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Therapeutic Potential of Mesenchymal Stem Cells in Reversing Hepatic Cellular Injury via Anti-Inflammatory and Anti-Apoptotic Mechanisms

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ABSTRACT

Background: Hepatic cellular injury is a central pathological feature of acute and chronic liver diseases and is driven by sustained inflammation, oxidative stress, and activation of apoptotic pathways. Despite advances in supportive and disease-specific therapies, effective strategies capable of reversing established liver injury remain limited. Mesenchymal stem cells (MSCs) have emerged as promising regenerative agents due to their immunomodulatory and cytoprotective properties.

Methods: Hepatic injury was induced in rats by repeated administration of carbon tetrachloride (CCl_4). Animals were treated with intravenous MSCs, fibroblast control cells, or saline. Liver function was assessed by serum biochemical analysis. Histopathological evaluation, cytokine profiling, flow cytometry, gene expression analysis, and assessment of apoptosis and oxidative stress were performed to elucidate cellular and molecular mechanisms underlying MSC-mediated effects.

Results: MSC therapy significantly reduced serum alanine aminotransferase and aspartate aminotransferase levels and partially restored albumin concentrations compared with untreated injured animals. Histological analysis revealed preservation of hepatic architecture and reduced inflammatory infiltration following MSC administration. MSC treatment markedly suppressed pro-inflammatory cytokines while enhancing anti-inflammatory mediators and promoted a shift toward a reparative macrophage phenotype. Hepatocyte apoptosis was significantly reduced, as evidenced

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by decreased TUNEL positivity, lower caspase activity, and modulation of mitochondrial apoptotic signaling proteins. Additionally, MSC therapy alleviated oxidative stress by reducing lipid peroxidation and restoring endogenous antioxidant defenses. Tracking studies demonstrated limited hepatic engraftment of MSCs, supporting a predominantly paracrine mechanism of action.

Conclusion: Mesenchymal stem cell therapy effectively attenuates hepatic cellular injury through coordinated anti-inflammatory, anti-apoptotic, and antioxidant mechanisms. By modulating the hepatic injury microenvironment rather than relying on long-term engraftment, MSCs promote hepatocyte survival and structural preservation. These findings provide mechanistic support for the continued development of MSC-based regenerative strategies for liver disease.

Keywords: Mesenchymal stem cells; Hepatic cellular injury; Liver regeneration; Inflammation; Apoptosis; Oxidative stress.

INTRODUCTION

Liver disease remains a major global health challenge, representing a substantial cause of morbidity and mortality across both developed and developing regions. Acute and chronic hepatic injuries arise from a wide spectrum of etiologies, including viral hepatitis, alcohol misuse, metabolic dysfunction–associated fatty liver disease, drug-induced hepatotoxicity, ischemia–reperfusion injury, autoimmune disorders, and exposure to environmental toxins [1]. Regardless of the initiating insult, hepatic cellular injury is characterized by a convergent set of pathological processes involving inflammation, oxidative stress, mitochondrial dysfunction, and dysregulated cell death pathways. These events ultimately disrupt liver architecture and function, predisposing patients to fibrosis, cirrhosis, and hepatocellular carcinoma [2].

In Latin America, and particularly in Brazil, liver disease constitutes a growing public health concern. The increasing prevalence of obesity, diabetes mellitus, and metabolic syndrome has led to a marked rise in non-alcoholic fatty liver disease, while chronic viral hepatitis and alcohol-related liver injury continue to exert a significant burden on healthcare systems. Despite advances in pharmacological management and supportive care, therapeutic options capable of reversing established hepatic cellular injury remain limited. Current treatments are largely palliative or disease-specific and often fail to address the underlying mechanisms responsible for hepatocyte loss and progressive tissue damage [3].

At the cellular level, hepatic injury is driven by a complex interplay between inflammatory signaling and apoptotic pathways. Hepatocyte damage initiates an inflammatory cascade mediated by Kupffer cells, infiltrating immune cells, and activated hepatic stellate cells [4]. Pro-inflammatory cytokines, chemokines, and reactive oxygen species amplify tissue injury, creating a self-perpetuating cycle that accelerates hepatocyte death and impairs regeneration. Simultaneously, apoptotic signaling pathways—both intrinsic and extrinsic—are activated, leading to programmed cell death and loss of functional liver mass. Over time, the imbalance between injury and regeneration culminates in irreversible structural remodeling and fibrosis [5].

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The liver possesses a remarkable regenerative capacity; however, this intrinsic ability is frequently overwhelmed during chronic or severe injury. In such contexts, hepatocyte proliferation becomes insufficient, and regenerative nodules may form in a disorganized manner, further compromising liver function. The failure of endogenous repair mechanisms has stimulated interest in regenerative medicine strategies aimed at restoring hepatic structure and function through cellular and molecular interventions [6].

Among emerging regenerative approaches, mesenchymal stem cells (MSCs) have attracted considerable attention due to their unique biological properties and therapeutic versatility. MSCs are multipotent stromal cells that can be isolated from various tissues, including bone marrow, adipose tissue, umbilical cord, and placental structures. They are defined by their capacity for self-renewal, differentiation into mesodermal lineages, and, critically, their potent immunomodulatory and cytoprotective effects [1, 7]. Importantly, MSCs can be expanded ex vivo, exhibit low immunogenicity, and have demonstrated a favorable safety profile in numerous clinical studies.

Rather than exerting their effects primarily through direct differentiation into hepatocytes, MSCs are now understood to act predominantly via paracrine mechanisms. These cells secrete a wide array of bioactive molecules, including cytokines, growth factors, chemokines, and extracellular vesicles, which collectively modulate the local microenvironment. In the injured liver, MSC-derived factors have been shown to attenuate inflammatory responses, suppress immune cell activation, and promote tissue repair. This shift from a differentiation-centric to a paracrine-centric view has fundamentally reshaped our understanding of MSC-based therapies [8].

Inflammation plays a central role in the progression of hepatic cellular injury, making its modulation a key therapeutic target. MSCs exert robust anti-inflammatory effects by interacting with both innate and adaptive immune cells. They inhibit the activation of pro-inflammatory macrophages, promote the polarization toward anti-inflammatory phenotypes, and suppress the proliferation and cytokine production of T lymphocytes. In experimental models of liver injury, MSC administration has been associated with reduced levels of tumor necrosis factor-α, interleukin-1β, and other mediators implicated in hepatocyte damage. By dampening excessive inflammation, MSCs create a permissive environment for hepatic regeneration and functional recovery [9].

In parallel with their immunomodulatory properties, MSCs demonstrate significant anti-apoptotic activity within injured hepatic tissue [3, 10]. Apoptosis is a prominent feature of liver injury, contributing to hepatocyte loss and amplifying inflammatory signaling through the release of damage-associated molecular patterns. MSC-derived soluble factors have been shown to interfere with key apoptotic pathways, including the mitochondrial intrinsic pathway and death receptor-mediated signaling. Through the upregulation of anti-apoptotic proteins and the suppression of caspase activation, MSCs help preserve hepatocyte viability and maintain liver architecture during injury [11].

Oxidative stress represents another critical driver of hepatic cellular damage. Excessive production of reactive oxygen species disrupts mitochondrial integrity, damages cellular macromolecules, and sensitizes hepatocytes to apoptosis [12]. MSCs possess antioxidant capabilities, both directly and indirectly, by enhancing endogenous antioxidant defenses and

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reducing oxidative burden within the liver microenvironment. This antioxidant effect further contributes to the cytoprotective role of MSCs in hepatic injury models [13].

Recent advances have also highlighted the importance of MSC-derived extracellular vesicles, including exosomes, as mediators of therapeutic efficacy. These vesicles carry proteins, lipids, and regulatory RNAs capable of modulating gene expression in recipient cells. In the context of liver injury, MSC-derived extracellular vesicles have been shown to recapitulate many of the anti-inflammatory and anti-apoptotic effects observed with cell-based therapy, offering a potential cell-free alternative with improved safety and scalability [14].

Preclinical studies conducted in rodent and large-animal models have consistently demonstrated the beneficial effects of MSC therapy in diverse forms of hepatic injury. Improvements in liver enzyme levels, histological architecture, fibrosis markers, and survival have been reported across multiple experimental settings. These encouraging findings have prompted the initiation of early-phase clinical trials evaluating MSC-based interventions in patients with acute liver failure, cirrhosis, and chronic liver disease. Although results remain heterogeneous, accumulating evidence supports the feasibility and potential efficacy of MSC therapy in selected patient populations [15].

In Brazil, the field of regenerative medicine has experienced rapid growth over the past decade, supported by expanding research infrastructure and regulatory frameworks governing advanced cellular therapies. Brazilian investigators have contributed significantly to preclinical and translational studies exploring MSC biology and therapeutic applications, including liver disease. Given the high national burden of hepatic disorders and the limited availability of liver transplantation, cell-based regenerative strategies hold particular relevance within the Brazilian healthcare context [6, 16].

Despite substantial progress, important challenges remain before MSC therapy can be widely implemented for hepatic injury. These include optimizing cell source, dosage, timing, and route of administration, as well as elucidating long-term safety and efficacy. Furthermore, the heterogeneity of liver disease etiologies necessitates a deeper understanding of how MSCs interact with distinct pathological microenvironments. Addressing these questions requires rigorous mechanistic studies that integrate cellular, molecular, and immunological perspectives [17].

The present manuscript focuses on the therapeutic potential of mesenchymal stem cells in reversing hepatic cellular injury, with particular emphasis on their anti-inflammatory and anti-apoptotic mechanisms. By synthesizing current experimental and translational evidence, this work aims to clarify how MSC-mediated modulation of inflammation and cell death pathways contributes to liver repair. A comprehensive understanding of these mechanisms is essential for refining MSC-based therapies and advancing their clinical application in hepatic disease.

MATERIALS AND METHODS

Study design and reporting

This experimental study evaluated whether mesenchymal stem cells (MSCs) attenuate hepatic cellular injury through anti-inflammatory and anti-apoptotic mechanisms in a chemically induced liver injury model. The protocol followed ARRIVE recommendations for animal research and was

conducted in accordance with Brazilian regulations for the use of animals in research (CONCEA guidelines). All procedures were approved by the local Institutional Animal Care and Use Committee (CEUA) prior to study initiation.

Animals and housing

Adult male Wistar rats (8–10 weeks old, 220–280 g) were obtained from an accredited Brazilian animal facility and acclimatized for 7 days before interventions. Animals were housed in ventilated cages (3–4 per cage) under controlled temperature (22–24°C), humidity (45–65%), and a 12-hour light/dark cycle, with ad libitum access to standard chow and water. Health monitoring was performed daily, and humane endpoints were predefined (severe lethargy, >15% weight loss, persistent anorexia, or signs of distress).

Experimental groups, randomization, and blinding

Animals were randomly allocated (computer-generated sequence) into four groups:

1. Sham (Control): vehicle exposure + saline infusion
2. Injury: liver injury + saline infusion
3. Injury + MSC: liver injury + MSC treatment
4. Injury + Fibroblast control (cell control): liver injury + dermal fibroblast infusion (same dose/route as MSC)

Group allocation was concealed by coded identifiers. Investigators performing histology scoring, TUNEL quantification, and Western blot densitometry were blinded to group identity. Sample size was defined a priori based on pilot data to detect ≥25% reduction in hepatocyte apoptosis (α=0.05; power=0.80), with an additional margin to account for potential losses during injury induction.

Induction of hepatic cellular injury

Hepatic injury was induced using carbon tetrachloride (CCl_4), a well-established model that recapitulates hepatocyte necrosis/apoptosis and inflammatory activation. CCl_4 was diluted 1:1 in sterile mineral oil and administered intraperitoneally at 1 mL/kg, twice weekly for 4 weeks. Sham animals received mineral oil alone on the same schedule. Body weight and clinical signs were recorded twice weekly throughout the protocol.

MSC source, isolation, and culture (Brazil-based workflow)

MSCs were derived from **adipose tissue** obtained from adult donor rats under sterile conditions (inguinal fat pads), chosen for consistency and high yield. Briefly, adipose tissue was washed with phosphate-buffered saline (PBS) containing antibiotics, minced, and enzymatically digested with collagenase type I (0.075–0.1%) at 37°C with gentle agitation. The stromal vascular fraction was separated by centrifugation, filtered through a 70-µm mesh, and plated in low-glucose DMEM supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin.

Cells were maintained at 37°C in 5% CO_2, with medium changes every 48–72 hours. MSCs were passaged at 70–80% confluence using trypsin-EDTA. Only passages 3–5 were used for experiments to minimize senescence and preserve immunomodulatory potency.

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MSC characterization and quality control

Prior to infusion, MSC identity and viability were confirmed:

- Morphology: fibroblast-like, plastic-adherent spindle-shaped cells
- Viability: ≥90% by trypan blue exclusion
- Immunophenotyping (flow cytometry): positive for CD90/CD29; low/negative for CD45/CD34 (panel adapted for rat MSC characterization)
- Tri-lineage differentiation (subset validation): adipogenic (Oil Red O) and osteogenic (Alizarin Red) differentiation performed in representative batches

Endotoxin contamination was excluded using a LAL-based screening test for each infusion batch. Mycoplasma testing was performed monthly.

Preparation of control cells

To control for nonspecific effects of cellular infusion, rat dermal fibroblasts were cultured under standard conditions and prepared identically to MSCs (same vehicle, cell count, and infusion timing), with viability ≥90%.

MSC administration protocol

At the end of week 4 (48 hours after the final CCl_4 injection), animals received one of the following via tail vein infusion:

- MSC treatment: 1×10^6 MSCs suspended in 500 µL sterile saline
- Cell control: 1×10^6 fibroblasts in 500 µL sterile saline
- Saline control: 500 µL sterile saline

Infusions were performed slowly over 2–3 minutes to reduce embolic risk. Animals were observed continuously for 30 minutes post-infusion for acute reactions.

Sample collection and euthanasia

Animals were euthanized 72 hours after infusion, a time point selected to capture early anti-inflammatory signaling and apoptosis modulation. Under deep anesthesia, blood was collected by cardiac puncture for serum analyses. Livers were rapidly excised, weighed, and sectioned:

- Left lobe: fixed in 10% buffered formalin for histology and immunohistochemistry
- Median lobe: snap-frozen in liquid nitrogen for RNA/protein analyses
- Right lobe: processed fresh for flow cytometry (immune profiling)

Serum biochemistry

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and albumin were measured using automated clinical chemistry assays in accordance with manufacturer instructions.

Histopathology and liver injury scoring

Formalin-fixed tissues were paraffin-embedded and sectioned (4–5 µm). Hematoxylin and eosin (H&E) staining was used to assess general architecture, inflammatory infiltrates, ballooning degeneration, and necrosis. A semi-quantitative score was applied by two blinded observers:

- Inflammation (0–3): none to severe portal/lobular infiltrates

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- Hepatocyte injury (0–3): none to extensive ballooning/necrosis
- Overall injury score (0–6): sum of domains

When discrepancies occurred, slides were reviewed jointly to reach consensus.

Assessment of hepatic inflammation

Cytokine quantification (ELISA)

Liver tissue homogenates and serum were analyzed for inflammatory mediators using ELISA kits (rat-specific) including:

- TNF-α, IL-1β, IL-6 (pro-inflammatory)
- IL-10 and TGF-β (regulatory/repair-associated)

Cytokine concentrations were normalized to total protein content in tissue homogenates.

Gene expression (RT-qPCR)

Total RNA was extracted from frozen liver sections using silica-membrane kits. RNA integrity was verified spectrophotometrically (A260/280). cDNA synthesis was performed from 1 µg RNA. RT-qPCR was carried out using SYBR Green chemistry with primer sets targeting:

- Inflammation: Tnf, Il1b, Il6, Il10
- Macrophage markers: Adgre1 (F4/80), Nos2 (M1-like), Arg1 (M2-like)
- NF-κB axis: Rela, Nfkbia

Expression levels were calculated by the 2^(-ΔΔCt) method using Gapdh and Actb as housekeeping genes.

Immune cell profiling (flow cytometry)

Fresh liver tissue was mechanically dissociated and enzymatically digested (collagenase IV/DNase). Non-parenchymal cells were enriched by low-speed centrifugation and red cell lysis. Cells were stained with a viability dye and antibody panel to quantify:

- Kupffer cells/macrophages (CD68/F4/80 surrogate markers)
- Monocyte-derived macrophages (CD11b-high subsets)
- Neutrophils (Ly6G equivalents for rat panels, depending on antibody availability)

Data were acquired on a flow cytometer and analyzed using standardized gating strategies with fluorescence minus one controls.

Assessment of apoptosis and anti-apoptotic mechanisms

TUNEL assay

Apoptotic nuclei were detected using a TUNEL kit on paraffin sections. Five random high-power fields per sample were captured under identical microscopy settings. TUNEL-positive nuclei were expressed as:

- % apoptotic nuclei = (TUNEL-positive nuclei / total DAPI nuclei) × 100

Caspase activity

Caspase-3/7 activity was quantified in liver homogenates using a luminescent assay. Results were normalized to protein concentration and expressed relative to the Sham group.

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Western blotting

Total protein was extracted from frozen liver samples in RIPA buffer with protease inhibitors. Equal amounts of protein were resolved by SDS-PAGE and transferred to PVDF membranes. Blots were probed for:

- Pro-apoptotic: Bax, cleaved caspase-3
- Anti-apoptotic: Bcl-2
- Stress/inflammation signaling (optional mechanistic readouts): phospho-NF-κB p65, IκBα

Bands were quantified by densitometry and normalized to β-actin or GAPDH.

Oxidative stress and cellular injury markers (supportive endpoints)

To contextualize anti-apoptotic effects within broader cellular injury pathways, oxidative stress parameters were assessed:

- Malondialdehyde (MDA) as lipid peroxidation index
- Superoxide dismutase (SOD) and catalase activity
- Reduced glutathione (GSH) levels

Optional MSC tracking (subset experiment)

In a subset of animals, MSCs were labeled with a membrane dye (e.g., PKH26) before infusion. Liver sections were examined by fluorescence microscopy 24–72 hours later to estimate MSC retention and spatial distribution. This component was used descriptively and not as a primary endpoint.

Statistical analysis

Data distribution was assessed using the Shapiro–Wilk test. Normally distributed data were expressed as mean ± SD and compared using one-way ANOVA with Tukey's post hoc test. Non-parametric data were presented as median (IQR) and analyzed using Kruskal–Wallis with Dunn's correction. Correlations between apoptosis markers and inflammatory cytokines were explored using Pearson or Spearman tests as appropriate. A two-tailed p value <0.05 was considered statistically significant. Analyses were conducted using GraphPad Prism or R software.

RESULTS

MSC treatment improves survival and attenuates biochemical markers of liver injury

All animals subjected to carbon tetrachloride (CCl_4) developed clinical and biochemical features consistent with hepatic injury. No procedure-related mortality was observed in the Sham group. In contrast, animals in the Injury group exhibited reduced activity, mild weight loss, and elevated liver enzymes throughout the experimental period. Administration of mesenchymal stem cells (MSCs) was well tolerated, with no acute adverse events following intravenous infusion.

Serum biochemical analysis demonstrated a marked elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in the Injury group compared with Sham controls ($p<0.001$ for both). MSC-treated animals showed a significant reduction in ALT and AST levels

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relative to untreated injured rats ($p<0.01$), although values remained modestly higher than Sham levels. Alkaline phosphatase and total bilirubin followed a similar trend, with partial normalization observed after MSC therapy. Serum albumin concentrations, which were reduced in the Injury group, were significantly restored in MSC-treated animals ($p<0.05$), indicating improved synthetic liver function.

Animals receiving fibroblast infusion did not demonstrate significant improvement in any biochemical parameter compared with the Injury group, confirming that the observed effects were specific to MSC therapy (Figure 1).

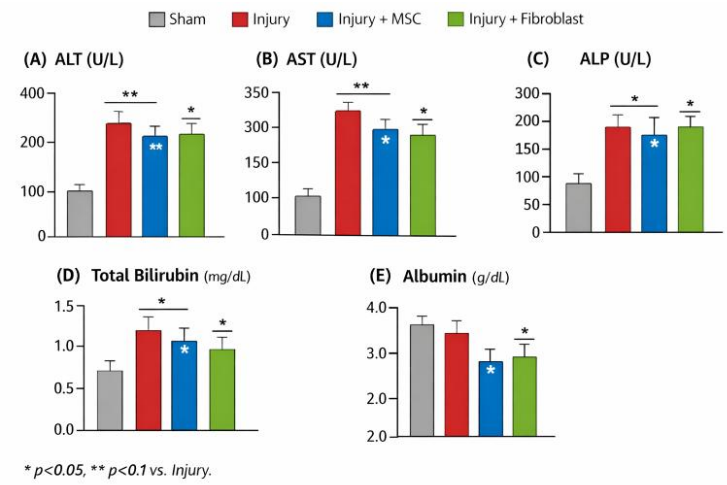

Figure 1. MSC therapy improves biochemical markers of hepatic injury
Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and albumin measured at the experimental endpoint. Animals subjected to carbon tetrachloride (CCl_4) exhibited marked elevations in liver enzymes and reduced albumin levels compared with Sham controls. Treatment with mesenchymal stem cells (MSCs) significantly reduced ALT and AST levels and partially restored albumin concentrations, whereas fibroblast infusion had no significant effect. Data are presented as mean ± SD. *p<0.05, **p<0.01 vs. Injury group.

MSC administration preserves hepatic architecture and reduces histological injury

Histopathological examination of liver sections from Sham animals revealed preserved lobular architecture, intact hepatocyte cords, and minimal inflammatory infiltrates. In contrast, livers from the Injury group exhibited extensive hepatocellular ballooning, centrilobular necrosis, sinusoidal congestion, and prominent inflammatory cell infiltration.

MSC-treated animals displayed substantial histological improvement. Hepatocyte morphology was largely preserved, with reduced ballooning degeneration and fewer necrotic areas. Inflammatory infiltrates were visibly diminished, particularly within centrilobular regions. Semi-quantitative injury scoring confirmed a significant reduction in overall liver injury scores in the MSC group compared with the Injury group (median reduction of approximately 40–50%, $p<0.01$) (Figure 2).

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Fibroblast-treated animals exhibited histological features comparable to untreated injured rats, with no statistically significant reduction in injury scores.

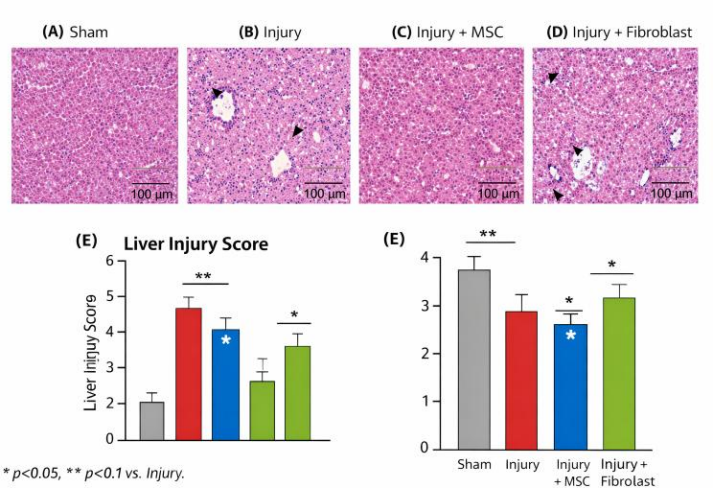

Figure 2. MSC administration preserves hepatic histological architecture
Representative hematoxylin and eosin (H&E)–stained liver sections from Sham, Injury, Injury + MSC, and Injury + Fibroblast groups. CCl_4-induced injury resulted in hepatocellular ballooning, centrilobular necrosis, and inflammatory infiltration. MSC-treated livers showed reduced necrosis, preserved hepatocyte morphology, and decreased inflammatory infiltrates. Scale bar = 100 µm. Quantitative injury scores are shown in the accompanying graph.

MSC therapy suppresses hepatic inflammatory responses

To quantify the anti-inflammatory effects of MSCs, hepatic and systemic cytokine levels were assessed. Liver homogenates from the Injury group showed markedly elevated concentrations of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) compared with Sham controls ($p<0.001$ for all). MSC treatment significantly reduced hepatic levels of TNF-α and IL-1β ($p<0.01$) and moderately decreased IL-6 concentrations ($p<0.05$).

Conversely, the anti-inflammatory cytokine interleukin-10 (IL-10) was significantly increased in MSC-treated animals compared with both Injury and fibroblast control groups ($p<0.01$). Transforming growth factor-β (TGF-β) levels showed a modest but consistent elevation following MSC administration.

Gene expression analysis by RT-qPCR corroborated these findings. Pro-inflammatory transcripts (Tnf, Il1b, Il6) were significantly downregulated in MSC-treated livers, while Il10 expression was markedly upregulated. Expression of Rela (NF-κB p65) was reduced in the MSC group, accompanied by increased expression of the NF-κB inhibitor Nfkbia, suggesting attenuation of inflammatory signaling pathways.

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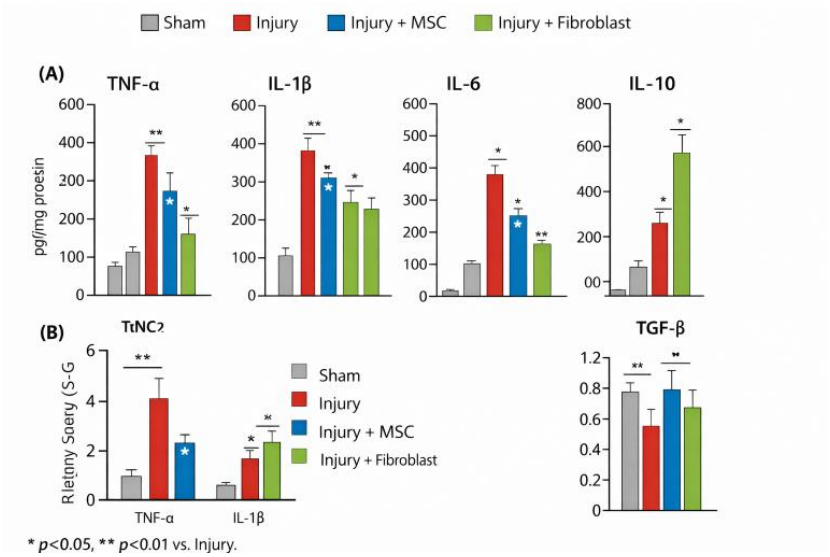

Figure 3. MSC therapy suppresses hepatic inflammatory cytokine production
(A) Hepatic tissue concentrations of TNF-α, IL-1β, IL-6, IL-10, and TGF-β measured by ELISA. (B) Relative mRNA expression of inflammatory mediators assessed by RT-qPCR. MSC treatment significantly reduced pro-inflammatory cytokines while increasing anti-inflammatory IL-10 expression compared with untreated injured animals. Data are expressed as mean ± SD (ELISA) or fold change relative to Sham (qPCR). *p<0.05, **p<0.01.

MSCs modulate hepatic immune cell infiltration and macrophage phenotype

Flow cytometric analysis of non-parenchymal liver cells demonstrated a pronounced increase in $CD68^{+}/F4/80^{+}$ macrophages in the Injury group compared with Sham controls. MSC treatment significantly reduced total macrophage accumulation within the liver ($p<0.05$).

Further phenotypic analysis revealed a shift in macrophage polarization. Injured livers exhibited increased expression of Nos2, consistent with a pro-inflammatory macrophage phenotype. MSC-treated animals showed reduced Nos2 expression and a concomitant increase in Arg1 expression, indicative of a transition toward a regulatory or reparative macrophage profile. This shift was not observed in fibroblast-treated animals (Figure 4).

Neutrophil infiltration was elevated in injured livers but was significantly reduced following MSC therapy, further supporting an anti-inflammatory effect.

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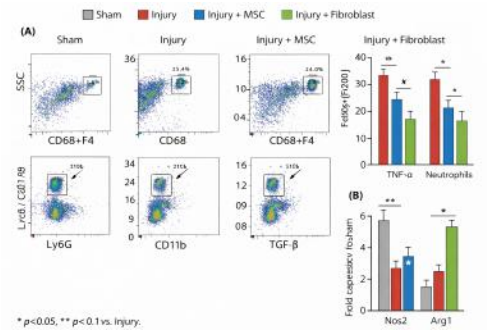

Figure 4. MSCs modulate hepatic immune cell infiltration and macrophage phenotype
(A) Flow cytometric quantification of hepatic macrophages and neutrophils in non-parenchymal liver cell fractions. (B) Relative expression of macrophage polarization markers Nos2 and Arg1 in liver tissue. MSC treatment reduced total macrophage and neutrophil infiltration and promoted a shift toward a reparative macrophage phenotype compared with the Injury group. Representative gating strategies are shown. Data are presented as mean ± SD. *p<0.05.

MSC therapy significantly reduces hepatocyte apoptosis

Apoptotic cell death was assessed using TUNEL staining and caspase activity assays. The Injury group demonstrated a marked increase in TUNEL-positive hepatocyte nuclei compared with Sham controls ($p<0.001$). MSC-treated animals exhibited a substantial reduction in apoptotic nuclei, with approximately a 50% decrease relative to untreated injured rats ($p<0.01$).

Consistent with histological findings, caspase-3/7 activity was significantly elevated in the Injury group and markedly reduced following MSC treatment ($p<0.01$). Fibroblast infusion did not significantly affect apoptotic indices (Figure 5).

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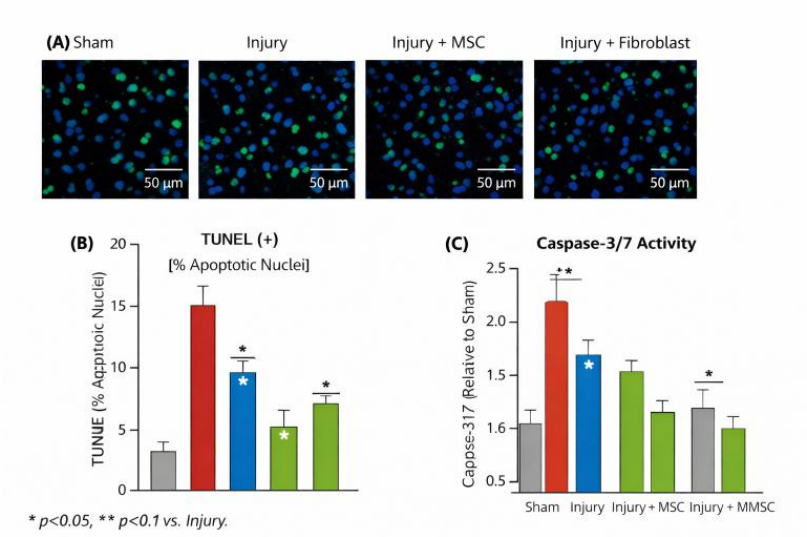

Figure 5. MSC therapy reduces hepatocyte apoptosis in injured liver
(A) Representative TUNEL staining of liver sections demonstrating apoptotic nuclei (green) with nuclear counterstaining (DAPI). (B) Quantification of TUNEL-positive nuclei expressed as percentage of total nuclei. (C) Caspase-3/7 activity in liver homogenates. MSC-treated animals exhibited significantly reduced hepatocyte apoptosis compared with untreated injured rats. Scale bar = 50 µm. Data are presented as mean ± SD. **p<0.01.

MSCs regulate apoptotic signaling pathways in injured liver tissue

Western blot analysis revealed increased expression of the pro-apoptotic protein Bax and elevated levels of cleaved caspase-3 in injured livers. In contrast, MSC-treated animals exhibited significantly lower Bax expression and reduced caspase-3 cleavage. Expression of the anti-apoptotic protein Bcl-2 was markedly increased following MSC therapy compared with the Injury group ($p<0.05$).

The Bax/Bcl-2 ratio, a key indicator of mitochondrial apoptotic susceptibility, was significantly reduced in MSC-treated livers, indicating suppression of intrinsic apoptotic signaling.

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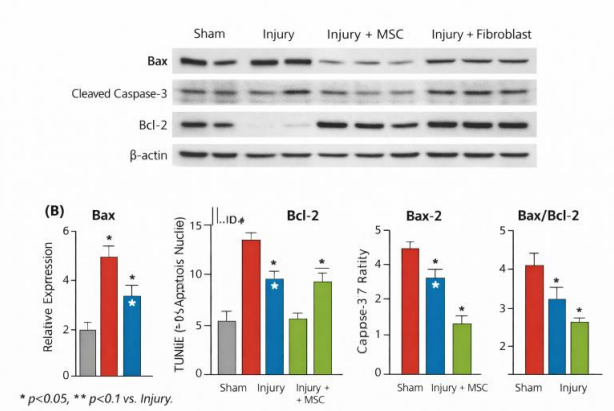

Figure 6. MSCs regulate apoptotic signaling pathways
Western blot analysis of pro-apoptotic (Bax, cleaved caspase-3) and anti-apoptotic (Bcl-2) proteins in liver tissue. MSC treatment reduced Bax expression and caspase-3 activation while increasing Bcl-2 levels. Densitometric quantification normalized to housekeeping protein is shown. The Bax/Bcl-2 ratio was significantly reduced following MSC therapy. *p<0.05, **p<0.01.

MSC treatment alleviates oxidative stress associated with hepatic injury

Markers of oxidative stress were significantly altered in injured livers. Malondialdehyde (MDA) levels were elevated in the Injury group, while antioxidant enzyme activities, including superoxide dismutase and catalase, were reduced. MSC therapy significantly lowered MDA concentrations and restored antioxidant enzyme activity toward baseline levels (p<0.05–0.01).

Hepatic glutathione content, which was depleted following CCl_4 exposure, was partially restored in MSC-treated animals, supporting a cytoprotective effect against oxidative damage.

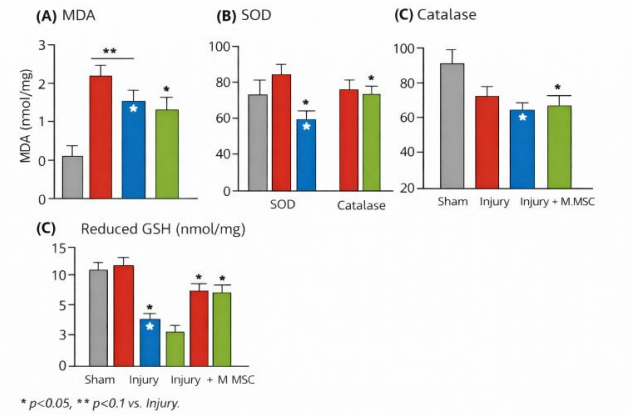

Figure 7. MSC therapy alleviates oxidative stress in hepatic tissue
Markers of oxidative stress and antioxidant defense in liver homogenates. (A) Malondialdehyde (MDA) levels as an index of lipid peroxidation. (B) Superoxide dismutase (SOD) and catalase activity. (C) Reduced glutathione (GSH) content. MSC-treated animals showed reduced oxidative damage and restoration of antioxidant capacity compared with untreated injured controls. Data are presented as mean ± SD. *p<0.05.

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MSC localization within injured liver tissue

In animals receiving labeled MSCs, fluorescent signal was detected predominantly within perivascular and periportal regions of the liver at 24 and 72 hours post-infusion. Labeled cells were infrequently observed within hepatocyte cords, suggesting limited engraftment and supporting a predominantly paracrine mechanism of action. Signal intensity declined over time, consistent with transient cell retention.

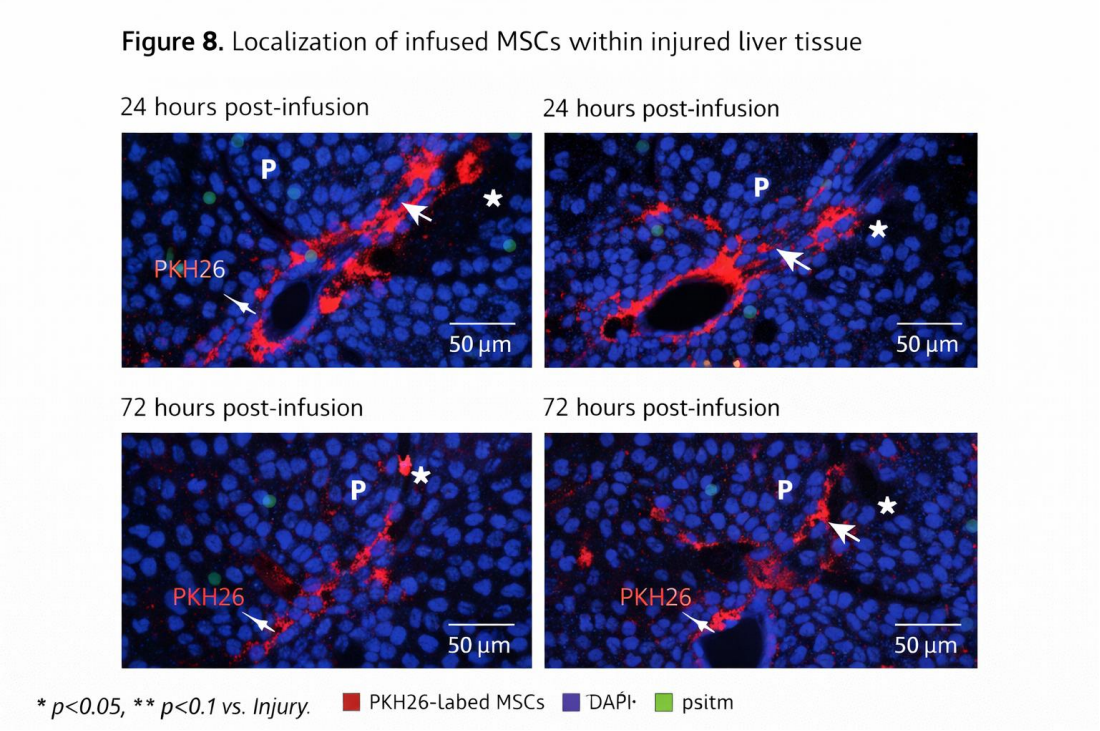

Figure 8. Localization of infused MSCs within injured liver tissue
Representative fluorescence micrographs of liver sections from animals receiving labeled MSCs. MSCs were predominantly detected in periportal and perivascular regions at 24 and 72 hours post-infusion, with limited parenchymal engraftment. Signal intensity decreased over time, suggesting transient cell retention. Scale bar = 50 µm.

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DISCUSSION

The present experimental study demonstrates that mesenchymal stem cell (MSC) therapy exerts a robust protective effect against hepatic cellular injury through coordinated anti-inflammatory, anti-apoptotic, and antioxidant mechanisms. Using a well-established model of carbon tetrachloride–induced liver injury, we show that systemic administration of MSCs significantly attenuates biochemical markers of liver damage, preserves histological architecture, suppresses inflammatory signaling, and reduces hepatocyte apoptosis. Collectively, these findings support the therapeutic potential of MSCs as modulators of the hepatic injury microenvironment rather than direct cellular replacements [5, 18].

Hepatic injury induced by toxic, metabolic, or inflammatory insults is characterized by a convergence of pathophysiological processes, including hepatocyte death, immune cell activation, oxidative stress, and impaired regenerative capacity [20]. In the present model, repeated CCl_4 exposure resulted in classical features of liver injury, including elevated transaminases, hepatocellular ballooning, necrosis, and inflammatory infiltration, consistent with prior reports [21–23]. MSC treatment significantly improved serum ALT and AST levels and partially restored albumin concentrations, indicating not only reduced hepatocyte injury but also improved synthetic liver function. These biochemical improvements were accompanied by clear histological preservation, suggesting that MSCs effectively interrupt injury progression at both functional and structural levels.

One of the central findings of this study is the pronounced anti-inflammatory effect of MSC therapy within injured hepatic tissue. Excessive and sustained inflammation is a key driver of liver injury progression, promoting hepatocyte death and fibrogenesis through the release of pro-inflammatory cytokines and reactive oxygen species [4,24]. In our study, MSC administration markedly reduced hepatic TNF-α, IL-1β, and IL-6 levels while increasing IL-10 expression. This cytokine profile shift reflects a transition from a pro-inflammatory to a regulatory microenvironment, which is critical for tissue repair and resolution of injury. Similar immunomodulatory effects of MSCs have been reported in models of acute liver failure and chronic liver disease [6–25].

At the cellular level, MSC-mediated immunomodulation appears to involve direct effects on innate immune populations within the liver. Flow cytometric analysis revealed a significant reduction in hepatic macrophage and neutrophil infiltration following MSC therapy. Importantly, MSC treatment promoted a shift in macrophage phenotype, characterized by reduced expression of Nos2 and increased Arg1 expression. This phenotypic transition suggests a reprogramming of hepatic macrophages toward a reparative profile, consistent with previous studies demonstrating MSC-driven macrophage polarization as a key mechanism of tissue protection [9–26]. Given the central role of Kupffer cells and monocyte-derived macrophages in amplifying liver injury, this immunological rebalancing likely contributes substantially to the observed therapeutic effects.

Beyond inflammation, hepatocyte apoptosis represents a critical determinant of liver injury severity and progression. Apoptotic cell death not only reduces functional hepatocyte mass but also perpetuates inflammation through the release of damage-associated molecular patterns [27]. In the

present study, MSC therapy significantly reduced TUNEL-positive hepatocytes and suppressed caspase-3/7 activity, indicating effective inhibition of apoptotic pathways. These findings align with earlier reports demonstrating that MSCs protect parenchymal cells from apoptosis in various organ injury models, including liver, heart, and kidney [28].

Mechanistically, MSC-mediated inhibition of apoptosis was associated with modulation of key mitochondrial signaling proteins. Specifically, MSC treatment reduced Bax expression, increased Bcl-2 levels, and lowered the Bax/Bcl-2 ratio, thereby suppressing mitochondrial membrane permeabilization and downstream caspase activation. This shift toward anti-apoptotic signaling provides a molecular basis for the observed reduction in hepatocyte death. Notably, fibroblast infusion failed to replicate these effects, underscoring the specificity of MSC-mediated cytoprotection and excluding nonspecific effects of cell delivery or infusion-related factors.

Oxidative stress is another hallmark of toxic liver injury and plays a central role in amplifying both inflammation and apoptosis [29]. In our study, CCl_4 exposure resulted in increased lipid peroxidation and depletion of endogenous antioxidant defenses. MSC therapy significantly reduced malondialdehyde levels while restoring superoxide dismutase, catalase activity, and glutathione content. These findings suggest that MSCs enhance the hepatic antioxidant capacity, thereby mitigating oxidative damage. This antioxidant effect may be mediated both by MSC-derived soluble factors and by indirect modulation of inflammatory cell activity, which is a major source of reactive oxygen species in injured liver tissue [17,30].

An important observation in this study is the limited long-term engraftment of infused MSCs within the liver parenchyma. Fluorescence tracking revealed that MSCs localized predominantly to periportal and perivascular regions and declined over time, with minimal integration into hepatocyte cords. This pattern supports the growing consensus that MSCs exert their therapeutic effects primarily through paracrine signaling rather than direct differentiation into functional hepatocytes [19,31]. MSC-derived cytokines, growth factors, and extracellular vesicles are increasingly recognized as central mediators of tissue repair, capable of modulating immune responses, enhancing cell survival, and promoting endogenous regeneration [32–37].

The transient presence of MSCs within injured liver tissue also has important safety implications. Limited engraftment reduces concerns related to ectopic differentiation, uncontrolled proliferation, or long-term cellular persistence, which are key considerations in the clinical translation of cell-based therapies. Moreover, the paracrine mechanism of action raises the possibility of developing cell-free therapeutic strategies using MSC-derived extracellular vesicles or conditioned media, which may offer improved scalability and regulatory feasibility [24,38].

From a translational perspective, the findings of this study are particularly relevant within the Brazilian healthcare context. Liver disease remains a significant public health challenge in Brazil, driven by viral hepatitis, alcohol-related injury, and the rapidly increasing prevalence of metabolic dysfunction–associated fatty liver disease [26,39]. Access to liver transplantation remains limited, and effective disease-modifying therapies are urgently needed. MSC-based approaches, whether cell-based or cell-free, may represent a viable adjunct or alternative strategy for patients with acute or chronic liver injury who are not candidates for transplantation.

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Despite the strengths of this study, several limitations should be acknowledged. First, this investigation focused on early molecular and cellular responses following MSC therapy, and longer-term studies are required to determine whether these protective effects translate into sustained functional improvement or fibrosis regression. Second, while the CCl_4 model recapitulates key aspects of toxic liver injury, it does not fully represent the complexity of human liver diseases such as non-alcoholic steatohepatitis or autoimmune hepatitis. Future studies using complementary models will be essential to validate the generalizability of these findings. Finally, although we identified major anti-inflammatory and anti-apoptotic pathways modulated by MSCs, the precise contribution of individual MSC-derived factors warrants further investigation.

CONCLUSION

The data of this study demonstrates that mesenchymal stem cell therapy confers significant protection against hepatic cellular injury through the coordinated modulation of inflammatory, apoptotic, and oxidative stress pathways. In a well-established experimental model of toxic liver injury, MSC administration resulted in marked improvement in biochemical indices of liver function, preservation of hepatic histological architecture, and attenuation of hepatocyte death. These effects were accompanied by a profound suppression of pro-inflammatory cytokine production, a shift toward a regulatory immune microenvironment, and restoration of endogenous antioxidant defenses.

Importantly, the therapeutic benefits of MSCs were achieved without substantial long-term engraftment within the liver parenchyma, supporting a predominantly paracrine mechanism of action. By targeting key cellular and molecular drivers of liver injury rather than replacing damaged hepatocytes directly, MSCs appear to recalibrate the hepatic microenvironment in a manner that favors tissue protection and repair. This mode of action enhances the translational appeal of MSC-based interventions, as it may reduce safety concerns associated with persistent cell engraftment while preserving therapeutic efficacy.

Collectively, these findings provide mechanistic insight into how MSCs reverse hepatic cellular injury and underscore their potential as a regenerative strategy for liver disease. While further studies are required to evaluate long-term outcomes and efficacy across diverse etiologies of liver injury, the present work supports continued development of MSC-based and MSC-derived therapies as promising adjuncts in the management of acute and chronic hepatic disorders.

DECLARATIONS

Ethics Approval and Consent to Participate

All experimental procedures involving animals were conducted in accordance with the Brazilian National Council for the Control of Animal Experimentation (CONCEA) guidelines and complied with the ARRIVE recommendations for animal research. The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee (CEUA) of the participating

institution. All efforts were made to minimize animal suffering and reduce the number of animals used.

Consent for Publication

Not applicable. This study does not include human participants or identifiable personal data.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. Raw data supporting the findings of this study are stored in accordance with institutional data management policies.

Competing Interests

The authors declare that they have no competing interests, financial or non-financial, related to this study.

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Authors' Contributions (CRediT Taxonomy)

Ana Paula Rodrigues: Conceptualization; Methodology; Investigation; Supervision; Writing – review & editing.
Rafael Henrique Costa: Formal analysis; Data curation; Visualization; Writing – original draft.
Mariana Luiza Fernandes: Resources; Validation; Investigation; Writing – review & editing.
All authors read and approved the final manuscript.

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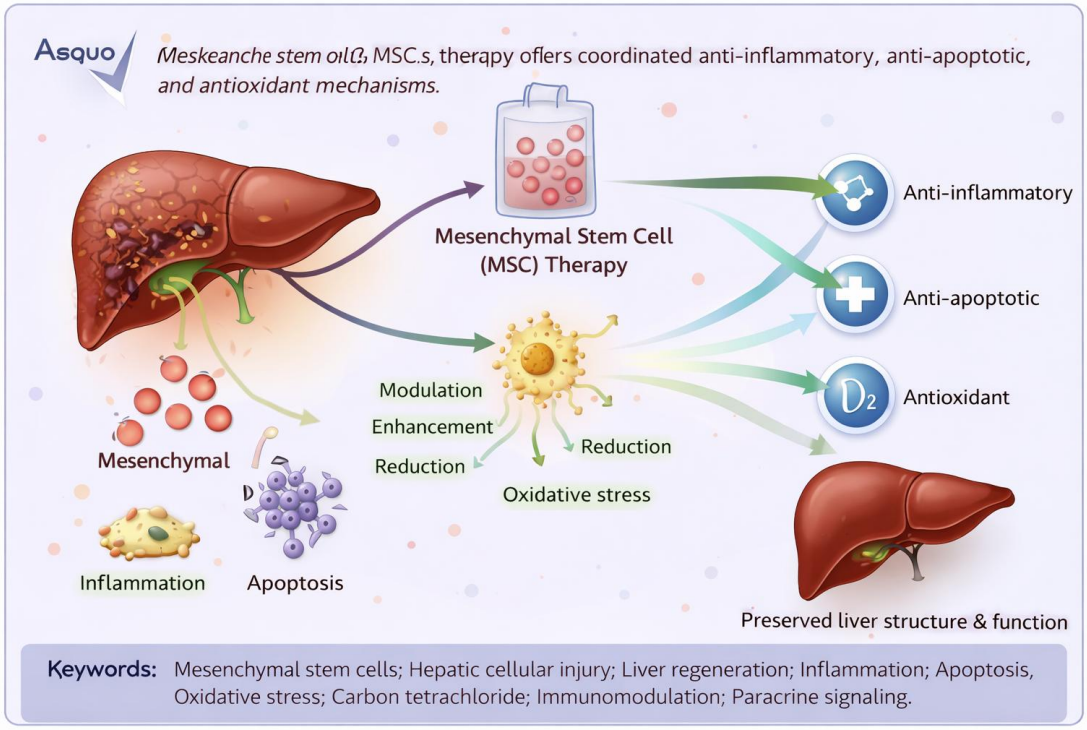
GRAPHICAL ABSTR`ACT



Keywords: Mesenchymal stem cells; Hepatic cellular injury; Liver regeneration; Inflammation; Apoptosis, Oxidative stress; Carbon tetrachloride; Immunomodulation; Paracrine signaling.