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Original article

Reducing the Effects of Strawberry Juice's Antioxidant Qualities on Rabbits' Renal and Hemotoxic Reactions Caused by Carbon Tetrachloride

Fayrouz Khaled*[1], Ramadan Ali[2], Tahani Aboulqassim[3]

[1]*Department of Chemistry, Faculty of Science, Omar Al-Mokhtar University, El-Beida, Libya*
[2]*Department of Zoology, Faculty of Science, Omar Al-Mokhtar University, El-Beida, Libya*
[3]*Department of Zoology, Libyan Academy for Postgraduate Studies, Ajdabiya, Libya*
Corresponding Email. *fayalzobair@yahoo.com*

Abstract
Strawberries (*Fragaria × ananassa*) are rich in polyphenols and antioxidants that may protect against oxidative stress, while carbon tetrachloride (CCl_4) is a well-known hepatotoxin used experimentally to induce liver and kidney injury. This study evaluated the protective effects of strawberry juice against CCl_4-induced hepatic and renal dysfunction in male rabbits. Biochemical analysis revealed that CCl_4 significantly elevated serum levels of aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALK), indicating hepatic injury. Specifically, AST and ALT levels were markedly increased in the CCl_4 group compared to controls, while treatment with strawberry juice alone significantly reduced these enzymes below control values. Co-administration of strawberry juice with CCl_4 resulted in AST and ALT levels nearly normalized to the control, indicating a hepatoprotective effect. Interestingly, ALK activity was highest in the strawberry juice group, suggesting enhanced biliary function, while the lowest ALK activity in the CCl_4 group implied possible cholestasis. In combination, ALK levels returned to near-normal values. Renal and metabolic parameters also demonstrated notable changes. CCl_4 significantly elevated plasma glucose, creatinine, and urea levels, indicative of metabolic disruption and renal impairment. Strawberry juice alone lowered these markers significantly, while co-administration with CCl_4 restored glucose, creatinine, and urea levels toward control values. These findings suggest that strawberry juice exerts both hepatoprotective and renoprotective effects, potentially through its antioxidant and anti-inflammatory properties.
Keywords: Strawberry Juice, Carbon Tetrachloride, Rabbits, Biochemical Parameters.

Introduction

Glycogen storage, lipid and protein synthesis, bile salt creation, hormone production, and detoxification are just a few of the many roles that the liver, the body's biggest internal organ and gland, plays in complicated metabolism [1]. Numerous pathogenic causes, including hepatic viruses and chemical hepatotoxins, can cause liver damage. Fatty livers also cause the down-regulation of numerous enzymes involved in drug metabolism [2]. Toxic hepatopathy, another name for drug or chemical-induced liver damage, is a serious clinical issue [3]. In addition to affecting growth and nutritional status, liver impairment can result in acute, chronic, or end-stage liver disease [1], which can then change how many medications behave pharmacologically [4]. According to the study [5], CCl_4 poisoning has been linked to reactive oxygen species (ROS), such as superoxide and hydroxyl radicals, which are known to be significant in the pathophysiology and progression of liver disease.

Numerous clinical and experimental findings in recent years have demonstrated that oxidative stress, which results from an imbalance between the body's oxidant and antioxidant systems favoring the oxidants, should be a major apoptotic stimulus in the various forms of acute and chronic liver injury as well as hepatic fibrosis [6]. CCl_4-induced hepatic fibrosis is linked to increased lipid peroxidation and decreased antioxidant status [7]. Thus, effective antioxidant treatments that have caught the attention of researchers provide information about postponing or avoiding the onset and progression of hepatic fibrosis. As a result, these treatments might be a viable therapeutic approach for hepatic fibrosis prevention and treatment [8]. The antioxidant defense system and nutrition are closely related since the diet may provide some exogenous low molecular weight antioxidants. To prevent oxidative stress events, these two primary antioxidant defenses systems work in tandem and control each other's levels [9]. A sizable class of compounds that are common in plants has gained attention in recent years. Significant clinical and experimental evidence in recent years has demonstrated that oxidative stress results from an imbalance between the body's oxidant and antioxidant systems [10].

Numerous studies show that natural compounds derived from medicinal and culinary plants have potent antioxidant properties that may protect against liver toxicity brought on by different toxicants [11]. Among those potential plants is the strawberry. The high concentrations of vitamin C, folate, and phenolic components in strawberries (Fragaria ananassa) make them an important source of bioactive chemicals. [12]. Flavonoids (primarily anthocyanins, with flavonols contributing as a minor component) comprise the largest class of phenolic compounds, followed by hydrolyzable tannins (gallotannins and ellagitannins) and phenolic acids (hydroxybenzoic and hydroxycinnamic acids), with condensed tannins (proanthocyanidins) as minor constituents [13]. According to earlier research, strawberries high in flavonoids—which give them

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their antioxidant qualities—and chemicals extracted from the whole plant have shown promise in cancer chemopreventive treatment. Polyunsaturated fatty acids are abundant in berry seeds. The human body cannot produce these acids; instead, it must get them from food [14]. Several additional vitamins, including thiamin, riboflavin, niacin, vitamin B6, vitamin K, vitamin A, and vitamin E, are also found in strawberries. Additionally, it has been recognized as a good supplier of iron, copper, phosphorus, magnesium, and iodine [15]. The purpose of this study is to ascertain whether strawberry (F. ananassa) juice protects rabbits' livers against CCl_4-induced damage.

Methods

Tested Compounds

In this study, the effect of CCl_4 with or without A muricata on hematological parameters, biochemical parameters including liver function, and free radicals of male rabbits was investigated. CCl_4 (1mg/ml) was brought from the chemistry department, Faculty of Science. Fresh strawberries (F. ananassa) were collected from the market of Ajdabiya in March–May, 2023.

Experimental Animals

We purchased twenty healthy, robust male rabbits from reputable local farms. The room in which these rabbits were kept was suitable for the trial period and was equipped in compliance with US-EPA 2004. The principles and standards of the Libyan Ministry of Agriculture, as well as the US-EPA 2004 for animal care, were followed in the care of the rabbits. Every rabbit was housed in an appropriate steel cage that had a 12-hour light cycle, a temperature between 22 and 26°C, and a humidity level between 40 and 70%. A suitable diet comprising clean water and balanced feed has been provided for the duration of the study. After being divided into four groups of five rabbits each at random, the animals were given the following treatment: Group I: Rabbits were used as controls and received an equivalent 1 ml of the vehicle (corn oil) alone by oral gavage twice per week for 6 successive weeks. Group II: Rabbits were treated with strawberry, which was given daily by gavage at a dose of 100 mg/kg BW [16], dissolved in corn oil for six successive weeks. Group III: Rabbits were treated with CCl_4 1.5 ml/kg BW in olive oil by gavage daily [17]. Group IV: Rabbits were given CCl_4 at a dose of 0.5ml/kg BW by gavage, like group III, and given strawberry at a dose of 100 mg/kg BW by gavage, like group II, for six successive weeks.

Blood biochemical parameters and enzyme activities

The remaining portion of the divided blood samples was immediately placed on ice. Samples were centrifuged for 20 minutes at 860 xg to produce plasma. After that, the plasma was kept at -20°C until it was time for analysis**.** Techniques were used to measure the concentrations of creatinine, urea, and plasma glucose. The [18] method was used to measure the activity of plasma aspartate transaminase (AST; EC 2.6.1.1) and alanine transaminase ("ALT"; EC 2.6.1.2). The method described in [19] was used to test the alkaline phosphatase ("AlP"; EC 3.1.3.1) activity in plasma.

Statistical analysis

When necessary, statistical analysis was performed using GraphPad Prism 8 or Minitab software (version 17). After determining that the data had a normal distribution, an ANOVA analysis was conducted using the Tukey multiple comparison test to achieve a significance level of $P < 0.05$.

Graphs

The Microsoft Excel 2007 program was used to plot the logarithmic scales for strawberry juice, carbon tetrachloride, and their combination.

Results

The data presented in Table 1 and Figures 1 to 3 highlight the changes in the activities of key hepatic enzymes—AST (aspartate transaminase), ALT (alanine transaminase), and ALK (alkaline phosphatase)—following exposure to CCl_4, strawberry juice, and their combination. These enzymes serve as important biomarkers for liver function and tissue integrity, particularly in evaluating hepatocellular injury. The CCl_4-treated group showed a marked elevation in both AST (60.59 ± 5.75 U/L) and ALT (54.26 ± 2.39 U/L) levels when compared to the control group (43.86 ± 0.81 U/L and 43.60 ± 2.80 U/L, respectively), with statistically significant differences ($p<0.05$). In contrast, rabbits treated with strawberry juice alone exhibited significantly lower AST (38.96 ± 1.86 U/L) and ALT (36.80 ± 1.83 U/L) levels compared to both the control and CCl_4 groups. Interestingly, the combination group (CCl_4 + Straw.J) showed a significant reduction in AST (43.11 ± 1.01 U/L) and ALT (44.23 ± 1.25 U/L) levels compared to the CCl_4-only group, bringing the values close to the control levels. This partial reversal of enzyme elevation supports the hypothesis that strawberry juice can attenuate CCl_4-induced liver damage, likely by enhancing antioxidant defenses and scavenging free radicals.

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Regarding alkaline phosphatase (ALK), a different trend was observed. The highest ALK activity was in the Straw. J group (53.35 ± 2.78 U/L), significantly higher than the control and CCl_4 groups. Since ALK is involved in biliary function, this rise may indicate a stimulatory effect of strawberry juice on bile secretion or liver regeneration rather than damage. The CCl_4 group had the lowest ALK activity (36.97 ± 2.64 U/L), suggesting possible cholestasis or suppression of ALK expression due to liver injury. In the combination group, ALK levels (44.81 ± 1.59 U/L) were comparable to the control, indicating a normalization effect due to strawberry juice co-administration.

Table 1. The activities of plasma enzymes of male rabbits treated with CCL_4, Straw.J, and their combination.

Parameter	***Experimental groups***			
Enzyme	**CON**	***CCL_4***	***Straw.J***	**CCL_4+Straw.J**
AST (U/L)	43.86 ± 0.819^b	60.59±5.754^a	38.96± 1.862^b	43.11 ±1.015^b
ALT (U/L)	43.60 ± 2.807^b	54.26 ± 2.396^a	36.8 0 ± 1.825^c	44.23±1.254^b
ALK (U/L)	44.65± 3.309^b	36.97±2.640^b	53.35±2.789^a	44.81±1.590^{ab}

The means ± SE for each treatment group is provided; n = 5. When mean values within a row did not share a common superscript letter (a, b, or c), significant differences ($p<0.05$) were observed.

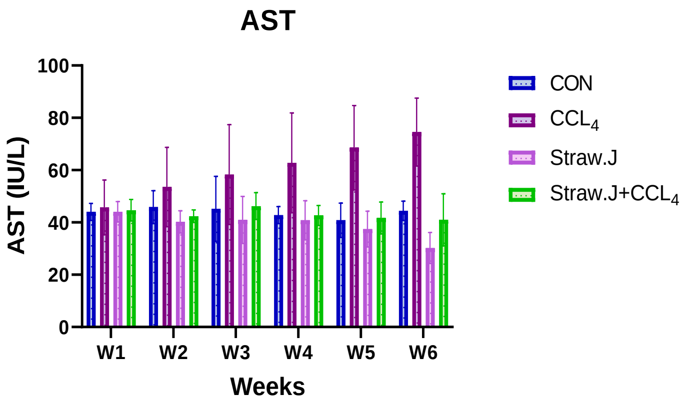

Figure 1. Changes in aspartate transaminase AST during treatment of male rabbits with CCL_4, Straw. J, and their combination

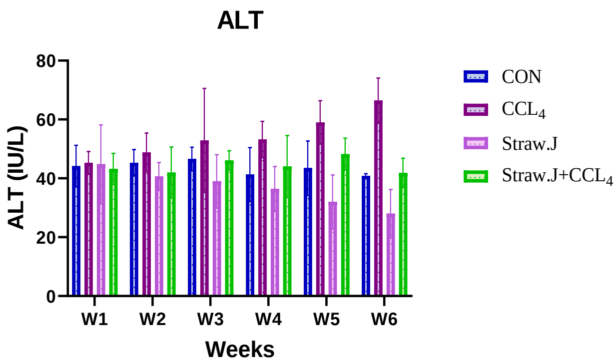

Figure 1.Changes in alanine transaminase ALT during treatment of male rabbits with CCL4, Straw. J, and their combination.

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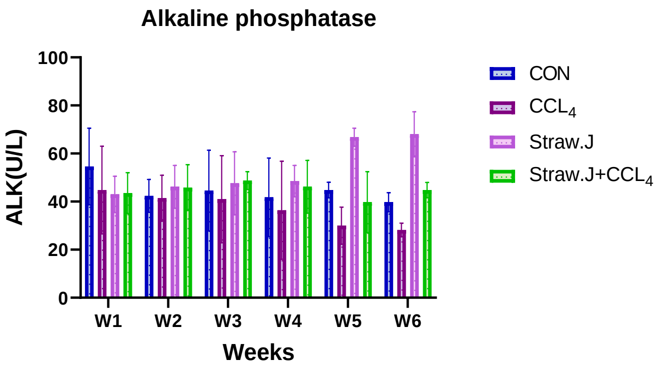

Figure 2. Changes in Alkaline Phosphatase ALK during treatment of male rabbits with CCL_4, Straw, J, and their combination.

The biochemical analysis presented in Table 2 and Figures 4–6 reflects the impact of CCl_4, strawberry juice, and their combination on plasma glucose, creatinine, and urea levels, which are key indicators of metabolic and renal function.
CCl_4 administration significantly increased glucose levels (123.3 ± 2.57 mg/dl) compared to both the control (113.5 ± 3.89 mg/dl) and strawberry juice group (102.51 ± 2.09 mg/dl), suggesting that CCl_4 exposure may disrupt glucose homeostasis. The combination group (112.12 ± 1.80 mg/dl) showed glucose levels comparable to the control, suggesting that strawberry juice mitigated the CCl_4-induced glucose imbalance.
Plasma creatinine, a marker of renal function, was significantly elevated in the CCl_4 group (1.13 ± 0.043 g/dl) compared to all other groups. Conversely, the strawberry juice group exhibited significantly lower creatinine levels (0.67 ± 0.064 g/dl), demonstrating its renoprotective properties. In the combination group (0.76 ± 0.087 g/dl), creatinine levels returned close to the control value (0.77 ± 0.049 g/dl), further supporting the idea that strawberry juice counteracts CCl_4-induced renal toxicity.
Similar to creatinine, urea levels were highest in the CCl_4 group (53.13 ± 4.96 mg/dl), indicating reduced renal clearance and impaired protein metabolism. The strawberry juice group had the lowest urea levels (33.78 ± 0.48 mg/dl), while the combination group (43.04 ± 1.25 mg/dl) was close to the control group (42.7 ± 0.83 mg/dl).

Table 2. Plasma biochemistry of male rabbits treated with CCL_4, Straw.J, and their combination.

Parameter	***Experimental groups***			
	CON	***CCL_4***	***Straw.J***	***CCL_4+Straw.J***
Glucose (mg/dl)	113.5 ± 3.891^{ab}	123.3 ± 2.565^{a}	102.51 ± 2.087^{b}	112.12 ± 1.801^{b}
Creatinine (g/dl)	0.77 ± 0.049^{b}	1.13 ± 0.043^{a}	0.67 ± 0.064^{b}	0.76 ± 0.087^{a}
Urea (mg/dl)	42.7 ± 0.825^{bc}	53.13 ± 4.964^{a}	33.78 ± 0.484^{c}	43.04 ± 1.250^{b}

The means ± SE for each treatment group is provided; n = 5. When mean values within a row did not share a common superscript letter (a, b, or c), significant differences ($p<0.05$) were observed.

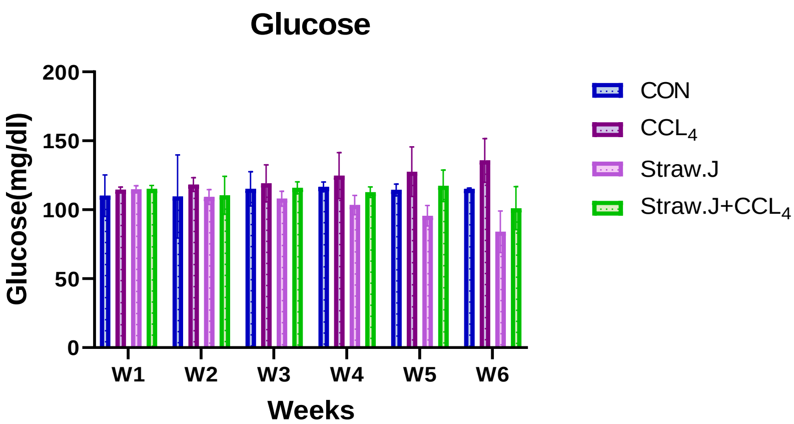

Figure 4. Variations in plasma glucose levels while male rabbits were treated with and CCL_4, Straw. J, and their combination.

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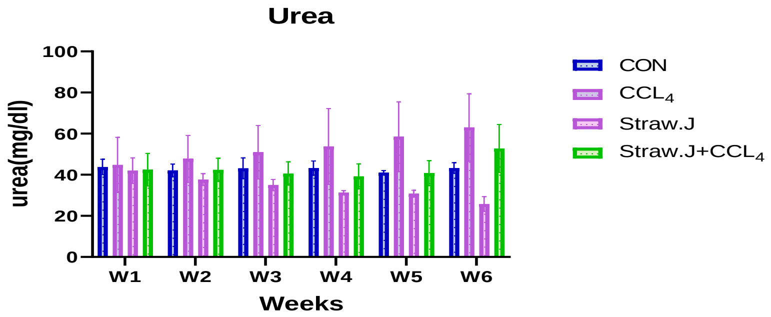

Figure 5. Effects of CCL_4, Straw. J, and their combination on urea levels in male rabbits.

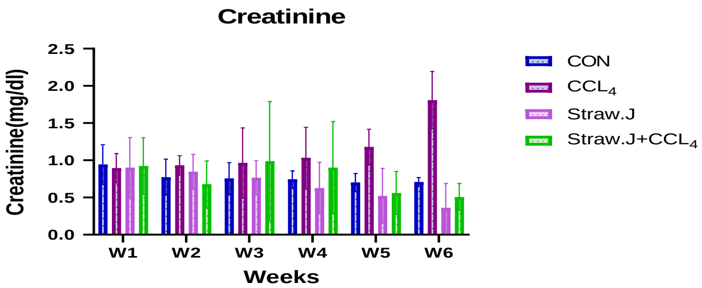

Figure 6. Alterations in Creatinine levels after male rabbits were treated with CCL4, Straw, J, and their combination.

Discussion

The elevation of AST (aspartate aminotransferase) levels in the CCl_4-treated group compared to the control confirms hepatocellular injury, a known outcome of carbon tetrachloride toxicity [20]. Carbon tetrachloride induces liver damage primarily through the formation of reactive trichloromethyl radicals, leading to lipid peroxidation and cell membrane damage in hepatocytes, thereby causing enzyme leakage into the bloodstream [21]. This enzymatic elevation is a hallmark of liver injury and is consistent with previously reported studies on CCl_4-induced hepatotoxicity in animal models [22]. Interestingly, AST activity in the group receiving strawberry juice alone was significantly lower than in both the control and CCl_4 groups, suggesting that strawberry juice might have a suppressive or stabilizing effect on transaminase release [23]. The antioxidant properties of strawberries, particularly due to anthocyanins, flavonoids, and vitamin C, have been documented to improve liver function by reducing oxidative stress and membrane damage. In the combination group (CCl_4 + Straw.J), AST levels were nearly restored to control values, indicating a protective effect of strawberry juice against CCl_4-induced hepatotoxicity. This supports the hypothesis that strawberry-derived antioxidants may effectively scavenge free radicals and reduce lipid peroxidation initiated by CCl_4 metabolites [24].

Similar hepatoprotective effects have been observed with other polyphenol-rich fruits in models of chemically-induced liver injury [25]. The ALT (alanine aminotransferase) profile closely mirrors that of AST, with significant elevation in the CCl_4 group and substantial reduction in the combination group. ALT is a more liver-specific enzyme than AST, and its rise directly reflects hepatocellular membrane disruption [26]. The lower ALT levels in the strawberry juice group again highlight the juice's potential to stabilize liver cell membranes and enhance intracellular antioxidant status [27].

Unlike AST and ALT, alkaline phosphatase (ALK) showed a different pattern, where the highest activity was recorded in the strawberry juice group, significantly higher than both the control and CCl_4 groups. This could be attributed to a potential stimulatory effect of strawberry juice on biliary function or hepatocyte regeneration. Enhanced ALK activity may indicate improved bile flow or enzyme synthesis under antioxidant influence, as observed in previous studies on polyphenol-rich plant extracts [28]. Notably, the ALK level in the combination group was close to the control group, further supporting the hypothesis that strawberry juice normalizes altered enzyme activity. The restoration of ALK to physiological levels might be due to the inhibition of oxidative stress pathways and upregulation of detoxification enzymes. These findings align with evidence suggesting that dietary antioxidants can aid in hepatic enzyme regulation during chemical toxicity [29].

The elevation of plasma glucose levels in the CCl_4-treated group compared to the control suggests hepatic dysfunction and impaired glucose metabolism, likely resulting from oxidative damage to hepatocytes. CCl_4 is known to interfere with carbohydrate metabolism by altering insulin sensitivity and inducing hepatic gluconeogenesis due to hepatocellular injury. This hyperglycemic state has been widely documented in models of CCl_4-induced liver injury [30]. In contrast, rabbits receiving strawberry juice alone showed a significant decrease in plasma glucose, indicating a hypoglycemic effect. This may be attributed to the high

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polyphenolic content of strawberries, especially anthocyanins, which have been shown to enhance insulin sensitivity and suppress hepatic gluconeogenesis [31]. Similar findings were reported by [32], who demonstrated that strawberry supplementation improved postprandial glycemic responses in healthy individuals. Interestingly, the combination group (CCl_4 + Straw.J) exhibited glucose levels comparable to the control, suggesting a protective role of strawberry juice against CCl_4-induced hyperglycemia [33]. This normalization may result from the antioxidant action of strawberry polyphenols, which likely mitigated oxidative damage to insulin-sensitive tissues and restored normal glucose homeostasis [34]. The rise in plasma creatinine in the CCl_4 group reflects renal impairment due to oxidative damage to kidney tissues. CCl_4 is known to generate free radicals that damage renal tubular cells and glomerular structures, leading to decreased glomerular filtration rate (GFR) and accumulation of nitrogenous waste in the blood [35].
Elevated creatinine is a classical biomarker of nephrotoxicity. However, in the strawberry juice group, creatinine levels were significantly reduced, even lower than the control group. This suggests that strawberry juice may have renoprotective properties, possibly due to its antioxidant constituents that neutralize CCl_4-derived free radicals. A study by [36] found that polyphenolic-rich diets improved renal function by reducing oxidative damage and preserving tubular integrity. Regarding urea levels, the CCl_4 group showed a significant increase compared to the control, again indicating compromised renal excretory function. Accumulation of urea is a common result of impaired glomerular filtration, which often accompanies tubular necrosis caused by CCl_4 toxicity [37].

Conclusion

The current findings indicate that CCl_4 induces significant liver and kidney dysfunction, as shown by elevated AST, ALT, creatinine, urea, and glucose levels. Strawberry juice administration alone or in combination with CCl_4 significantly improved these parameters, suggesting its potent protective effects. These results highlight the antioxidant potential of strawberry juice in mitigating CCl_4-induced toxicity.

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Conflict of interest. Nil

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الملخص

الفراولة غنية بالبوليفينولات ومضـادات الأكسـدة التي قد تحمي من الإجهاد التأكسـدي، في حين أن رابع كلوريد الكربون (CCl_4) هو سـم كبدي معروف يُسـتخدم تجريبيًا لإحداث تلف في الكبد والكلى. قيّمت هذه الدراسـة الآثار الوقائية لعصـير الفراولة ضـد الخلل الكبدي والكلوي الناجم عن CCl_4 لدى ذكور الأرانب. كشف التحليل الكيميائي الحيوي أن CCl_4 رفع بشكل ملحوظ مستويات مصل إنزيم ناقلة أمين الأسبارتات (AST) وإنزيم ناقلة أمين الألانين (ALT) وإنزيم الفوسـفاتيز القلوي(ALK) ، مما يشـير إلى تلف الكبد. وبشـكل أكثر تحديدًا، ارتفعت مسـتويات إنزيمي ناقلة أمين الأسـبارتات (AST) وإنزيم ناقلة أمين الألانين (ALT) بشـكل ملحوظ في مجموعة CCl_4 مقارنةً بمجموعة الضـوابط، بينما أدى العلاج بعصـير الفراولة وحده إلى انخفاض كبير في هذه الإنزيمات إلى ما دون قيم مجموعة الضـوابط. أدى تناول عصـير الفراولة مع CCl_4 إلى مسـتويات إنزيمي ناقلة أمين الأسـبارتات (AST) وإنزيم ناقلة أمين الألانين (ALT) تقريبًا إلى مسـتويات مجموعة الضـوابط، مما يشـير إلى تأثير وقائي على الكبد. من المثير للاهتمام أن نشـاط ALK كان أعلى في مجموعة عصـير الفراولة، مما يشـير إلى تحسـن وظائف القناة الصـفراوية، بينما كان أدنى نشاط ALK في مجموعة CCl_4 يدل على احتمالية حدوث ركود صفراوي. وبالجمع بين هذين العاملين، عادت مستويات ALK إلى قيم قريبة من المعدل الطبيعي. كما أظهرت المؤشرات الكلوية والأيضية تغيرات ملحوظة. فقد أدى CCl_4 إلى ارتفاع ملحوظ في مستويات الجلوكوز والكرياتينين واليوريا في البلازما، مما يدل على وجود خلل في الأيض وضـعف كلوي. وقد خفض عصـير الفراولة وحده هذه المؤشرات بشـكل ملحوظ، بينما أعاد تناوله مع CCl_4 مستويات الجلوكوز والكرياتينين واليوريا إلى مستوياتها الطبيعية. وتشير هذه النتائج إلى أن عصير الفراولة له تأثيرات وقائية للكبد والكلى، ربما من خلال خصائصه المضادة للأكسدة والالتهابات.

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