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Myocardial Structural Remodeling and Histological Recovery Following Acetaminophen Exposure: Comparative Effects of Rutin and Mesenchymal Stem Cells in Male Rats

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ABSTRACT

Acetaminophen (APAP) is a commonly used analgesic and antipyretic drug, but excessive exposure can cause tissue injury and may affect organs beyond the liver. This study investigated myocardial (MYO) histopathological alterations associated with repeated APAP exposure in male albino rats and compared the protective effects of rutin (RUT) and bone marrow-derived mesenchymal stem cells (BM-MSCs). Fifty adult male rats were randomly assigned to control and experimental groups. APAP was administered orally at 750 mg/kg b.wt., every 72 hours for 21 days. Following APAP exposure, animals were either monitored for spontaneous recovery or treated with RUT, BM-MSCs, or their combination for 30 and 60 days. Heart tissues were processed and stained with hematoxylin and eosin for histopathological examination, and the observed alterations were evaluated using semi-quantitative grading. APAP exposure resulted in progressive MYO injury, characterized by MYO degeneration, subendocardial and interstitial edema, focal hemorrhage, and inflammatory cell infiltration, with more pronounced alterations after 60 days. RUT treatment was associated with progressive improvement in MYO structure, reaching complete histological normalization after 60 days. BM-MSC treatment resulted in well-preserved MYO architecture at both examination periods, with no detectable histopathological alterations. Combined treatment also maintained relatively preserved MYO architecture; however, mild focal degeneration persisted at both time points. Overall, RUT and BM-MSCs demonstrated substantial histological protective effects against APAP-associated MYO injury, although the combined regimen did not provide an additional histological advantage over the individual treatments.

1. INTRODUCTION

Acetaminophen (APAP), also known as paracetamol, is a widely used analgesic and antipyretic drug with an established safety profile at therapeutic doses. However, its toxicity is dose-dependent, and excessive intake can lead to significant tissue injury (Yoon et al., 2016; Alshailabi et al., 2024). While hepatotoxicity is the most extensively studied effect of APAP overdose, emerging clinical and experimental evidence suggests that high-dose exposure may also be associated with cardiovascular alterations. It remains unclear whether these changes reflect direct myocardial (MYO) injury or secondary effects of systemic or hepatic toxicity (Yoon et al., 2016; Abdalally et al., 2021).

Moreover, at toxic levels, APAP metabolism shifts toward generating the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). Under normal conditions, NAPQI is detoxified by conjugation with reduced glutathione; however, excessive exposure depletes glutathione reserves, leading to accumulation of reactive intermediates and induction of oxidative stress (OS) (Yoon et al., 2016; Elduob et al., 2023a). Although this mechanism is well established in the liver, the resulting oxidative and inflammatory responses may also affect extrahepatic tissues, including the myocardium. Reports of MYO degeneration and necrosis following APAP intoxication support the possibility of cardiac involvement, although direct evidence remains limited (KhabazianZadeh et al., 2019; Khalid et al., 2026). Furthermore, histopathological evaluation provides a reliable approach for detecting structural MYO alterations, including cardiomyocyte degeneration, vascular congestion, interstitial edema, and inflammatory changes (Nagai et al., 2023). Histopathological assessment enables direct evaluation of tissue architecture and the distribution of MYO damage. Moreover, MYO injury is a dynamic process, with histological features evolving from early edema and inflammatory responses to tissue repair and fibrosis. Therefore, temporal assessment of MYO tissue changes is important for distinguishing persistent injury from structural recovery (Fernández-Jiménez et al., 2015; Khalid et al., 2026). Rutin (RUT) is a naturally occurring flavonoid glycoside that has received considerable attention because of its broad biological activities, particularly its antioxidant and anti-inflammatory properties. Experimental evidence has demonstrated that RUT can attenuate cardiac tissue injury in different models of MYO stress. In a rat model of experimentally induced cardiac contusion, RUT administration reduced biochemical and histopathological alterations and was associated with preservation of cardiac tissue integrity (Meng et al., 2022; Elduob et al., 2023b). Similarly, RUT treatment attenuated MYO histopathological damage in rats exposed to pirarubicin, a model of drug-associated cardiac toxicity (Wang et al., 2018). Although these experimental models differ from APAP exposure, their findings provide relevant evidence that RUT may help preserve MYO structure under conditions associated with cellular oxidative and inflammatory stress (Elduob et al., 2023b). In addition, bone marrow-derived mesenchymal stem cells (BM-MSCs) have shown promise in cardiac repair through paracrine signaling, immunomodulation, and promotion of tissue remodeling and angiogenesis (Jiang et al., 2006; Sid-Otmane et al., 2020; Mabotuwana et al., 2022). These approaches may offer complementary mechanisms to mitigate MYO injury and enhance recovery. Accordingly, the present study aimed to evaluate MYO structural alterations following repeated APAP exposure and to assess the histological response to RUT, BM-MSCs, and their combined administration in male rats. Emphasis was placed on comparative analysis of tissue injury and recovery across treatment groups over time.

2. METHOD

Chemicals

RUT ($C_{27}H_{30}O_{16}$) and APAP ($C_8H_9NO_2$) were purchased from Sigma Chemical Company (USA). BM-MSCs were isolated and cultured at the Medical Research Center, Ain Shams University, Egypt.

Experimental Animals

Seventy male albino rats were used in this study. Twenty young rats (100 g) were used as donors for BM-MSCs, while fifty adult rats (150–160 g) were used for the experimental procedures. Animals were obtained from the Animal House (Giza, Egypt) and acclimatized for two weeks under standard laboratory conditions (24 ± 2°C, standard diet, and water *ad libitum*).

Isolation and Characterization of BM-MSCs

BM-MSCs were isolated from femoral and tibial bone marrow of young male rats (6 weeks; 100 g) under sterile conditions using flushing techniques, then cultured in DMEM supplemented with fetal bovine serum and antibiotics at 37° C in a humidified 5% CO_2 incubator. Following cell adhesion, non-adherent elements were discarded and adherent spindle-shaped cells were expanded through successive medium changes until near-confluence. MSC identity was verified by flow cytometry (NAVIOS, Beckman Coulter), showing CD44/CD105 positivity and CD34 negativity (El-Nahrawy et al., 2017). Cell viability was confirmed by trypan blue exclusion, and suspensions were adjusted to 1.5×10^6 viable cells in 0.5 mL PBS per animal. Oral treatments were delivered via gavage, while BM-MSCs were administered intravenously through the tail vein under aseptic conditions following standard transplantation protocols (Jiang et al., 2006).

Experimental Design

The fifty adult rats were randomly divided into two main groups:

1. **Control Group:** Animals in this group received no pharmacological treatment and were maintained under standard laboratory conditions throughout the experimental period.
2. **APAP-Induced Recovery Group:** Animals were administered APAP orally at a dose of 750 mg/kg b.wt. (Anbarasu et al., 2011) every 72 hours for 21 days. Following cessation of exposure, no therapeutic intervention was given, and animals were monitored for spontaneous recovery over two periods (30 and 60 days).
3. **APAP + RUT Treatment Group:** Animals were first exposed to the same APAP protocol described above. Thereafter, RUT was administered orally at 25 mg/kg b.wt. (Shenbagam and Nalini, 2011) once daily for 30 and 60 consecutive days.
4. **APAP + BM-MSCs Group:** Following APAP intoxication for 21 days, animals received a single intravenous injection of BM-MSCs (1.5×10^6 cells suspended in 0.5 mL PBS; Oskouei et al., 2012) via the lateral tail vein under aseptic conditions for 30 and 60 consecutive days.
5. **Combined Therapy Group (APAP + BM-MSCs + RUT):** Animals were first exposed to APAP as previously described. Subsequently, a single intravenous injection of BM-MSCs was administered, followed by daily oral administration of RUT for either 30 or 60 days to evaluate the potential combined therapeutic effects of BM-MSCs and RUT.

Histological Processing and Tissue Examination

For histological assessment, heart tissue samples were carefully collected and immediately preserved in 10% neutral buffered formalin to maintain structural integrity (Lillie, 1954). After adequate fixation, the specimens were processed using a conventional paraffin-embedding technique. Heart tissues were gradually dehydrated through increasing concentrations of ethanol, cleared in xylene, and then infiltrated with molten paraffin wax maintained at 56°C. The resulting blocks were allowed to solidify before sectioning. Thin sections of approximately 6 µm were obtained using a sliding microtome and mounted onto clean glass slides for further examination. For general histological evaluation, the sections were stained with hematoxylin and eosin (H&E) following standard laboratory procedures (Bancroft & Stevens, 1996). Tissue alterations in heart sections were evaluated in a semi-quantitative manner using a simple grading system, where absence of changes was recorded as (−), while mild, moderate, and severe alterations were classified as (+), (++), and (+++), respectively (EL-Dab and Alshailabi et al., 2024; Ahmed et al., 2026).

3. ETHICS APPROVAL

Ethical approval for the animal experiments was obtained from the Al-Mukhtar Bioethics Committee, the Libyan National Committee for Biosafety and Bioethics, Omar Al-Mukhtar University, Libya (NBC: 007. A. 26. 96). All procedures complied with applicable institutional ethical guidelines for the use of laboratory animals.

4. RESULT

Histopathological Findings of the Myocardium

Histological examination of the myocardium of control rats revealed normal cardiac architecture, characterized by intact and regularly arranged MYO fibers with no detectable histopathological alterations (Fig. 1). In contrast, APAP-exposed rats showed evident MYO structural alterations. After 30 days, subendocardial edema, MYO damage, and focal hemorrhage between the MYO bundles were observed (Fig. 2). At 60 days, these alterations became more pronounced, with severe subendocardial edema, MYO damage, and inflammatory cell infiltration (ICI) (Fig. 3). Moreover, the RUT treatment was associated with progressive improvement in MYO morphology. After 30 days, vascular congestion with prominent erythrocytes within dilated blood vessels was observed, together with interstitial edema and ICI (Fig. 4). By 60 days, the MYO architecture was preserved, with no detectable histopathological alterations (Fig. 5). In addition, the APAP + BM-MSCs group showed a well-preserved MYO architecture at both examination periods. No detectable histopathological alterations were observed after either 30 or 60 days (Figs. 6 and 7).

In the combined-treatment group, only mild focal degeneration of a limited number of MYO fibers was observed at both 30 and 60 days, while the surrounding MYO architecture remained relatively preserved (Figs. 8 and 9).

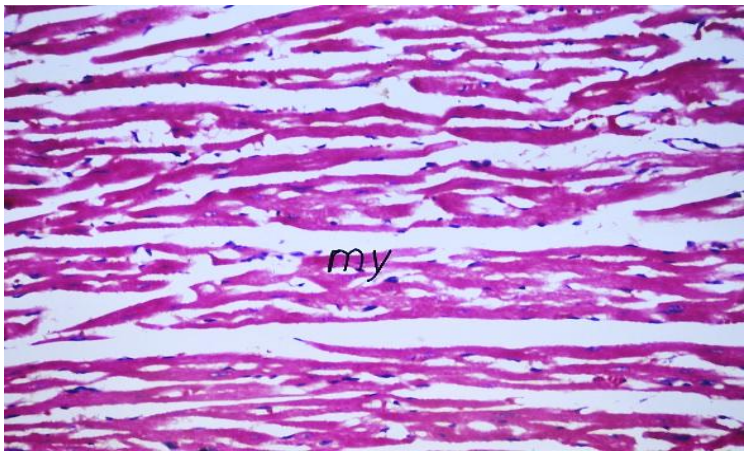


Fig. 1. Heart section from control rats showing normal MYO architecture with intact cardiac muscle fibers (my) and no observable histopathological alterations (H&E, ×400).

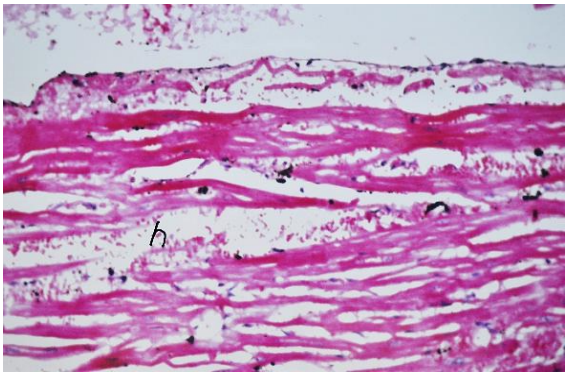


Fig. 2. Heart section from APAP-treated rats after 30 days showing subendocardial edema with MYO damage and focal hemorrhage between MYO bundles (h) (H&E, ×400).

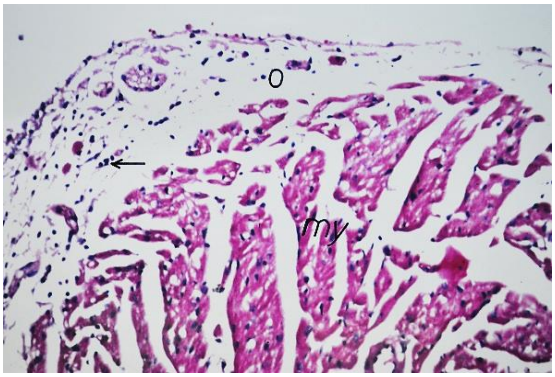


Fig. 3. Heart section from APAP-treated rats after 60 days showing severe subendocardial edema with MYO damage (my) and ICI (arrow) (H&E, ×400).

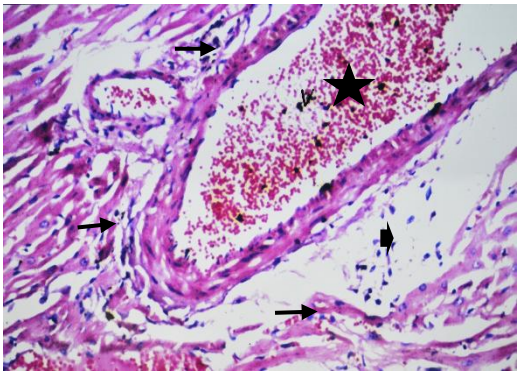


Fig. 4. Heart section from APAP + RUT-treated rats after 30 days, showing vascular congestion with prominent erythrocytes within dilated blood vessels (star), accompanied by interstitial edema (arrowhead) and ICI in the surrounding tissue (arrows). (H&E, ×400).

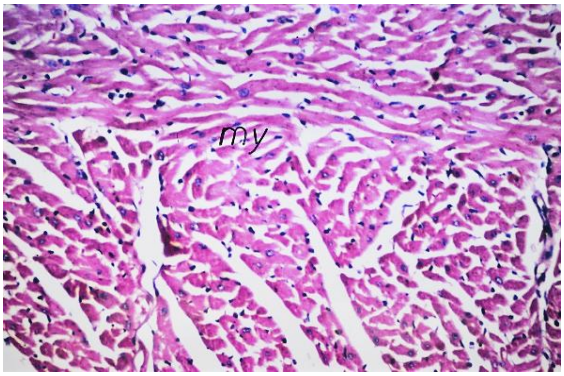


Fig. 5. Heart section from APAP + RUT-treated rats after 60 days showing preserved MYO architecture with no detectable histopathological alterations (my). (H&E, ×400).

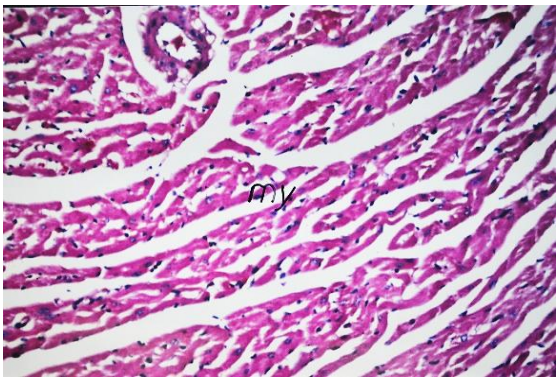


Fig. 6. Heart section from APAP + BM-MSC-treated rats after 30 days, showing conserved MYO architecture with no detectable histopathological alterations (my). (H&E, ×400).

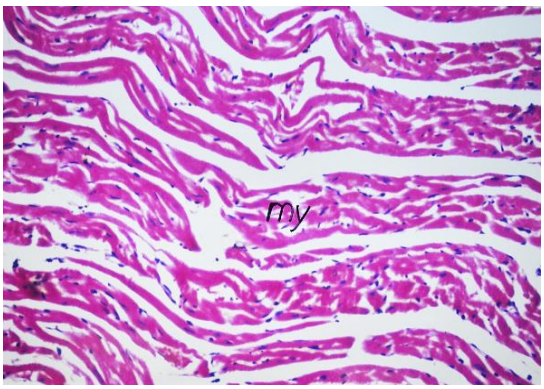


Fig. 7. Heart section from APAP + BM-MSC-treated rats after 60 days, showing well-preserved MYO architecture with no detectable histopathological alterations (my). (H&E, ×400).

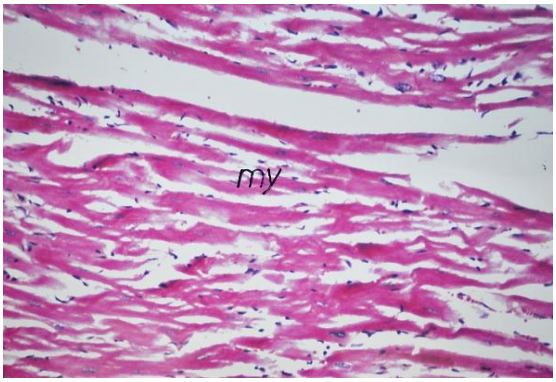


Fig. 8. Heart section of a combined-therapy rat after 30 days showing focal degenerative changes affecting a limited number of MYO fibers (my), while the surrounding MYO architecture remains relatively preserved (H&E, ×400).

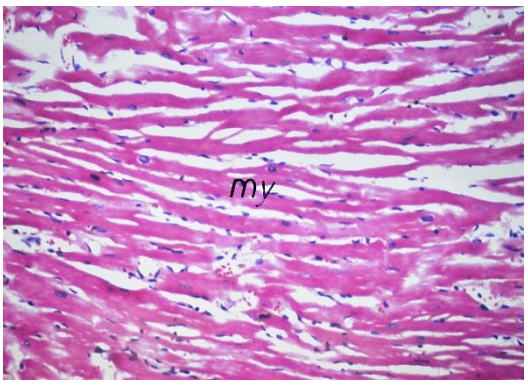


Fig. 9. Heart section from a combined-therapy rat after 60 days showing focal degeneration of a few MYO fibers, with preservation of the surrounding cardiac architecture (my) (H&E, ×400).

Semi-quantitative Histopathological Assessment

Semi-quantitative assessment of the MYO sections demonstrated a greater severity of histopathological alterations in the APAP group, particularly after 60 days (Table 1). At 30 days, the APAP group showed mild-to-moderate MYO degeneration, moderate edema, and mild hemorrhage. At 60 days, MYO degeneration increased to moderate-to-severe, accompanied by severe edema and moderate ICI. Furthermore, in the APAP + RUT group, mild edema, moderate vascular congestion, and mild ICI were detected at 30 days, whereas no detectable alterations were recorded at 60 days. In contrast, the APAP + BM-MSCs group showed no detectable alterations in any of the assessed parameters at either time point. The combined-treatment group showed only mild MYO degeneration at both 30 and 60 days, with no detectable edema, congestion, hemorrhage, or ICI (Table 1). Overall, the histopathological assessment indicated that APAP exposure was associated with progressive MYO structural alterations, whereas treatment with RUT or BM-MSCs was associated with marked preservation of MYO architecture. The BM-MSC-treated group showed no detectable histopathological alterations at either examination point, while the RUT-treated group showed complete histological normalization by 60 days. The combined-treatment group also exhibited largely preserved MYO architecture, although mild focal MYO degeneration persisted.

Table 1. Semi-quantitative scoring of histopathological alterations in the myocardium of control and experimental rats

Group	Time	Degeneration	Edema	Congestion	Hemorrhage	ICI
Control	–	–	–	–	–	–
APAP	30 d	++	++	–	+	–
APAP	60 d	+++	+++	–	–	++
APAP + RUT	30 d	+	+	++	–	+
APAP + RUT	60 d	–	–	–	–	–
APAP + BM-MSCs	30 d	–	–	–	–	–
APAP + BM-MSCs	60 d	–	–	–	–	–
Combined-therapy	30 d	+	–	–	–	–
Combined-therapy	60 d	+	–	–	–	–

Values represent the semi-quantitative histopathological grading of the examined MYO sections. (−) = no detectable histopathological alteration; (+) = mild alteration; (++) = moderate alteration; (+++) = severe alteration.

5. DISCUSSION

The present histopathological findings demonstrate that prolonged APAP exposure was associated with progressive structural alterations in the myocardium. While the control hearts showed normal organization of cardiac muscle fibers, APAP-treated animals exhibited subendocardial edema, MYO damage, and focal hemorrhage at 30 days, followed by more pronounced edema and ICI at 60 days. The semi-quantitative assessment supported this progression, particularly for MYO degeneration and edema. Although APAP is primarily recognized for its hepatotoxicity, cardiac abnormalities have been reported following severe APAP exposure, including MYO injury, arrhythmias, and cardiac dysfunction (KhabazianZadeh et al., 2019; Abdalally et al., 2021). However, the extent to which these changes result from a direct cardiac effect or from systemic consequences of APAP toxicity remains uncertain (Khalid et al., 2026). The present findings therefore provide morphological evidence of MYO involvement without implying that the heart represents the primary target of APAP toxicity. Moreover, a possible explanation for the observed MYO alterations is the disturbance of cellular redox homeostasis associated with excessive APAP exposure. When the capacity for APAP detoxification is exceeded, its reactive metabolite NAPQI can contribute to glutathione depletion, mitochondrial dysfunction, and oxidative and nitrosative stress (Ramachandran & Jaeschke, 2017; Elduob et al., 2023a; Alshailabi et al., 2024). Such disturbances may be particularly relevant to the myocardium because cardiac muscle has a high and continuous energy requirement. The increasing severity of the lesions at 60 days, together with the appearance of ICI, may therefore reflect persistent cellular stress and an associated tissue response. Nevertheless, OS and inflammatory mediators were not directly measured in the present study, and these mechanisms should consequently be regarded as plausible interpretations rather than demonstrated pathways.

The MYO response to RUT was considerably more favorable. At 30 days, some vascular congestion, edema, and ICI remained detectable, whereas by 60 days the MYO architecture appeared completely preserved. This gradual normalization is consistent with the reported antioxidant and anti-inflammatory activities of RUT (EL-Dab and Alshailabi et al., 2024). RUT has been shown to enhance endogenous antioxidant defenses and reduce oxidative damage, with involvement of cellular protective pathways such as Nrf2/HO-1 (Rahmani et al., 2023). More specifically, experimental studies have demonstrated cardioprotective effects of RUT, including reduction of lipid peroxidation and preservation of antioxidant defenses in models of MYO injury (Karthick and Prince, 2006; Annapurna et al., 2010). These findings provide a reasonable biological basis for the progressive improvement observed in the present study.

The complete preservation of MYO architecture after 60 days of RUT treatment may therefore reflect attenuation of the processes contributing to APAP-associated tissue injury. RUT has also been reported to protect cardiac mitochondria against oxidative damage and to preserve mitochondrial antioxidant and energy-related functions (Karthick and Prince, 2010). However, because the present investigation relied primarily on histological examination, it cannot establish whether mitochondrial protection or modulation of oxidative pathways directly contributed to the observed morphological recovery. Previous studies have demonstrated that APAP can induce molecular alterations related to oxidative stress and inflammation in cardiac tissue that may not be apparent by conventional histopathological examination (Jin et al., 2012). Further biochemical and molecular investigations are therefore warranted to clarify the mechanisms underlying the observed tissue recovery (El-Dab & Alshailabi, 2024). The histological findings should consequently be interpreted as evidence of structural protection rather than direct proof of a particular molecular mechanism.

Moreover, the BM-MSC-treated animals showed an even more consistent preservation of MYO morphology. No detectable histopathological abnormalities were observed at either 30 or 60 days. This early preservation may be related to the multifaceted actions of mesenchymal stem cells within injured tissues. Current evidence indicates that the therapeutic effects of MSCs are mediated substantially through paracrine and immunomodulatory mechanisms rather than through differentiation into replacement cardiomyocytes alone. MSCs release trophic factors and extracellular vesicles capable of influencing inflammation, cell survival, angiogenesis, and tissue repair (Sid-Otmane et al., 2020; Mabotuwana et al., 2022). Such effects could create a more favorable local environment for maintaining MYO integrity following APAP exposure. On the other hand, the absence of inflammatory and degenerative changes in the BM-MSC group is also compatible with the immunomodulatory properties of these cells. MSCs can interact with immune cells and modify inflammatory responses, potentially limiting persistent inflammation and supporting tissue recovery (Mabotuwana et al., 2022). This may partly explain the difference between BM-MSCs and RUT at 30 days, when residual edema and ICI were still present in the RUT-treated myocardium. Nevertheless, this finding should not be interpreted as evidence that BM-MSCs are universally superior to RUT; rather, under the specific experimental conditions of the present study, BM-MSC treatment was associated with earlier and more sustained morphological preservation.

The combined-treatment group produced a different and somewhat unexpected pattern. Mild focal degenerative changes remained detectable at both examination periods, whereas no detectable abnormalities were observed in the BM-MSC group and no abnormalities remained in the 60-day RUT group. Thus, the combined regimen did not demonstrate an additional histological advantage over the individual treatments. This does not necessarily indicate an antagonistic interaction, since the outcome of combined interventions can depend on dose, timing, duration, and interactions between their respective biological effects. Importantly, the lesions in the combined group were focal and limited, suggesting that the treatment was still associated with substantial preservation of MYO structure rather than widespread tissue injury. The present findings indicate a clear difference between prolonged APAP exposure and the therapeutic interventions. APAP was associated with progressive MYO degeneration, edema, hemorrhage, and ICI, whereas RUT was accompanied by gradual restoration of MYO architecture and BM-MSCs by early and sustained structural preservation. These observations are consistent with the proposed antioxidant and anti-inflammatory actions of RUT and the paracrine and immunomodulatory properties of BM-MSCs (Karthick and Prince, 2006; Sid-Otmane et al., 2020; Rahmani et al., 2023). The persistence of only mild focal degeneration following combined treatment suggests that the response to the combined regimen was more complex than expected and did not translate into superior histological protection. Because the present assessment was morphological, further studies incorporating OS indices, inflammatory markers, apoptosis-related proteins, mitochondrial markers, and quantitative morphometry would help clarify the mechanisms responsible for the observed MYO protection.

6. CONCLUSION

The present study demonstrated that acetaminophen exposure was associated with progressive histopathological alterations in the rat myocardium, characterized mainly by edema, MYO degeneration, hemorrhage, and ICI. These alterations were more pronounced after 60 days, indicating persistent MYO injury. Treatment with RUT resulted in marked histological improvement, with complete absence of detectable MYO abnormalities after 60 days. Similarly, treatment with the BM-MSCs showed well-preserved MYO architecture at both observed time points.

The combined treatment produced only mild focal degenerative changes, suggesting that both interventions had protective potential, although their combination did not result in an additional histological benefit under the conditions of the present study. Overall, the findings support the potential of RUT and BM-MSCs as promising protective approaches against APAP-associated MYO alterations. However, the study was limited to histopathological and semi-quantitative tissue assessment. Further investigations incorporating biochemical, molecular, oxidative stress, inflammatory, apoptotic, and cardiac functional markers are recommended to clarify the mechanisms underlying the observed protective effects. Longer exposure and follow-up periods, together with different treatment doses and schedules, may also provide further insight into the therapeutic potential of RUT and BM-MSCs.

In conclusion, RUT and BM-MSCs showed substantial histological protective effects on the myocardium following APAP exposure, supporting their potential for further investigation as complementary protective strategies against drug-associated cardiac tissue injury.

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