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Impact of Ottelione on Gamma-glutamyl Transferase and Hematological Markers in Mice with Liver Fibrosis

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Abstract

Ottelione is a natural product that has a powerful tubulin polymerization inhibitory effect and cytotoxicity in tumor cell lines. This study was planned to evaluate its therapeutic effect against hepatotoxicity induced by carbon tetrachloride. Fifty five mice were divided into six groups each of 11 mice: first group considered as control group injected i.p. with olive oil, second group injected i.p. with DMSO, 3rd group was treated with Ottelione injected i.p, 4th group injected by CCl4, and 5th group mice received CCL4 in olive oil i.p. 3 times/week for 6 weeks, followed by Ottelione injected i.p. daily for 15 days. CCl4 treatment causes an increase in Gamma-glutamyl transferase and significant changes in hematological parameters when compared with a negative control group. Treating the mice with Ottelione showed an enhancement in Gamma-glutamyl transferase and hematological parameters when compared with the positive CCl4 control group. In conclusion Ottelione succeeded in reducing hepatotoxicity in mice induced by CCL4 and it could restore the liver to normal.

Keywords: Hepatotoxicity; Ottelione; CCl4; Fibrosis; GGT.

Introduction

Liver is the backbone of the body which makes a lot of functions that are critical to maintaining homeostasis, (Rahim et al., 2020), and is responsible for the metabolism of drugs and toxic chemicals (Baradaran et al., 2019). The liver gets rid of foreign substances by detoxifying and eliminating drugs and other xenobiotics that enter the body through the gastrointestinal tract and after absorption enters the liver through the portal vein. it has a high concentration of toxin-metabolizing enzymes that can alter xenobiotics to substances with low toxicity and defecate them (Ben Hsouna et al., 2019). Liver toxicity is the most reason that leads to death whole the world (Paik et al., 2020). The hepato-toxicological problem is an injury caused by toxic chemicals and some drugs (Tighe et al., 2020) and virus infiltration from ingestion or infection (Khan and Nabavi, 2019).The hepatotoxicity results from the

oxidative stress that occurred by the accumulation of reactive oxygen species (ROS) that affect macromolecules in the liver (Elbakry et al., 2019). This oxidative stress results from the imbalance between the free radical and antioxidant defenses (Wang et al., 2020).

Fibrosis is an indicator of chronic inflammatory diseases (Ballestri et al., 2021). Its Characterized by loss of hepatocytes and change in hepatic construction following an imbalance between extracellular matrix synthesis, and also degradation and formation of scar tissue (Gabr and Alghadir,2021).

Carbon tetrachloride (CCl4) induced in mice caused fibrosis (Ernst et al., 2020). CCl4 is a xenobiotic substance that induces acute and chronic tissue damages, CCl4 dissociates by cytochrome P450 enzyme into trichloromethyl (CCl3) and trichloromethyl peroxyl (OOCCl3) highly toxic radicals (Tsuchida et al., 2018). The trichloromethyl radical reacts with necessary biomolecules such as fatty acids, proteins, lipids, nucleic acids, and amino acids to cause lipid peroxidation and damage DNA synthesis and division. So, causing cellular malfunction is proved by variations in biochemical and hematological parameters (Bagali et al., 2020).

Cellular gamma-glutamyl transfers (GGT) is mainly accountable for methods of metabolizing extracellular reduced glutathione (GSH), permitting assimilation of basic amino acids for intracellular GSH production. Therefore, Serum GGT is an oxidative stress marker that results in GSH depletion (Corti et al., 2020). The test for gamma-glutamyl transfers (GGT) measures the blood GGT.GGT is a body-wide enzyme, although mainly present in the liver. GGT can seep into the circulation if the liver is injured. High GGT blood levels could be a symptom of liver illness or bile duct injury. Bile channels bring bile into the liver and outside of it. Bile is a liver-built fluid. Digesting it is essential (Affrin and Savitha, 2018).

Drugs used for liver treatment have many side effects, So it is crucial to find safe and economical alternates from a natural product (Aly et al., 2020). Bioactive compounds are secondary metabolites, that have a role in adaptability and survival, and have a multi-therapeutic effect, based on their anti-oxidant (Nile et al., 2018). Anti-inflammatory (Meng et al., 2018), antimicrobial (Takó et al., 2020), and antitoxic properties (Hallajzadeh et al., 2020) because of the different therapeutical effects, using natural agents to treat liver diseases.

In this context, Ottelia alismoides is a freshwater plant that propagates in partly flooded water; it has fluctuating leaves on extended petioles. In Egypt, it blooms annually in rice fields and irrigation channels during the summer months (El-Missiry et al., 2012). This plant contains different natural compounds such as glycosides, alkaloids, flavonoids, terpenoids, tannins, and phenolic compounds (Banu and Cathrine, 2015). Major chemical components of Ottelia alismoides are two diastereomeric 4-methylene-2-cyclohexenones, otteliones A (OTTE), and B, ten new diarylheptanoids (2,3,4,5a-d,6,7&8) together with 3a-hydroxy ottelione, a hydroxylated derivative of otteliones A and B (Hoye et al., 2013). The entire plant has been used as a drug for a lot of applications (Navale and Paranjape, 2018). More specifically, OTTE itself has a powerful tubulin polymerization inhibitory effect and cytotoxicity in tumor cell lines in vitro (Ayyad et al., 1998 and Chang et al., 2012).

Material and methods

Chemicals

Chemicals were of excellent quality, as methanol, petroleum ether, chloroform, acetone, diethyl ether, and CCl4 were acquired from BDH Chemicals, Ltd., Poole, England. Boric acid powder and vanillin were acquired from El-Gomhouria Company for Drugs and Chemicals in Egypt. Sigma-Aldrich Chemical Co. provided the dimethyl sulfoxide (DMSO), ethanol, and ethyl acetate (St Louis, MO, USA). Fisher Scientific UK provided acetylacetone, hydrochloric acid, and sodium sulphate

Plant Extract Preparation

During the summer, whole plants of O. alismoides (350 g) were gathered from canals of the River Nile in Delta, Egypt. Plants were air-dried at ambient temperature and kept at -20 degrees Celsius until extracted. Ottelia alismoides extract was obtained by utilizing petroleum ether and a few purification procedures, including preparative TLC to get pure chemicals. The extract was diluted after being dissolved in 1% DMSO. It was utilized

because of its anticancer and antioxidant properties.

Experimental Animals

Male adult Swiss albino mice (n=55) with an average weight (22-25 gm) were provided from the Zoology Department, Damietta Faculty of Science, Egypt. The animals were kept in wire-mesh cages (11 mice per cage) at the Animal House of the Faculty of Science and were fed and given filtered water for a week before the experiment began.

Animal grouping and Drug treatment

55 Swiss male adult albino mice, as seen in Figure 1, were divided into 5 groups (11 mice/each). Following the end of the experimental phase, the whole of the blood was collected by heart penetration for hematological examination and then slaughtered for 12 hours by ether inhalation. Dissected and washed with isotonic saline, the liver has been stored at –20°C for biochemical examination.

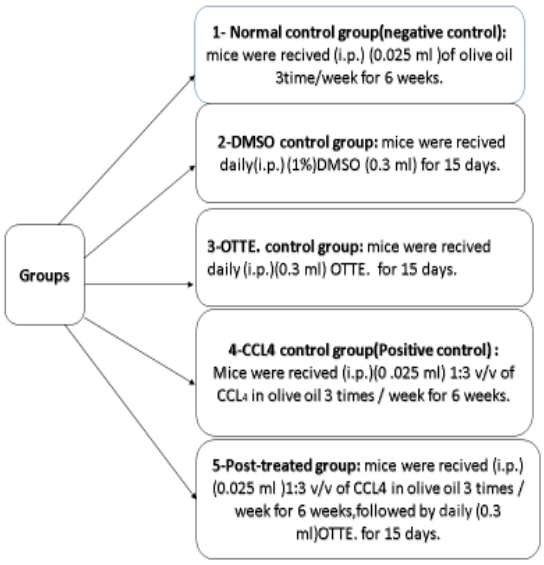

Figure 1. Animal grouping and Drug treatment **Abbreviations**: **DMSO**: dimethyl sulfoxide, **i.p:** intraperitoneally, **OTTE.** : OTTELIONE, **CCl_4**: carbon tetrachloride.

Biochemical analysis

The plasma gamma-glutamyl transferase (GGT) was measured according to the method of (Szasz *et al*., 1974) by using a kit purchased from Centronic GmbH Co., Wattenberg, Germany.

Complete blood count (CBC)

The HORIBA Hematology Assessment (model: MICROS 60 OT) collection has been carried out on a portion of retro-orbital blood samples from every animal that was used to fully count blood cells (white blood cells, Red Blood cells, and platelets) (France).

Statistical analysis

Data were evaluated by one-way variance analysis (ANOVA) of "SPSS" 14.0 for Microsoft Windows, SPSS Inc., and considered statistically significant at two-sided $P < 0.05$. Numerical data expressed as average ± SD.

Result

Gamma-glutamyl transferase (GGT)

Figure 2 showed the influence of OTTE.on GGT. There was a non-significant increase in GGT in treated mice either with DMSO or OTTE compared to negative control group. Also, Administration of CCl_4 resulted in a simultaneous elevation in GGT hepatic enzyme activities when compared to negative control group mice (p=0.0001). On the other hand, treating mice with OTTE in post-treated group exhibited significant improvement in hepatic enzymes compared to positive control group (CCl_4) (p=0.0001).

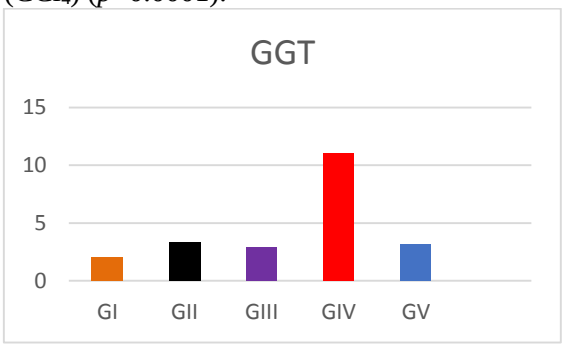

Figure 2: Effect of CCl_4 and OTTE treatment on GGT in albino mice

Abbreviations :(GI) Normal group (Negative control)**, (GII)** DEMSO group**, (GIII)** OTTELIONE group**, (GIV)** CCL4 group (positive control)**, (GV)** Post- treated group**.**

Haematological parameters:

Treatment with CCl_4 significantly increase the white blood cells (WBCs) to (19.8±0.7 x

$10^3/mm^3$), reduced platelets count to (274±9.7 x $10^3/mm^3$), Red blood cells (RBCs) levels to (5.7±0.63 $x10^6/mm^3$), Hematocrit levels to (35.5±1.09%), ($p<0.001$) and Hemoglobin concentration to (8.3±0.51g/dl), ($p<0.05$) in the blood compared to negative control group (12.0±0.79 x $10^3/mm^3$, 540±20.1 x $10^3/mm^3$, 8.4±0.45 $x10^6/mm^3$, 40.9±0.96 %, ($p<0.001$), and 12.0±0.59 g/dl, ($p<0.05$) respectively. On the other hand; white blood cells significantly decreased in the post-treated group ($p<0.001$) compared to the positive control group. platelet counts, hemoglobin concentration, red blood cells, and hematocrit counts significantly increased compared to the positive control group as shown in Table 1.

Table 1: Effect of CCl_4 and OTTE treatment on hematological parameters in albino mice

	Normal	OTTE	DMSO	CCl_4	Post OTTE
RBCs ($10^6/mm^3$)	8.4 ± 0.45	7.6 ± 0.47 [a]	8.6 ± 0.56	5.7 ± 0.63 [a]	8.0 ± 0.25 [b]
WBCs ($10^3/mm^3$)	12.0 ± 0.79	12.8 ± 0.65	14.6 ± 0.97[a]	19.8 ± 0.7 [a]	10.6 ± 0.54 [a,b]
HCT %	40.9 ± 0.96	39.1 ± 0.57[a]	41.6 ± 0.73	35.5 ± 1.09[a]	40.4 ± 0.84 [b]
Hgb (g/dl)	12.0 ± 0.59	12.7 ± 0.6	12.8 ± 0.75	8.3 ± 0.51 [a]	11.1 ± 0.77 [a,b]
PLT ($10^3/mm^3$)	540 ± 20.1	491 ± 19.3 [a]	587 ± 8.2 [a]	274 ± 9.7 [a]	495 ± 10.8 [a,b]

Data represented as mean ± SD
a =significant when compared with the control healthy mice group.
b =significant when compared with the CCl_4 treated mice group.
Abbreviations: RBCs: Red blood cells; WBCs: White blood cells; HCT: Hematocrit; HGB: Hemoglobin; PLTs: Platelets.

Correlations between different studied Parameters among the studied group

All the possible correlations between the studied parameters were investigated. Only the significant correlations are described in table 2.

Correlations with GGT

GGT is negatively correlated with RBCs (r= -0.815, $p<0.001$), HCT (r = - 0.850, $p<0.0001$), Hgb (r = - 0.797, $p<0.0001$), PLTs (r = -0.922, $p<0.0001$). WBCs (r= -0.757, $p<0.0001$) that showed in table 2.

Correlations with RBCs

RBCs is positively correlated with HCT (r = 0.777, $p<0.0001$), Hgb(r = 0.826, $p<0.0001$), PLTs (r =0.873, $p<0.0001$). And also showed that RBCs is negatively correlated with WBCs (r= -0.469) that showed in table 2.

Correlations with WBCs

WBCs is negatively correlated with HCT (r = -0.58), Hgb(r = -0.347, p= 0.004), PLTs (r = -0.585) that showed in table 2.

Correlations with HCT

HCT is positively correlated with Hgb (r = 0.713, $p<0.0001$), PLTs (r =0.912, $p<0.0001$). that showed in table 2.

Correlations with Hgb

Hgb is positively correlated with PLTs (r = 0.829, $p<0.0001$) (table 2).

Table 2. Pearson's correlations analysis between GGT, RBCs, WBCs, HCT, Hgb, PLT in all studied groups.

Variable	GGT	RBCs	WBCs	HCT	Hgb	PLT
GGT	-	-.815	.757	-.850	-.797	-.922
RBCs	-.815	-	-.469	.777	.826	.873
WBCs	.757	-.469	-	-.580	-.347	-.585
HCT	-.850	.777	-.580	-	.713	.912
Hgb	-.797	.826	-.347	.713	-	.829
PLT	-.922	.873	-.585	.912	.829	-

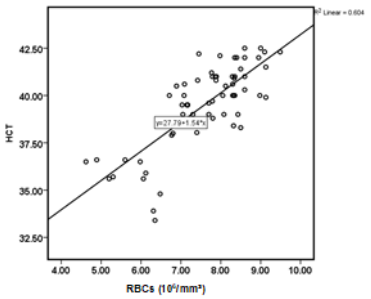

Figure 3. The correlation between RBCs and HCT in all studied groups

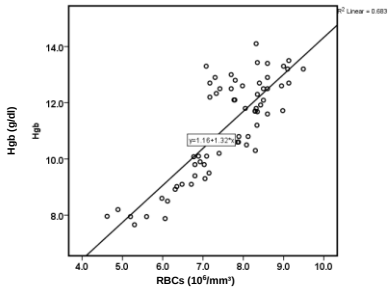

Figure 4. The correlation between RBCs and Hgb in all studied groups.

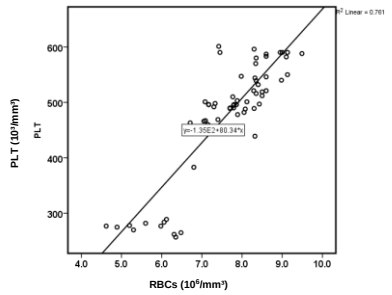

Figure 5. The correlation between RBCs and PLT in all studied groups.

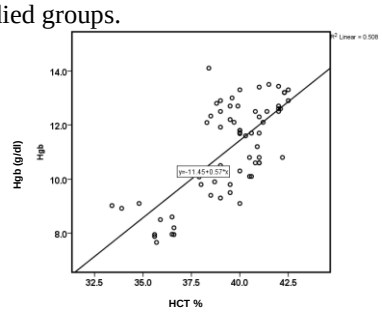

Figure 6. The correlation between HCT and Hgb in all studied groups.

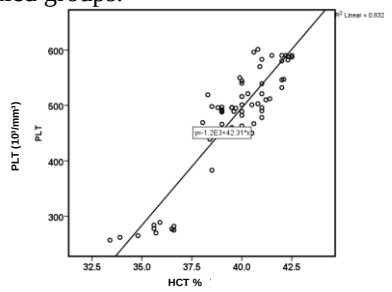

Figure 7. The correlation between HCT and PLT in all studied groups.

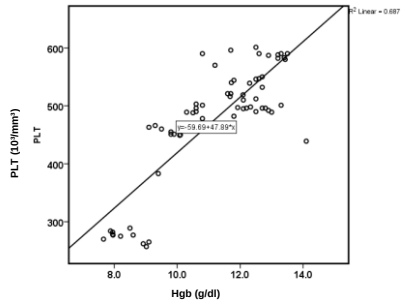

Figure 8. The correlation between Hgb and PLT in all studied groups.

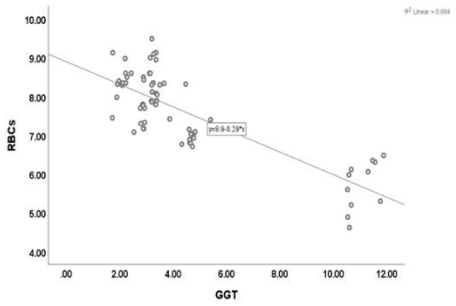

Figure 9. The correlation between GGT and RBCs in all studied groups

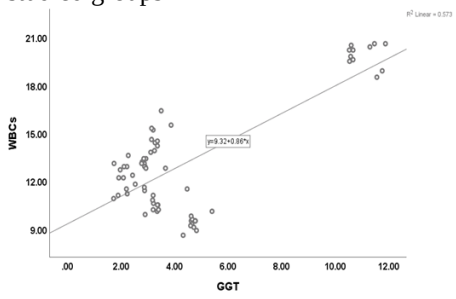

Figure10. The correlation between GGT and WBCs in all studied groups

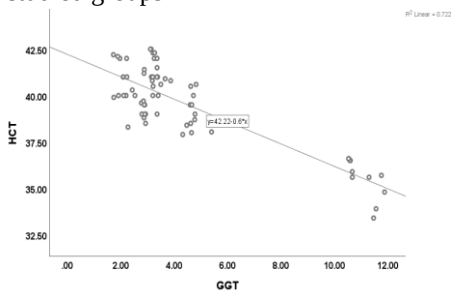

Figure11. The correlation between GGT and HCT in all studied groups

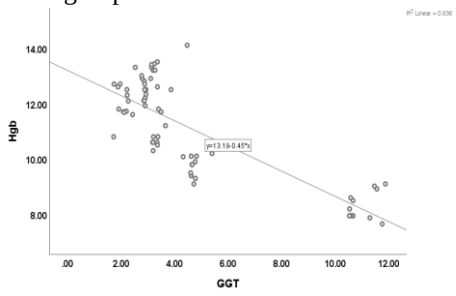

Figure12. The correlation between GGT and Hgb in all studied groups

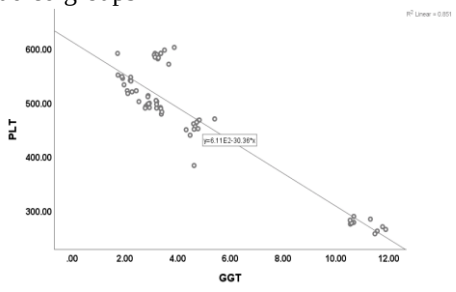

Figure13. The correlation between GGT and PLT in all studied groups

Discussion:

The present study was focused on exploring the hepatoprotective action of OTTE against CCl_4-induced liver toxicity in mice. hepatoprotective compounds obtained from plant sources are of great interest due to their have a negative rather than positive effect inside an animal's body, distinct from synthetic drugs (Hira et al., 2021). In this study, ottelione was prepared for higher yield and higher purity.

Metabolic activation is one of the major mechanisms for drug-induced hepatotoxicity and has been received more and more attention in recent years (Yang et al., 2017). Reactive metabolic intermediates generated play a critical role in drug-induced hepatotoxicity by adduction with liver protein (Guo et al., 2019). Carbon tetrachloride ($CC1_4$), a halogenated hydrocarbon, causes hepatic lipid peroxidation, inflammation, and fibrosis **(**Harrisa et al., 2016). CCl_4 is known to be converted to the trichloromethyl radical ($CC1_3$) by the liver microsomal cytochrome P450, which acts as a drug-metabolizing enzyme. ($\bullet CC1_3$) produced in hepatocytes from CCl4 quickly interacts with oxygen to produce a trichloromethyl peroxy radical (Takó et al., 2020).

Oxidative stress is the result of an Inequality of highly reactive oxygen generation and the effective removal of antioxidant, superoxide anion (O2), H202, and hydroxyl ion ('OH) by the antioxidant system. They can be made by mitochondria in enormous quantities **(Ahmad *et al*., 2017).** At lower quantities, ROSs key cell proliferation, migration, and death signaling molecules are implicated **(Forrester *et al*., 2018)**. These chemicals might be of benefit against the pathogens at greater concentrations and lead to enhanced activation of leukocyte and platelet and increased leukocyte recruitment **(Shukla *et al*., 2019).** Although this happens in connection with innate immunity and inflammatory signals in cells, most ROS are detrimental for cells because of the build-up of irreversible damage that results in mutations and cell death **(Morgillo *et al*., 2018).** In numerous illnesses, containing fibrosis and cancer, ROS and oxidative stress are involved **(Moldogazieva *et al*., 2019)**. ROS is the major cause of oxidative stress that has been discovered as an NADPH enzyme that promotes important processes to produce fibrotic disorders (**De Minicis and Brenner, 2007**).

Hepatic fibrosis is essentially a pathophysiological process for liver damage, tissue regeneration, and wound healing **(Parola and Pinzani, 2019)**. It shows chronic inflammatory disorders, which are defined by loss of hepatocytes and changes in a hepatic structure after the imbalance between extracellular matrix synthesis and scar tissue development **(Zhan *et al*., 2019)**. The degree of hepatic damage and protection are determined by estimating the serum levels of liver biomarkers such as GGT (Asija et al., 2014). Liver biomarkers are present in the mitochondria of hepatocytes. The transferases in the hepatic cells are ALT, AST and GGT. These enzymes are cytoplasmic, but owing to increased membrane permeability, while there is liver damage, they enter the circulatory system. The raised GGT serum values indicated hepatotoxicity **(Ying *et al*., 2017)**. Because GGT enzymes increase greatly in the group CCL_4 and drop in the group pretreated. Our finding accords with **(Eltahir *et al*., 2020)**, who found that CCL_4 therapy led to substantial increases in blood GGT levels as compared with normal control. However, CCL_4 damages the hepatocyte membrane, leading to loss of structural integrity and leakage of liver enzymes from the mitochondrion into the blood circulation. Significant rises in the ranks of liver biomarkers GGT. However, these increases were inverted by treatment with OTTE through diminished two-fold elevations in the transaminase activities in mice *vs* CCl_4 positive control mice at post-treatment which indicated normalization of liver functions This provides evidence that OTTE showed a hepatotoxic protective effect in mice.

The complete CBC, also defined as a hemogram or blood panel, is utilized as a crucial test for a range of infections such as anemia, infection, and leukemia. Estimate the quantity of all blood cell components: red blood cells (RBCs), white blood cells (WBCs), and platelets (PLT). Any anomaly (rises or reductions) in the number of blood cells or related indices shown by the CBC might indicate a medical issue underlying the diagnosis **(Yassin, 2013).** The data of the present study shows that the number of RBCs, hemoglobin concentration (p0.05), hematocrit concentration, and platelet concentration in the positive control group (p0.001) has all decreased significantly when compared to the negative control group and the amount of WBCs has risen significantly. These results

agree with **(Sun *et al*., 2018)** in which, therapy with CCl_4 led to substantial platelet reductions and increased counts of WBCs. Furthermore, coagulation system activation and fibrin deposition.

The present findings are in line with that of **Zahran *et al*., (2021)**.

This is owing to CCl_4's toxicity, which has been linked to hepatic damage in mice due to the production of highly reactive CCl3• and CCl3OO• radicals during CCL_4 metabolism **(Elshater *et al*., 2013).** According to **(Rahmouni *et al*., 2017)**, the drop in RBC count and Hb level caused by CCL_4 therapy might be ascribed to disrupted hematopoiesis, erythrocyte destruction, a decrease in the rate of erythrocyte production, and/or a greater clearance circulation. Furthermore, it was shown that the suppression of both erythropoietic and thrombopoietic activities of the bone marrow might explain the reduction of RBC and PLT levels.

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الملخص العربي

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يعتبر الاوتيليا منتج طبيعي له تأثير مثبط قوي لبلمرة التوبولين والسمية الخلوية في خطوط الخلايا السرطانية. صممت الدراسة الحالية لإثبات تأثيرها العلاجي ضد السمية الكبدية التي يسببها رابع كلوريد الكربون. وقد اشتملت الدراسة علي ٥٥ فأرًا مقسمين إلى خمس مجموعات (ن = ١١): المجموعة الأولى مجموعة التحكم السلبي حيث تم حقن الفئران بزيت الزيتون في الغشاء البريتوني ، المجموعة الثانية مجموعة داي ميثيل سالفواكسيد، المجموعة الثالثة مجموعة الاوتيليون ، المجموعة الرابعة المجموعة الضابطة الإيجابية التي تلقت فيها الفئران رابع كلوريد الكربون للحث على تسمم الكبد ، وتلقت فئران المجموعة الخامسة مجموعة ما بعد العلاج رابع كلوريد الكربون في زيت الزيتون ثلاث مرات في الأسبوع لمدة ستة أسابيع ، ثم تم حقنها بالاوتيليون يوميا لمدة ١٥ يوم . وقد أظهرت المجموعة الضابطة الإيجابية زيادة في جاما جلوتاميل ترانس فيريز وتغيرات في دلالات أمراض الدم عند مقارنتها بالمجموعة الضابطة السلبية. ولقد أظهر علاج الفئران باستخدام الاوتيليون تحسنا ملحوظا في نشاط إنزيم جاما جلوتاميل ترانس فيريز وفي دلالات أمراض الدم عند مقارنتها بالمجموعة الضابطة الإيجابية. الخلاصة: أظهرت هذه الدراسة نجاح الاوتيليون في الحد من السمية الكبدية في الفئران التي سببها رابع كلوريد الكربون، حيث يمكن أن يعيد الكبد إلى طبيعته.