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Article

Evaluating of the Protective Effect of Vitamin E Against the Histological and Biochemical Effects of Methamphetamine on the Rat Liver

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Abstract: Methamphetamine is a powerful central nervous system stimulant belonging to the amphetamine class, it increases the release of dopamine and norepinephrine, causing feelings of energy and euphoria. It is considered a highly addictive substance, and its use is associated with psychiatric and neurological disorders, as well as cardiovascular and immune system diseases. Chronic use can also lead to changes in brain function that affect memory and behavior, making it a significant health and social problem. The study aims to evaluate the protective effect of vitamin E against the toxic effects of methamphetamine on the histological structure of the liver in male rats and on liver function through the analysis of liver enzymes (ALT, AST, ALP) over different time periods. This study included 28 male Sprague-Dawley rats, divided into 7 groups of 4 animals each. The first group served as the control group and was fed a standard diet and water throughout the experiment. The second group was administered methamphetamine at a concentration of 0.1 mg/kg for 15 days, in addition to water and food. The third group was administered methamphetamine at a concentration of 0.1 mg/kg for 30 days, The fourth group was administered vitamin E at a concentration of 0.1 mg in two drops for 15 days; the fifth group was administered vitamin E at a concentration of 0.1 mg in two drops for 30 days; the sixth group was administered methamphetamine at a concentration of 0.1 mg/ kg along with vitamin E as a protective agent at a concentration of 0.1 mL for 15 days, and the seventh group was administered methamphetamine at a concentration of 0.1 mg/kg along with vitamin E at a concentration of 0.1 mL for 30 days, Microscopic examination of the tissue sections revealed numerous histological changes in the liver, including cellular necrosis and degeneration accompanied by hepatocyte hypertrophy, with some nuclei appearing enlarged and surrounded by cytoplasmic vacuoles, as well as hemorrhage and significant infiltration of inflammatory cells, as well as detachment of endothelial cells from the central vein lining and an increase in the number and size of Kupffer cells. Biochemical test results for blood samples measuring liver function showed abnormalities in ALT and AST levels, leading to a decrease that persisted as the duration of treatment increased. This decrease in activity, despite cellular swelling, may be attributed to the depletion of enzymatic reserves within hepatocytes or to the inhibition of protein synthesis resulting from the severe oxidative stress caused by the drug; However, the alkaline phosphatase (ALP) enzyme

showed a sharp increase with prolonged treatment duration, as elevated ALP levels are a significant indicator of obstruction or irritation of the bile ducts resulting from inflammation, This study concludes that the use of methamphetamine for varying periods of time causes liver damage that becomes more severe over time, progressing from minor structural abnormalities (15 days) to cellular necrosis, complete tissue death, and blood clots (30 days). Vitamin E, on the other hand, provides good protection during the short-term period (15 days) by improving liver function and reducing enzyme levels (AST, ALT); however, this efficacy diminishes in the face of chronic toxicity over the long term.

Keywords: Methamphetamine, Vitamin E, Rat liver, Hepatotoxicity, Hepatocellular damage, Liver toxicity.

Introduction

Methamphetamine is a potent central nervous system stimulant and belongs to the amphetamine class of drugs, which are highly addictive and can cause a variety of toxic effects in different organs of the body. Scientific interest in studying its pathological effects has increased due to the growing prevalence of its use and the associated serious structural and functional disorders. Recent studies indicate that chronic exposure to methamphetamine leads to cellular and metabolic disorders associated with oxidative stress, inflammation, and increased free radical production, which negatively impacts tissue integrity and the functions of various organs [1].

The liver is one of the organs most vulnerable to the toxic effects of drugs and chemicals, given its essential role in metabolism and detoxification. Numerous studies have shown that methamphetamine causes mitochondrial dysfunction and increased production of reactive oxygen species (ROS), leading to liver cell damage and pathological changes in liver tissue. Chronic exposure to methamphetamine is also associated with inflammatory responses and oxidative stress, which may contribute to cellular degeneration, necrosis, and congestion in various tissues [2].

Assessing liver function is an important method for detecting the extent of liver damage caused by exposure to toxic substances, as elevated levels of liver enzymes such as ALT, AST, and ALP indicate damage to the cell membranes of liver cells and the leakage of their contents into the bloodstream. Histological examination also provides direct evidence of pathological changes in liver tissue, such as cellular degeneration, inflammatory infiltration, congestion, and necrosis [3].

Therefore, this study aimed to evaluate the toxic effects of methamphetamine on the histological structure of the liver in male rats, to measure changes in liver function by analyzing liver enzymes (ALT, AST, ALP) in serum, comparing the severity of histological and biochemical changes among the different experimental groups, investigating the protective role of vitamin E in reducing methamphetamine-induced liver damage, and analyzing the effect of exposure duration (15 days and 30 days) on the degree of liver damage.

2- Material and methods

2-1 Preparation of animals

In this study, 28 healthy male Sprague-Dawley rats, with a weight rate (150-200)g and aged (2-4) months, were in good health and were subjected to appropriate and stable environmental conditions (25 ºC) and provided with nutrition and water.

Study design

Rats used in the study were randomly divided into six groups of experiments, as well as the control group, and the weights of each group were taken into account as much as possible before the start of the study.

Groups

A total of 28 rats were randomly assigned to seven groups, with four rats in each group, as follows:

1- The first group (G1), which served as the control group: This group consisted of 4 rats that were given their regular diet as well as sterilized water daily for 30 days.

2- The second group (G2): This group consisted of 4 rats that were given food and water daily and administered methamphetamine orally after dissolving it in 1 mL of distilled water at a concentration of 0.1 mg/kg per animal for 15 days.

3- The third group (G3): This group consisted of 4 rats, which were given food and water daily and administered methamphetamine orally after dissolving it in 1 mL of distilled water at a concentration of 0.1 mg/kg per animal for 30 days.

4- The fourth group (G4): This group consisted of 4 rats, which were given food and water daily and administered vitamin E at a concentration of 0.1 mg orally in two drops per animal for 15 days.

5- The fifth group (G5): This group consisted of 4 rats, which were given food and water daily and administered vitamin E at a concentration of 0.1 mg orally (two drops per animal) for 30 days.

6- The sixth group (G6): This group consisted of 4 rats, which were given food and water daily and administered methamphetamine after dissolving it in 1 mL of distilled water at a concentration of 0.1 mg/kg per animal orally, along with vitamin E at a concentration of 0.1 mL for 15 days.

7- The seventh group (G7): This group consisted of (4) rats, which were given food and water daily and administered methamphetamine orally after dissolving it in (1) mL of distilled water at a concentration of (0.1) mg/kg per animal, along with vitamin E at a concentration of (0.1) mL, for a period of (30) days.

2-2 Histological Sections Preparation

The tissue sections was prepared in histology Lab., college of Science, Tikrit University, and prepared the microscopical sections according the method of Al Hajj (2010), which include the following processes:

The collected tissues segments of liver was taken and immersed in 10 % formalin for 24 hours followed by immersion in graded series of alcohol from 70, 80, 90 and 100 %, then clearing with xylene and embedded in paraffin wax at 60ºC. Blocking of the samples were done and the sectioning were performed using a rotary microtome. The thickness of the sections were 6 μm. The tissue sections after application of staining with Hematoxylin and Eosin (H&E) were mounted on the slides using D.P.X and covered by cover slides. The slides were examined using light microscope and photographed by manipulated camera prepared for this purpose.

As for the measurement of biochemical tests of liver function (ALT, ALP, AST) using the UV-Vis Double Beam Spectrophotometer.

3-Results and Discussion

3-1- The effect of the drug Methamphetamine and the role of vitamin E as a protective agent on the histological structure of the liver.

Microscopic examination of the hepatic lobules hepaticlobules in the liver tissue showed that each lobule contained in its center the central vein central vein devoid of blood, into which the blood sinusoid sinusoids pour at its periphery and contain the cells of the kupffer cells, and those sinusoids are surrounded by rows of polygonal polygonal hepatocytes in the form of radial columns arranged and each cell has a central spherical in addition, the central vein has a wide lumen lined with simple squamous epithelial cells, simple squamous epithelial cells, are endothelial cells endothelial cells based on the basement membrane basement membrane, as shown in figures (1), (2). Histological sections of the rat liver treated with methamphetamine for 15 days also showed marked hypertrophy of Hepatocellular hypertrophy hepatocytes with their agglutination and loss of normal architectural dysarray, the nuclei of many cells also looked pale chromosomal Nuclear hypochromasia, indicating degenerative changes Degenerative changes and branching of Bile ducts were observed Bale ductules lined with Cubic epithelial cells and surrounded by an inflammatory infiltrate of white blood cells in

the Portal Portal inflammatory infiltration area, vascular vascular congestion was also found, represented by the fullness of both the central vein and the portal vein In addition to the decomposed blood, hepatic sinusoids appeared in the hepatic sinuses, narrow-Lumen Sinusoidal narrowing and containing erythrocytes with a marked increase in Kupffer cell activation cells, as shown in figures (3),(4). While the results of histological sections of the rat liver treated with methamphetamine for 30 days showed a pronounced hypertrophy of Hepatocellular hypertrophy hepatocytes with some nuclei appearing spherical and enlarged Nuclear inclusion, while the majority of nuclei appeared with a ghostly Ghost-like nuclei appearance indicating degenerative or necrotic changes, stenosis of the hepatic sinusoidal narrowing was also observed accompanied by the presence of hypertrophied and dark-pigmented activated Kupffer cells, a partial loss of the integrity of the liver capsule disruption with degeneration of neighboring hepatocellular degeneration was also observed, while in the Portal Portal area there was The branch of the portal vein appeared congested and filled with blood Portal vein congestion along with the branches of the Bile ducts Bile ductules surrounded by a dense inflammatory infiltrate formed by white blood cells and macrophages .Inflammatory infiltration with macrophages, as shown in figures (5),(6) .

The results of histological sections of the rat liver treated with vitamin E for 15 days also showed the presence of polygonal hepatocytes on the liver, where some cells appeared to be separated from each other, while others appeared in the form of Cell clustering cellular aggregates that included hypertrophied Hepatocellular hypertrophy hepatocytes along with other cells together, and the appearance of some cells was observed with a honeycomb pattern nuclear hypochromasia, the network of hepatic sinusoids hepaticsinusoids seemed to be filled with enlarged Kupffer cell activation cells, and a wide portal vein branch appeared in the Portal Portal area The Lumen is lined with endothelial lining endothelial cells, and the presence of Bile ductules bile duct branches surrounded by infiltrates of Inflammatory cell infiltration white blood cells is also observed, as shown in figures (7) ,(8). The results of histological sections of the rat liver treated with vitamin E for 30 days also showed the presence of necrosis and degeneration in hepatocellular necrosis and degeneration accompanied by an oversize of hepatocellular hypertrophy cells, where thickening of some nuclei of Nuclear pyknosis was observed while other nuclei appeared hypertrophied, with cytoplasmic explosions around the cytoplasmic vacuolation nuclei, enlarged and dark-pigmented Kupffer cell activation cells also appeared inside some hepatic sinusoidal Hepaticsinusoids. As for the Portal Portal area, the portal vein branch appeared free of blood, along with the presence of Bile ductules bile duct branches lined with simple cubic cells, in addition to the hepatic artery hepaticarter branch, these structures were surrounded by infiltration of Inflammatory cell infiltration white blood cells, as shown in figures (9) ,(10). While the results of histological sections of the rat liver showed treatment with methamphetamine and vitamin E for 15 days, the liver body showed the presence of polygonal hepatocytes with spherical nuclei with faded chromatin pigments, the appearance of hepatocytes with a honeycomb pattern-like pattern was also observed, indicating a disturbance in the normal histological structure. Hepatic sinusoids also appeared regular in the form of a branched network of vascular channels, which contained enlarged and dark-pigmented Kupffer cells, while some pockets appeared wide-lumened and filled with oversized Kupffer cells, an indication of their activation., The occurrence of dissection and partial loss of the liver capsule capsule disruption accompanied by dense infiltration of white blood cells inflammatory cell infiltration between hepatocytes was also observed, along with the appearance of degenerative changes degenerative changes in a number of hepatocytes adjacent to the areas of inflammation, as shown in figures (11),(12).

The results of histological sections of the rat liver treated with methamphetamine and vitamin E for 30 days also showed extensive degeneration of hepatocellular degeneration in the liver with the presence of cytoplasmic vacuolation around the cytoplasmic vacuolation nuclei, thickening of some nuclei of Nuclear pyknosis with the disappearance of nuclei in other cells of Nuclear loss, an indication of necrotic changes. The hepatic sinusoids appeared as channels that contained some degenerated hepatocytes as well as Kupffer cells. As for the Portal Portal area, the portal vein appeared congested and contained multiple thromboses with the presence of some white blood cells, and a thickening of the basement membrane was observed in the Basement membrane thickening based on

endothelial endothelial cells. Branches of Bile ductules bile ducts surrounded by inflammatory infiltration of white blood cells inflammatory infiltration also appeared, in addition, there was a branch of the hepatic artery Hepaticartery, and periportal edema inflammatory edema was observed around the portal vein. Degenerated hepatocytes with vacuolated cytoplasm and hypertrophied nuclei also appeared in the vicinity of the portal zone, as shown in figures (13),(14).

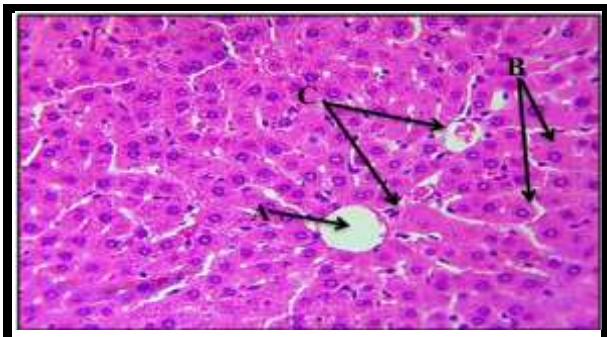

Figure (1): A histological section of a rat liver from the control group, showing a hepatic lobule with a central vein (A), rows of polygonal hepatocytes with spherical nuclei (B), and blood sinusoids containing Kupffer cells (C) (H&E, 40×).

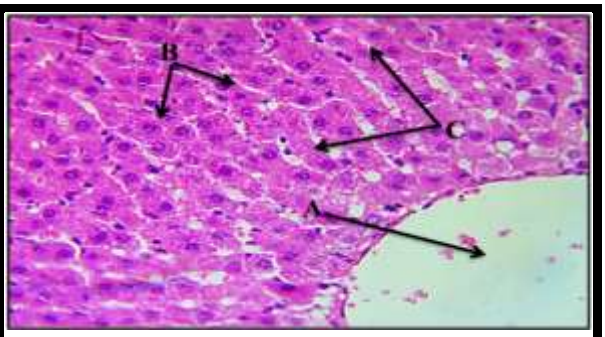

Figure (2): A histological section of a rat liver from the control group, showing the central vein of the liver (A), rows of hepatocytes (B), and blood sinusoids containing Kupffer cells (C) (H&E, 40×).

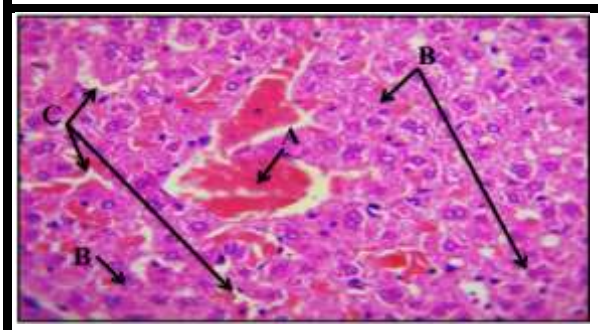

Figure (3): A histological section of a rat liver from the second group treated with methamphetamine at a concentration of 0.1 mg/kg for 15 days, showing - Central vein with a blood clot (A) Hepatocytes showing hypertrophy (B) Narrow hepatic sinusoids (C) (H&E, 40×).

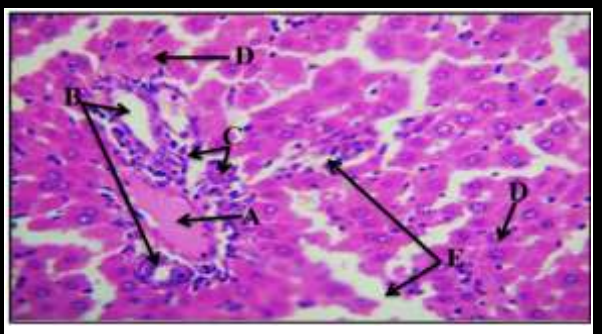

Figure (4): A histological section of a rat liver from the second group treated with methamphetamine at a concentration of 0.1 mg/kg for 15 days, showing the portal area - A blood-filled branch of the portal vein (A), branches of the bile duct (B), infiltration of white blood cells (C), clusters of hypertrophic hepatocytes (D), and blood sinusoids containing Kupffer cells (E) (H&E, 40×).

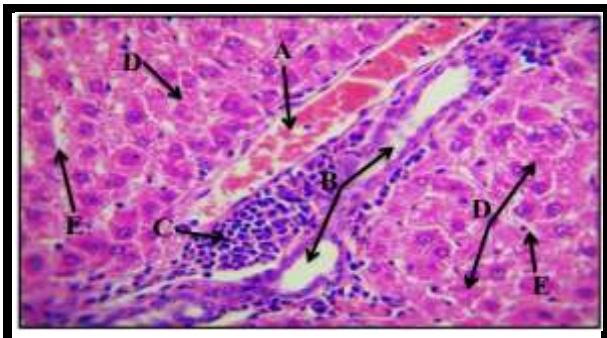

Figure (5): A histological section of a rat liver from the third group treated with methamphetamine at a concentration of 0.1 mg/kg for 30 days, showing the portal area of the liver - Portal vein filled with (A) branches of the bile duct (B) massive infiltration of white blood cells in the portal area (C) hepatocytes showing hypertrophy (D) some blood sinusoids are narrowed and contain Kupffer cells (E) (H&E, 40×).

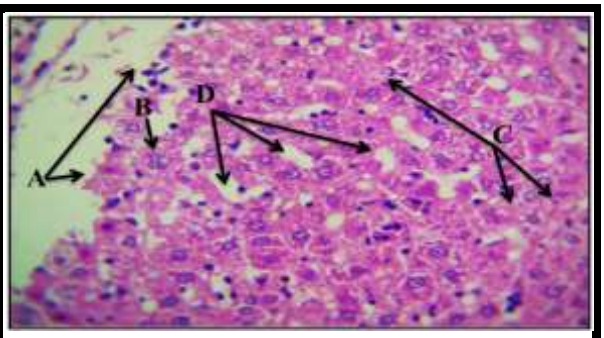

Figure (6): A histological section of a rat liver from the third group treated with methamphetamine at a concentration of 0.1 mg/kg for 30 days, showing the liver tissue—the liver parenchyma (A) exhibits hepatocellular degeneration (B) Hypertrophy of hepatocytes with ghost nuclei (C) Sinusoids containing Kupffer cells (D) (H&E, 40×).

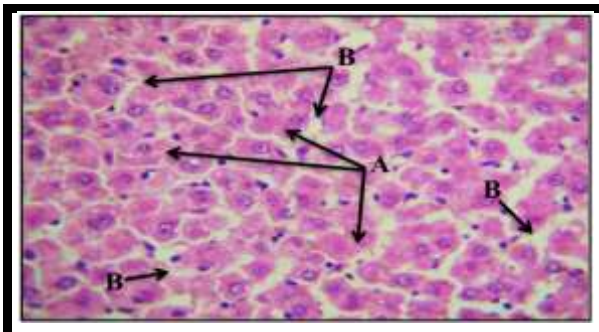

Figure (7): A histological section of a rat liver from fourth group, treated with vitamin E at a concentration of 0.1 mg for 15 days, showing the liver tissue - Polygonal liver cells with spherical nuclei, appearing honeycomb-like (A); a network of sinusoids containing Kupffer cells (B) (H&E, 40×).

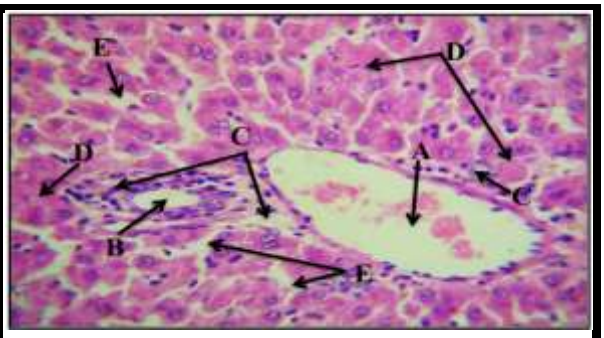

Figure (8): A histological section of a rat liver from fourth group, treated with vitamin E at a concentration of 0.1 mg for 15 days, showing the portal area - Lumen-widened portal vein (A) Bile duct (B) Infiltration of white blood cells in the portal area (C) Hypertrophy of hepatocytes (D) Sinusoids containing Kupffer cells (E) (H&E, 40×).

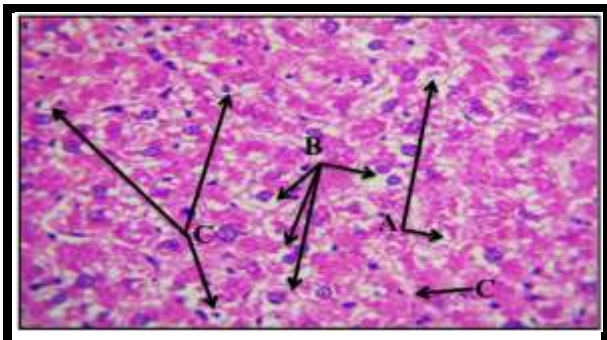

Figure (9): A histological section of a rat liver from fifth group, treated with vitamin E at a concentration of 0.1 mg for 30 days, showing the liver tissue - Hepatocellular necrosis with loss of nuclei (A) Hepatocellular degeneration with nuclear hypertrophy (B) Kupffer cells (C) (H&E, 40×).

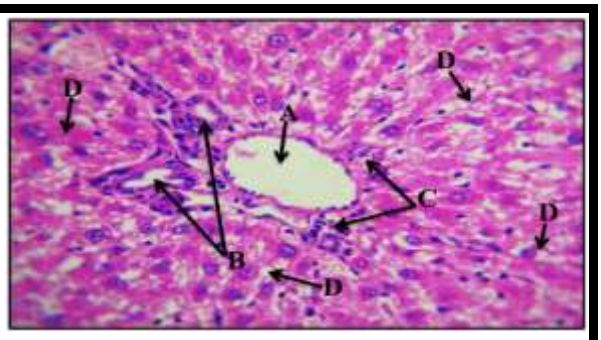

Figure (10): A histological section of the liver of a rat from the fifth group treated with vitamin E concentration (0.1) ml for (30) days, showing the portal region - the portal vein (A), the branch of the bile duct (B), infiltration of white blood cells (C), hypertrophy of hepatocytes with cytoplasmic bloating (D) (H&E, 40×).

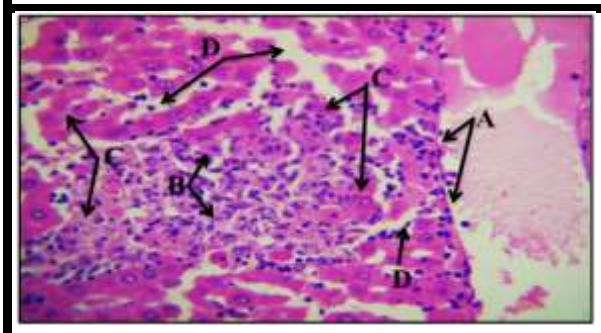

Figure (11): A histological section of the liver of a rat from the sixth group treated with methamphetamine (0.1) mg/kg and vitamin E (0.1) ml for (15) days, showing the periphery of the liver - loss of the liver capsule (A), massive infiltration of white blood cells in the liver parenchyma (B), degeneration of liver cells (C), dilatation of blood sinusoids containing Kupffer cells (D) (H&E, 40×).

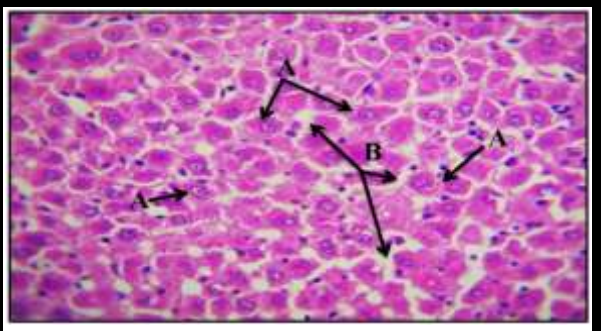

Figure (12): A histological section of the liver of a rat from the sixth group treated with methamphetamine (0.1) mg/kg and vitamin E (0.1) ml for (15) days, showing the parenchyma of the liver tissue - large multi-ribbed cells with pale-stained spherical nuclei (A). The blood sinusoids appeared in the form of branched hives and contained Kupffer cells (B) (H&E, 40×).

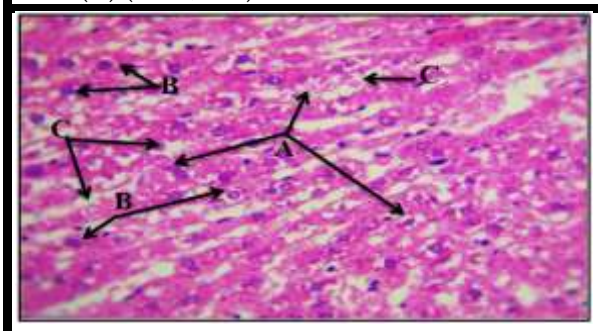

Figure (13): A histological section of the liver of a rat from the seventh group treated with methamphetamine at a concentration of (0.1) mg/kg with vitamin E at a concentration of (0.1) ml for (30) days. The liver parenchyma shows the presence of extensive degeneration in the hepatic cells with perinuclear cytoplasmic

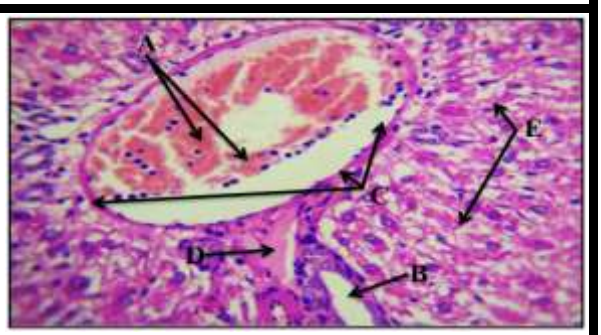

Figure (14): Histological section of the liver of a rat from the seventh group treated with methamphetamine (0.1) mg/kg and vitamin E (0.1) ml for (30) days, showing the portal region - the portal vein branch, which contains a blood clot with some white blood cells (A) Bile duct branch (B) Thickening of the basal membrane of

vacuolation (A) and nuclear thickening of some hepatocytes. condensation (B) and hepatic sinusoids appear to contain some Kupffer cells (C) (H&E, 40×).	the portal vein (C) Perfusion Hemorrhagic infiltration around the vein (D) Hepatocellular degeneration around the portal zone (E) (H&E, 40×).

The current histological results showed that the administration of methamphetamine to rats for 15 days caused obvious pathological changes in the liver tissue, represented by hepatocellular hypertrophy and loss of normal architectural organization, attributed to oxidative stress resulting from increased production of free electrolytes that lead to damage to cell membranes and disruption of the functioning of ion pumps, causing swelling of cells and narrowing of the hepatic sinuses, which is consistent with Kiatkin and Sharma [4]. The appearance of ghostly or faded pigment nuclei also indicates the occurrence of hepatic necrosis and chromatin degradation as a result of depletion of natural antioxidants inside the cell, which was indicated by Al-Ghareeb [5]. The results also showed the activation of Kupffer cells and the presence of inflammatory infiltrate in the Portal area with pronounced vascular congestion, reflecting the occurrence of acute hepatitis caused by the activation of the immune response by endotoxins and free electrolytes, which corresponds to Zhang et al. [6]. The appearance of branching of the bile ducts and a partial loss of the integrity of the liver capsule were also noted, which indicates a compensatory attempt to repair tissue damage**.** In the 30-day group, the changes were more severe, extensive necrosis appeared with an increase in Ghost nuclei, severe congestion and obvious loss of the normal structure of the liver, which indicates worsening oxidative damage and depletion of cellular defense mechanisms as a result of chronic exposure to methamphetamine. The intensity of inflammatory infiltration, activation of Kupffer cells and the appearance of ductal reflux also increased, which are indicators of the onset of the development of cirrhosis, which is consistent with Li and Zhao [7]. The comparison between the two groups indicates a direct correlation between the duration of methamphetamine exposure and the severity of hepatic tissue damage, as the injury progressed from minor degenerative and inflammatory changes on Day 15 to severe structural damage and extensive necrosis on day 30.

While the histological results of the group of rats treated with vitamin E for 15 days showed a clear preservation of the normal structure of the liver, as the hepatocytes appeared regular and polygonal with the integrity of blood vessels and portal vein, which indicates the protective role of vitamin E in protecting cell membranes and reducing oxidative stress [8]. Also, the appearance of the honeycomb pattern indicates an increase in glycogen storage and an improvement in the metabolic state of hepatocytes. Minor activation of Kupffer cells and mild inflammatory infiltration around the bile ducts were also observed, which is explained as a physiological immune response that enhances the liver's defense ability without causing tissue damage [9]. As for 30 days after treatment with vitamin E, degenerative changes appeared, represented by necrosis of hepatocytes, hypernucleosis, cytoplasmic explosiveness, which indicates a disturbance in the oxidative balance as a result of long-term exposure to the vitamin, as it may turn from an antioxidant to an oxidation-stimulating agent with excessive or prolonged use [9]. Hepatocellular hyperplasia with increased activity of Kupffer cells and inflammatory infiltration around the portal region also appeared, reflecting the liver's response to an attempt to metabolize cumulative doses of vitamin [8]. The comparison of the two groups showed that the protective effect of vitamin E was pronounced within 15 days, while the use for 30 days led to the appearance of degenerative and inflammatory changes as a result of the cumulative effects of the vitamin, which indicates that the duration of exposure plays an important role in determining the nature of the histological effects of the liver [10].

Histological results also showed that the administration of vitamin E as a prophylactic agent with methamphetamine for 15 days partially contributed to reducing the severity of liver damage, as the tissue maintained the regularity of the hepatic sinuses and the overall structure of the liver. This is attributed to the ability of vitamin E to inhibit lipid oxidation and protect cell membranes from the influence of free electrolytes generated by methamphetamine, which is consistent with Wang

et al. [11]. However, the appearance of a hives pattern and fading of the nuclei indicates the continued presence of cellular stress and limited degenerative effects as a result of the oxidative toxicity of the drug [5]. Activation of Kupffer cells and inflammatory infiltration around the damaged areas have also been observed, this is explained as a defensive immune response aimed at removing cellular debris and reducing the spread of tissue damage, which is indicated by Saleh and El-Janabi [12]. As for 30 days after the combined treatment, more severe histological changes appeared, represented by extensive hepatic degeneration, cytoplasmic explosiveness, thickening and loss of nuclei, which indicates the occurrence of advanced necrosis and the failure of vitamin E's ability to counteract the cumulative effect of methamphetamine [7]. Blood clots, vascular congestion and edema also appeared around the Portal area with dense inflammatory infiltrate, reflecting the occurrence of vascular damage and chronic inflammation as a result of persistent oxidative stress [13]. A comparison of the 15-and 30-day periods shows that the effectiveness of vitamin E was clearer in the short term, as it helped to relatively preserve the histological structure of the liver, while this Protection declined with prolonged exposure to methamphetamine, which led to the development of damage from minor degenerative changes to necrosis and severe vasculitis.

3-2 The effect of the drug methamphetamine, the role of vitamin E as a prophylactic agent on chemobiological tests of liver function.

3-2-1 The results of a statistical analysis of a group of rats treated with Methamphetamine for 15 and 30 days compared to the control group.

Table (1): statistical analysis of liver function of a group of rats treated with Methamphetamine for 15 and 30 days compared to the control group.

Variable	Tested Mean ± SD		Control Mean ± SD
	15 Days	30 Days	
AST	113.6 ± 2.7*	122.8 ± 1.92*	165.0 ± 4.64
ALT	33.2 ± 1.92*	42.8 ± 1.92*	64.8 ± 2.39
ALP	123.6 ± 2.07*	304.6 ± 2.3*	236.2 ± 27.99

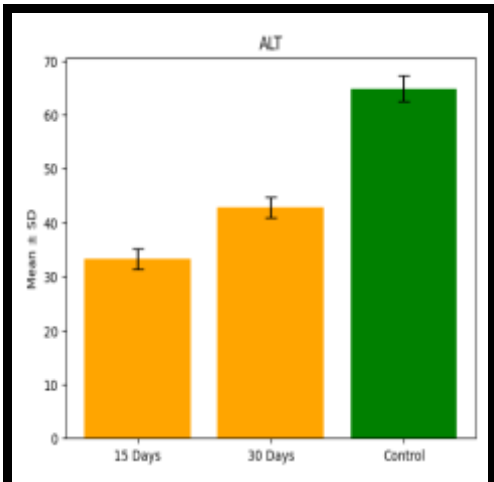

Figure (15): statistical analysis of liver function (ALT) of a group of rats treated with Methamphetamine

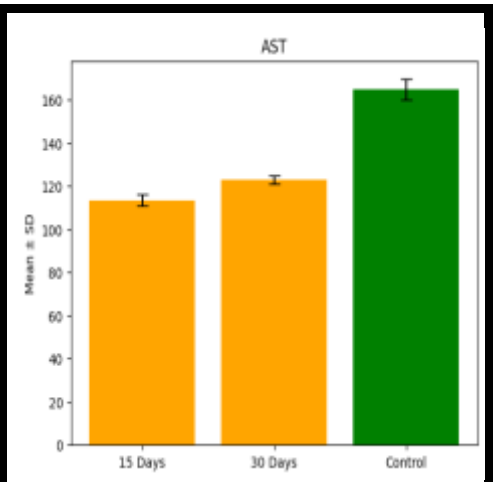

Figure (16): statistical analysis of liver function (AST) of a group of rats treated with Methamphetamine

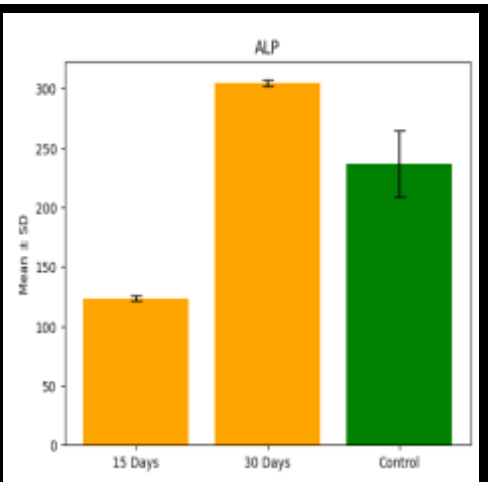

Figure (17): statistical analysis of liver function (ALP) of a group of rats treated with Methamphetamine

for 15 and 30 days compared to the control group.	for 15 and 30 days compared to the control group.	for 15 and 30 days compared to the control group.

3-2-2 The results of a statistical analysis of a group of rats treated with vitamin E for 15 and 30 days compared to the control group.

Table (2): statistical analysis of liver function of a group of rats treated with vitamin E for 15 and 30 days compared to the control group.

Variable	Tested Mean ± SD		Control Mean ± SD
	15 Days	30 Days	
AST	133.2 ± 1.92*	154.4 ± 3.21*	165.0 ± 4.64
ALT	43.0 ± 2.24*	42.6 ± 2.41*	64.8 ± 2.39
ALP	154.0 ± 2.74*	281.2 ± 1.92*	236.2 ± 27.99

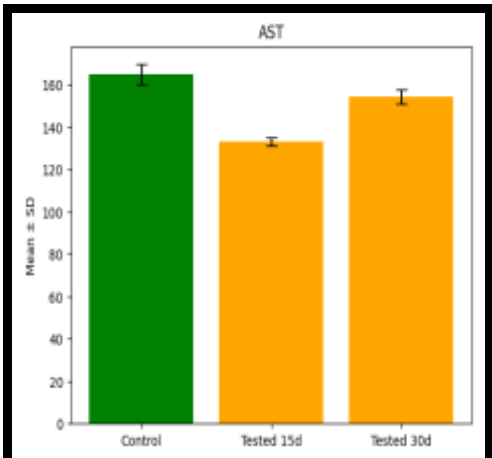

Figure (18): statistical analysis of liver function (AST) of a group of rats treated with vitamin E for 15 and 30 days compared to the control group.

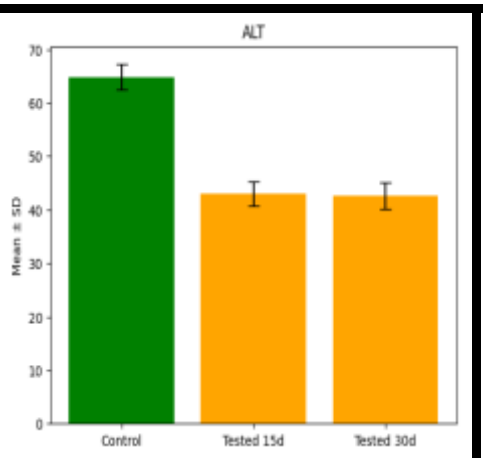

Figure (19): statistical analysis of liver function (ALT) of a group of rats treated with vitamin E for 15 and 30 days compared to the control group.

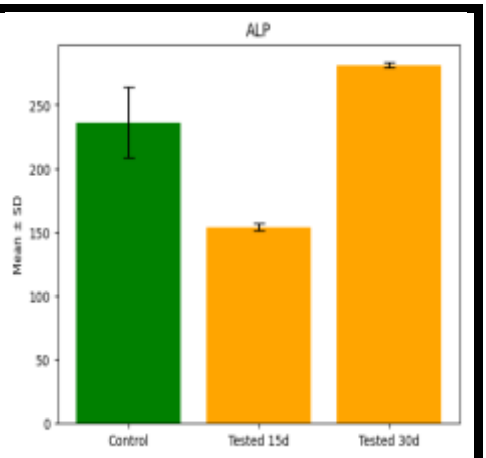

Figure (20): statistical analysis of liver function (ALP) of a group of rats treated with vitamin E for 15 and 30 days compared to the control group.

3-2-3 The results of a statistical analysis of a group of rats treated with methamphetamine and vitamin E for 15 and 30 days compared to the control group.

Table (3): statistical analysis of liver function of a group of rats treated with methamphetamine and vitamin E for 15 and 30 days compared to the control group.

Variable	Tested Mean ± SD		Control Mean ± SD
	15 Days	30 Days	

AST	**163.0 ± 2.24**	**94.6±2.07***	**165.0 ± 4.64**
ALT	**52.0 ± 1.58***	**35.400±2.07***	**64.8 ± 2.39**
ALP	**173.8 ± 2.59***	**256.6±2.07**	**236.2 ± 27.99**

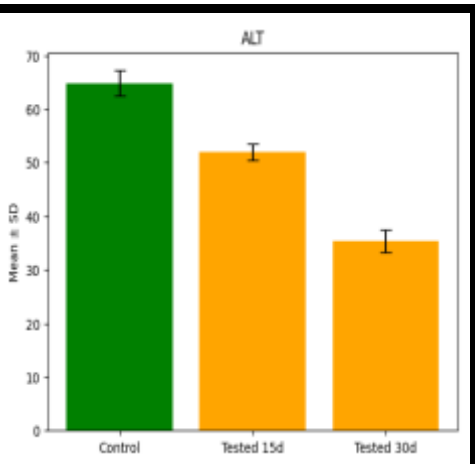

Figure (21): statistical analysis of liver function (ALT) of a group of rats treated with methamphetamine and vitamin E for 15 and 30 days compared to the control group.

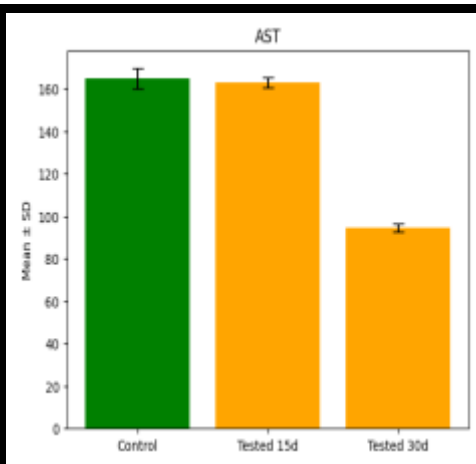

Figure (22): statistical analysis of liver function (AST) of a group of rats treated with methamphetamine and vitamin E for 15 and 30 days compared to the control group.

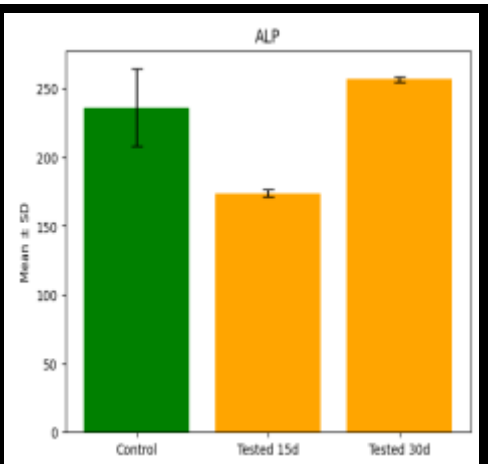

Figure (23): statistical analysis of liver function (ALP) of a group of rats treated with methamphetamine and vitamin E for 15 and 30 days compared to the control group.

The results of the current study of a group of rats treated with Methamphetamine for 15 and 30 days compared to the control group show a close and consensual correlation between biochemical deterioration and histopathological changes in the liver of rats treated with methamphetamine, where the statistical values of liver enzymes reflect the magnitude of structural damage seen microscopically. The significant decrease in the levels of AST and ALT enzymes in the groups (15 and 30 days) compared to the control group, despite the presence of cytomegaly (Hepatocellular hypertrophy) and degenerative changes (Degenerative changes), may be attributed to depletion of the enzyme stock inside hepatocytes or inhibition of protein synthesis as a result of severe oxidative stress caused by the drug, which is consistent with what recent studies have indicated that the chronic toxicity of methamphetamine leads to the consumption of defense mechanisms and enzymatic properties of the liver [14].

The biochemical results of a group of rats show treatment with vitamin E for 15 and 30 days compared to the control group.The effect of vitamin E depends on the duration of exposure; in the 15-day group, reduced levels of liver enzymes (AST, ALT, ALP) maintained the normal structure of hepatocytes and reduced oxidative damage, due to the role of vitamin E in stabilizing cell membranes and preventing lipid oxidation, which reduces the leakage of enzymes into the blood [15]. The appearance of cytomegaly and honeycomb pattern is also interpreted as an adaptive response to increased metabolic activity of the liver [16]. In the 30-day Group, a clear increase in the ALP enzyme was recorded (281.2), which was accompanied by inflammatory infiltration around the bile ducts, indicating the occurrence of cholestasis and inflammatory stress caused by the cumulative effect of vitamin [10]. The appearance of necrosis, nuclear hypertrophy, cytoplasmic detonation also explains the high AST enzyme compared to the 15-day period, which indicates the transformation of the vitamin effect with prolonged use into a reverse oxidant effect (Pro-oxidant effect) led to damage to hepatocytes and loss of integrity of the liver tissue [17].

The results of the current study also show a group of rats treated with methamphetamine and vitamin E for 15 and 30 days compared to the control group. There is a clear correlation between

biochemical variables and histological changes in the liver of rats treated with methamphetamine and vitamin E. A gradual significant decrease in the AST and Walt enzymes was observed with the continuation of treatment with vitamin E until Day 30, reaching the lowest values (94.6 ±2.07) and(35.40 ±2.07), respectively, due to the antioxidant role of vitamin E in stabilizing cell membranes and reducing the leakage of enzymes into the blood [18]. Histologically, the hepatic sinuses retained their organization on Day 15, however, the appearance of a hives pattern and inflammatory infiltrate indicates persistent oxidative stress and partial methamphetamine effect [19]. As for the ALP enzyme, it showed a pronounced rise on day 30 exceeding the control group, which was associated with thickening of the basement membrane, inflammatory edema, infiltration around the bile ducts, indicating cholestasis and damage to the portal [20]. Also, the appearance of cytoplasmic explosiveness, thickening of nuclei, their loss on day 30 reflects the progression of damage towards cellular necrosis as a result of the cumulative toxicity of methamphetamine. Despite the activation of kupffer cells as a defensive response, vascular congestion and blood clots contributed to the aggravation of tissue damage. The results suggest that vitamin E provided partial functional protection, but did not completely prevent the structural damage caused by chronic methamphetamine exposure.

Conclusions

The study proved that the methamphetamine drug causes liver damage that becomes more and more serious over time, progressing from minor structural Disorders (Day 15) to cellular necrosis, complete tissue death and blood clots (day 30).Vitamin E was able to provide good protection during the short period (15 days) by improving liver function and reducing enzymes (AST,ALT), but this effectiveness declined in the face of chronic toxicity in the long term.As it turned out at day 30, the destructive ability of methamphetamine surpassed the protective ability of vitamin E, which led to the appearance of vascular lesions and blockage of the bile ducts (elevated ALP enzyme), which confirms that antioxidants alone are not enough to treat chronic intoxication .As well as The liver showed an active defense reaction represented by hypertrophy of the "cover" cells and inflammatory infiltration, an attempt by the organ to reduce the effect of toxins and cleanse the tissue, the severity of this response increased with the length of exposure . It turned out that the toxicity of the drug was not limited to hepatocytes only, but extended to the destruction of the external liver portfolio and caused thrombosis in the blood vessels, indicating a comprehensive collapse in the blood perfusion of the organ.

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