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Histopathological evaluation of the potential ameliorating effects of stem cells and rutin against acute renal toxicity induced by acetaminophen in male rats

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Abstract:
The present investigation aims at a histopathological assessment of the potential ameliorating effects of stem cells and rutin against acute renal toxicity by acetaminophen in male rats. Two main experiments were conducted using seventy rats. Twenty immature rats were used in the primary investigation as a source of bone marrow. In the second investigation, fifty mature rats were split into two groups: G (1) served as the control group, and G (2) received 750 mg/kg b.w./72 hours of oral acetaminophen (APAP) for three weeks. This group was divided into four subgroups: (A) rats receiving APAP for three weeks, then left for two months without treatment; (B) rats receiving APAP for three weeks, followed by treatment with rutin (RUT) (25 mg/kg b.w./d) for two months; (C) rats receiving APAP for three weeks, then the rats were injected in their tail vein by mesenchymal cells (MS) (1.5x 106 cells in 0.5 PBS) for two months; and (D) rats received APAP for three weeks, then MS injected in the tail vein, and received RUT for two months. After taking tissue sections of the kidneys: it was found that the rats receiving APAP alone had perivascular edema with blood vessel congestion, tubular deterioration, glomerulus deteriorating lesions, and inflammatory cell penetration in their renal tissues. Whereas the APAP RUT and APAP-MS-RUT groups showed few tubular deteriorations. Moreover, APAP MS displayed the typical kidney histological structure. The results of the investigation showed that MS significantly lowers acute renal toxicity.

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Keywords: kidney; rutin; histopathology; mesenchymal cell; acetaminophen.

التقييم النسيجي المرضي للتأثيرات التحسينية المحتملة للخلايا الجذعية والروتن ضد التسمم الكلوي الحاد الناجم عن الأسيتامينوفين في ذكور الجرذان.

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الملخص:
يهدف البحث الحالي إلى دراسة التقييم النسيجي المرضي للتأثيرات التحسينية المحتملة للخلايا الجذعية والروتين ضد السمية الكلوية الحادة للأسيتامينوفين في ذكور الجرذان. تم إجراء تجربتين رئيسيتين باستخدام سبعين من الجرذان السليمة. تم استخدام عشرين جرذ غير ناضج في الجزء الأول كمصدر للنخاع العظمي. في الجزء الثاني، تم تقسيم خمسين جرذ من الذكور الناضجة إلى مجموعتين: المجموعة (1) كانت بمثابة المجموعة الضابطة، والمجموعة (2) مجموعة تلقت 750 ملجم/كجم من وزن الجسم/72 ساعة من الأسِيتامينُوفين عن طريق الفم لمدة ثلاثة أسابيع. تم بعد ذلك تقسيم هذه المجموعة إلى أربع مجموعات فرعية: (أ) الجرذان التي تلقت أسِيتامينُوفين لمدة ثلاثة أسابيع، ثم بقيت لمدة شهرين دون علاج؛ (ب) مجموعة تلقت فيها الجرذان أسِيتامينُوفين لمدة ثلاثة أسابيع، يليها العلاج بالروتين (25 ملغم/كغم من وزن الجسم/اليوم) لمدة شهرين؛ و (ج) تلقت الجرذان أسِيتامينُوفين لمدة ثلاثة أسابيع، وبعد ذلك تم حقنها في الوريد الذيلي بواسطة الخلايا الجذعية (1.5×10^6 خلية في 0.5 PBS) لمدة شهرين، و (د) تلقت الجرذان أسِيتامينُوفين لمدة ثلاثة أسابيع، و حقنت بالخلايا الجذعية في الوريد الذيلي، وتلقت الروتين لمدة شهرين. بعد أخذ مقاطع نسيجية من الكلى وجد أن الجرذان التي تلقت أسِيتامينُوفين فقط تعاني من وذمة حول الأوعية الدموية مع احتقان الأوعية الدموية، تدهور الأنابيب، آفات الكبيبة المتدهورة، واختراق الخلايا الالتهابية في أنسجة الكلى. بينما

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مجموعات أسِيتاميـنُوفين مع الروتين والاسِيتاميـنُوفين مع الخلايا الجذعية والروتين معا أظهرت القليل من التدهور الأنبوبي. وعلاوة على ذلك، فان مجموعة أسِيتاميـنُوفين مع الخلايا الجذعية أعادت التركيب السليم للنسيج الكلوي. أظهرت النتائج أن المعاملة بالخلايا الجذعية مع الأسِيتاميـنُوفين يقلل بشكل ملحوظ من السمية الكلوية الحادة.

الكلمات المفتاحية: الكلى؛ روتين. التشريح المرضي. الخلية الوسيطة أسِيتاميـنُوفين.

1. Introduction:

In clinical practice, acetaminophen (APAP), a frequently given analgesic and antipyretic medication, is the greatest dangerous medication among those having hypothetically injurious effects (Kaplowitz, 2004). However, when it is administered in overdose, it can cause acute renal toxicity (Abdallah *et al.*, 2016, Elduob *et al.*, 2023). Blood urea nitrogen and creatinine levels are increased in serum by renal toxicity and reduction in kidney epithelial structure caused taken APAP (Benhelima *et al.*, 2016, Alshailabi *et al.*, 2021). Additionally, there is evidence that the causes of hepatic and renal toxicity may not be the same in these organs, since N-acetyl-cysteine has been used to protect against hepatotoxicity but not renal toxicity (Alshailabi *et al.*, 2021). The reactive oxygen species (ROS) relate to macromolecules including membrane lipids, proteins, and nucleic acids, they have the potential to compromise the antioxidant defense system, result in significant tissue damage, and impair cell function. On the other hand, elevated ROS production and/or lowered antioxidant defense may result in oxidative stress (OS) (Farooqui *et al.*, 2016, Abdalally *et al.*, 2021).

Rutin (RUT) is a citrus flavonoid glycoside that is made up of the disaccharide rutinose and the flavonol quercetin. It is a polyphenolic bioflavonoid with significant antioxidant and pharmacological activity (Qu *et al.*, 2019). In addition to myocardial protection and immunomodulating events, it possesses antioxidant features and performs anticancer, anti-inflammatory (Khan *et al.*, 2012, Ganeshpurkar and Saluja, 2017), antihyperpietic, antiapoptotic, and antiautophagic agent (Qu *et al.*, 2019), and reduced the OS (Kandemir *et al.*, 2015).

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Several studies employing mesenchymal stem cell (MS) therapy to treat experimental acute renal damage are generally positive (Klinkhammer *et al.*, 2014). Also, MS has numerous helpful properties on the kidneys, including anti-inflammation, angiogenesis promotion, endogenous stem cell mobilization, antiapoptotic, antioxidation, antifibrosis, and encouraging cell reprogramming (de Almeida *et al.*, 2013). These cells are measured by clonogenicity, self-renewal, discrepancy in different ancestries, and by renewing organs with positive lesions (Sávio-Silva *et al.*, 2020). Thus, the present study inspected the histopathological evaluation of the potential ameliorating effects of stem cells and rutin against the acute renal toxicity of acetaminophen in male albino rats.

2. Materials and Methods:

2.1. Chemical materials:

Rutin (RUT) ($C_{27}H_{30}O_{16}$) and acetaminophen (APAP) ($C_8H_9NO_2$) were obtained from Sigma Chemical Company (USA). Mesenchymal stem cells (MS) were isolated and cultivated at the Medical Research Center in Aleibbasiuh, Ain Shams University to use in this study.

2.2. Animals

In this investigation, seventy male albino rats were used. Bone marrow-derived MS were obtained from twenty young male albino rats (100 g) and fifty older male albino rats (150–160 g). Rats were obtained from the Animal House of Giza, Cairo, Egypt, and they spent two weeks becoming used to the lab environment. They were kept in cages with 24± 2°C temperatures, and a standard laboratory feed and water.

2.3. Study groups

Seventy healthy male rats were used in two main investigations. In the initial study, bone marrow-derived (MS) was obtained from twenty young male albino rats weighing 100g. Through the tail vein, the rats received an injection of BM-MS (1.5x 106 cells in 0.5 PBS). At Ain Shams University's Medical Research Center, the cultured

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BM-MS were evaluated using a BECKMAN COULTER NAVIOS flow cytometer (Elduob *et al.*, 2023). Bone marrow MS is positive for CD44, CD105, and CD19 but CD34 is negative while hematopoietic cells are CD34 positive (Bobis *et al.*, 2006).

Fifty adult male rats were divided into two groups for the second study:

- Group 1 served as the control group (CN). Rats were kept as controls and were given unlimited access to diet and drink.
- Group 2 received 750 mg/kg b.w./72 hours of oral APAP (Anbarasu et al., 2011) for three weeks. This group was divided into four subgroups:
- (A): (APAP) rats receiving APAP for three weeks, then went for two months without any treatment.
- (B): (APAP-RUT) rats receiving APAP for three weeks, then given RUT (25 mg/kg b.w/d) orally (Shenbagam and Nalini., 2011) for two months.
- (C): (APAP-MS) rats receiving APAP for three weeks, then injected in their tail vein by MS (1.5x 106 cells in 0.5 PBS) for two months.
- (D): (APAP-MS-RUT) rats received APAP for three weeks, then the MS was injected in their tail vein, and the rats received RUT treatment for two months.

The rats were sacrificed one month from the beginning of the study, and at the end of the experiment, to compare the potential treatment effects. Animal kidneys were removed for histopathological analysis.

2.4. Histopathological investigation:

Kidney specimens were fixed in Bouin's solution then imbedded in paraffin wax, after dehydrated in alcohol, and cleaned in xylol. Hematoxylin and eosin were used to stain sections after they were cut at a thickness of 5 µm (Dey, 2018). The following was a grading system for alterations to the experimental histopathologic parameters for kidney tissues: (+), (++), and (+++) denoting mild, moderate, and severe alterations, respectively, and (-) denoting no variations (Moshaie-Nezhad *et al.*, 2021, Alshailabi *et al.*, 2021).

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3. Results:

The CN group's kidney section presented a normal histological stru cture (Figure. 1). While the APAP rats' kidneys for one month demonstrated perivascular edema with blood vessel congestion, tubular deterioration with intratubular hemorrhage, widened blood vessels with fibrotic zone surrounding them, glomerulus deteriorating lesions, and penetration of inflammatory cells (Figure 2). Moreover, APAP rats' kidneys for two months showed intratubular hemorrhage, blood vessel congestion, glomerulus deterioration with the tubular deterioration, and permeation of inflammatory cells (Figure. 3). On the other hand, the rats treated with APAP-RUT for one month demonstrated deteriorative change in glomerulus and tubular (Figure 4). In addition, the APAP-RUT rats' kidney sections for two months represented normal glomerulus, congestion in the vortical blood vessel, and a few tubular deteriorations (Figure 5). Whereas, the rats treated by APAP-MS in the kidney section displayed the typical histological structure (Figures 6 & 7). Similarly, APAP-MS-RUT rats' kidney tissues demonstrate the typical histological structure of the glomeruli with degeneration in the lining epithelium of a few tubules (Figures 8 & 9). The alterations to the kidney tissues' histopathological structure were graded as shown in Table. 1, where lessening was found in the histopathologic changes in the renal tissues in the rats treated with RUT, while the MS rats showed significantly less renal toxicity with normal histological kidney structure when compared with the RUT and APAP groups.

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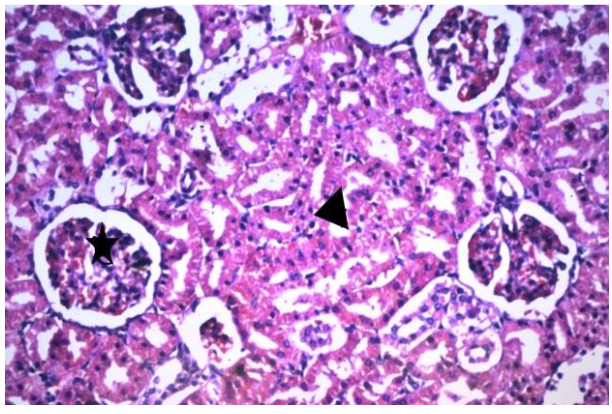

Figure 1: CN rats' kidney cortex section displaying the typical histological structure of the glomeruli (star) and tubules (head arrow) (H & E, X400).

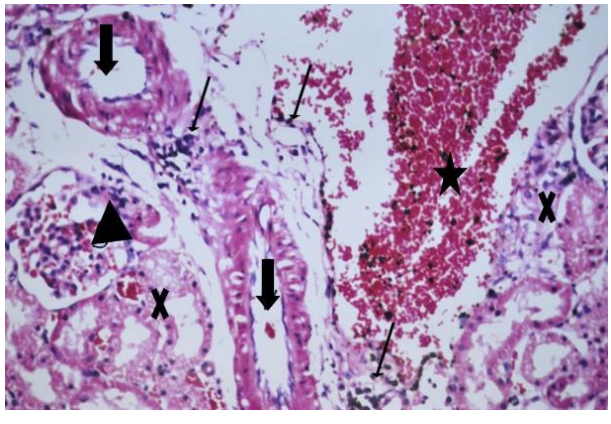

Figure 2: APAP rats' kidney cortex section for one month demonstrating perivascular edema with blood vessel congestion (star), tubular deterioration with intratubular hemorrhage (X), widened blood vessels with fibrotic zone surrounding them (thick arrows), glomerulus deteriorating lesions (head arrow), and penetration of inflammatory cells (thin arrows) (H & E, X400).

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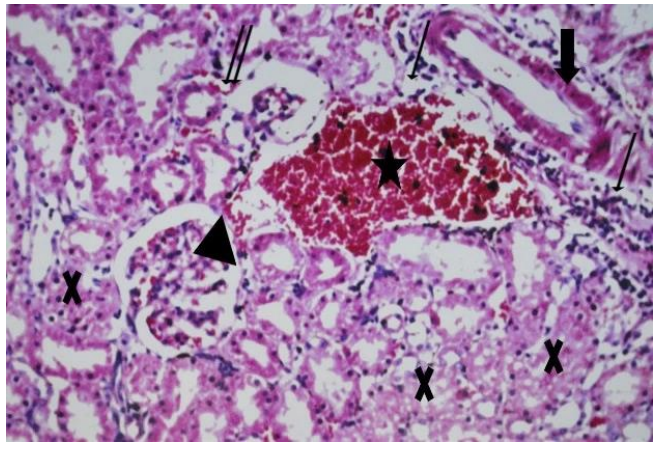

Figure 3: APAP rats' kidney cortex section for two months demonstrating intratubular hemorrhage (double arrow), blood vessel congestion (star), glomerulus deterioration (head arrow), widened blood vessels with fibrotic zone surrounding them (thick arrows), tubular deterioration (X), and permeation of inflammatory cells (thin arrows) (H & E, X400).

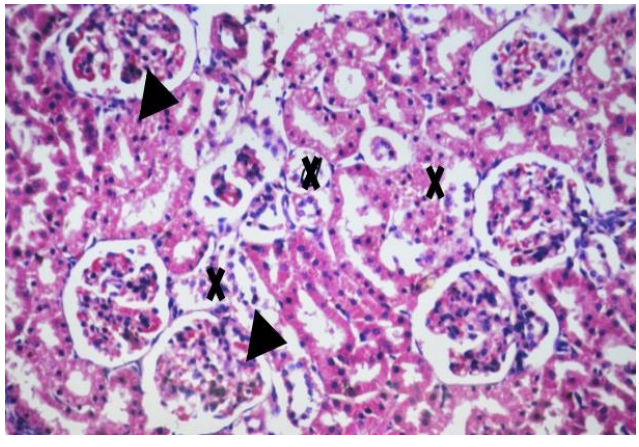

Figure 4: APAP-RUT rats' kidney cortex section for one month demonstrating the deteriorative change in glomerulus (head arrow) and tubular (X) (H & E, X400).

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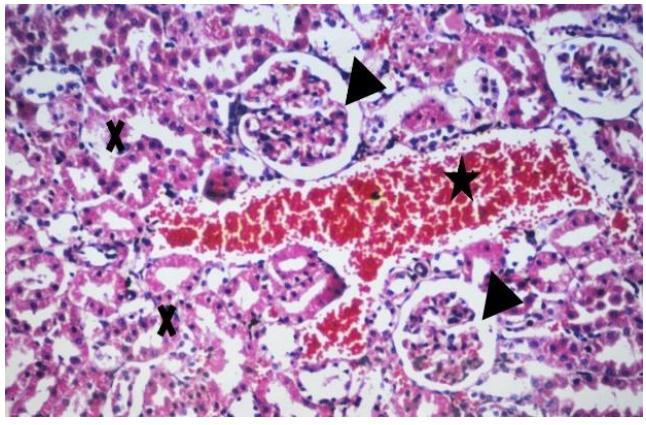

Figure 5: APAP-RUT rats' kidney cortex section for two months demonstrating normal glomerulus (head arrow), congestion in the vortical blood vessel (star), and few tubular deteriorations (X) (H & E, X400).

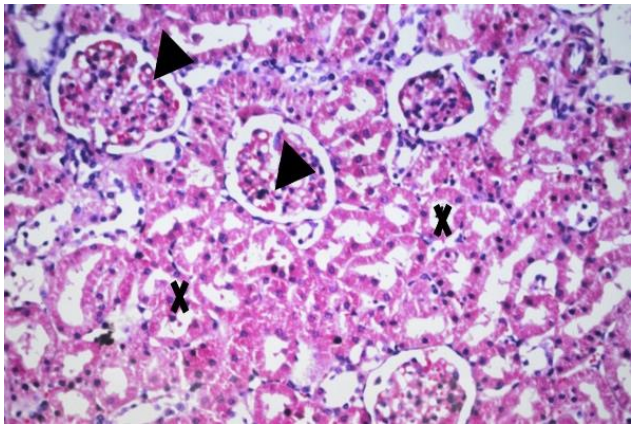

Figure 6: APAP-MS rats' kidney cortex section for one month demonstrating the typical histological structure of the glomeruli (head arrows) and tubules (X) (H & E, X400).

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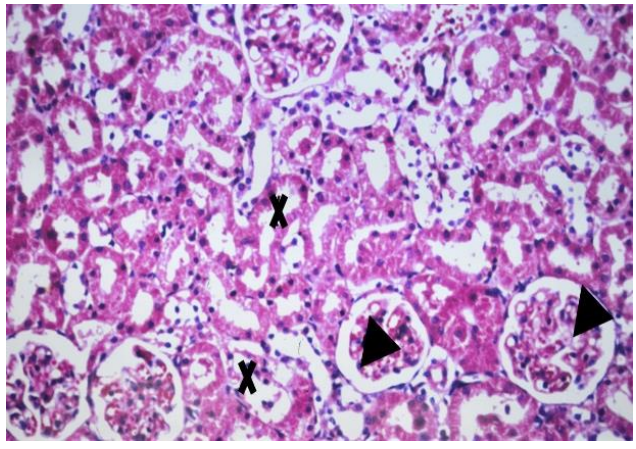

Figure 7: APAP-MS rats' kidney cortex section for two months demonstrating the typical histological structure of the glomeruli (head arrows) and tubules (X) (H & E, X400).

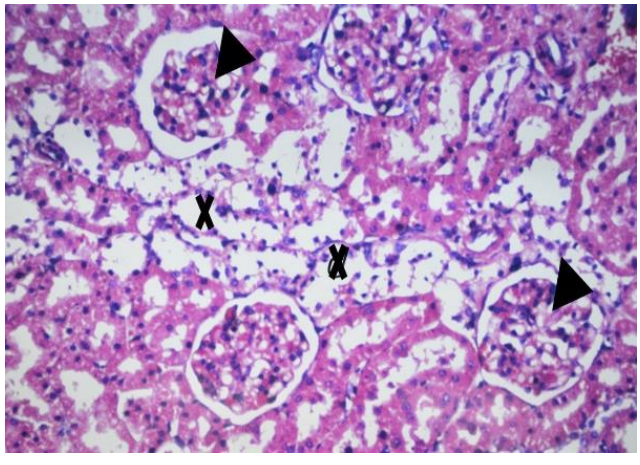

Figure 8: APAP-MS-RUT rats' kidney cortex section for one month demonstrating the typical histological structure of the glomeruli (head arrows) and degeneration in the lining epithelium of some few tubules (X) (H & E, X400)

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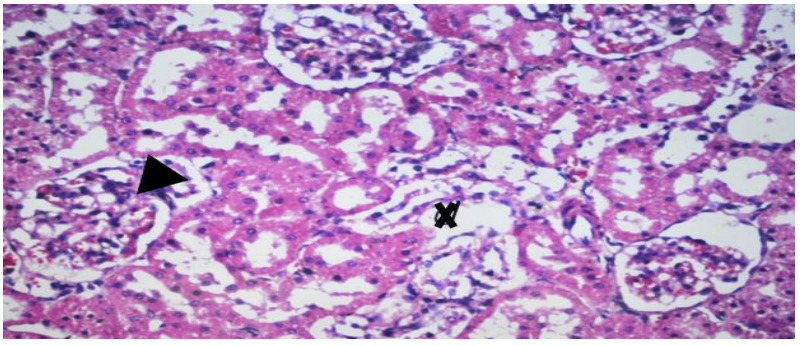

Figure 9: APAP-MS-RUT rats' kidney cortex section for two months demonstrating the typical histological structure of the glomeruli (head arrows) and degeneration in the lining epithelium of some tubules (X) (H & E, X400).

Table (1): Histopathologic changes in renal tissues:

Histo-pathologic changes	CN	APAP		APAP-RUT		APAP-MS		APAP-MS-RUT	
Time		One M	Two M	One M	Two M	One M	Two M	One M	Two M
Infla-mmatory cell penetration	-	+++	++	-	-	-	-	-	-
Congestion	-	+++	++	-	+	-	-		
Deteriora-tion	-	+++	++	+	+	-	-	+	+
Hemorrhage	-	+	+	-	-	-	-	-	-
Oedema	-	++	-	-	-	-	-	-	-

4. **Discussion:**

The study showed that the renal tissues of the rats showed a variety of histological alterations, including perivascular edema with blood vessel congestion, tubular deterioration with intratubular hemorrhage, widened blood vessels, glomerulus deteriorating lesions, and penetration of inflammatory cells. These results were corroborated by the results of Reshi *et al.*, (2020), Alshailabi *et al.*, (2021), and Aboshama et al., (2024) who said that the APAP metabolic activation to the reactive metabolite N-acetyl- p-benzoquinone-imine (NAPQI) causes renal toxicity. Additionally,

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Reshi *et al.* (2020) and Aboshama et al. (2024) stated that when high doses of APAP are consumed, more NAPQI is produced, which causes a more severe glutathione deficiency. Where this accumulation of NAPQI causes it to covalently bind with cellular proteins and macromolecules. This procedure throws off homeostasis, starts tissue necrosis, and finally leads to tissue failure. Also, APAP poisoning significantly reduced kidney ATPase activity, which may have resulted from abnormal alterations in mitochondria and cell membrane permeability (Nirala and Bhadauria, 2008; Jaswal *et al.*, 2016). Furthermore, APAP-induced renal toxicity involves the induction of inflammation, which may increase levels of the pro-inflammatory cytokine renal tumor necrosis factor-α (TNF-α) (Alshailabi *et al.*, 2021). It has been demonstrated that APAP can increase the production of ROS, trigger the nuclear factor-kappa B (NF-kB), protein kinase, and mitogen-activated protein kinase pathways, in addition to elevating levels of cytokines such as TNF-α and interleukin-1α (Bashandy *et al.*, 2016). Also, Reshi et al. (2020) suggested that elevated lipid peroxidation may play a role in the development of APAP-induced kidney damage. On the other hand, the rats were administered APAP-RUT and demonstrated few tubular deteriorations. These are because RUT contains phenolic compounds and flavonoid glycosides and has a variety of pharmacological activities, such as anti-inflammatory, vasoactive, and inhibitory effects on membrane lipid peroxidation (Rahmani *et al.*, 2023; Elduob *et al.*, 2023). In addition to protecting against renal toxicity, RUT has been shown to repair the histological structure (Ali *et al.*, 2023).

The rats treated with APAP-MS showed a normal histological structure of kidney tissues. This suggests that MS has the aptitude to grow into renal parenchyma cells, which can then repair the kidney (Wanyan *et al.*, 2023). Furthermore, MS can release cytokines against the primary inflammatory setting of acute kidney damage, including interleukin-6, interleukin 10, transforming growth factor-β, and other cytokines (Wang *et al.*, 2012). Also, MS interrelates with these immune cells intercellularly and secretes cytokines, chemokines, and growth factors that have an effective

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immunomodulatory impact on them, thus meaningfully refining renal function (Sávio-Silva *et al.*, 2020; Wanyan *et al.*, 2023). Besides, the animals that were treated with APAP-MS-RUT demonstrated a normal histological structure of the glomeruli with degeneration in the lining epithelium of a few tubules. In addition, the histopathologic changes of the experimental parameters were compatible with the histopathological results of the kidney tissues in the all-treated rats.

5. Conclusions:

The current findings suggest that the increase in the acute renal toxicity of APAP-induced in rats was effectively reduced and controlled via the administration of antioxidant activities and anti-inflammatory effects of PUT. Also, the study's results demonstrated that MS considerably reduces acute renal toxicity. Accordingly, this study implies that long-term treatment with RUT and MS may consequently control or prevent the development of acute renal toxicity that is due to APAP.

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