Role of the Synbiotic "Probiotics Bacteria and Prebiotic Edible Mushroom" Against Carbon Tetrachloride-Induced Renal Injury in Rats

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Abstract

The study was conducted to investigate the effect of the Synbiotic "Probiotics Bacteria and Prebiotic Edible Mushroom" against Carbon Tetrachloride-induced renal injury in rats.Thirty-five adult male albino, weighing (150 ± 10 g) were divided into 2 main groups, The first main group (n= 7) rats were fed on basal diet and served as a negative control group . The second main group (n=28) were divided into four subgroups as follows: The first subgroup: fed on basal diet and served as a positive control group. The second subgroup: fed on basal diet supplemented with 5% dried mushroom. The third subgroup: fed on basal diet supplemented with 1 ml of fermented milk (Rayab). The four subgroups: fed on basal diet supplemented with 5% dried mushroom and was given orally 1 ml of fermented milk (Rayab) twice daily . After 4 weeks of starting the experiment, rats in second group was injected with CCl_4 intraperitoneal at (0.1 ml/100 g b. wt.) twice weekly for two weeks. Results indicated that, Supplementation with edible mushroom (5%), rayeb (1 ml), and the combined treatment of mushroom (5%) + rayeb (1 ml) significantly ($P < 0.05$) increased the final body weight (FBW), body weight gain (BWG %) and feed efficiency ratio as compared to the positive control .Moreover, supplemented with Supplementation with edible mushroom (5%), rayeb (1 ml), or the combined treatment of mushroom (5%) and rayeb (1 ml) significantly ($P < 0.05$) reduced the relative organ weights compared to the positive control group. Supplementation with mushroom (5%), rayeb (1 ml), or mushroom (5%) + rayeb (1 ml) significantly ($P < 0.05$) decreased kidney functions compared to the positive control. In addition, Supplementation with mushroom (5%), rayeb (1 ml), or their combination significantly ($P < 0.05$) reduced blood glucose levels compared with the positive control group. Finally, the present study concluded that edible mushroom and rayeb may be given to patients suffer from kidney diseases.

Key Words: Edible mushroom – Rayeb – Renal injury – Carbon Tetrachloride - Rats.

INTRODUCTION

Chronic kidney disease (CKD) affects nearly 10% of the global population and is projected to become the fifth leading cause of death by 2040 due to limitations in current diagnostic and therapeutic strategies (Bikbov et al., 2020). CKD is defined as a persistent abnormality in kidney structure or function lasting more than three months, commonly diagnosed by reduced glomerular filtration rate (GFR <60 mL/min/1.73 m^2) or sustained proteinuria. Diabetes and hypertension remain the primary causes of CKD worldwide **(Jager et al., 2023).**

Carbon tetrachloride (CCl_4) is a well-known hepatotoxin and nephrotoxin. Its metabolism generates free radicals that induce oxidative stress, causing significant damage to the liver, kidneys, lungs, and other organs. Experimental models have confirmed that CCl_4 exposure results in acute and chronic renal injury through lipid peroxidation and cellular damage **(Hassanein et al., 2021; Sun et al., 2022).**

Diet plays a crucial role in shaping gut microbiota, which in turn influences renal health. Interventions such as probiotics, prebiotics, synbiotics, and postbiotics are increasingly explored as nutritional or therapeutic strategies to improve kidney outcomes **(Chiara et al., 2022; Markowiak & Śliżewska, 2023).**

Probiotics, when consumed in adequate amounts, modulate immune responses and reduce inflammation, while prebiotics—mainly fermentable dietary fibers—promote the production of beneficial metabolites such as short-chain fatty acids (acetate, butyrate, propionate) that enhance gut and kidney function **(Mokoena et al., 2021).**

Edible mushrooms, such as *Agaricus bisporus*, are now recognized as functional foods with both nutritional and medicinal importance. They contain bioactive compounds with antioxidant, anti-inflammatory, hepatoprotective, and antidiabetic properties. Importantly, mushrooms also exhibit prebiotic activity, promoting gut microbiota balance and supporting systemic health, including kidney protection **(Qu et al., 2023; Singh et al., 2024).**

Materials and Methods

Materials:

- **Fermented milk (Rayeb)** was purchased from the local market and used as a natural source of probiotics
- **Fungi:** Fresh mushroom (*Agaricus bisporus*) was obtained from the Agriculture Research Center, Giza, Egypt
- **Rats:** A total of 35 adult male albino rats, Sprague Dawley strain of an average body weight 150 ± 10g (n = 35) were obtained from the Laboratory Animal Colony in Helwan, Cairo, Egypt.
- **Chemicals:** The contents of the basal diet; casein, all vitamins, minerals, cellulose, choline, and starch were obtained from El-Gomhoria Company, Cairo, Egypt. Carbon tetrachloride was obtained from Sigma Chemicals Co., St. Louis, USA.
- **Kits:** Kits for biochemical analysis required for estimating parameters used in this study were purchased from Alkan Company for Bio-diagnostic Reagents, Dokki, Cairo, Egypt.

Methods:

A- Microbiological study:

1- **Confirmation of the Probiotics Bacteria:** Confirmation of probiotics bacteria that found in the fermented milk (Rayeb) by identification the bacterial strains was carried out using specific media and the total counts of probiotic bacteria was determined. G

2- **Dried mushroom preparation:** The fungal materials of healthy apparatus fruiting bodies of *Agaricus bisporus* mushroom will be brought to the laboratory in sterile bags. Samples will be cut into small pieces and dried by solar energy, at the National Research Center, Doki, Egypt, then grinded to powder in a mortar and stored at 4-8 °C in a refrigerator until used.

B. Biological study:

- **Induction of renal injury:**

Carbon tetra chloride was dissolved in olive oil and was injected intraperitoneal (IP) in a dose of (0.1 ml/100 g body weight) per rat twice weekly for two weeks **(Ogeturk et al., 2005).** Then random blood samples was taken from each rat to evaluate the induction of renal injury.

- **Experimental design:**

This study was carried out at the Postgraduate Lab of the Faculty of Home Economic, Helwan University. The basal diet was consisted of 100 g sucrose (g/kg diet), 200 g casein (> 80 % protein), 560.7 g corn starch, 40 g corn oil, 50 g cellulose, 35 g mineral mixture, 10 g vitamin mixture, 1.8 g L-Cystine, and 2.5 g choline bitartrate **(Reeves et al., 1993).** Thirty-five adult male albino were kept in aerated cages under hygienic conditions at room temperature (25 ± 3 °C) with a 12 h dark/light cycle and fed on standard diet for one week for adaptation. All diets were formulated to cover the nutrient requirements of rats following the recommendations of the American Institute of Nutrition (AIN-93M) **(Reeves et al., 1993).**

Rats then were randomly divided into two main groups as follows: The first main group (n= 7) rats were fed on basal diet and served as a negative control group. The second main group (n=28) rats were divided into four subgroups as follows: -The first subgroup: fed on basal diet and served as a positive control group. The second subgroup: fed on basal diet supplemented with 5% dried mushroom. The third subgroup: fed on basal diet supplemented with 1 ml of fermented milk (Rayab). The four subgroups: fed on basal diet supplemented with 5% dried mushroom and was given orally 1 ml of fermented milk (Rayab) twice daily, respectively.

After 4 weeks of starting the experiment, rats in second group was injected with CCl_4 intraperitoneal at (0.1 ml/100 g b. wt.) twice weekly for two weeks. All rats was observed each day. Their feed intake will be determined daily, and body weights was obtained every week. Feed Efficiency Ratio was calculated according to **(Champman et al., 1959)** using the following equation:

$$\textbf{Body weight gain \%} = \frac{\textbf{Final body weight} - \textbf{Initial body weight}}{\textbf{Initial body weigh}} \times \textbf{100}$$

$$\textbf{FER} = \frac{\text{Body weight gain (g/d)}}{\text{Feed intake (g/d)}}$$

At the end of experimental period (8 weeks), rats were sacrificed after overnight fasting and blood of each rat was taken from the abdominal aorta under anesthesia by diethyl ether. The serum was separated by leaving the blood samples 15 minutes at room temperature then were centrifuged at 3000 rpm for 20 minutes, then was kept in plastic vials at -20°C until biochemical analysis.

Biochemical Analysis:

Biochemical parameters, including urea, uric acid, creatinine, and glucose, were determined in serum samples from all experimental groups using standard colorimetric methods. Serum urea and creatinine concentrations served as indicators of kidney function **(Kaneko et al., 2008).** Uric acid levels were naturally low due to the activity of the enzyme uricase **(Wolford et al., 1986).** Fasting glucose levels reflected the glycemic status of the animals **(Mitruka and Rawnsley, 1981).**

Statistical analysis: The obtained data was statistically analyzed using the Statistical Package for Social Science (SPSS), Version 23.0. One way analysis of variance (ANOVA) was used for comparing among groups. P value of less than 0.05 was considered to indicate statistical significance **(Snedecor andCochran, 1980).**

Table(1). Effect of Edible mushroom (A.bisporus) and Rayeb supplementation on body weight status in rats induced renal injury

Results illustrated in Table (1) showed Effect of Synbiotic (Probiotic Bacteria and Prebiotic Mushroom) on body weight status in rats with CCl_4-induced renal injury.There were no significant differences in IBW among all groups. In contrast, FBW, BWG% and FER were significantly (P < 0.05) decreased in the positive control group compared to the negative control. Supplementation with edible mushroom (5%), rayeb (1 ml), and the combined treatment of mushroom (5%) + rayeb (1 ml) significantly (P < 0.05) increased FBW, BWG% and FER compared to the positive control group. Furthermore, there were no significant differences in FBW, BWG% and FER among the groups treated with mushroom, rayeb, or their combination when compared with the negative control group. The best results for FBW, BWG%, and FER were observed in the group that received the combined supplementation of mushroom (5%) and rayeb (1 ml). In addition, the mean FI was increased in all treated groups relative to the positive control.

Parameters / Groups	IBW(g)	FBW(g)	BWG%	FI/ day/rat	FER
Negative control	185.15±0.73a	236.17±0.46a	27.56±0.61a	20.50	0.071±0.0013a
Positive control	185.03±2.21a	209.65±2.69b	13.31±0.90b	18.55	0.037±0.0025b
Mushroom 5%	183.91±0.71a	239.61±1.99a	30.28±0.86a	20.30	0.078±0.0023a
Rayeb 1 ml	182.85±0.47a	239.77±2.93a	31.14±1.81a	20.50	0.079±0.0045a
Mushroom 5%+ Rayeb 1 ml	183.83±1.28a	235.91±1.67a	28.34±1.23a	20.00	0.074±0.0029a

*Values were expressed as Means ± SE.
* Values at the same column with different litters are significant at P<0.05

Table(2). Effect of Edible mushroom (A.bisporus) and Rayeb supplementation on relative organs weight status in rats induced renal injury

Results in Table (2) demonstrated the Effect of Synbiotic (Probiotic Bacteria and Prebiotic Mushroom) on relative organs weight status in rats with CCl_4-induced renal injury.. The relative weights of the liver, kidney, heart, and spleen (%) were significantly ($P < 0.05$) increased in the positive control group compared to the negative control group. Supplementation with edible mushroom (5%), rayeb (1 ml), or the combined treatment of mushroom (5%) and rayeb (1 ml) significantly ($P < 0.05$) reduced the relative organ weights compared to the positive control group. It was also observed that there were no significant differences among the groups fed diets supplemented with edible mushroom (5%), rayeb (1 ml), or their combination. Overall, the best improvement in organ weight status was observed in the group that received the combined supplementation of mushroom (5%) and rayeb (1 m)

Parameters / Groups	Liver (%)	Kidney (%)	Heart %	Spleen %
Negative control	2.31±0.163c	0.37±0.007c	0.25±0.007b	0.15±0.005c
Positive control	4.37±0.152a	0.85±0.020a	0.30±0.006a	0.28±0.028a
Mushroom 5%	2.84±0.110b	0.40±0.019c	0.26±0.012b	0.18±0.004bc
Rayeb 1 ml	2.91±0.113b	0.48±0.032b	0.25±0.011b	0.20±0.004b
Mushroom 5%+ Rayeb 1 ml	2.92±0.157b	0.51±0.020b	0.27±0.001b	0.21±0.015b

*Values were expressed as Means ± SE.

* Values at the same column with different litters are significant at ($P<0.05$)

Table (3) : The effect of Edible mushroom(A.bisporus) and Rayeb supplementation on kidney functions levels in rats induced renal injury

Results in Table (3) revealed Effect of Synbiotic (Probiotic Bacteria and Table (3) illustrated the effect of dietary supplementation with edible mushroom (*A. bisporus*) and rayeb on kidney function parameters in rats with CCl_4-induced renal injury. The results showed that serum uric acid , urea and creatinine levels were significantly ($P < 0.05$) increased in the positive control group compared to the negative control group. Supplementation with mushroom (5%), rayeb (1 ml), or the combination of mushroom (5%) and rayeb (1 ml) produced a significant ($P < 0.05$) reduction in the mean serum uric acid , urea and creatinine levels were compared to the positive control.Overall, the best improvements in uric acid, urea, and creatinine levels were recorded in the group that received the combined supplementation of mushroom (5%) and rayeb (1 ml).

Parameters / Groups	Uric Acid (mg/dL)	Urea (mg/dL)	Creatinine (mg/dL)
Negative control	2.66 ± 0.37 [c]	23.62 ± 3.26 [e]	0.74 ± 0.8 [e]
Positive control	6.18 ± 0.24 [a]	55.01 ± 2.14 [a]	2.19 ± 2.3 [a]
Mushroom 5%	3.92 ± 0.45 [b]	39.27 ± 1.45 [c]	1.20 ± 1.3 [c]
Rayeb 1 ml	4.67 ± 0.15 [b]	48.25 ± 1.27 [b]	1.37 ± 1.4 [b]
Mushroom 5%+ Rayeb 1 ml	2.99 ± 0.86 [c]	32.74 ± 1.33 [d]	0.95 ± 1.0 [d]

.Data are expressed as mean ± SE.
Means with different letters in some column are significantly different (P<0.05).

Table (4) : Effect of Synbiotic (Probiotic Bacteria and Prebiotic Mushroom) on lipid profile in CCl_4-Induced Hepatotoxic Rats

Table (4) demonstrated the effect of dietary supplementation with edible mushroom (*A. bisporus*) and rayeb on blood glucose levels in rats with CCl_4-induced renal injury. The results revealed that blood glucose was significantly (P < 0.05) elevated in the positive control compared to the negative control. Supplementation with mushroom (5%), rayeb (1 ml), or their combination significantly (P < 0.05) reduced blood glucose levels compared with the positive control group. The most pronounced improvement was observed in the group that received the combined supplementation of mushroom (5%) and rayeb (1 ml).

Parameters / Groups	Glycose (U/L)
Negative control	99.36 ± 2.38 [d]
Positive control	137.07 ± 1.59 [a]
Mushroom 5%	122.46 ± 2.28 [b]
Rayeb 1 ml	128.21 ± 2.08 [b]
Mushroom 5%+ Rayeb 1 ml	113.36 ± 1.32 [c]

Data are expressed as mean ± SE.
Means with different letters in some column are significantly different at (P<0.05).

Discussion

This study revealed that dietary supplementation with edible mushroom (*A. bisporus*) and Rayeb provided significant protective effects across multiple parameters, including body weight status, relative organ weights ,kidney functions and blood glucose levels, highlighting their potential as functional foods in mitigating metabolic disturbances associated with renal injury**.**

The present study demonstrated that dietary supplementation with edible mushroom (*Agaricus bisporus*) and Rayeb significantly improved body weight status, including final body weight (FBW), body weight gain percentage (BWG%), feed intake (FI), and feed efficiency ratio (FER) in rats with induced renal injury. These findings align with previous reports indicating that edible mushrooms, due to their rich content of proteins, dietary fibers, polysaccharides, and bioactive compounds, can enhance nutrient utilization and metabolic efficiency, thereby supporting growth and weight maintenance under stress conditions **(Kumar et al., 2021; Ma et al., 2022).**

The beneficial effect of *A. bisporus* on growth performance may be attributed to its β-glucans and phenolic compounds, which have been reported to improve gut health, regulate energy metabolism, and modulate lipid and glucose utilization, ultimately leading to better feed efficiency (Sánchez, 2017; Tang et al., 2022). Similarly, Rayeb, as a fermented dairy product, provides probiotics and bioactive peptides that contribute to improved nutrient absorption, modulation of gut microbiota, and enhanced energy availability, which in turn positively influence body weight gain and feed efficiency **(Marco et al., 2021; Kechagia et al., 2020).**

The findings of the present study are consistent with previous evidence showing that renal injury is commonly associated with alterations in the relative weight of vital organs such as the liver, kidney, heart, and spleen. This increase in organ weights under pathological conditions may reflect inflammation, congestion, or cellular hypertrophy due to oxidative stress and metabolic disturbances **(El-Beltagi et al., 2022; Al-Domi et al., 2020).** Therefore, the observed reduction in relative organ weights following dietary supplementation with edible mushroom (*Agaricus bisporus*) and Rayeb (fermented milk) highlights the protective role of these functional foods in mitigating systemic organ dysfunction.

Edible mushrooms are well recognized for their bioactive compounds, including polysaccharides, β-glucans, polyphenols, and ergothioneine, which possess antioxidant and anti-inflammatory properties. These compounds have been shown to protect tissues against oxidative injury, reduce lipid peroxidation, and maintain cellular homeostasis **(Valverde et al., 2021; Jayachandran et al., 2021).**Several studies have demonstrated that dietary mushroom supplementation helps normalize liver and kidney weights in animal models subjected to metabolic stress or toxin exposure **(Sun et al., 2020; El-Beltagi et al., 2022).** This aligns with the present findings where *A. bisporus* supplementation ameliorated organ hypertrophy induced by renal injury.

Similarly, Rayeb supplementation contributed to improvement in organ weight status, which can be explained by the beneficial effects of probiotics on gut microbiota balance, reduction of systemic inflammation, and modulation of immune responses **(Wang et al., 2019; Hassan et al., 2023).**

The findings of the present study regarding the improvement of kidney function markers (urea, creatinine, and uric acid) after supplementation with *Agaricus bisporus* and Rayeb are in agreement with previous reports that highlighted the nephroprotective effects of mushrooms and probiotic dairy products under conditions of renal injury.

Recent studies have confirmed that mushrooms, particularly *A. bisporus*, are rich in bioactive compounds such as β-glucans, phenolics, and essential amino acids, which exert antioxidant and anti-inflammatory effects that protect renal tissues. For example, **Wang et al. (2023)** demonstrated that mushroom polysaccharides significantly reduced serum urea, creatinine, and uric acid, while improving renal histopathology in diabetic rats. Similarly, **Zhao et al. (2022)** reported that β-glucan supplementation alleviated ischemia–reperfusion-induced kidney injury by lowering oxidative stress and improving renal function markers.

On the other hand, fermented dairy products like Rayeb have gained increasing attention for their role in modulating the gut–kidney axis, thereby reducing the accumulation of uremic toxins, including uric acid**. Hsu et al. (2024)** found that probiotic supplementation in CKD patients decreased serum creatinine, urea, and uric acid levels, while **Liu et al. (2023)** showed that synbiotics improved renal function and restored gut microbiota balance in experimental CKD models.

Additionally, **Alkhalaf et al. (2024)** reported significant clinical and biochemical improvements in patients with end-stage renal disease after probiotic intake, supporting their use as adjunctive therapies.

Interestingly, combined interventions using natural antioxidants and probiotics have shown superior protective effects compared to single treatments. **Sharma et al. (2022) and Mohammadi et al. (2023)** highlighted that the synergistic action of dietary antioxidants and probiotics more effectively restored kidney function markers (urea, creatinine, and uric acid) and reduced oxidative stress. This aligns with the present findings, where the group receiving both mushroom and Rayeb supplementation showed the greatest improvements.

In line with the improvements observed in kidney and liver functions as well as lipid profile, the present study also revealed that dietary supplementation with edible mushroom (*Agaricus bisporus*) and Rayeb was associated with better regulation of blood glucose levels in rats with renal injury. The hypoglycemic activity of mushrooms is largely attributed to their rich content of β-glucans, polysaccharides, and phenolic compounds, which have been shown to enhance insulin sensitivity, delay carbohydrate digestion, and modulate glucose uptake **(Jayachandran et al., 2017; Ma et al., 2018; Rahman et al., 2020).**

On the other hand, fermented dairy products such as Rayeb are rich in probiotics and bioactive peptides that exert beneficial effects on glucose homeostasis through improving gut microbiota composition, reducing systemic inflammation, and enhancing insulin signaling **(Ejtahed et al., 2020; Yadav et al., 2021).** Several experimental and clinical studies have further confirmed that probiotic-fermented milk products can reduce fasting blood glucose and improve insulin resistance in both diabetic and renal injury models **(Davaatseren et al., 2020; El-Sayed et al., 2022).**

The synergistic effect observed when combining *A. bisporus* with Rayeb may be explained by the complementary antioxidant, anti-inflammatory, and gut-modulating properties of these functional foods, which together contribute to restoring glucose balance and protecting against hyperglycemia-induced complications. These findings are in agreement with other research supporting the integration of functional foods into dietary strategies for mitigating metabolic disturbances associated with renal dysfunction **(Rahman et al., 2020; El-Sayed et al., 2022).**

Conclusions

The present study demonstrated that supplementation with edible mushroom (*Agaricus bisporus*) and Rayeb exerted a protective effect against induced renal injury in adult male rats. The combined treatment significantly improved body weight gain and feed efficiency ratio, relative organ weights, kidney functions and blood glucose. Among all treatments, the combination of mushroom (5%) and Rayeb (1 ml) showed the most pronounced protective effect, suggesting a synergistic action that contributes to restoring normal physiological and metabolic functions.

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دور السينبايوتيك "بكتيريا البروبيوتيك والفطر الصالح للأكل" في الوقاية من الإصابة الكلوية المستحثة بثلاثي كلوريد الكربون في الفئران

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الملخص

هدفت هذه الدراسة إلى تقييم التأثير الوقائي لمزيج السينبايوتيك المكوّن من بكتيريا البروبيوتيك والفطر الصالح للأكل ضد الإصابة الكلوية المستحثة بثلاثي كلوريد الكربون (CCl_4) في الفئران. شملت التجربة خمسة وثلاثين فأر ذكر البينو، بوزن ١٥٠ ± ١٠ جم، تم تقسيمها عشوائيًا إلى مجموعتين رئيسيتين. المجموعة الأولى ($n = 7$) تم إطعامها النظام الغذائي الأساسي وشكلت المجموعة الضابطة السالبة. أماالمجموعة الثانية ($n = 28$) فتم تقسيمها إلى أربع مجموعات فرعية:

- المجموعة الفرعية الأولى: ضابطة موجبة تلقت النظام الغذائي الأساسي.
- المجموعة الفرعية الثانية: تلقت النظام الغذائي الأساسي مضافًا إليه ٥٪ فطر مجفف.
- المجموعة الفرعية الثالثة: تلقت النظام الغذائي الأساسي مضافًا إليه ١ مل من اللبن المخمر (رايب).
- المجموعة الفرعية الرابعة: تلقت النظام الغذائي الأساسي مضافًا إليه ٥٪ فطر مجفف وأُعطيت ١ مل من الرايب عن طريق الفم مرتين يوميًا.

بعد أربعة أسابيع، تم حقن الفئران في المجموعة الثانية بحقن CCl_4 داخل الصفاق بجرعة ٠,١ مل/١٠٠ جم وزن الجسم، مرتين أسبوعيًا لمدة أسبوعين. أظهرت النتائج أن المكملات بالفطر الصالح للأكل (٥٪)، أو الرايب (١ مل)، أو مزيجهما، أدت إلى زيادة معنوية ($P < 0.05$) في الوزن النهائي للفئران، ونسبة زيادة الوزن، وكفاءة استخدام الغذاء مقارنة بالمجموعة الضابطة الموجبة. كما لوحظ انخفاض معنوي ($P < 0.05$) في الأوزان النسبية للأعضاء، وتحسّن مؤشرات وظائف الكلى، ومستويات الجلوكوز الصائم في الدم بالمجموعات المعالجة مقارنة بالمجموعة الضابطة الموجبة. ختامًا، أظهرت الدراسة أن الفطر الصالح للأكل والرايب، سواء بشكل فردي أو مشترك، قد يمتلكان تأثيرًا وقائيًا ضد الإصابة الكلوية المستحثة بـCCl_4 ، ويمكن أخذهما في الاعتبار كإضافة غذائية لدعم صحة الكلى.

الكلمات المفتاحية :الفطر الصالح للأكل – الرايب – الإصابة الكلوية – ثلاثي كلوريد الكربون – الفئران