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In-Vitro Evaluation of an Injectable Umbilical Cord-Derived Bioscaffold: A Translational Approach for Repair and Regeneration of Cartilage

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Abstract

Background and objectives: Articular cartilage injuries remain difficult to treat due to the tissue's limited regenerative capacity and the inconsistent outcomes of current surgical interventions. This study presents a novel injectable bio-scaffold derived from decellularized human umbilical cord extracellular matrix (ECM) enriched with umbilical cord–derived mesenchymal stem cells (UC-MSCs) for cartilage repair.

Materials and Methods: Human umbilical cords were decellularized using enzymatic and detergent-based protocols. Decellularization efficacy was confirmed via histological staining, DAPI imaging, DNA quantification. The ECM was processed into an injectable formulation. UC-MSCs were isolated, expanded, and evaluated for scaffold adhesion, proliferation (under varying serum and EGF conditions), and chondrogenic differentiation using Alcian Blue staining at days 1, 6, and 15. Student's t-test was used for statistical analysis (P-value < 0.05).

Results: Decellularization resulted in > 90% removal of nuclear content, evidenced by near-complete loss of DAPI-positive nuclei, reduction of DNA concentration from ~14–15 ng/µl in native tissue to ~1 ng/µl in decellularized samples, and markedly faint DNA bands on agarose gel. H&E staining confirmed preservation of ECM architecture with complete cellular clearance. UC-MSCs seeded on the ECM scaffold exhibited enhanced adhesion and significantly increased proliferation compared to cells cultured without scaffolds, reaching > 3×10^6 cells by 72 h. The combination of EGF (10 ng/mL) with 20% FBS yielded the highest proliferation and surface coverage. Chondrogenic differentiation assays demonstrated progressive extracellular matrix accumulation, with Alcian Blue staining showing a substantial increase in glycosaminoglycan (GAG) deposition by day 15, confirming successful scaffold-mediated chondrogenesis.

Conclusion: The decellularized human UC-derived injectable scaffold provides a biocompatible microenvironment that promotes UC-MSC proliferation and chondrogenic differentiation. This platform demonstrates strong translational potential for minimally invasive cartilage repair and future clinical application. Future *in-vivo* studies and clinical translation will establish an advanced regenerative strategy for cartilage repair and osteoarthritis management.

Keywords: Umbilical cord, UCMS, ECM, Cartilage, Chondrocytes.

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1. Introduction

Articular cartilage injuries are prevalent in orthopedic conditions and sports-related trauma, often progressing to osteoarthritis due to a lack of vasculature, nerves, and lymphatics. Current clinical interventions, including microfracture, autologous chondrocyte implantation (ACI), and osteochondral grafting, have shown variable efficacy, often resulting in fibrocartilage formation rather than true

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hyaline cartilage and carrying risks of donor-site morbidity or immune rejection (1, 2). This indicates the pressing need for alternative regenerative approaches that mimic native cartilage microarchitecture and support long-term functionality. Human umbilical cord-derived scaffolds have gained significant attention due to their extracellular matrix (ECM) composition, immune-privileged status, and ability to support the tri-lineage differentiation of mesenchymal stem cells (MSCs), particularly towards the chondrogenic lineage (3). When combined with stem cells, these scaffolds create a biomimetic niche conducive to cartilage regeneration through enhanced cellular adhesion, matrix synthesis, and anti-inflammatory modulation, making them an ideal candidate for translational cartilage repair (4). Among several sources of stem cells, the human umbilical cord (UC) offers a distinctive, ethically acceptable, and readily available tissue that is typically discarded postpartum. It has been proven that UC tissue, particularly Wharton's jelly, is rich in structural ECM components like collagen, fibronectin, hyaluronic acid, and laminin, which play key roles in supporting cell attachment, proliferation, and differentiation (5). Furthermore, UC-derived mesenchymal stem cells (UC-MSCs) and their secretome have been shown to exert immunomodulatory, pro-angiogenic, anti-fibrotic, and antimicrobial effects that can accelerate tissue repair and reduce inflammation and infection (6). While many decellularized ECM-based scaffolds have gained increasing attention for their clinical potential, very few injectable formulations derived from human UC are currently used in therapeutic interventions. Injectable scaffolds are advantageous as they offer leverage to fit any geometry, allowing access to the damaged microenvironment with minimal invasiveness (7). To address this translational gap, the present study aims to develop and evaluate a novel injectable bio-scaffold derived from decellularized human UC tissue, embedded with UC-MSCs that can differentiate into chondrocytes, with the potential to lead to advanced healing of damaged cartilage following animal studies and human clinical trials.

2. Materials and Methods

2.1. Collection of the umbilical cord

Human umbilical cord tissues were obtained from healthy donors post-normal delivery at the Department of Gynecology of Krishna Institute of Medical Sciences (KIMS) Hospitals, India, with due written informed consent. The study protocols were reviewed and approved by the institutional ethics committee (IEC) in accordance with national guidelines (ICMR-Indian Council and Medical Research) and the Declaration of Helsinki.

2.2. DNA quantification

DNA isolation and purification were performed using the DNeasy Blood & Tissue kit (QIAGEN GmBH, Germany) following the manufacturer's protocol. Briefly, 10 mg of each native (cellularized) and decellularized umbilical cord tissue was used for DNA isolation. Tissue was lysed using 180 µL of buffer ATL and 20 µL of proteinase K in a 1.5 ml tube. After vortexing, tubes were incubated in a water bath at 56°C till a clear solution was visible. Again, tubes were briefly vortexed briefly, and 200 µL of buffer AL and 200 µL of ethanol were added and mixed vigorously. The above mixture was added to the DNeasy mini spin column placed in a 2 ml collection tube (CT) and centrifuged at 8000 rpm for 1 min, followed by another centrifugation at the same speed as after adding the buffer AW1 to a new collection tube. The flowthrough was discarded, and the column was placed in a new CT, and 500 µL of buffer AW2 was added, followed by centrifugation at 14000 rpm for 3 min. The flowthrough was again discarded, and 200 µL of buffer AE was added and incubated at room temperature for 1 min. DNA was collected after centrifugation at 8000 rpm for 1 min and suspended in deionized water for further quantification. DNA was quantified using EON nanodrop (BioTek) at a 260/280 ratio. Further quantified DNA (25 µL of each cellularized and decellularized) was visualized on a 1% agarose gel made in 1X TAE buffer with ethidium bromide (EtBr) under the GBox GelDoc system (Syngene, Synoptics, UK).

2.3. 4,6-diamidino-2-phenylindole (DAPI) staining

Paraffin blocks of cellularized and decellularized umbilical cord tissues were cross-sectioned using a microtome (Leica Biosystems). Tissue sections on the slide were subjected to dewaxing, followed by xylene and graded ethanol (100% through 70%) treatment. After thorough washing, the slides were air-dried and stained by adding enough 4',6-diamidino-2-phenylindole (DAPI) mounting medium (Vector Laboratories Inc.) and incubated for 30 min at 4°C. The slides were imaged at 20X under a fluorescence microscope (Olympus BX53) at 380-400 nm. The images were processed using CellSense software version 4.5.

2.4. Hematoxylin and Eosin Y (H&E) staining

Dewaxing of cellularized and decellularized umbilical cord tissues was performed as mentioned in the DAPI staining protocol. After washing the slides with water, they were submerged in hematoxylin (Mayer's from SRL company) for 10 minutes. They were again rinsed with water for 2 minutes and were briefly dipped in 1% acid alcohol and then quickly rinsed with water. Further slides were placed in 1% sodium bicarbonate solution (Sigma Aldrich, Merck KGaA, USA) for 30 seconds. After washing under running tap water, the slides were counterstained with Eosin Y (SRL) solution for 1-2 minutes. Slides were then dehydrated by dipping them in increasing concentrations of alcohol (70% through 100%). Briefly, the slides were dipped in xylene and mounted using DPX (FINAR reagents) mounting solution. The slides were imaged at 20X under a fluorescent microscope at 380-400 nm. The images were processed using CellSense software version 4.5.

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2.5. Preparation of bio-scaffold

The umbilical cords were cleaned and decellularized using a sequential enzymatic and detergent protocol involving 0.25% trypsin-EDTA solution (Thermo Fisher Scientific) and 1% Triton X-100 (Sigma Aldrich) in phosphate-buffered saline (PBS). This method ensures the removal of immunogenic cellular components while preserving the structural integrity of the ECM. The ECM was then lyophilized using a lyophilizer (Lyovapour L300) and solubilized using HCl and pepsin (Sigma Aldrich) to facilitate injectable scaffold fabrication.

2.6. Isolation of umbilical cord-derived mesenchymal stem cells

The umbilical cord tissues were thoroughly cleaned with phosphate-buffered saline (PBS), cut into several small pieces (2-3 cm in size, 10-15 explants), and seeded into 90 mm Petri dishes. These were placed in a CO_2 incubator (Eppendorf) at 37°C with 5% CO_2 for 30 minutes to facilitate attachment. Complete medium (F12) (Gibco) supplemented with 10% FBS, 0.1% FGF (R&D Systems), and 1% of Penicillin-Streptomycin (10,000 U/mL) antibiotic solution (Thermo Fisher Scientific) was added, and then cultures were incubated for five days without disturbance. Thereafter, the medium (complete) was changed every alternate day, and cell movement from the explants was monitored under a microscope. The migrated cells (with fibroblastic, elongated) would be stem cells that were trypsinized at 70-80% confluency using trypsin-EDTA (0.25%) and subcultured as Passage zero (P0), then further subcultured and maintained up to passage 4 (P4). Passage 2 (P2) stem cells were used for chondrogenic differentiation. Umbilical cord-derived stem cell isolation and maintenance were performed as described in our previous work (8). The isolated stem cells were characterized, and the results were published as supplementary material, which could be referred to (8) for this work.

2.7. Stem cell proliferation by EGF and FBS

For stem cell biocompatibility analysis and proliferation potential, umbilical cord-derived mesenchymal stem cells were seeded (1×10^5) on umbilical cord-derived ECM coated on 22 mm cover slips kept in a 30 mm cell culture disk. Epidermal Growth Factor (EGF) treatment was done to enhance the proliferation and therapeutic potential of stem cells on a scaffold (9). Stem cell proliferation was tested on four culture conditions: (1) Dulbecco Modified Eagle Medium with high glucose (DMEM) (Gibco) + 10% Fetal Bovine Serum (FBS) (Gibco) + 10 ng/ml Epidermal Growth Factor (EGF) (R&D Systems), (2) DMEM + 20% FBS + 10 ng/ml EGF, (3) DMEM + 10% FBS (no EGF), and (4) DMEM only.

2.8. Stem cell seeding on ECM and chondrogenic differentiation

Stem cell (1×10^5) seeding on an umbilical cord-derived scaffold (ECM), followed by adhesion and proliferation, was monitored by Giemsa staining (Merck Millipore). Chondrogenic differentiation was induced using commercially available chondrogenic induction media by following the manufacturer's protocol. Differentiation of stem cells into chondrocytes and their integration with the ECM were assessed using Alcian Blue (Sigma Aldrich) staining on days 1, 6, and 15 to detect glycosaminoglycan (GAG)-rich cartilage matrix (9). The image (40X) was taken using a fluorescence microscope with a 40X objective in bright field view mode. All the images were processed using Cellsense software version 4.5.

2.9. Statistics Statistical Analysis

All the experiments were done in triplicate, and the significance of the data was assessed using a Student' t-test between the control and experimental groups ($^*P < 0.05$).

3. Results

3.1. H&E staining, DAPI staining, and DNA quantification

Hematoxylin and Eosin (H&E) staining demonstrated a substantial reduction in cellular content following decellularization of umbilical cord tissue. Quantitative analysis showed that native tissue contained approximately 120 cells per field, whereas decellularized tissue showed only a minimal residual cellular presence (Figure 1A). Morphologically, cellularized samples exhibited abundant nuclei and intact stromal cells, while decellularized samples retained only the extracellular matrix architecture with no visible nuclear structures. DAPI staining corroborated the loss of nuclear material after decellularization. Native tissue presented dense, brightly fluorescent nuclei with a mean count of approximately 100 per field. In contrast, decellularized tissue showed almost complete absence of DAPI-stained nuclei (Figure 1B). DNA quantification revealed a marked reduction in total DNA content following decellularization. Native tissue exhibited a mean concentration of ~14–15 ng/µl, whereas decellularized tissue showed a significantly lower value of ~1 ng/µl (Figure 1C). Agarose gel electrophoresis showed the quantitative findings: cellularized tissue displayed a prominent DNA band, while the decellularized tissue only had a faint band, indicating efficient removal of genomic material.

3.2. Growth of stem cells on a scaffold

Umbilical cord–derived stem cells (UCSC) exhibited progressive growth under normal culture conditions, with distinct differences observed between cells cultured on the scaffold and those grown without scaffold support.

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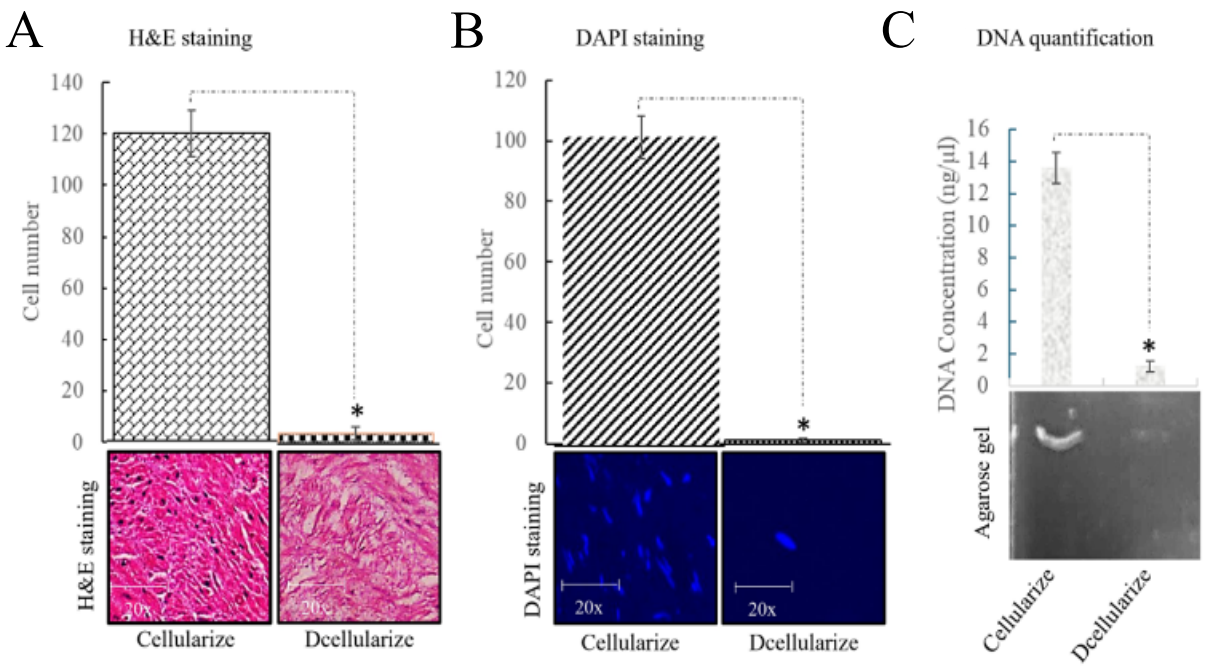

Figure 1. A) H&E staining and quantitative cell counts, B) DAPI fluorescent staining and nuclear quantification, C) Quantitative DNA analysis on agarose gel electrophoresis. Data are presented (*) indicate a statistically significant difference compared to the cellularized control ($P < 0.05$). Scale bars = 20 µm.

Microscopic evaluation demonstrated that UCSC seeded on the scaffold showed enhanced attachment and surface coverage starting at 24 h, with increased cellular density at 48 h, and a uniformly confluent cell layer by 72 h (Figure 2A). The scaffold-supported cultures showed compact cellular organization and extensive matrix interaction. Quantitative assessment of UCSC proliferation revealed significantly higher cell numbers in the scaffold group at all measured time points. At 24 h, scaffold-supported UCSC exhibited greater initial attachment than cells cultured alone. By 48 h, the scaffold group showed enhanced proliferation with cell numbers exceeding the non-scaffold group. At 72 h, cells on the scaffold reached the highest proliferation levels, with values surpassing 3 × 10^6 cells, whereas UCSC cultured without the scaffold exhibited comparatively lower cell counts (Figure 2B). Overall, scaffold incorporation consistently promoted higher cell yield across all time intervals.

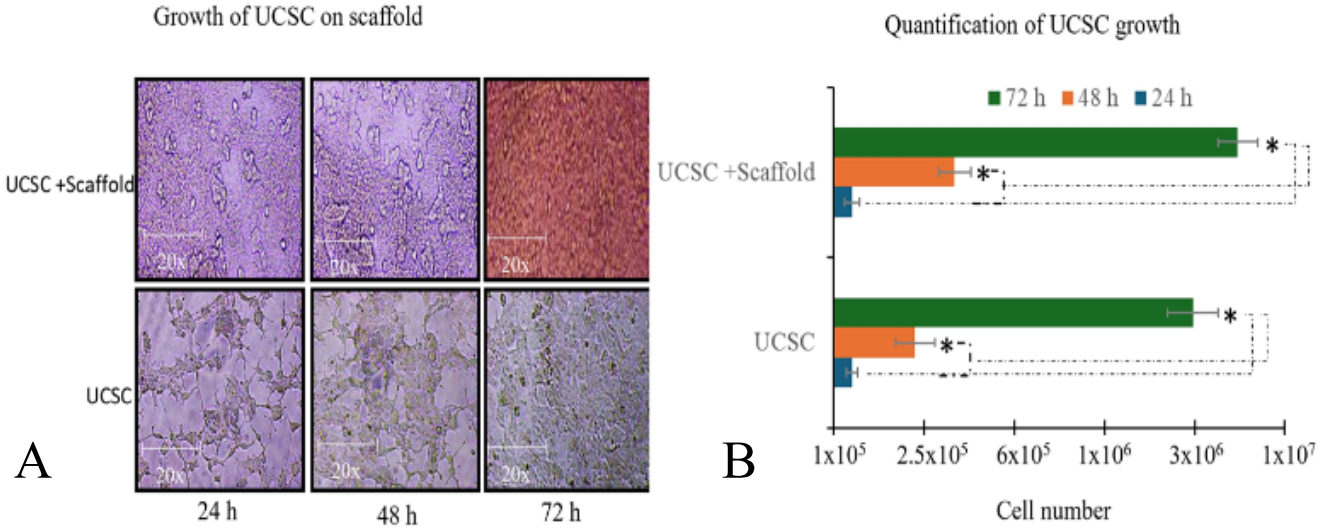

Figure 2. A) Representative micrographs (20×) and 72 h Giemsa staining show cell morphology, attachment, and colony density across the control. B) Time-dependent cell counts (24, 48, 72 h) demonstrate a significant increase (*$P < 0.05$) in final yield when increasing FBS from 10% to 20% in the presence of EGF. Scale bars = 20 µm.

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3.3. Enhancement of stem cell proliferation by EGF and FBS on scaffold materials

The effect of growth factors on stem cell proliferation demonstrates that the combination of Epidermal Growth Factor (EGF) and varying concentrations of Fetal Bovine Serum (FBS) significantly enhances the proliferation of stem cells cultured on scaffolds. Microscopic analysis at 24, 48, and 72 hours revealed increasing cell density over time, with enhanced proliferation in cells treated with EGF (10 ng) combined with 20% FBS (Figure 3A). Giemsa staining further supported these observations by illustrating higher cellular density and more extensive spreading in the same group. Quantitative cell counting confirmed these findings, showing a statistically significant increase in cell numbers at 72 hours in the EGF + 20% FBS group compared to control conditions (Figure 3B). Collectively, these data suggest that EGF complements FBS to promote stem cell growth on scaffolds.

3.4. Chondrogenic differentiation of UCSC on scaffold

The differentiation of human umbilical cord stem cells (UCSCs) into chondrocytes was monitored over a 15-day period. Without staining, the cells exhibited a progressive morphological change indicative of chondrogenic differentiation, with increased extracellular matrix depositionevident by day 15 (Figure 4, top row). Alcian blue staining confirmed the presence of glycosaminoglycans (GAGs) in the extracellular matrix, with a marked increase in matrix observed from day 6 to day 15 (Figure 4, bottom row). Specifically, the blue staining intensity, which correlates with GAG content, was significantly higher on day 15 than on days 1 and 6, indicating successful chondrogenic differentiation of UCSC on the scaffold over time.

4. Discussion

The development of bio-scaffolds derived from human tissues, particularly the umbilical cord, has gained significant attention in recent years due to their regenerative properties and potential to treat various tissue injuries (10). The umbilical cord is an abundant and ethically sourced tissue known for its rich content of mesenchymal stem cells (MSCs), growth factors, and extracellular matrix components (11). These factors are essential for facilitating tissue repair and regeneration, making it an attractive candidate for integrating with bio-scaffolds for cartilage damage repair (12). The injectable bio-scaffold developed in this study, derived from human umbilical cord tissue enriched with stem cell secretome, demonstrated promising biocompatibility *in-vitro*. The scaffold's ability to support cellular attachment and proliferation suggests that it provides an ideal microenvironment for stem cell differentiation and cartilage

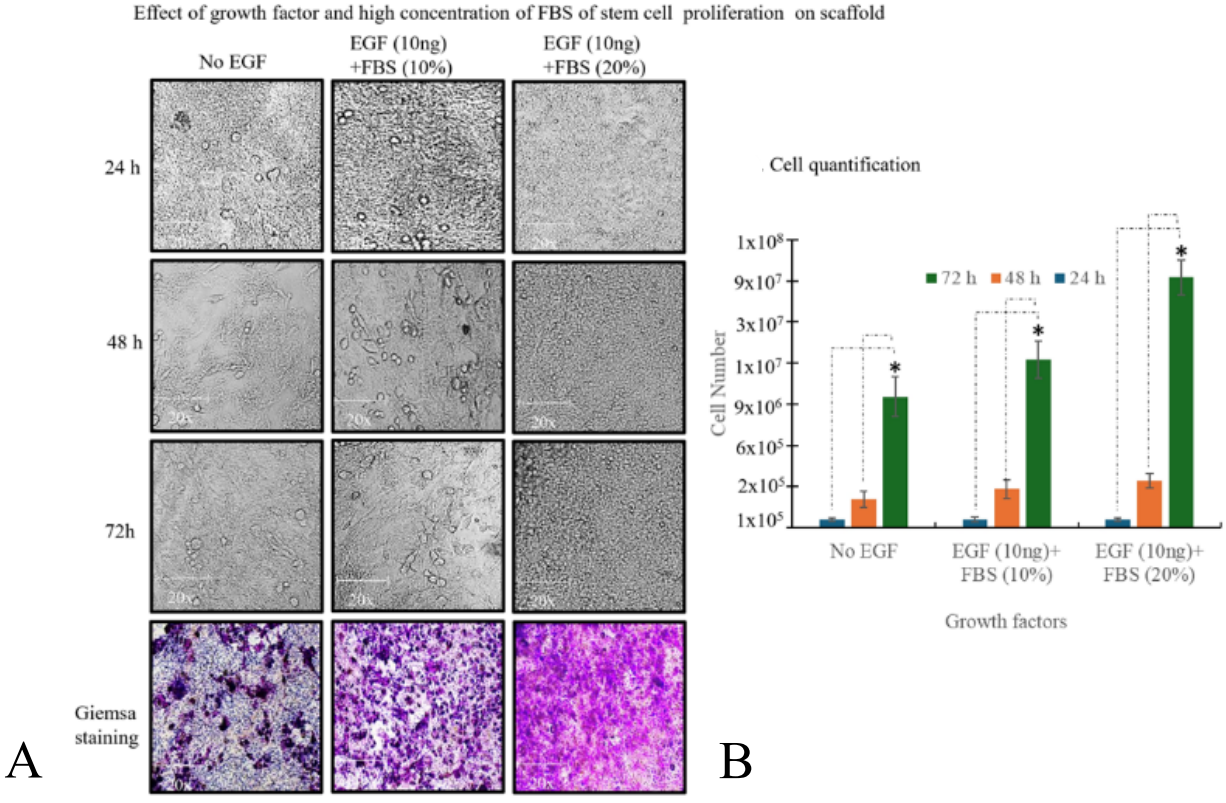

Figure 3. A) Micrographs (20×) and 72 h Giemsa staining show cell morphology and colony density across control, 10% FBS + EGF, and 20% FBS + EGF groups. B) Cell counts over time show that increasing FBS to 20% with EGF significantly maximizes final yield (*$P < 0.05$); scale bars = 20 µm.

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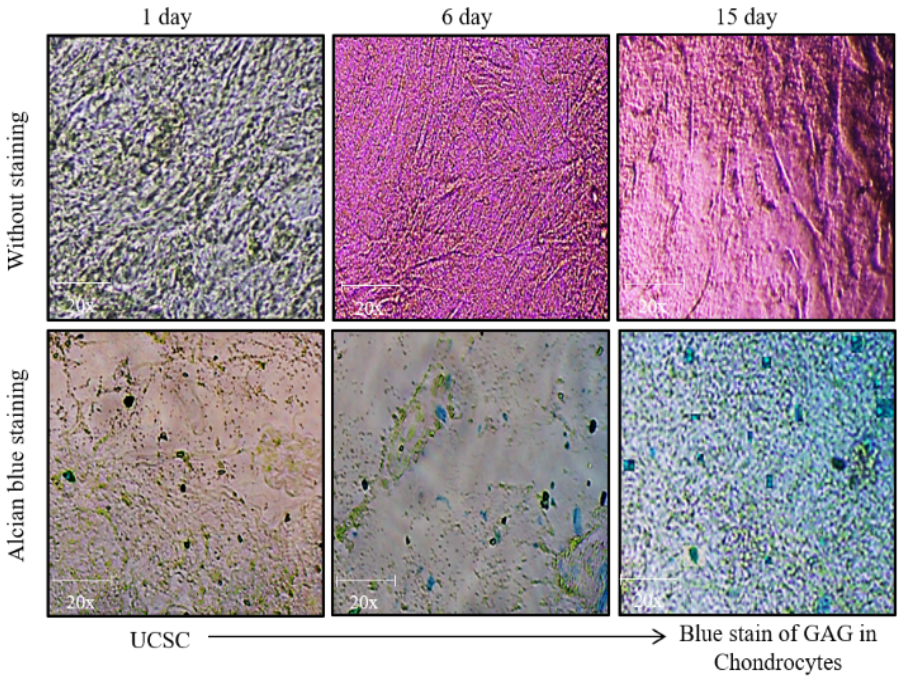

Figure 4. Differentiation of stem cells into chondrocytes over the 15-day period. Alcian Blue staining (bottom row) confirms enhanced chondrogenesis via a time-dependent increase in staining intensity. The advancing signal directly correlates with successful glycosaminoglycan (GAG) accumulation within the matrix; scale bars = 20 μm.

Umbilical-cord-derived bioscaffolds exhibit stronger chondrogenic regeneration than most conventional scaffolds because they provide a native extracellular matrix enriched with collagens, sulfated GAGs, and growth factors that stimulate SOX9, COL2A1, and aggrecan expression while simultaneously downregulating inflammatory and hypertrophic pathways (14). Compared with hyaluronic acid (HA) hydrogels, which offer excellent injectability but require biochemical augmentation to achieve robust hyaline-like cartilage formation, UC-derived hydrogels show inherently higher bioactivity and stronger induction of type II collagen deposition (15). Gelatin-methacrylate (GelMA) hydrogels allow tenable stiffness and good printability but lack the intrinsic growth factor content present in UC tissue, leading to lower spontaneous chondrogenesis (16). Alginate and chitosan hydrogels offer biocompatibility and encourage rounded chondrocyte morphology but have limited cell-adhesive motifs and weaker chondrogenic signaling compared with UC bioscaffolds (17). PEG-based synthetic hydrogels provide precise mechanical control but are biologically inert and require extensive biochemical modification to match the native ECM, which is found in UC-derived materials (18). PCL/PLGA composite scaffolds possess superior mechanical strength, ideal for load-bearing defects, but their hydrophobicity and limited bioactivity necessitate blending with ECM-rich materials, such as UC components, to enhance chondrogenesis (19).

Moreover, our findings are consistent with previous reports that have highlighted the potential of umbilical cord-derived MSCs for tissue repair due to their immunomodulatory properties and ability to differentiate into various cell types (20). In addition to cellular support, the scaffold exhibited chondrogenic differentiation potential, which is of particular importance in applications involving cartilage regeneration, showing the therapeutic scope of the umbilical cord tissue-derived bio-scaffold for cartilage injuries and joint repair. However, challenges such as scaffold degradation rate, long-term biocompatibility, and optimal delivery mechanisms *in-vivo* remain to be addressed. Animal studies are necessary to understand the role of the scaffold in modulating the immune response during the regeneration of cartilage, which should be explored, as it could play a critical role in preventing chronic inflammation and ensuring tissue integration (21).

5. Limitations

Although this study demonstrated promising *in-vitro* findings for the use of umbilical cord-derived bio-scaffold, there are few limitations that should be addressed. First, these are only *in-vitro* findings on the therapeutic efficacy of the bio-scaffold. Hence, animal model studies should be conducted to assess its performance in a complex biological system and to assess efficacy in terms of chondrogenesis, angiogenesis, and immune response modulation. This indigenous, cost-effective technology has the potential to address a major clinical need across the globe.

6. Conclusion

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This study demonstrates the feasibility of developing a human umbilical cord-derived injectable ECM scaffold embedded with stem cells for cartilage repair applications. The scaffold supports stem cell proliferation and its chondrogenic differentiation and is amenable to minimally invasive delivery.

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Ethics
The IEC approval code for the project is KIMS/EC/2020/66-03 from Krishna Institute of Medical Sciences (KIMS) Hospitals, India.

Using artificial intelligence (AI)
AI was not used to generate image or text.

Author contributions
Vinod Kumar Verma: Conceptualization, Methodology, Formal analysis, Writing - Original draft
Radhika Chowdary Darapuneni: Resources and Writing - Original draft
Tirupura Sundari: Investigation, Data curation
Syed Sultan Beevi: Conceptualization, Methodology, Formal analysis - Writing - riginal draft

Conflict of interest
There are no conflicts of interest.

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