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Paracetamol-Associated Testicular Microarchitectural Disturbances and Their Histological Amelioration by Rutin and Mesenchymal Stem Cells in Male Rats

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اضطرابات البنية المجهرية للخصية المرتبطة بالباراسيتامول وتحسنها النسيجي بواسطة الروتين والخلايا الجذعية الوسيطة في ذكور الجرذان

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Abstract:
Paracetamol (PCM) is widely used as an analgesic and antipyretic agent, but excessive exposure may induce tissue injury beyond the liver, including alterations in testicular structure. This study investigated the histopathological effects of PCM on the testes of adult male rats. It evaluated the ameliorative potential of rutin (RUT) and bone marrow-derived mesenchymal stem cells (BM-MSCs), administered separately or in combination. Fifty adult male albino rats were randomly allocated to control and experimental groups. PCM was administered orally at 750 mg/kg body weight every 72 h for three weeks. Following PCM exposure, rats received RUT (25 mg/kg/day), a single intravenous dose of BM-MSCs (1.5×10^6 cells), or both treatments for one or two months. PCM exposure produced progressive testicular damage characterized by seminiferous tubular degeneration and atrophy, reduced tubular diameter, vascular congestion, interstitial edema, disruption of the germinal epithelium, and marked reduction or absence of spermatogenesis. RUT treatment promoted gradual structural recovery, whereas BM-MSC administration produced more evident preservation of seminiferous architecture and spermatogenic activity. The combined treatment resulted in the greatest histological improvement, with testicular organization approaching that of controls after two months. These findings indicate that RUT and BM-MSCs may have therapeutic potential against PCM-induced testicular injury, particularly when used in combination.

Keywords: Paracetamol; Testis; Rutin; Mesenchymal stem cells; Histopathology.

الملخص
يُستخدم الباراسيتامول على نطاق واسع كمسكن وخافض للحرارة، إلا أن التعرض المفرط له قد يؤدي إلى حدوث أذى نسيجي يتجاوز الكبد، بما في ذلك إحداث تغيرات في بنية الخصية. هدفت هذه الدراسة إلى تقييم التأثيرات النسيجية المرضية للباراسيتامول في خصى ذكور الجرذان البالغة، ودراسة التأثير التلطيفي المحتمل للروتين والخلايا الجذعية الوسيطة المشتقة من نخاع العظم، عند إعطائهما بصورة منفردة أو بالاشتراك معًا. استُخدم 50 جرذًا بالغًا من ذكور الجرذان البيضاء، ووزعت عشوائيًا إلى مجموعات ضابطة وتجريبية. أُعطي الباراسيتامول فمويًا بجرعة مقدارها 750 ملغم لكل كغم من وزن الجسم كل 72 ساعة لمدة ثلاثة أسابيع. وبعد التعرض للباراسيتامول، عولجت الجرذان بالروتين بجرعة 25 ملغم لكل كغم يوميًا، أو بجرعة واحدة من الخلايا الجذعية الوسيطة المشتقة من نخاع العظم عن طريق الحقن الوريدي، أو بكلا العلاجين لمدة شهر أو شهرين. أدى التعرض للباراسيتامول إلى حدوث تلف تدريجي في الخصية، تمثل في تنكس وضمور الأنابيب المنوية، وانخفاض أقطارها، واحتقان الأوعية الدموية، والوذمة الخلالية، واضطراب الظهارة الجرثومية، مع انخفاض ملحوظ أو غياب تكوين الحيوانات المنوية. أدى العلاج بالروتين إلى تحسن تدريجي في البنية النسيجية، في حين أظهر العلاج بالخلايا الجذعية الوسيطة حفاظًا أوضح على بنية الأنابيب المنوية ونشاط تكوين الحيوانات المنوية. وحقق العلاج المشترك

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أكبر تحسن نسيجي، مع اقتراب بنية الخصية من الحالة الطبيعية بعد شهرين. وتشير هذه النتائج إلى الإمكانات العلاجية الواعدة للروتين والخلايا الجذعية الوسيطة في الحد من إصابة الخصية الناجمة عن الباراسيتامول، خاصة عند استخدامهما معًا.

الكلمات المفتاحية: الباراسيتامول؛ الخصية؛ الروتين؛ الخلايا الجذعية الوسيطة؛ علم الأنسجة المرضية.

Introduction

The testis is a highly specialized organ in which the structural integrity of the seminiferous tubules (SFT) is essential for normal spermatogenesis. The seminiferous epithelium consists of developing germ cells supported by Sertoli cells (Sc), while Leydig cells and blood vessels occupy the interstitial compartment [1, 2, 3]. Because germ cells undergo continuous proliferation and differentiation, this tissue is particularly susceptible to chemical and pharmacological insults, which may cause tubular disorganization, degeneration, germ-cell loss, and atrophy [4, 5]. Therefore, histopathological assessment provides a useful approach for detecting and characterizing testicular structural injury [3, 5]. Paracetamol (PCM; acetaminophen) is one of the most widely used analgesic and antipyretic drugs worldwide. Although it has a well-established safety profile at therapeutic doses, excessive exposure can result in cellular injury associated with the formation of the reactive metabolite N-acetyl-p-benzoquinone imine, glutathione depletion, oxidative imbalance, and disruption of cellular homeostasis [6, 7, 8]. While hepatotoxicity remains the best-characterized consequence of PCM overdose, experimental evidence indicates that PCM-associated injury can extend beyond the liver and affect other tissues [7]. The testis appears to be among the tissues susceptible to such effects. Experimental studies have reported degenerative changes in SFT, alterations in Sc organization, abnormalities of spermatogenic cells, and vascular or interstitial changes following PCM administration [9, 10]. More recent histological observations have similarly demonstrated SFT atrophy and degeneration, and alterations in Sc following PCM exposure in rats [10]. Moreover, the structural consequences of PCM exposure are also consistent with its capacity to induce tissue-level disturbances in several organs. Recent histopathological studies have documented cellular edema, vascular congestion, inflammatory-cell infiltration, and disruption of tissue architecture following PCM exposure in some tissues [11, 12]. Although these morphological responses differ according to the affected organ, they collectively indicate that PCM-associated cellular stress can be expressed as measurable alterations in tissue architecture. In the testis, such alterations are of particular interest because disruption of SFT organization directly reflects damage to the specialized cellular environment supporting spermatogenesis [10]. Furthermore, previous experimental evidence has demonstrated that PCM-associated testicular injury can be attenuated by protective interventions. In a rat model, antioxidant administration reduced PCM-induced SFT degeneration, atrophy, cellular debris, and alterations affecting germ cells and Sc [10]. These observations support the possibility that modulation of cellular stress may preserve testicular architecture following PCM exposure. Accordingly, naturally occurring compounds with antioxidants and cytoprotective properties have attracted increasing attention as potential protective agents. Rutin (RUT), a naturally occurring flavonoid glycoside of quercetin, has been extensively investigated because of its antioxidant, anti-inflammatory, anti-apoptotic, and cytoprotective activities [13, 14, 15]. These properties are particularly relevant to testicular injury because oxidative imbalance, inflammatory signaling, and excessive apoptosis can compromise the integrity of the seminiferous epithelium and its cellular components [4, 16]. Recent experimental studies provide increasing evidence for the protective effects of RUT on testicular tissue. RUT has been reported to attenuate testicular structural and cellular alterations induced by hexachlorobenzene, with improvement in histological organization accompanied by modulation of oxidative and apoptotic responses [17]. Similar protective effects have been observed in rats exposed to cyclophosphamide, in which RUT reduced testicular histological damage and oxidative disturbances [18]. RUT has also attenuated testicular alterations associated with deltamethrin exposure, supporting its potential to counteract chemically induced testicular injury through multiple complementary mechanisms [19]. Mesenchymal stem cells (MSCs) represent another promising approach for tissue protection and repair. Their therapeutic effects are mediated through complex paracrine and immunomodulatory activities involving regulation of inflammatory responses, promotion of cell survival, angiogenesis, and stimulation of endogenous tissue-repair mechanisms [20, 21]. Experimental studies have demonstrated beneficial effects of MSC-based interventions in models of testicular injury, including improvement of histopathological abnormalities following chemically induced damage [22]. More recently, stem-cell-derived conditioned medium has also been reported to attenuate chemically induced testicular injury, supporting the importance of paracrine mechanisms in tissue recovery. In addition, previous experimental work in PCM-exposed male rats demonstrated beneficial effects of RUT and MSCs on reproductive parameters, while related histopathological investigations showed improvement of PCM-induced renal tissue alterations following these interventions [15]. However, functional or biochemical improvement does not necessarily demonstrate restoration of the microscopic organization of the testis. Moreover, previous

studies have established that PCM can produce structural alterations in the testis and that several protective or reparative interventions can attenuate chemically induced tissue damage. However, the histological response of PCM-exposed testicular tissue to RUT and MSC-based treatment requires further direct characterization [10, 15]. The present study therefore aimed to evaluate the histopathological alterations induced by PCM in the testes of adult male rats and to determine the potential ameliorative effects of RUT and mesenchymal stem cells administered individually or in combination. Particular emphasis was placed on the preservation of SFT organization and the integrity of the cellular components of the testicular tissue.

Material and methods

Chemicals

PCM and RUT were obtained from Sigma Chemical Co. (USA). Bone marrow-MSCs (BM-MSCs) were also isolated and cultured at the Medical Research Center, Ain Shams University, Egypt.

Experimental animals and study design

The experimental design and treatment protocol were based on the study by Elduob et al. [15]. Briefly, 70 male albino rats were used: 20 young rats served as donors for BM-MSC isolation, and 50 adult rats weighing approximately 150–160 g were allocated to the experimental groups. Animals were obtained from the Animal House, Giza, Egypt, and acclimatized for two weeks under standard laboratory conditions (24 ± 2°C) with free access to standard chow and water.

The adult rats were randomly assigned to five experimental groups. The control group received no pharmacological treatment. The PCM-exposed group received PCM orally at 750 mg/kg B.Wt., every 72 h [23], for 3 weeks and was subsequently maintained without treatment for one & two months. The PCM + RUT group received the same PCM regimen followed by oral RUT at 25 mg/kg B.Wt./day [24] for one & two months. The PCM + BM-MSCs group received PCM followed by a single intravenous administration of BM-MSCs (1.5×10^6 cells/0.5 mL PBS) through the tail vein, followed by one & two months. The combined-treatment group received PCM followed by BM-MSC administration and daily oral RUT for the corresponding one & two months. The animal experiments were conducted following approval from the Al-Mukhtar Bioethics Committee at Omar Al-Mukhtar University. All procedures were performed in accordance with applicable institutional guidelines for the care and use of laboratory animals.

BM-MSC preparation

BM-MSCs were obtained from the femoral and tibial bone marrow of young male rats and cultured under sterile conditions in DMEM supplemented with fetal bovine serum and antibiotics at 37°C in a humidified atmosphere containing 5% CO_2. Following removal of non-adherent cells, the adherent cell population was expanded by successive medium changes. Cell characterization was performed by flow cytometry, demonstrating positivity for CD44 and CD105 and negativity for CD34, as previously described [15, 25]. Cell viability was assessed by trypan blue exclusion, and viable cells were prepared at a concentration of 1.5×10^6 cells/0.5 mL PBS for intravenous administration.

Testicular tissue collection and histological processing

At the end of each designated experimental period, the animals were euthanized according to the approved experimental protocol. Testes were carefully excised and immediately immersed in 10% neutral buffered formalin for fixation. Following fixation, the tissues were processed using standard paraffin-embedding procedures, including graded ethanol dehydration, xylene clearing, and paraffin infiltration. Paraffin blocks were sectioned at approximately 6 µm thickness using a sliding microtome. The sections were mounted on glass slides and stained with hematoxylin and eosin (H&E) according to standard histological procedures [26]. H&E-stained sections were examined microscopically to assess the general architecture of the testicular tissue.

Results and discussion

Histological examination of the control group revealed normal testicular architecture with intact SFT and complete spermatogenic series. The germinal epithelium showed orderly arrangement of spermatogonia (Sg), spermatocytes (Sc), and spermatids (St), with abundant spermatozoa (Sz) filling the lumina of SFT (Figure 1). In contrast, the PCM-exposed group exhibited marked time-dependent degenerative changes. After one month of PCM withdrawal, the testes showed severe structural disruption characterized by degeneration and necrosis of SFT, significant reduction in tubular diameter, pronounced vascular congestion, and interstitial edema (Figure 2). These alterations worsened after two months, when extensive tubular atrophy, loss of germinal epithelium integrity, and complete or near-complete absence of spermatogenesis were observed in many SFT (Figure 3). In the other sections, in the PCM + RUT-treated group, partial histological improvement was observed

compared to the PCM group. After one month, degenerative changes in SFT persisted, including reduced tubular diameter and loss of spermatogenic activity in several tubules (Figure 4). However, after two months of rutin treatment, a noticeable recovery was observed, with most SFTs showing preserved architecture, although occasional tubules still exhibited mild degeneration and reduced spermatogenesis (Figure 5). Similarly, the PCM + BM-MSCs group demonstrated a more pronounced regenerative effect. After one month, SFTs were largely preserved with near-normal tubular diameter and active spermatogenesis, with only minimal degenerative changes in a few tubules (Figure 6). This recovery was further enhanced after two months, when most tubules exhibited normal histoarchitecture and complete spermatogenic activity (Fig. 7). The combined-treatment group showed the most prominent restoration of testicular structure. After one month, the testes displayed nearly normal histological organization with intact SFT and abundant Sz within the lumina (Fig. 8). After two months, complete restoration of normal testicular architecture was observed, with well-organized germinal epithelium and active spermatogenesis comparable to the control group (Fig. 9).

The present study demonstrated marked structural alterations in the testes of PCM-exposed rats, whereas the control group maintained normal SFT architecture and active spermatogenesis. PCM exposure resulted in progressive tubular degeneration, reduced tubular diameter, vascular congestion, interstitial edema, tubular atrophy, and marked loss of the germinal epithelium. These findings are consistent with the observations of [9] and [10], who reported altered and degenerating SFT and structural abnormalities in Sc and St following paracetamol administration in rats. The greater severity of the lesions after two months of PCM withdrawal suggests that testicular injury persisted beyond the exposure period and was not followed by rapid spontaneous structural recovery. Such persistent damage may interfere with the highly organized process of spermatogenesis, which depends on continuous germ-cell development and an intact seminiferous microenvironment [15]. The current analysis provides additional evidence at the tissue level, demonstrating that the reproductive alterations were accompanied by substantial disruption of testicular microarchitecture. In addition, our previous histopathological study showed that PCM induced marked testicular damage and that vitamin C attenuated these changes [10]. These findings strengthen the evidence for PCM-associated testicular injury and support the potential value of antioxidant and regenerative interventions.

RUT treatment produced a progressive improvement in testicular architecture, which was more evident after two months than after one month. The persistence of some degenerative changes during the first month followed by improved tubular organization at two months suggests a gradual tissue response to treatment. This finding is consistent with previous experimental studies showing that RUT attenuates testicular histopathological damage induced by different toxicants, with reported improvements in seminiferous architecture and reductions in oxidative and apoptotic alterations [17, 18]. These findings support the structural improvement observed in the present RUT-treated group, although the molecular mechanisms underlying this improvement were not directly examined in the current study. Additionally, BM-MSC treatment produced a more pronounced histological recovery than PCM alone. Most SFT were relatively preserved after one month, and the improvement became more evident after two months. Similar regenerative effects of BM-MSCs have been reported in experimental models of testicular injury, where MSC administration improved seminiferous architecture and was associated with modulation of oxidative, inflammatory, and apoptotic responses [22]. The beneficial response may therefore be related, at least in part, to the paracrine and immunomodulatory properties of MSCs; however, these mechanisms were not directly investigated in the present study and should consequently be considered possible explanations rather than demonstrated mechanisms. Also, the combined BM-MSC + RUT treatment produced the most pronounced morphological improvement, with nearly normal testicular organization after one month and restoration of well-organized seminiferous epithelium and active spermatogenesis after two months. The greater improvement observed with the combined treatment may reflect complementary effects of RUT-associated antioxidant protection and the regenerative and immunomodulatory potential of BM-MSCs. Experimental studies have independently demonstrated the protective effects of RUT against oxidative and apoptotic testicular injury and the regenerative effects of BM-MSCs in damaged testicular tissue [18, 22]. Nevertheless, the present findings should be interpreted as enhanced histological recovery rather than evidence of pharmacological synergy, since a formal interaction analysis was not performed. Overall, the results indicate that PCM produced persistent testicular structural injury, whereas RUT and BM-MSCs promoted morphological recovery, with the combined treatment showing the greatest degree of improvement.

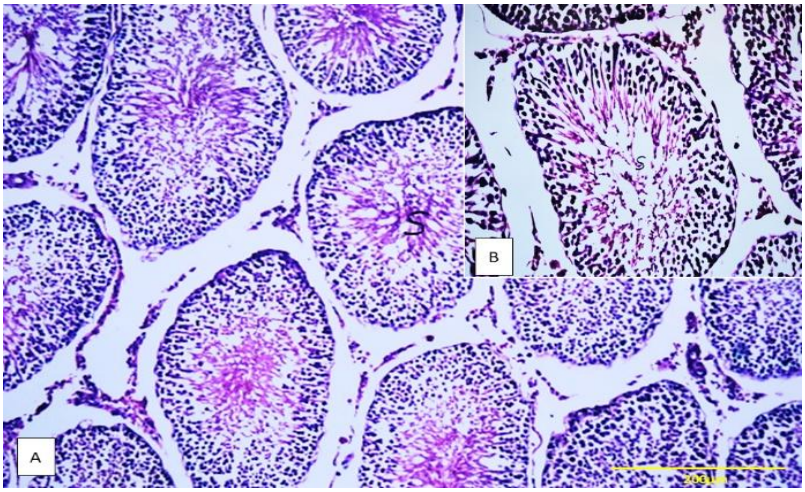

Figure 1. Normal histological structure of the testis in control rats showing intact SFT with abundant Sz (S) in the lumen. St, Sc, and Sg are clearly visible along the germinal epithelium.

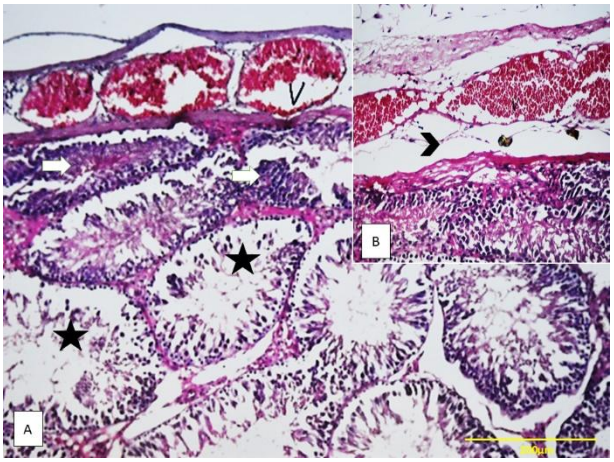

Figure 2. Testis section from PCM-treated rats after 1 month, showing marked degeneration and necrosis of SFT (white arrows), reduced tubular diameter (stars), severe vascular congestion (V), and interstitial edema (arrowhead).

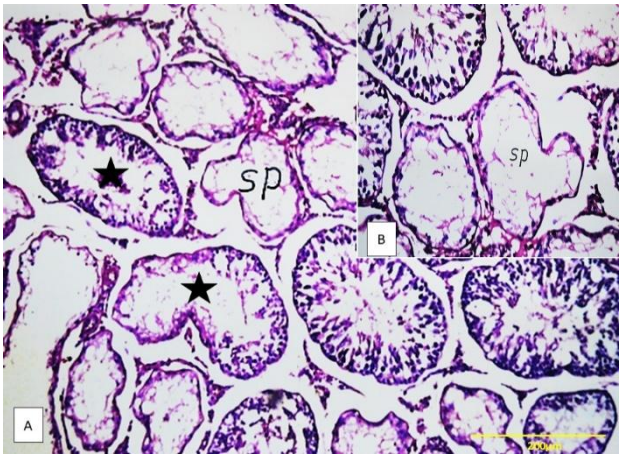

Figure 3. Testis section from PCM-treated rats after 2 months, showing atrophy and degeneration of SFT (stars), reduced tubular diameter, and absence of spermatogenesis (SP) in many tubules.

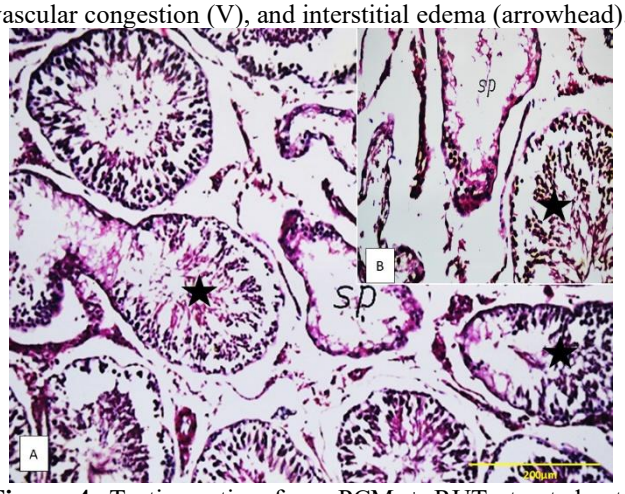

Figure 4. Testis section from PCM + RUT- treated rats after 1 month, showing marked degeneration of SFT (stars), reduced tubular diameter, and absence of spermatogenesis (SP) in some SFT.

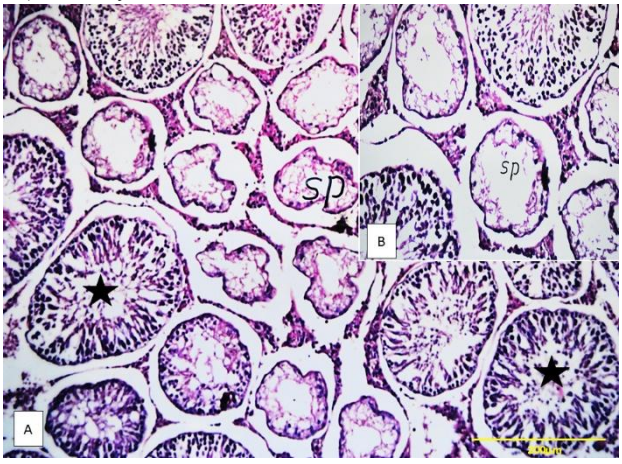

Figure 5. Testis section from PCM + RUT- treated rats after 2 months, showing largely preserved SFT (stars) with some tubules exhibiting degeneration and reduced tubular diameter, and absence of spermatogenesis (SP) in some SFT.

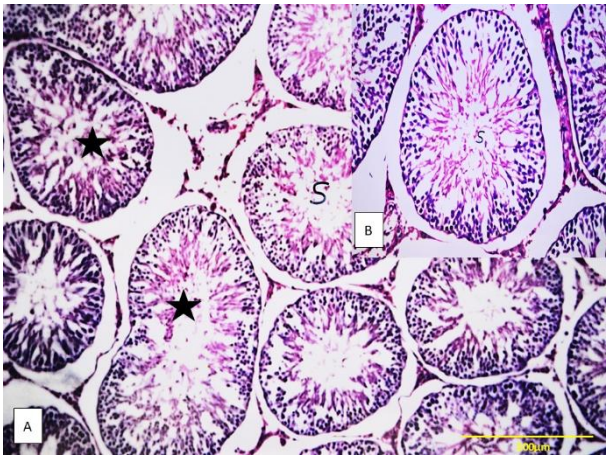

Figure 6. Testis section from PCM + BM-MSCs-treated rats after 1 month, showing well-preserved SFT with normal tubular diameter and active spermatogenesis (S), with few degenerative changes observed in some SFT (stars).

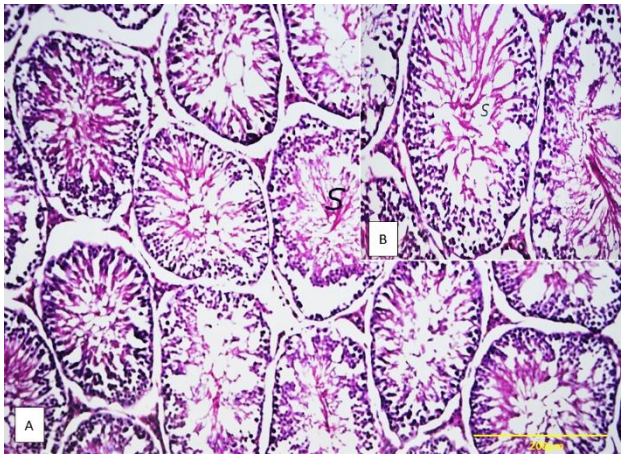

Figure 7. Testis section from PCM + BM-MSCs- treated rats after 2 months, showing well-preserved SFT with normal tubular diameter and normal spermatogenesis, and a few degenerations in some SFT (S).

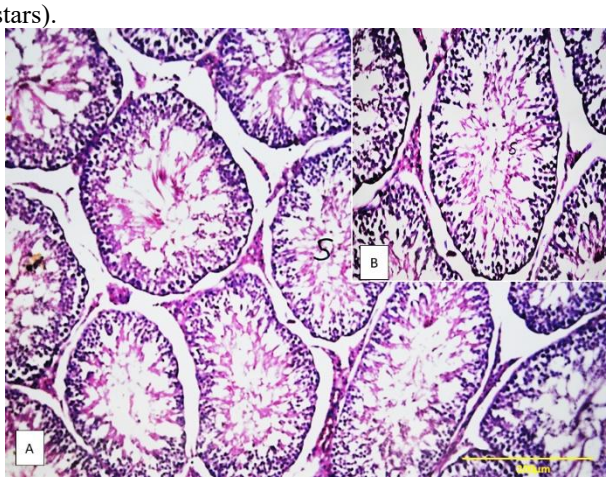

Figure 8. Testis section from combined-treatment group rats after 1 month, showing normal histological architecture with intact SFT and abundant Sz (S) in the lumen. Sg, Sc, and St are clearly observed along the germinal epithelium.

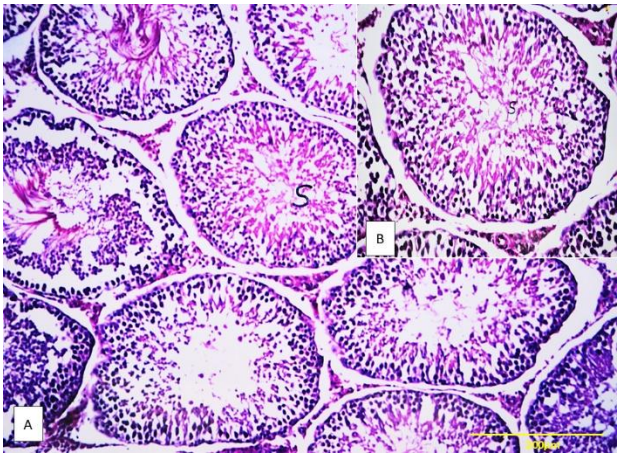

Figure 9. Testis section from combined-treatment group rats after 2 months, showing normal histological structure of the testis with intact SFT and abundant Sz (S) in the lumen. St, Sc, and Sg are clearly visible along the germinal epithelium.

Note for Figures 1–9: (A) ×100; (B) ×400; H&E staining; scale bar = 200 µm.
Abbreviations: SFT, seminiferous tubules; Sz, spermatozoa; Sg, spermatogonia; Sc, spermatocytes; St, spermatids;

Conclusion

The present study demonstrated that PCM exposure induced marked and persistent histopathological alterations in the testes of male rats. These alterations included SFT degeneration and atrophy, reduced tubular diameter, vascular congestion, interstitial edema, disruption of the germinal epithelium, and marked impairment or absence of spermatogenesis. The persistence and increased severity of these lesions after two months of PCM withdrawal indicate that testicular injury was not rapidly reversed following cessation of exposure.

Treatment with RUT resulted in progressive improvement of testicular histoarchitecture, with more evident recovery after two months of treatment. BM-MSCs produced a more pronounced regenerative response, with substantial preservation of SFT structure and restoration of spermatogenic activity. Notably, the combined BM-MSC + RUT treatment produced the greatest degree of morphological recovery, with testicular architecture and spermatogenesis approaching those observed in the control group after two months. These findings suggest that RUT and BM-MSCs have potential protective and regenerative effects against PCM-induced testicular injury, while their combined administration may provide greater histological recovery than either treatment alone. However, because the present study was based primarily on histopathological assessment, the underlying molecular mechanisms and the possibility of a synergistic interaction between

RUT and BM-MSCs could not be established. Further studies incorporating oxidative stress, inflammatory, apoptotic, and reproductive biomarkers, together with quantitative assessment of spermatogenesis and fertility outcomes, are recommended to clarify the mechanisms underlying the observed tissue recovery.

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