

Toxic effects of fumonisin B1 in mice and its detoxification by cabbage seed extract

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Abstract:

The main objective of this research study the toxic effects by fumonisin B1 (FB1) in mice by studying on haematological parameters (Hb, PCV, RBC, WBC and DWBC), mitotic index and histopathological changes of liver and kidney. The following results which obtained from the current research:

The effects of FB1 alone on blood picture were caused significant decrease in Hb, PCV and RBCs count. Total WBCs, neutrophil and eosinophil counts were found to be increased significantly; lymphocytes and basophils were decreased significantly and monocytes were not affected significantly, whereas, no significant differences were noticed in mice treated with cabbage seed extract alone or plus FB1. The results of toxic effects on cytogenic study showed a significant decrease in mitotic index for mice treated FB1 alone, but there were no significant in mice treated with FB1 in combination with cabbage seed extract and no significant difference between mice treated cabbage seed extract alone in comparison with control group. While the histopathological changes, In liver: Showed congestion of central vein with vacuolation of hepatocyte, apoptotic cells and accumulation of inflammatory cells in necrotic areas, also the formation of mitotic figure and single necrotic hepatocyte in group which treated with FB1 alone, whereas mice treated with FB1 in combination with cabbage seed extract showing regeneration most hepatocytes normal structure. The histopathological study of kidney: Showed atrophy of glomerular tuft, degeneration and necrosis of epithelial lining of proximal and distal convoluted tubules with congestion of blood vessels and wide areas of necrosis in parenchyma, in addition the presences of hyaline casts in urinary tubules due to urinary failure in mice treated with FB1 alone, while in mice treated FB1 plus cabbage seed extract showed just congestion and cuffing in mice treated with FB1 in combination with cabbage seed extract which indicate that the cabbage seed extract has a protective effects.

keyword: *Fumonisin B1, Cabbage, Detoxification, Fumonisin toxicity.*

Introduction:

Mycotoxins are a structurally diverse group of mostly small molecular weight compounds that contaminate the whole food chain, from the harvested products to the plate of consumers (1). Mycotoxins occur sporadically both seasonally and geographically, environmental factors such as light, temperature, pH and water activity (aw), either as single factors or in combination are effect on mycotoxin production (2, 3). Fumonisin are a group of toxic metabolites produced by fungi of the genus *Fusarium*, especially *F. verticillioides* and *F. proliferatum*, these species have been found in several agricultural products worldwide, especially in maize (4). Among the fumonisins identified so far, fumonisin B1 (FB1) is considered

to be the most toxic and the most abundant, representing 70% of the total concentration in naturally contaminated food and feeds, followed by fumonisins B2 (FB2) and B3 (FB3) (5). Different toxic effects of FB1 were evaluated in many kinds of animals, such as Equidae, swine, rat, mice, rabbit, chicken and others. Ingestion of FB1 causes a variety of toxicosis in animals, including leukoencephalomalacia in horses, porcine pulmonary edema, and hepatocarcinoma, liver disease in rats, body weight and average daily weight gain have been shown to decrease in chicks in parallel with increasing dietary FB1 (6, 7). Hepatic and renal toxicity can be observed in several species, including rats, broilers, turkeys and ducks, additionally, the occurrence of FB1 in foods has been statistically associated with a high incidence of human esophageal cancer (8). On the basis of existing toxicological evidence, the International Agency for Research on Cancer (IARC) has declared that *F. verticillioides* toxins are potentially carcinogenic to humans

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(Group 2B carcinogens) (9). Structurally, fumonisins resemble sphingolipids and can alter sphingolipid biosynthesis suggesting that sphingolipid alterations play an important role in disease and carcinogenesis in DNA damage. FB1 disrupts the sphingolipid metabolism on many types of cells and tissues through the inhibition of ceramide synthase, a key enzyme in sphingolipid biosynthesis and reacylation of free sphingosine (10).

Material and Methods:

Maize Samples: Samples of maize were randomly collected from Baghdad city markets.

Isolation of *Fusarium verticillioides*: Isolation and identified on potato dextrose agar (PDA) according to (11).

Production of Fumonisin B1: According to the procedure by (12) used rice grains as a substrate for Fumonisin B1 production.

Extraction and Cleanup of Fumonisin B1: The procedure described by (13).

ELISA Kit Analysis: The *Fusarium verticillioides* mycotoxin was analyzed by using (Enzyme Linked Immune Absorbent Assay) ELISA kit for the quantitative determination of Fumonisin B1 in maize and grains from DIAGNOSTIC AUTOMATION, INC.USA.

Laboratory Animals: Sixty mice were used and maintained at the animal house laboratory in Iraqi center of cancer and medical genetic researches. The median lethal dose (LD50) of FB1 in mice described by (14) about (50mg/kg body weight) equivalent 1.25 mg/ mouse and about (5mg/kg body weight) for cabbage seed extracts was literature based (15) and giving orally for six months repeated every 48h. of fumonisin

B1 toxin and cabbage seed extracts. Mice were divided in to four groups each one contain 10 mice as follows: Group1: control mice (untreated), Group2: orally treated with crude toxin (FB1), Group3: orally treated with crude toxin (FB1) plus cabbage seed extract, Group4: orally treated with cabbage seed extract alone as control.

Cabbage Seed Extraction: According to (16).

Blood Collection: The blood samples were collected at the end of experiment from the groups according to (17).

Cytogenetic study (Mitotic Index): The sacrificed mice from each group of toxic study at the end of experiment were used for measuring mitotic index detected according to Allen method (18), used femur bone marrow.

Preparation of Tissues for Histopathological Studies: Were done according to (19).

Statistical Analysis: Statistical package for social sciences (SPSS) software version 16 was used for performing statistical analysis (20).

Results:

Three isolates of *Fusarium Verticillioides* were isolated from samples of maize were appeared macroscopically white in color (Fig.1). Macroconidia appeared microscopically long, straight. Apical cell morphology is curved. Microconidia were club shaped and usually no septate and as long chain (Fig.2). Three isolates of *Fusarium Verticillioides* were tested for FB1 production on rice medium, and the result demonstrated that the rice were a good medium for FB1 production and there was an obvious diversity among the isolates in FB1 production by using ELISA technique as in (Table 1).

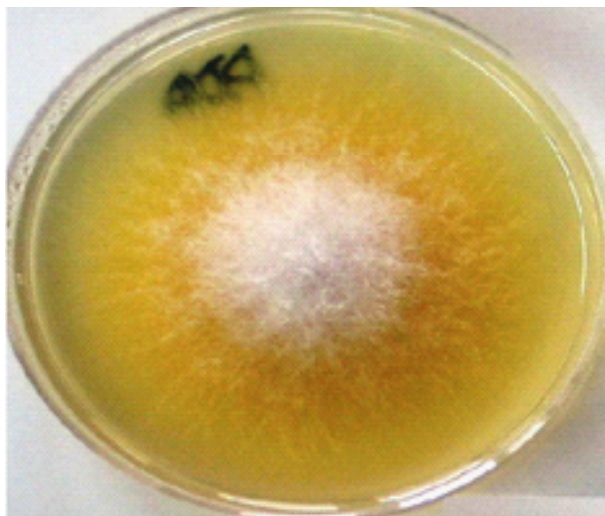


Figure (1) Macroscopically appearance of *Fusarium Verticillioides* on PDA at 7 days.



Figure (2) Microscopically appearance of *Fusarium Verticillioides* by using Lacto phenol Cotton blue Stain (X 40).

Table (1) The levels of FB1 (ng) detection by ELISA technique

Fusarium verticillioides isolates	Levels of FB1(ng/g)
Fusarium verticillioides (1)	More than 25 ng
Fusarium verticillioides (2)	25 ng
Fusarium verticillioides (3)	10 ng

The results of (MI) mitotic index in mice showed a significant decrease for mice treated FB1 alone when compared to mice untreated (control) and cabbage seed extract alone.

There were significant between mice treated FB1 alone

and mice treated with FB1 in combination with cabbage seed extract and no significant between mice treated with cabbage seed extract alone in comparison with control group (Table 2

Table (2) Mitotic index (%) in experimental mice (mean \pm SE).

Mitotic index %	Groups			
	Control	FB1alone	FB1+Cabbage seed extract	Cabbage seed extract alone
	^a 0.03 \pm 0.7	0.01 ^b \pm 0.3	^a 0.01 \pm 0.7	^a 0.02 \pm 0.8

Within each raw, values indicated by the same letter are not significantly different ($p \leq 0.05$).

The effects of fumonisin B1 on blood picture indicated that FB1 alone caused a significant decrease in Hb, packed cell volume (PCV %) and RBCs (Table 3), whereas, no significant differences were noticed in mice treated with cabbage seed extract alone or plus FB1 when compared with control. Total WBCs, neutrophil and eosinophil counts were found to be

increased significantly, lymphocytes and basophils were decreased significantly and monocytes were not affected significantly in the mice treated with FB1 alone (Table 4), whereas mice treated with cabbage seed extract alone or plus FB1 were comparable with the controls regarding the WBCs.

Table (3) Effect of cabbage seed extract on Hb, PCV and RBCs in mice given orally FB1 (50mg/kg body weight) for 6 months(mean \pm SE).

Parameter	Groups			
	Control	FB1alone	FB1+Cabbage seed extract	Cabbage seed extract alone
Hb gm/dl	^a 0.12 11.55 \pm	^b 1.37 \pm 8.4	^a 0.87 \pm 11.22	^a 0.96 \pm 11.46
% PCV	^a 0.31 37.40 \pm	^b \pm 1.14 12.32	^a 0.43 \pm 36.78	^a 0.89 \pm 37.36
RBC mm3/106	^a 0.24 \pm 7.48	^b 1.10 \pm 5.61	^a 0.64 \pm 7.10	^a 0.78 \pm 7.50

For each parameter, values indicated by the same letter are not significantly different ($p \leq 0.05$).

Table (4) Effect of cabbage seed extract on WBCs and differential count of leucocytes in mice given orally FB1 (50mg/kg b.w.) for 6 months (mean \pm SE).

Parameter	Groups			
	Control	FB1alone	FB1+Cabbage seed extract	Cabbage seed extract alone
WBCs 109/L	^a 0.1 \pm 7.05	^b 0.40 \pm 10.82	^a 0.30 \pm 7.24	^a 0.10 \pm 7.08
%Lymphocyte	^a 0.12 \pm 52.13	^b 0.22 42.01 \pm	^a 0.11 \pm 51.38	^a 0.21 \pm 52.10
% Neutrophil	^a 0.22 \pm 32.32	^b 0.21 \pm 43.36	^a 0.13 \pm 32.43	^a 0.20 \pm 32.33
% Monocytes	^a 0.16 \pm 8.68	^b 0.13 \pm 8.31	^a 0.30 \pm 8.64	^a 0.17 \pm 8.66
% Eosinophil	^a 0.06 \pm 3.40	^b 0.04 \pm 3.85	^a 0.05 \pm 3.35	^a 0.04 \pm 3.43
% Basophils	^a 0.02 \pm 3.40	^b 0.03 \pm 2.44	^a 0.01 \pm 3.68	^a 0.02 \pm 3.48

Within each raw, values indicated by the same letter are not significantly different ($p \leq 0.05$).

Microscopical examination of liver and kidney of mice treated orally FB1 (50 mg/kg body weight) and cabbage seed extract (5mg/kg body weight) showed the histopathological changes. Effects of fumonisin B1 on liver: Liver section of control untreated mice (Fig. 3) showed normal tissue (central vein surrounded with hepatic cord), while the mice treated with FB1 alone showed congestion of central vein with vacuolation of hepatocyte, apoptotic cells and accumulation of inflammatory cells in necrotic areas (Fig. 4) also (Fig. 5) show formation of mitotic figure and single necrotic hepatocyte. As shown in (Fig. 6), liver section from mice treated with FB1 in combination with cabbage seed extract showing regeneration of most hepatocytes normal structure. While the liver section (Fig. 7) of mice treated with cabbage seed extract alone showed normal tissue.

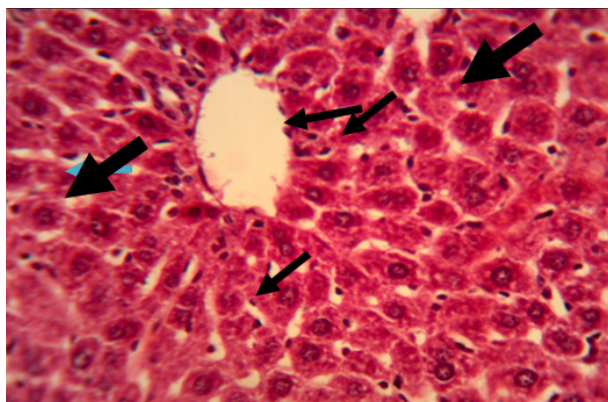


Figure (3) Histopathological section of liver for untreated mouse (control) showing central vein (↑) surrounded with hepatic cord (↑) (H&E X 200).

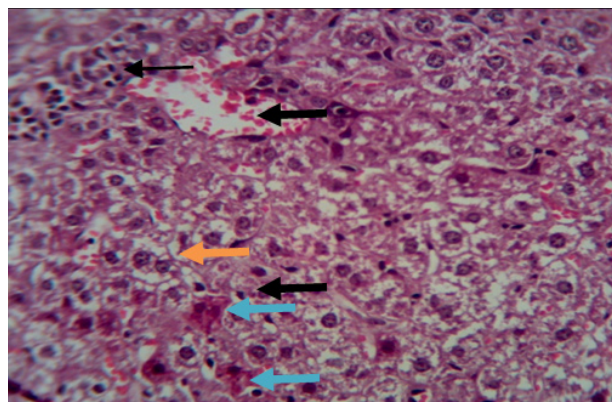


Figure (4) Histopathological section of liver for treated mouse FB1 alone showing congestion of central vein (↑) with vacuolation of hepatocyte (↑) and apoptotic cells (↑) and accumulation of inflammatory cells in necrotic areas (↑) (H&E X 200)

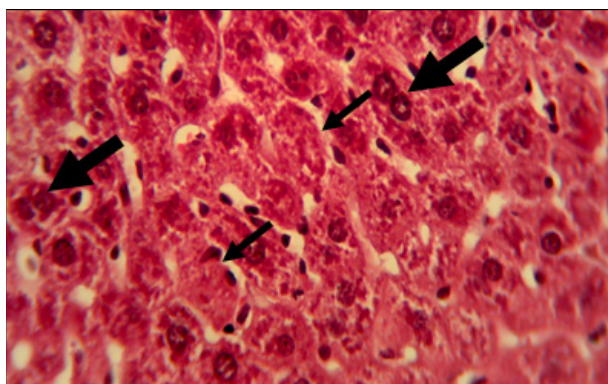


Figure (5) Histopathological section of liver for treated mouse FB1 alone showing single necrotic hepatocyte (↑) and mitotic figures of hepatocyte (↑) (H&E X 400).

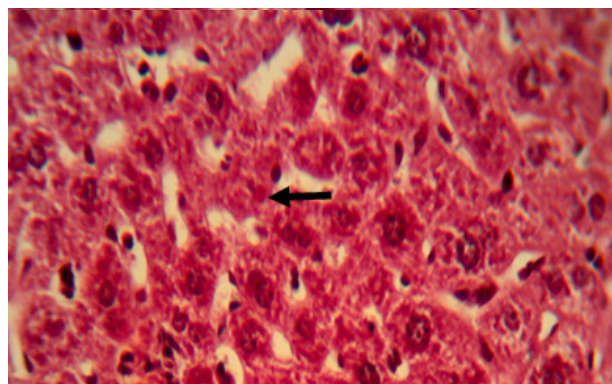


Figure (6) Histopathological section of liver for treated mouse FB1 + cabbage seed extract showing regeneration (↑) most hepatocytes normal structure (H&E X 400).

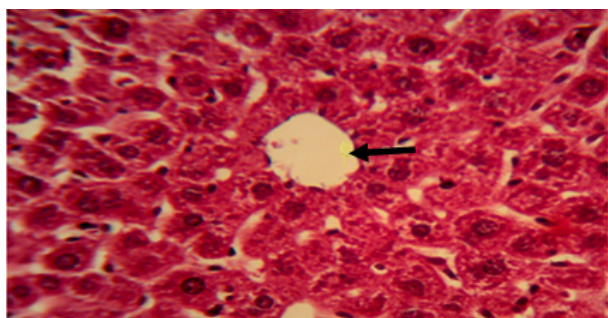


Figure (7) Histopathological section of liver for treated mouse cabbage seed extract showing normal hepatocyte central vein surrounded by hepatic cord (↑) (H&E X 400).

Effects of fumonisin B1 on kidney: Kidney section from control mice (Fig. 8) shows normal renal tubules, normal glomeruli and normal epithelial cells lining of the renal tubules. While kidney section from mice treated with FB1 alone (Fig. 9) revealed atrophy of glomerular tuft, degeneration and necrosis of epithelial lining of proximal and distal convoluted tubules with congestion of blood vessels

and wide areas of necrosis in parenchyma (Fig. 10) in addition for presences of hyaline casts in urinary tubules (Fig. 11) due to urinary failure. In (Fig. 12) show just congestion and cuffing in mice treated with FB1 in combination with cabbage extract. While kidney section from mice treated with cabbage seed extract alone show no abnormal changes (Fig. 13).

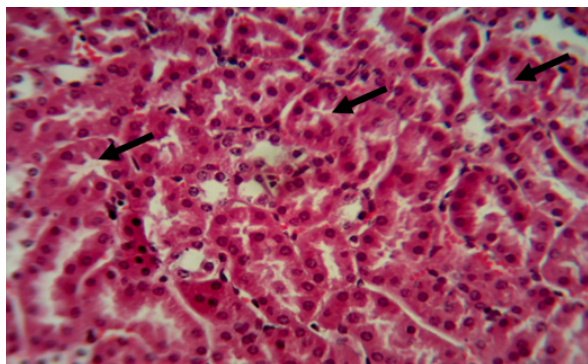


Figure (8) Histopathological section of kidney for untreated mouse (control) showing normal tubules (↑) (H&E X 400).

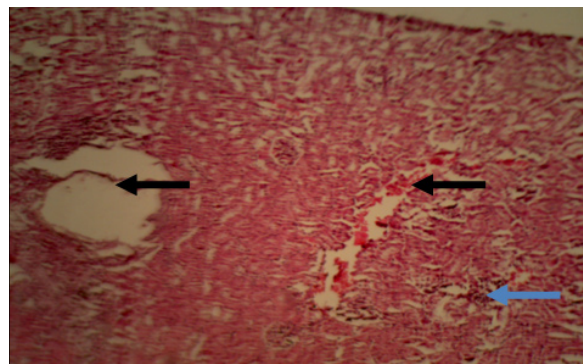


Figure (9) Histopathological section of kidney for treated mouse FB1 alone showing large area of necrosis (↑) infiltrated with inflammatory cell (↑) (H&E X 200)

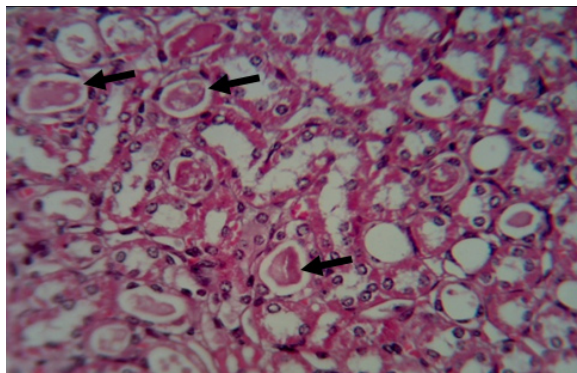


Figure (10) Histopathological section of kidney for treated mouse FB1 alone showing hyaline casts in the lumen of urinary tubules (↑) (H&E X 400)

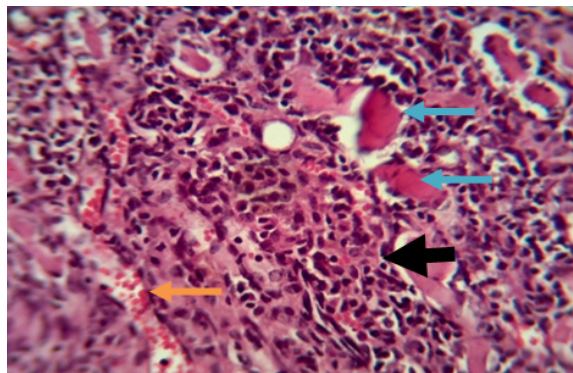


Figure (11) Histopathological section of kidney for treated mouse FB1 alone showing hyaline casts in the lumen of urinary tubules (↑), infiltrated with inflammatory cells (↑) and congestion of blood vessels (↑) (H&E X 400).

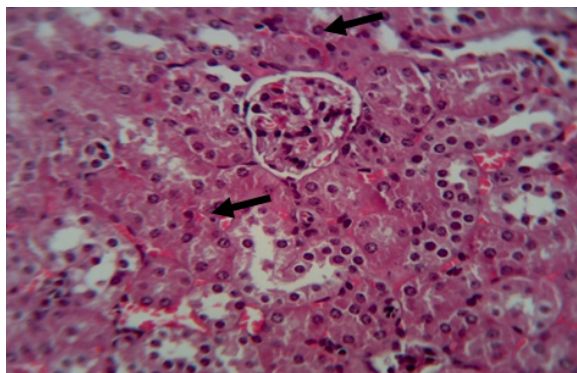


Figure (12) Histopathological section of kidney for treated mouse FB1 + cabbage seed extract showing congestion of blood vessels and glomerular capillaries (↑) (H&E X 400).

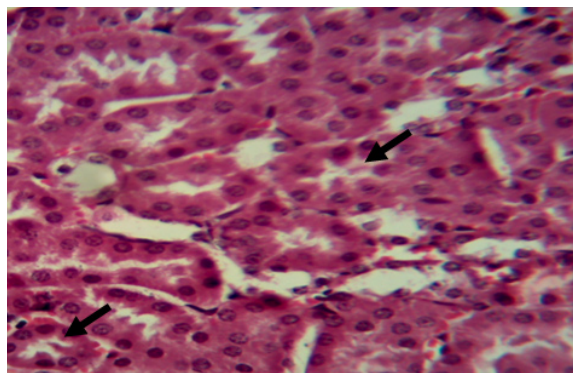


Figure (13) Histopathological section of kidney for treated mouse cabbage seed extract alone showing normal tubules (↑) (H&E X 400).

Discussion :

1. *Fusarium Verticillioides* is one of the most fungal species infect maize grains due to that maize have essential nutrients for growth of fungi, also the bad environmental condition during the storage may play an important role in growth of fungi and this results which in accordance to the finding of the literatures (21, 22) in Iraq, (23, 24) in Iran, (25) in Argentina, (26) in Romania, (27) in Copenhagen, (28) in Pakistan and (29) in Serbia. About 25% of the world storages of cereals are affected by moulds every year. The contamination of corn grains by fungi is to a large extent, determined by climatic parameters, particularly temperature and humidity, although moulds thus belong to the natural flora of maize, their wide occurrence is harmful because they may reduce the quality of maize (30). The variation for fumonisin production on rice substrates were high, progeny phenotypes in crosses number 57, 65, and 72 were sufficiently distinct to test the hypothesis that fumonisin biosynthesis can be controlled by a mutation in a single gene or in a group of closely linked genes (31, 32) The cytological observation reveals that FB1 are capable of reducing the (MI%), this result is in line with data of (33) which indicate that FB1 is capable of preventing the cell cycle in renal cells of the African green monkey, and also with (34) that noted the reduction in the values of (MI%) of bovine lymphocytes cultures. The (35) revealed that the FB1 and aflatoxin B1 causes blocking of cell division. The present results indicated that FB1-treated mice showed hematological picture typical to those reported during fumonisin toxicity (36). Also in this study was observed a decrease in hemoglobin concentration, PCV% and total RBCs resulting in normocytic normochromic anemia. This decrease in the hematopoietic parameters may be due to many factors, such as inhibition of protein synthesis as indicated by lower serum albumin and serum total proteins (37, 38). Previous reports indicated that FB1 decreases the total iron binding

capacity (39) and affects the metabolism of minerals such as Cu and Zn (15). Moreover, the results of (40), who stated that FB1 causes a depletion of lymphoid cells, supported our findings regarding the lymphocytopenia and monocytopenia in fumonisin-treated mice. There was a significant increase in the WBCs count, which mainly consisted of neutrophil. These increases in WBCs and the percentage of neutrophil suggested that the toxin is eliciting an inflammatory response, and in turn causes alterations in bone marrow and the function of the immune system (41). When compared the results of histopathological examination on liver with literatures showed the (42) who observed necrosis and hepatocytes undergo vacuolation, in addition to (43, 36) those reported that FB1 was induce liver lesions in rats, rabbits, horses and pigs which consist of one or more of the following features; single cell necrosis, hepatocellular cytoplasmic vacuolation, variation in nuclear size and staining properties, pyknosis, fibrosis and bile duct proliferation, mild to marked hepatocellular hyperplasia, mitotic figures, foci of cellular alteration. While (36) who clearly noticed that the cabbage seed extract has a protective role against FB1-induced liver damage as indicated by the improvement of the histological picture in the liver tissues. But the results of histopathological changes in kidney appears like the (19, 45) those clearly noticed that FB1 have adverse effects on the various body organs and systems (e.g. hepatoxins and nephrotoxins) and nephrotoxicity has been reported in several species, and the kidney appears to be the most sensitive target organ (19). While mice treated with FB1 in combination with cabbage extract those clearly noticed that the cabbage extract has a protective effects (36) may due to the radical scavenging activity of its components (glycosinolate). From this study we can conclude that fumonisin B1 caused pathological changes in the liver, kidney, brain and cabbage has a protective effect against the toxicity of FB1 and these protective effects may be due to the active components.

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التأثير السمي للفيومونيسين ب1 في الفئران وازالة سميتها بواسطة مستخلص بذور اللهانة

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الخلاصة

هدف البحث دراسة التأثير السمي للفيومونيسين ب1 في الفئران من خلال دراسة الصورة الدموية (خضاب الدم، حجم الخلايا المرصوصة، عدد كريات الدم الحمراء، كريات الدم البيض و العد التفرقي لخلايا الدم البيض)، معامل الانقسام لخلايا نخاع العظم مع دراسة التغيرات النسيجية لكل من الكبد، الكلية. تم الحصول على النتائج التالية:

أظهرت نتائج تأثير الفيومونيسين ب1 لوحده على الصورة الدموية قلة معنوية ($P \leq 0.05$) على كل من خضاب الدم، حجم الخلايا المرصوصة و عدد كريات الدم الحمراء. ولوحظ زيادة معنوية ($P \leq 0.05$) في عدد كريات الدم البيض الكلي، خلايا العدلة و الخلايا الحمضة وقلة معنوية ($P \leq 0.05$) للخلايا اللمفاوية والقاعدية وعدم تأثر خلايا النواة معنويًا، ولم تلاحظ اختلافات معنوية في الفئران المعاملة بالفيومونيسين ب1 و مستخلص بذور اللهانة والمعاملة بمستخلص بذور اللهانة لوحده عند مقارنتها بمجموعة السيطرة. بينت نتائج التأثير السمي على معامل الانقسام الخلوي قلة معنوية ($P \leq 0.05$) في الفئران المعاملة بالفيومونيسين ب1 لوحده بينما لم تظهر اي فروقات معنوية في المجموعتين المعاملتين بالفيومونيسين ب1 و مستخلص بذور اللهانة والمعاملة بمستخلص بذور اللهانة لوحده عند مقارنتها بمجموعة السيطرة.

أما التغيرات النسيجية التي ظهرت في كبد الفئران المعاملة بالفيومونيسين ب1 لوحده هي احتقان الوريد المركزي وتقجي سايتوبلازم الخلايا الكبدية وموت الخلايا المبرمج مع تجمع الخلايا الالتهابية في المناطق المتتخرة وتكون اشكال الانقسام الخلوي وتنخر احادي الخلية، اما المجموعة التي عوملت بالفيومونيسين ب1 و مستخلص بذور اللهانة فقد اظهرت عودة الخلايا الكبدية للنسيج الطبيعي. بينما اظهرت المقاطع النسيجية للكلية ظمور في الكبيبة، تنكس وتنخر الخلايا الظهارية المبطنة للنببيات الكلوية مع احتقان الاوعية الدموية م توسع المناطق المتتخرة بأضافة لتكون القوالب الشفافة في النببيات البولية نتيجة الفشل الكلوي في الفئران المعاملة بالفيومونيسين ب1 لوحده، بينما في المجموعة المعاملة بالفيومونيسين ب1 و مستخلص بذور اللهانة اظهرت التغيرات النسيجية احتقان الاوعية الدموية للكبيبة الذي يدل على التأثير الفعال لمستخلص بذور اللهانة.