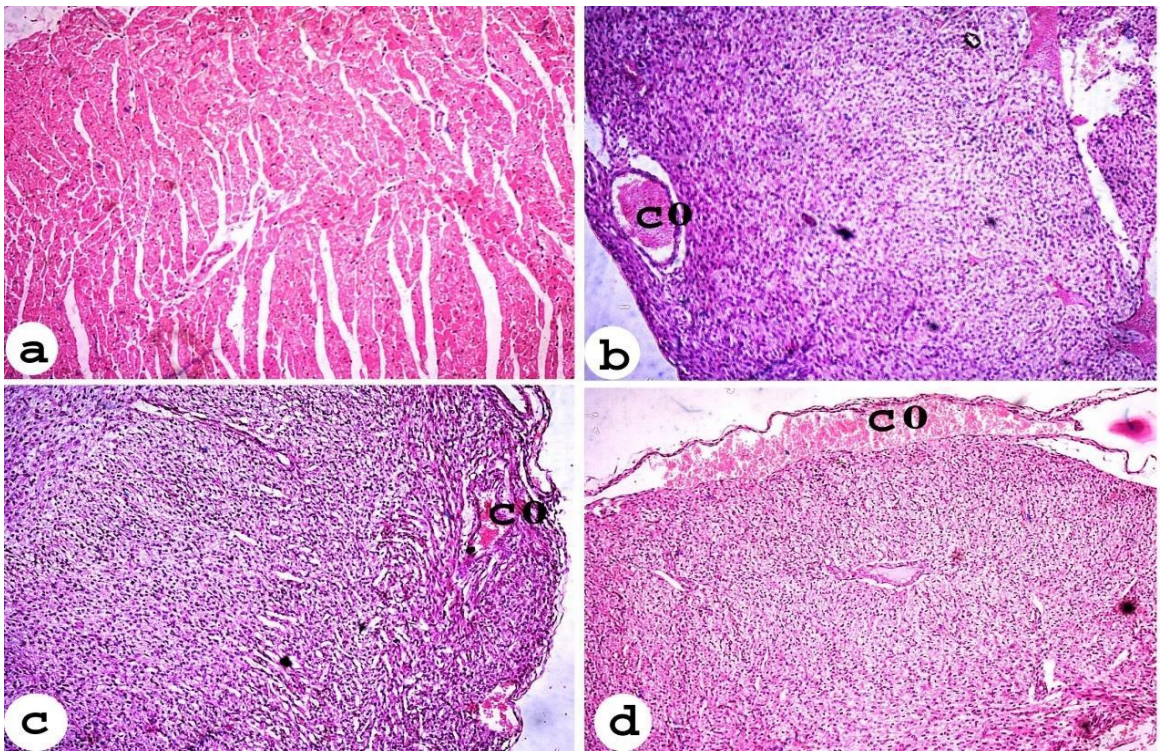

Figure 13. Heart of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing congestion of epicardial blood vessels and diffuse degeneration of heart. H&E. X 100.

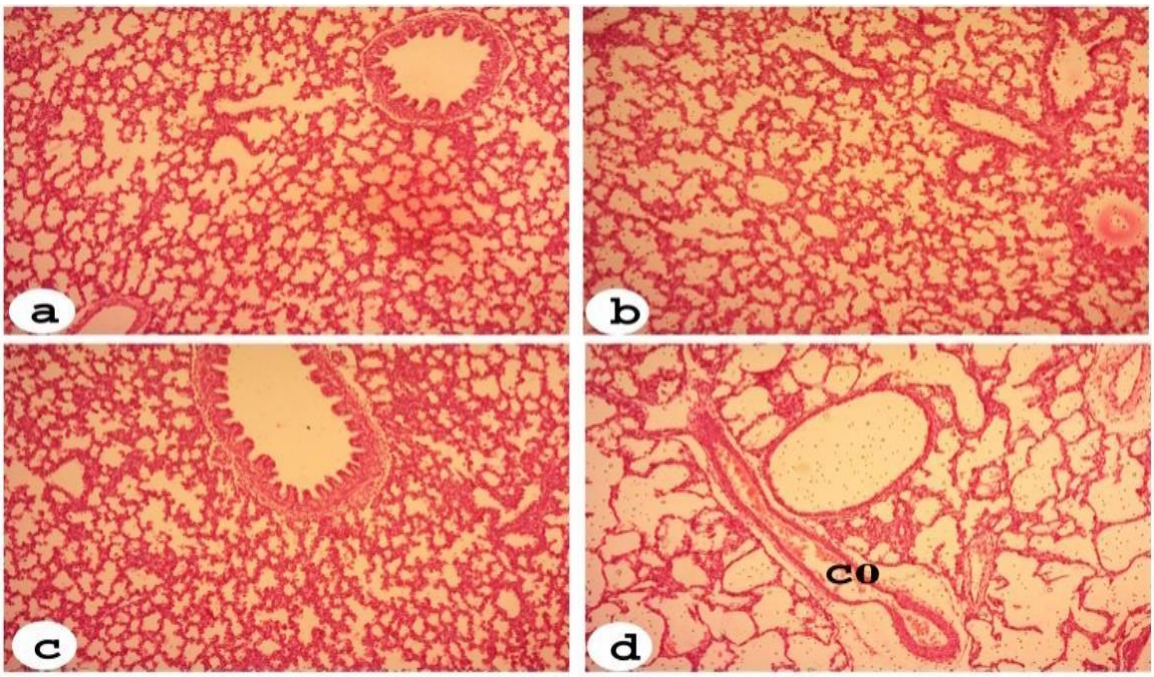

Figure 14. Lung of rabbit feti of control (a) and *Khat* treated dams (b- low dose, c- medium dose, d- high dose) showing congestion of peribronchial blood vessels (c). H&E. X 200.

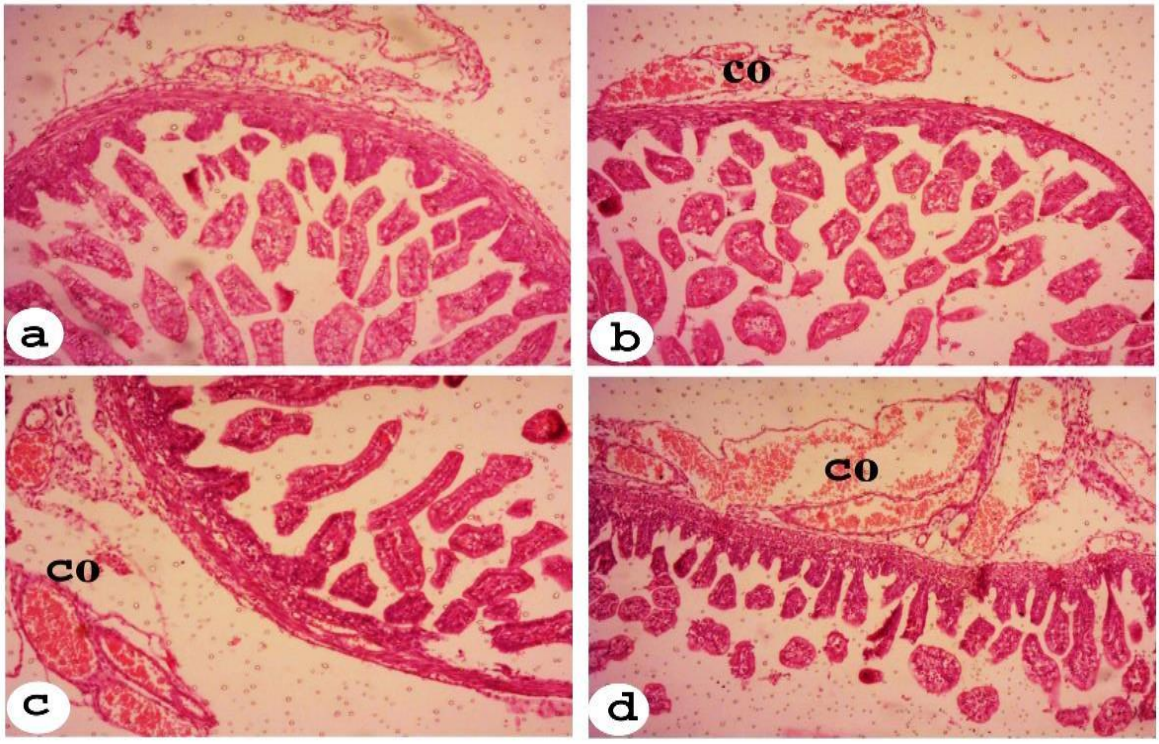

Figure 15. Intestine of rabbit feti of control (a) and *Khat* treated dams (b-low dose, c-medium dose, d-high dose) shoed severe congestion of serosal blood vessels (c). H&E. X 200.

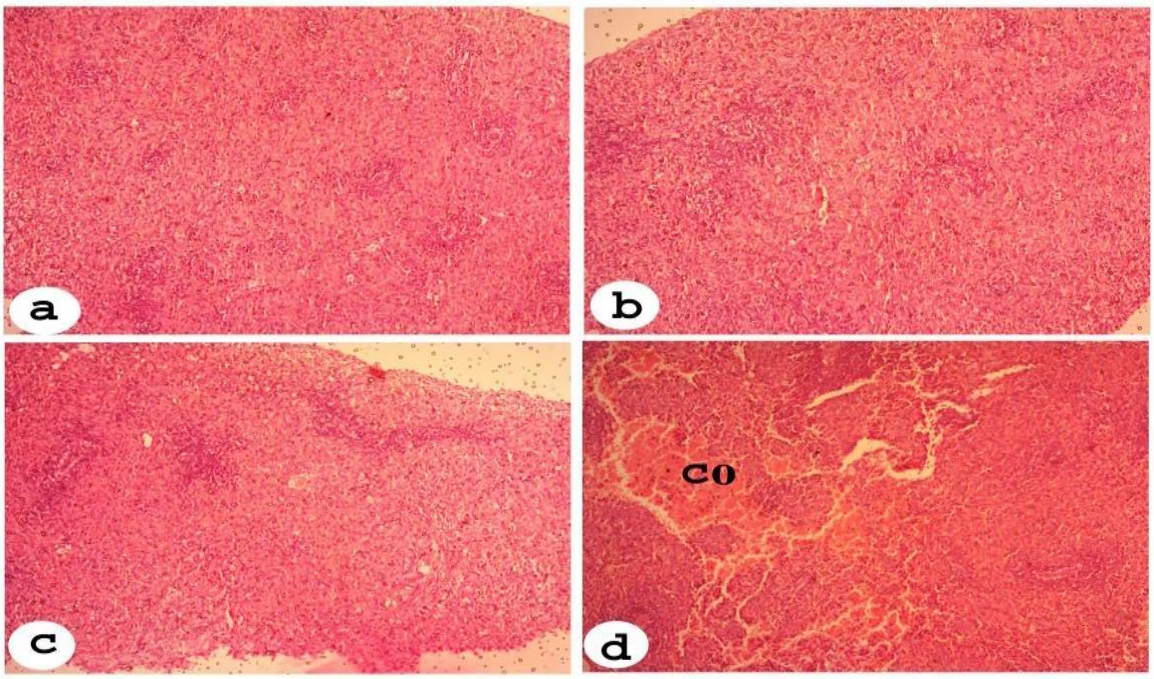

Figure 16. Spleen of rabbit feti of control (a) and khat treated dams (b- low dose, c- medium dose, d- high dose) showing congestion of sinusoids (C). H&E. X 200.

observed only with the highest dose only. Degenerative changes, swelling and necrotic changes of some nerve cells as well as supporting cells were observed mainly with the medium and high doses (**Figure 10-11**).

Spinal cord: Both grey matter and white matter of spinal cord of control group showed normal histological structure. Degeneration of nerve fibers in white matter and some neurons in grey matter was observed in treated animals (**Figure 12**). these changes were dose dependent and ranged from mild, medium to severe.

Heart: Heart of rabbit embryo treated with khat showed congestion of epicardial blood vessels and diffuse degeneration of heart muscles compared to normal control group that had either no congested blood vessels or degeneration of cardiac myocytes (**Figure 13**). Severity of both congestion and degeneration was dose dependent (**Figure 13**). Lung, digestive tract and spleen showed mild changes in treated embryos and the only change was the congestion of blood vessels (peri-brochial, serosal and sinusoids respectively). Congestion was observed mainly with the highest dose (**Figure 14-16**).

DISCUSSION

The prenatal effect of administration of *Khat* extract to pregnant rabbit form day 8 to 18 of gestation showed decrease in the weight of different fetal organs (liver and kidney and brain, heart, gall bladder, stomach and intestine) of feti of all doses compared to control fetuses on day 28. This decrease in organs weight may be due to that *Khat* decrease in the appetite of dams (Mwenda et al., 2003). Degenerative changes in fetal liver and kidney seen in this study included invasion of infiltrative inflammatory cells, cytoplasm vacuolization of hepatic and tubular cells; these results supported the findings of Nasher et al. (1995). The dege-nerative vacuolar lesions in liver of rabbit feti indicated direct hepatotoxicity of *Khat* on the liver cells as recoded by Alsalahi et al. (2012) in adult rat. Wafaa and Olfat (2013) observed focal area of necrosis, fatty degeneration of hepatic cells, congestion and dilation of the central vein and surrounding sinusoid in liver of rabbit; these results supported our findings.

In the current study, the observed changes in liver and kidney of rabbit feti included tubular cell invasion of infiltrative inflammatory cells and cytoplasmic vacuolation of hepatic cells, as supported by Al-Qirim et al. (2002), Motarreb et al. (2002) and Al-Hashem et al. (2011).

Histopathological findings of liver and kidney in this study were consistent with the changes as reported by Al-Habori et al. (2002) who described that periportal fibrotic changes may occue due to the long time (about 6 months) administration of *Khat* to adult rabbits. The toxic effects exerted by *Khat* on kidney and liver of rat can be menifested either by *Khat* itself or by the pesticides that

are sprayed on *Khat* trees leaves (Al-Akwa et al., 2009; John et al., 2011). However, in the present study, we confirmed that the effect was only due to the *Khat*, as the plant was tested to be free from any pesticide.

The current study showed that *Khat* caused vascular congession in liver, kidney, heart, lung, intestine, brain, spinal cord and spleen. The venus congession was explained by Brenneisenr et al. (1984) in human that *Khat* caused increase in blood pressure and heart rate. Also, Al-motarreb et al. (2002) in human recorded a direct vasoconstrictor action of *Khat* which leads to increase the amount of venous blood. our results were supported by Alsalahi et al. (2012) in adult rat and Wafaa and Olfat (2013) in adult rabbit that *Khat* caused vascular congession and dilation in central vein of liver.

Because of unavailability of the literatures about the degeneration of some neurons of brain and spinal cord and cardiac myocytes in human caused by *Khat* and its chemical group of cathinone (Choi, 1988; Bergeron, 1995).

Myocardial degeneration may be due to *Khat* that *Khat* caused increase in blood pressure and heart rate as mentioned by Brenneisenr et al. (1984) in human the increases heart rate leads to cellular edema and degeneration. Increased workload may result in zones of relative hypoxia in the heart leading to myocardial degeneration and necrosis as the workload-induced stress (Chang and Foote, 1973). The myocardial degeneration may be also direct toxicity of *Khat* on myocyte like the toxict effect of many plants like coffe senna as mentioned by Jones et al. (1997) and Jubb et al. (1993).

CONCLUSION

The current study shows that prenatal exposure of *Khat* during the period of organgenesis in rabbit induced numerous pathological lesion in defferent internal organs including liver, kidney, brain, spinal cord, spleen, intestine, heart and lung. These finding reflect adverse effect of *Khat* on the embryo and fetus.

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CONFLICT OF INTEREST

The authors declared no conflict of interests.

AUTHORS' CONTRIBUTION

El-Nahla, Hassan designed the plan of work. All authors share in fulfillment of the work and were involved in writing up of the manuscript as well as refined English of the draft. Finally, the manuscript was read and commissioned by all authors.

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