

## RESEARCH ARTICLE

### The Possible Protective Effect of Galantamine against Paracetamol Induced Hepatic and Renal Toxicity in Rats

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#### Abstract

Paracetamol (PCM) is a pain reliever that is also used as an antipyretic and an analgesic after surgery. Overdoses, such as those used in suicide attempts or unintentional mishaps, can produce hepatotoxicity, which can result in rapid liver failure and renal necrosis. Galantamine (GAL) is a reversible and competitive cholinesterase inhibitor that is used to treat Alzheimer's disease and other memory-related diseases. This study aimed to investigate the possible protective role of GAL (0.3 mg/kg P.O) for successive 28 days against PCM (2 g/kg BW P.O) toxicity on day 29 of the experiment. At day 30, blood samples were collected for evaluation of liver function such as serum alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), total protein, albumin, globulin, albumin/globulin (A/G) ratio and kidney function (urea and creatinine). The obtained results revealed that GAL decreased the levels of ALT, AST, ALP, urea, creatinine and improved the protein profile in comparison with PCM treated group. In conclusion, GAL had a protective effect against PCM toxicity by improving liver and kidney function against hepatic and renal toxicity induced by PCM in rats.

**Keywords:** Paracetamol, Galantamine, Renal toxicity, Hepatotoxicity, Liver and kidney enzymes.

#### Introduction

Paracetamol (PCM) was identified in Germany at the end of the nineteenth century, but it was not frequently used before the middle of the twentieth. PCM uses were limited due to caution about the cytotoxicity of more than analgesics, but PCM was judged to be acceptable at normal doses. There were no other reports of PCM misuse, and its use expanded gradually, replacing the more dangerous analgesics existing at the time (acetanilide and phenacetin) [1].

In Egypt, PCM was included in the Ministry of Health protocol for the short-term management of illnesses that required quarantine and nursing at home, as well as urgent patients that needed hospitalization [2]. As a result, the rate of PCM consumption expanded, as did the toxicity of PCM reliance. Taking just a slight bit more than the

authorized total daily dose of PCM (4 g) may provoke liver problems in certain users. The average quantity attributable to liver diseases was 5–7.5 g/day, approaching the authorized limit daily dose of 4 g. unusual cases of acute liver damage have been documented [3].

In the United States, Acute liver failure caused by PCM had become the leading cause of liver transplantation and the second leading cause of liver failure. PCM is catabolized by multiple routes: glucuronidation, sulfation, or the cytochrome P450 enzyme system. The alkylating metabolite N-acetyl-P-benzoquinone imine (NAPQI) is crucial for PCM's negative impacts [4].

When acetaminophen is taken in therapeutic doses, about 90% of the PCM goes through a mix of sulphate and glucuronide coupling. As harmless byproducts, these complexes are excreted. The urine excretes an additional 5% of the total compound. The

cytochrome P450 system mixed function oxidase system, principally enzyme CYP2E1, catalyzes the conversion of a small fraction to NAPQI, a highly reactive and poisonous compound. NAPQI employs native glutathione in the liver as a substrate, ending with the manufacture of mercapturic acid, a harmless residue discharged in the urine. When a person takes too much acetaminophen, the regular metabolic circuits become saturated, and more acetaminophen is shuffled through the P450 system. As a result, excess NAPQI is created, and when glutathione content is decreased by 70%, the extra NAPQI joins with hepatocytes, resulting in cellular toxicity and hepatic necrosis [5].

Although the precise mechanisms are uncertain, oxidative stress is thought to be involved in the pathogenesis of APAP-induced kidney injury, as revealed by accelerated lipid peroxidation and glutathione depletion [6].

Alzheimer's disease (AD) is amongst the most severe brain diseases to treat, with serious medical and social implications. The progression of dementia is linked to an increase in oxidative stress in the brain. GAL hydrobromide has been shown to be effective in treating Alzheimer's disease. GAL could be a multi-mode of action neurotherapeutic medication for the treatment of Alzheimer's disease. It's an Acetylcholinesterase (AChE) inhibitor that's reversible and competitive. It also increases the sensitivity of nicotinic acetylcholine receptors (nAChRs) to Ach by binding allosterically to them [7].

In hepatic stellate and renal cells, 7 nAChRs subtypes have been identified. Furthermore, the OH group of GAL is a protector of reactive oxygen species (ROS), indicating that it has antioxidant action [8].

This study aimed to examine the possible protective effects of GAL against hepatic and renal toxicity induced by PCM in rats.

## Materials and Methods

### Drugs

GAL (Famalzyl) tablets (each tablet containing 8 mg) was purchased from October

Pharma, Egypt. PCM (panadol) tablets (each tablet containing 500 mg) was purchased from GlaxoSmithKline, London, England.

### Animal model and study protocols

Sprague-Dawley male albino rats (n = 40) weighing 150 to 200 g were obtained from the Animal House of the Faculty of Veterinary Medicine, Zagazig University. The rats were randomly divided into 4 groups (n = 10/group). Negative control group 1: the animals were left without any treatment. The rats in the second group (GAL) were given oral doses of GAL (0.3 mg/kg BW) by gavage daily for 28 days [9]. Rats in the 3rd group (PCM) administered a single oral dose of PCM (2 g/kg BW) by gavage on day 29 of the experiment [10]. The 4th group (PCM + GAL): rats in this group administrated oral doses of GAL (0.3 mg/kg) daily by gavage for successive 28 days and PCM (2 g/kg BW) by gavage on day 29 of the experiment. The study was approved by the Institutional Animal Care and Use Committees of Zagazig University (ZU-IACUC) with approval No. ZU\_IACUC/2/F/186/2021.

### Sample collection and processing

The rats were fasted overnight before being anaesthetized the next day with 87 mg of ketamine/kg BW and 13 mg of xylazine/kg BW [11]. After blood samples were obtained from the vena cava, the blood was collected, permitted to coagulate, and then centrifuged at 3,000 rpm for 15 min. The serum samples were stored at -20 °C until needed.

### Determination of liver functions as markers of hepatic injury

The determination of ALT and AST concentrations in serum was performed by using enzymatic colorimetric kits (ALT Assay Kit abcam, USA, Catalog No: ab105134 and ab105135, respectively) [12]. ALP was determined by using enzymatic colorimetric kits (ALP Assay Kit abcam, USA, Catalog No: ab83369) [13]. Total proteins and albumin were determined by using enzymatic colorimetric kits from Spinreact, Girona, Spain

using the manufacturing instructions [14, 15]. Globulin was calculated as the difference between total proteins and albumin [15].

#### ***Determination of hepatorenal markers in serum***

Urea was determined by using enzymatic colorimetric kits (Urea Assay Kit abcam, Catalog No: ab83362) using the manufacturing instructions [16]. Creatinine was measured by using Creatinine Assay Kit abcam, Catalog No: ab65340 [17].

#### ***Data analysis***

The data was analysed using the computerized SPSS version 16 application. The results were reported as a mean standard deviation. One-way ANOVA was used to examine the data, and Duncan's test was used to determine significance.  $P < 0.05$  was considered significant [18].

### **Results**

#### ***Effect of oral administration of PCM, GAL and their combination on hepatic and renal markers***

##### ***Effect on liver functions enzymes***

The obtained result in Table (1) revealed a significant increase ( $P \leq 0.05$ ) in the serum level of ALT in the group of rats treated with PCM in comparison with the control group (Figure 1). Meanwhile, the group of rats administrated both PCM and GAL revealed a significant decrease ( $P \leq 0.05$ ) in the level of ALT in comparison with group 3, which was treated with PCM only. Moreover, the group of rats administered a GAL revealed no significant difference in the level of ALT in comparison with control one.

Our data represented in Table (1) and Figure (1) revealed a significant increase ( $P \leq 0.05$ ) in the serum level of AST in the group of rats treated with PCM in comparison with control. Meanwhile, the group of rats administrated both PCM and GAL revealed a significant decrease ( $P \leq 0.05$ ) in the level of AST in comparison with group 3 which was treated with PCM only. Moreover, the group of rats administered a GAL revealed no

significant difference in the level of AST in comparison with the control one.

The obtained results in Table (1) and Figure (1) revealed a significant increase ( $P \leq 0.05$ ) in the serum level of ALP in the group of rats treated with PCM in comparison with control. Meanwhile, the group of rats administrated both PCM and GAL revealed a significant decrease ( $P \leq 0.05$ ) in the level of ALP in comparison with group 3 which was treated with PCM only. Moreover, the group of rats administered a GAL revealed no significant difference in the level of ALP in comparison with the control one.

##### ***Determination of protein profile***

The obtained result in Table (2) and Figure (2) revealed a significant decrease ( $P \leq 0.05$ ) in the level of serum total protein in the group of rats treated with PCM in comparison with control. Meanwhile, the group of rats administrated both PCM and GAL revealed a significant increase ( $P \leq 0.05$ ) in the level of the total protein in comparison with group 3, which was treated with PCM only. Moreover, the group of rats administered a GAL showed no significant difference in the level of total protein in comparison with the control group.

A significant decrease ( $P \leq 0.05$ ) in the level of serum albumin was observed in the group of rats treated with PCM in comparison with control in in Table (2) and Figure (2). Meanwhile, the group of rats administrated both PCM and GAL revealed a significant increase ( $P \leq 0.05$ ) in the level of albumin in comparison with group 3, which was treated with PCM only. Furthermore, there was no significant difference in albumin levels between the GAL-treated rats and the control group.

The attained results in in Table (2) and Figure (2) revealed no significant difference in the level of total globulin between control and other treated groups.

The obtained result from in Table (2) and Figure (2) revealed a significant decrease ( $P \leq 0.05$ ) in the level of A/G ratio in the group of rats treated with PCM in comparison with

control. Also, the group of rats administrated both PCM and GAL revealed a significant difference in the level of A/G ratio in comparison with group 3, which was treated with PCM only and revealed a significant decrease ( $P \leq 0.05$ ) in A/G ratio in comparison with the control group. Furthermore, in comparison to the control group, rats given a GAL showed no significant difference in A/G ratio.

#### Effect on kidney function tests

As shown in Table (3) and Figure (3), urea levels increased significantly ( $P \leq 0.05$ ) in the PCM-treated rats compared to the control group. Meanwhile, the group of rats administered both PCM and GAL revealed a significant decrease ( $P \leq 0.05$ ) in the level of

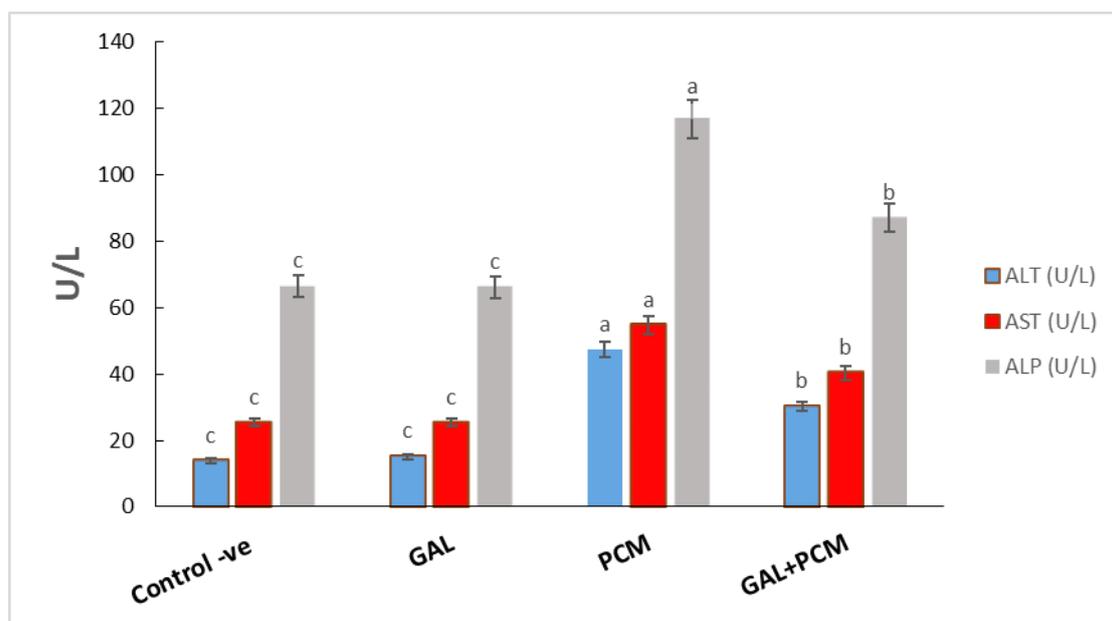
urea in comparison with group 3, which was treated with PCM only. Moreover, the group of rats administered a GAL revealed no significant difference in the level of urea in comparison with the control one.

The obtained result in Table (2) and Figure (3) revealed a significant increase ( $P \leq 0.05$ ) in the creatinine level in the group of rats treated with PCM in comparison with control. Meanwhile, the group of rats administrated both PCM and GAL revealed a significant decrease ( $P \leq 0.05$ ) in the level of creatinine in comparison with group 3, which was treated with PCM only. Moreover, the group of rats administered a GAL revealed no significant difference in the level of creatinine in comparison with the control one.

**Table 1. The effect of oral administration of PCM (2 g/kg BWBW), GAL (0.3 mg/kg BW) and their combination on ALT (U/L) in male albino rats.**

Group	ALT (U/L)	AST (U/L)	ALP (U/L)
G.1: Control -ve	13.92 <sup>c</sup> ± 0.89	25.44 <sup>c</sup> ± 1.48	66.48 <sup>c</sup> ± 2.12
G. 2 Rats (GAL)	15.12 <sup>c</sup> ± 0.97	25.45 <sup>c</sup> ± 1.49	66.10 <sup>c</sup> ± 2.88
G.3: Rats (PCM)	47.28 <sup>a</sup> ± 1.87	54.72 <sup>a</sup> ± 1.40	116.88 <sup>a</sup> ± 4.20
G: 4: Rats (GAL + PCM)	30.24 <sup>b</sup> ± 1.82	40.32 <sup>b</sup> ± 1.45	87.12 <sup>b</sup> ± 5.04

Mean within the same column carrying different superscripts are significantly different at  $P < 0.05$ . Paracetamol (PCM), Galantamine (GAL), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST).

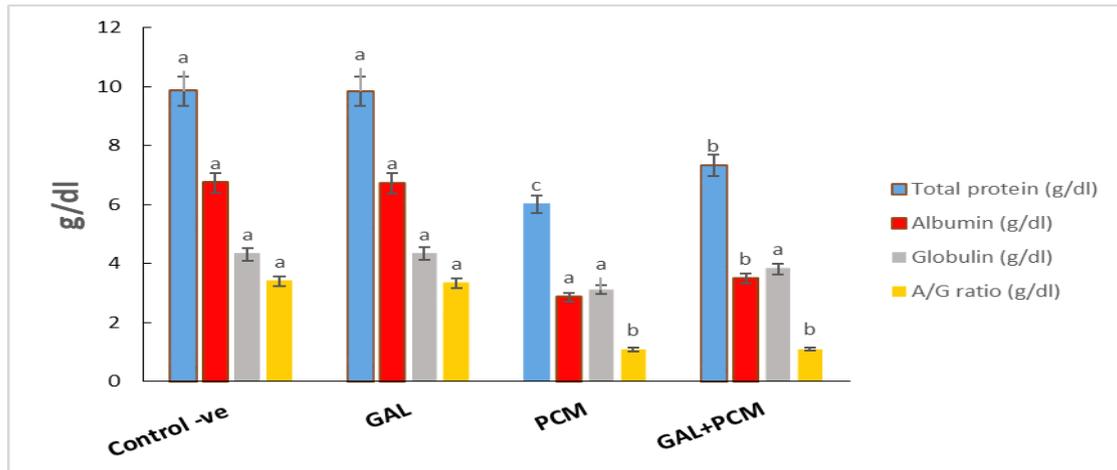


**Figure 1: The impact of oral administration of PCM (2 g/kg BW), GAL (0.3 mg/kg BW) and their combination on ALT, AST, ALP (U/L) in male albino rats.**

**Table 2. The effect of oral administration of PCM (2 g/kg BW), GAL (0.3 mg/kg BW) and their combination total protein (g/dl) in male albino rats.**

Group	Total protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)	A/G ratio (g/dl)
G.1: Control -ve	9.86 <sup>a</sup> ± 0.35	6.74 <sup>a</sup> ± 0.37	4.32 <sup>a</sup> ± 0.25	3.39 <sup>a</sup> ± 0.24
G: 2 Rats (GAL)	9.84 <sup>a</sup> ± 0.26	6.72 <sup>a</sup> ± 0.25	4.33 <sup>a</sup> ± 0.11	3.32 <sup>a</sup> ± 0.13
G.3: Rats (PCM)	6.02 <sup>c</sup> ± 0.53	2.86 <sup>c</sup> ± 0.24	3.11 <sup>a</sup> ± 0.31	1.09 <sup>b</sup> ± 0.052
G: 4: Rats GAL+ PCM)	7.34 <sup>b</sup> ± 0.25	3.50 <sup>b</sup> ± 0.16	3.82 <sup>a</sup> ± 0.17	1.102 <sup>b</sup> ± 0.058

Mean within the same column carrying different superscripts are significantly different at  $P < 0.05$ . Paracetamol (PCM), Galantamine (GAL), albumin/globulin (A/G).

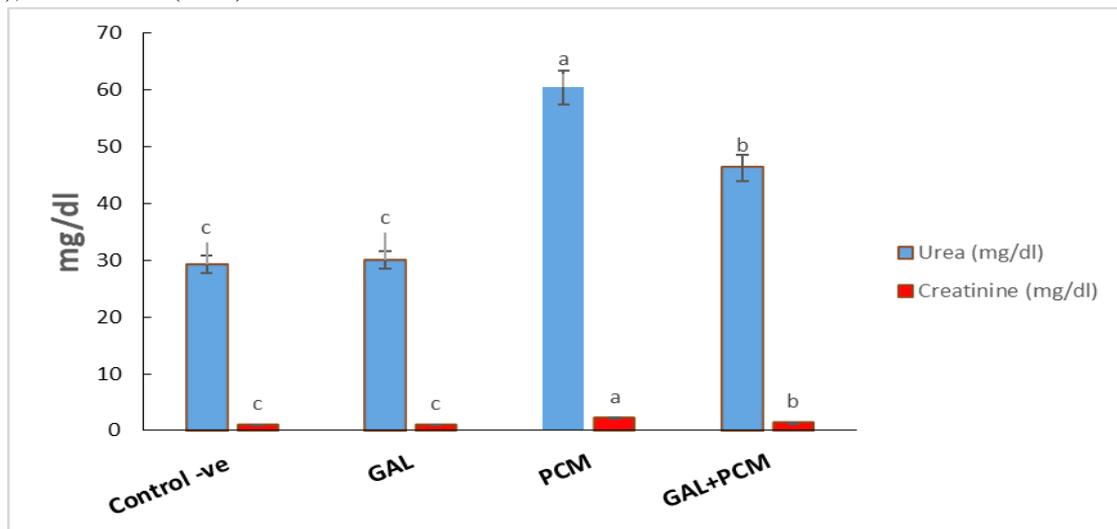


**Figure 2: The impact of oral administration of PCM (2 g/kg BW), GAL (0.3 mg/kg BW) and their combination on protein profile in male albino rats.**

**Table 3. The effect of oral administration of PCM (2 g/kg BW), GAL (0.3 mg/kg BW) and their combination on urea and creatinine (mg/dl) in male albino rats .**

Group	Urea (mg/dl)	Creatinine (mg/dl)
G.1: Control (C)	29.28 <sup>c</sup> ± 1.24	0.95 <sup>c</sup> ± 0.055
G: 2 Rats (GAL)	30.10 <sup>c</sup> ± 0.85	0.93 <sup>c</sup> ± 0.53
G.3: Rats (PCM)	60.48 <sup>a</sup> ± 6.010	2.11 <sup>a</sup> ± 0.31
G: 4: Rats (GAL + PCM)	46.32 <sup>b</sup> ± 5.48	1.25 <sup>b</sup> ± 0.13

Mean within the same column carrying different superscripts are significantly different at  $P < 0.05$ . Paracetamol (PCM), Galantamine (GAL).



**Figure 3: The impact of oral administration of PCM (2 g/kg BW), GAL (0.3 mg/kg BW) and their combination on urea & creatinine (mg/dl) in male albino rats.**

## Discussion

The liver is a major organ that manages different physiological reactions in the body and is involved in biochemical activity in the human being. It has a large capacity to detoxicate poisonous compounds and produce helpful substances, and it is employed in numerous critical functions such as metabolism, division, and storage. In addition, the kidney is one of the most prevalent excretory organs for medication and environmental toxins. The composition and structure of the liver have been found to be altered by a variety of medicines, chemicals, and pollutants. Some medicines cause broad kidney damage, including tubular damage [19].

The present study was designed to investigate the adverse effects of PCM and the effect of GAL against hepatic and renal disturbances induced in rats by PCM. Co-administration of PCM and GAL to male albino rats resulted in significant decrease in serum creatinine and urea levels when compared with the group treated with PCM.

ALT is found in many organs, particularly the liver, and its elevation indicates hepatic damage. AST is found in metabolically active tissues such as the kidney, brain, red blood cells, skeletal muscle, heart, and liver. When these cells are destroyed, AST is released. ALP levels are elevated in a variety of tissues, and this could be attributed to increased osteoplastic activity. Its rise is linked to a variety of organ ailments, including liver illness, hepatitis, and bile duct obstruction, making it a marker for hepatobiliary diseases. Its amount is enhanced since it is positioned on the hepatic canaliculus, especially when the bile duct is obstructed [20].

In animal and human studies, serum creatinine and urea levels have been routinely utilized as reliable measures of kidney dysfunction [21]. The decomposition result of creatine phosphate in muscle is creatinine, whereas urea is the chief nitrogenous end product of protein and amino acid breakdown secreted by the liver [22].

When a high dose of PCM was given to male albino rats, serum creatinine and urea levels increased significantly when compared to the control group. Kidney function metrics include serum creatinine and urea concentrations, with creatinine being more specific than urea concentrations. In another study suggested that at a dose of 1 g/kg, APAP can cause severe nephrotoxicity [6]. The findings are consistent with those reported by Wans *et al.* [23], who found an increase in serum urea and creatinine levels in rats given a single dosage of PCM (2 g/kg BW) and these findings corroborate our findings.

Dahiya *et al.* [24] demonstrated that PCM caused a gradual increase in the levels of AST and ALT enzymes. Also, the PCM's effects on renal function, blood urea, and serum creatinine levels were shown to rise gradually in the PCM-treated group in comparison with the control group. Hafez *et al.* [25] studied the toxicity of PCM in the liver and kidney. Their results revealed that in the group that was treated with PCM, there was a significant increase in AST, ALT, ALP, total bilirubin, urea, and creatinine.

Motawi *et al.* [26] studied the impact of PCM toxicity on the liver and kidney in rat models. When compared to the control group, PCM supplementation resulted in a significant increase in serum ALT, AST, and ALP. PCM causes kidney impairment by increasing serum levels of KIM-1, urea, creatinine, and uric acid. The same results were recorded by Madinah *et al.* [27], who observed an increase in serum creatinine and urea in male Wistar rats given a single oral dose of PCM at 1 g/kg BWn the eighth day of the experiment and found the same results.

The hepato-renal toxicity induced by PCM in rats was also evaluated and the results revealed that the PCM-treated group had a significant rise in serum creatinine and urea, indicating the severity of kidney damage caused by PCM. Also, there was a considerable increase in AST and ALT levels [28]. A previous investigation found that a male albino wistar rat administered an oral

dose of PCM (2 g/kg BW) on day 15 of the experiment resulted in a significant increase in serum creatinine and urea concentration [10].

The impact of PCM on hepato–renal damage was studied in Swiss albino mice by Singh and Mani [29]. The increased levels of serum AST, ALT, ALP, bilirubin, creatinine, urea, and uric acid in mice treated with PCM revealed that the drug's harmful effects had affected liver and renal functioning. Another experiment revealed the toxic impact of PCM on liver damage and renal impairment. In another study, PCM raised the blood creatinine, blood urea nitrogen, ALT, AST, and lactate dehydrogenase activity, white blood cells, and platelet count while dramatically lowering hemoglobin, serum total protein, albumin, and uric acid levels when compared to the control [30].

Askaripour *et al.* [31] studied the effects of GAL as a cholinergic agent on the acute and late phases of hepatic ischemia-reperfusion. In the acute phase of ischemia-reperfusion, pre-ischemic therapy with GAL reduced the levels of ALT, AST, and ALP. Post-ischemic therapy with GAL reduced all enzymes. It was suggested that pre-and post-ischemic GAL therapy could reduce hepatic ischemia-reperfusion injury in the acute versus late stages.

Satapathy *et al.* [32] demonstrated the impact of GAL in obesity models. At which point, the group of HFD-mice revealed an increase in ALT levels and lipid accumulation in the liver at the end of the 12-week research period, and GAL dramatically reduced ALT levels. The potential of GAL's as a potential anti-diabetic agent was evaluated in the diabetic n5-STZ rat model, and the result revealed that there was a significant increase in total cholesterol, free fatty acids, and serum AST and ALT in the diabetic model [33].

Simeonova *et al.* [34], studied the AChE inhibitor GAL and the antioxidant polyphenol curcumin hybrid that was developed and evaluated for significant AChE inhibition *in vitro*. When compared to the control, GAL ameliorated the levels of ALT, AST, and uric

acid. It was proved that GAL is a potential multitarget therapeutic candidate for the treatment of neurodegenerative illnesses since it is an AChE inhibitor with significant antioxidant action.

## Conclusion

In conclusion, these data can support the use of GAL to minimize toxicity for the therapeutic benefit in the management of hepatic and renal toxicity. The study points to the useful effect of GAL as a potential protective agent that may have benefits in the prevention of liver and renal disorders and also as an add-on drug with other oral standard drugs, a common trend for the time being for the management of hepatic and renal toxicity.

## Conflict of interest

The authors declare no conflict of interests.

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### الملخص العربي

#### التأثير الوقائي المحتمل للجالاتامين ضد التسمم الكبدي والكلوي الناجم عن الباراسيتامول في الفئران

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الباراسيتامول، هو مسكن للألام يستخدم أيضاً كمخفف للحرارة ومسكن عند البشر بعد الجراحة أو عند الإصابة بالحمى. يمكن أن تؤدي الجرعات الزائدة ، مثل تلك المستخدمة في محاولات الانتحار أو الحوادث غير المقصودة ، إلى تسمم الكبد ، مما قد يؤدي إلى فشل الكبد السريع والنخر الكلوي. الجالاتامين هو أحد مثبطات الكولينستيراز القابلة للعكس والتنافسية التي تستخدم لعلاج مرض الزهايمر والأمراض الأخرى المتعلقة بالذاكرة. هدفت هذه الدراسة إلى التحقيق في الدور الوقائي المحتمل للجالاتامين 0.3 مجم / كجم لمدة 28 يوماً على التوالي ضد سمية الباراسيتامول 2 جم / كجم في اليوم 29 من التجربة ، في اليوم 30 تم جمع عينات الدم لتقييم وظائف الكبد مثل الاسبرتاتامينوترانسفيريزوالالانينامينوترانسفيريزوالفوسفاتيز القلوية ، البروتين الكلي ، الألبومين ، الجلوبيولين ، نسبة الألبومين / الجلوبيولين ووظائف الكلى (اليوريا والكرياتينين) . وقد كشفت النتائج أن الجالاتامين قلل من مستويات الاسبرتاتامينوترانسفيريزوالالانينامينوترانسفيريزوالفوسفاتيز القلوية واليوريا والكرياتينين وحسن صورة البروتين مقارنةً بالمجموعة المعالجة بالباراسيتامول. الخلاصة أن الجالاتامين كان له تأثير وقائي للتخفيف من سمية الباراسيتامول عن طريق تحسين وظائف الكبد والكلى ضد السمية الكبدية والكلوية التي يسببها الباراسيتامول في الفئران.