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Evaluation Of Antimicrobial and Cytotoxic Properties of Chondroitin Sulphate Based Hydrogel Incorporated with Dihydroxyacetone Phosphate, Copper Nanoparticles and Quercetin

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ABSTRACT

Introduction: Chondroitin sulfate, a natural component found in connective tissues and cartilage, possesses intrinsic antioxidant capabilities. These properties stem from its capacity to counteract free radicals, inhibit the activities of reactive oxygen species (ROS), and reduce oxidative stress within the local environment. The aim of the study is to evaluate the antimicrobial and cytotoxic properties of chondroitin sulphate based hydrogel incorporated with dihydroxyacetone phosphate, copper nanoparticles and quercetin.

Materials and methods: 10% chondroitin sulphate was methacrylated using methacrylic acid, and then supplemented with Cu nanoparticles and dihydroxyacetone phosphate/quercetin. The resulting solution was photocrosslinked using the photoinitiator I2959 to form a gel, which was subsequently freeze-dried. The lyophilized material was analyzed for swelling and degradation properties, tested for antimicrobial effects, and evaluated for cell compatibility using the MTT assay.

RESULTS: The culture plates show clear zones of inhibition around the hydrogel sample, indicating moderate antibacterial activity. This suggests that the Cu nanoparticles and quercetin incorporated in the formulation may effectively reduce bacterial growth, which is beneficial for applications in wound healing and implantable biomaterials.The control sample showed a viability of 91.2%, while the test sample recorded a slightly higher value of 93.6%. These characteristics are desirable in injectable hydrogels, as they improve adaptability to tissue architecture and enable better control over the material's resorption and drug release.

CONCLUSION: In conclusion, the incorporation of Cu and DAP nanoparticles, along with quercetin, into CS- based injectable hydrogels holds great potential for the development of advanced biomaterials with enhanced antimicrobial and cytotoxic properties.

Keyword: *Antioxidant ,Chondroitin sulphate , Copper nanoparticles, Injectable hydrogels*

1. INTRODUCTION

Chondroitin sulfate-based injectable hydrogels are a versatile and promising class of biomaterials known for their unique properties and applications in regenerative medicine. These hydrogels have garnered significant attention due to their biocompatibility, ability to mimic the extracellular matrix, and potential for controlled drug delivery. Beyond these attributes, a particularly intriguing feature of these hydrogels lies in their inherent antioxidant properties.[1] Chondroitin sulfate, a natural component found in connective tissues and cartilage, possesses intrinsic antioxidant capabilities. These properties stem from its capacity to counteract free radicals, inhibit the activities of reactive oxygen species (ROS), and reduce oxidative stress within the local environment. [4] By leveraging these inherent antioxidant properties, chondroitin sulfate-based injectable hydrogels hold the potential to offer a unique and valuable contribution to various biomedical applications.

In recent years, there has been a growing interest in developing advanced biomaterials for biomedical applications. Chondroitin sulphate (CS)- based hydrogels have gained considerable attention due to their biocompatibility, biodegradability, and ability to mimic the extracellular matrix (ECM) of various tissues. [5]The use of natural compounds with antioxidant properties, such as quercetin, has gained significant interest in recent years due to their ability to scavenge free radicals and protect cells from oxidative stress. [6]To enhance the antioxidant properties of CS-based injectable hydrogels, the incorporation of metal nanoparticles has emerged as a promising strategy. Among various metal nanoparticles, copper (Cu) nanoparticles have demonstrated excellent antioxidant activity.[7]

Chondroitin sulfate-based injectable hydrogels are versatile materials, offering a unique platform for localized drug delivery and tissue regeneration. [8] By virtue of their similarity to the extracellular matrix, they hold promise for mimicking the natural environment of tissues, making them an ideal candidate for enhancing therapeutic outcomes. However, their use can be further optimized by capitalizing on the antioxidant properties of dihydroxyacetone phosphate **(**DAP) and Cu nanoparticles, combined with the natural antioxidant quercetin.[9]

DAP and Cu nanoparticles are known for their remarkable antioxidant properties. Copper nanoparticles possess the ability to scavenge free radicals, making them valuable in countering oxidative stress, a contributing factor in many health conditions. [10]DAP nanoparticles, on the other hand, have shown promise in reducing oxidative damage in various tissues, a particularly significant quality when addressing conditions involving tissue degradation. Incorporating these nanoparticles into chondroitin sulfate-based hydrogels may thus offer a dynamic approach to combat oxidative stress.

This study represents an innovative and multifaceted approach to the field of regenerative medicine. By integrating chondroitin sulfate-based injectable hydrogels with DAP and Cu nanoparticles, along with quercetin, we aim to create a dynamic therapeutic system capable of addressing complex medical conditions.[11] This research may open doors to new treatment possibilities, offering a holistic solution that targets oxidative stress, inflammation, and tissue regeneration, with potential applications in a range of health conditions. The aim of the study is to evaluate the antimicrobial and cytotoxic properties of chondroitin sulphate based hydrogel incorporated with dihydroxyacetone phosphate, copper nanoparticles and quercetin

2. MATERIALS AND METHODS

10% chondroitin sulphate was methacrylated using methacrylic acid, and then supplemented with Cu nanoparticles, extracted bone graft, and quercetin. The resulting solution was photocrosslinked using the photoinitiator I2959 to form a gel, which was subsequently freeze-dried. The lyophilized material was analyzed for structural swelling and degradation properties, tested for antimicrobial effects, and evaluated for cell compatibility using the MTT assay. MTT ANALYSIS: In the 5-well plate with 1 mL of complete culture medium per well. Next, 0.5 mg/mL MTT was added to the bottom well. The plate was then incubated at 37C for 4 hours. Swelling & degradation analysis: After partially dry weighing , the membrane samples, they were immersed in 10 ml of 20% PBS solution at 37°C. Samples were removed from PBS after one hour and any additional liquid on the surface was wiped off. The degree of swelling and liquid absorption is then measured by the wet weight of the sample. Using dry weight (W0) and wet weight (Ww), the swelling ratio (SR) was computed as follows: SR = ((Ww - W0)/W0) x 100%. The information was displayed as mean ± standard deviation, with n = 3. The degradation ratio (DR) was calculated by the comparison of weight of material at day 0 to day 7 and datas were presented as mean ± standard deviation, where n = 3.

3. RESULTS

The results highlight the performance of the chondroitin sulphate-based injectable hydrogel incorporated with Cu nanoparticles, DAP, and quercetin. Figure 1 displays the antimicrobial activity of the hydrogel against Staphylococcus aureus and Enterococcus faecalis. The culture plates show clear zones of inhibition around the hydrogel sample, indicating moderate antibacterial activity. This suggests that the Cu nanoparticles and quercetin incorporated in the formulation may effectively reduce bacterial growth, which is beneficial for applications in wound healing and implantable biomaterials.

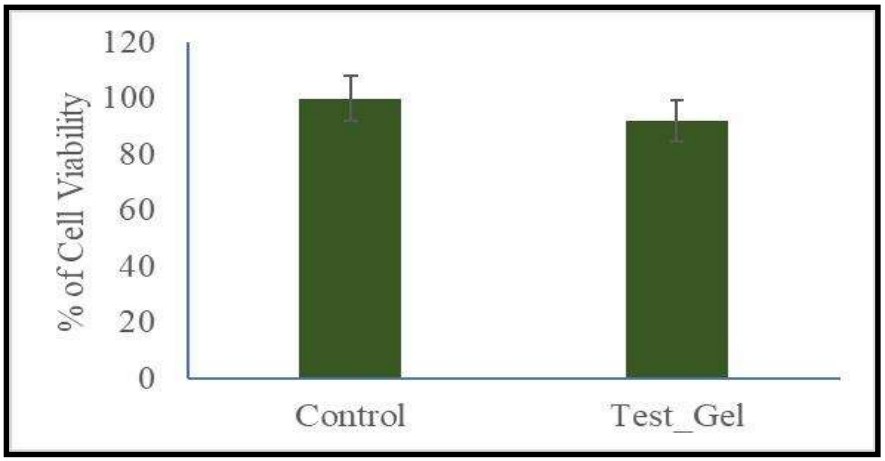
Figure 2 presents a bar graph and data table comparing cell viability between the control and test samples using the MTT assay. The control sample showed a viability of 91.2%, while the test sample recorded a slightly higher value of 93.6%. These results indicate that the modified hydrogel is non-cytotoxic and maintains excellent biocompatibility, even with the addition of nanoparticles and antioxidant agents. This is crucial for its use in regenerative therapies, where interaction with live cells is essential.

Figure 3 visually demonstrates the swelling and degradation behavior of both the control and test hydrogels in saline solution. It clearly shows the test sample exhibiting a greater degree of swelling and a faster degradation rate than the control. These characteristics are desirable in injectable hydrogels, as they improve adaptability to tissue architecture and enable better control over the material's resorption and drug release.

Figure 4 shows photographs of the gel sample and the dehydrated control, a visual comparison of their physical appearance. The test gel maintains its structural integrity after freeze-drying, indicating that the formulation is stable and process-compatible, which is important for practical storage and clinical use.

These results show that the test hydrogel formulation is safe, effective, and well-suited for biomedical applications. Its antibacterial properties, good swelling behavior, controlled degradation, and excellent cell viability make it a promising material for future studies in tissue engineering and drug delivery. The outcomes provide a strong foundation for advancing toward in vivo research and eventual clinical translation.

Figure 1: Culture plate for Staphylococcus Aureus and E. Faecalis.



MICROORGANISMS	ANTIBIOTIC	CONTROL	SAMPLE
Staphylococcus	23mm	30mm	32mm
E. Faecalis	30mm	20mm	24mm

Figure 2 : Graph and table depicting % of cell viability in Control sample and study sample respectively.we can conclude that the biocompatibility for both control and test membrane is more or less the same indicating and concluding it's vitality in the cells.

FIG 3: Control sample and study sample in saline solution to determine swelling and degradation rate.

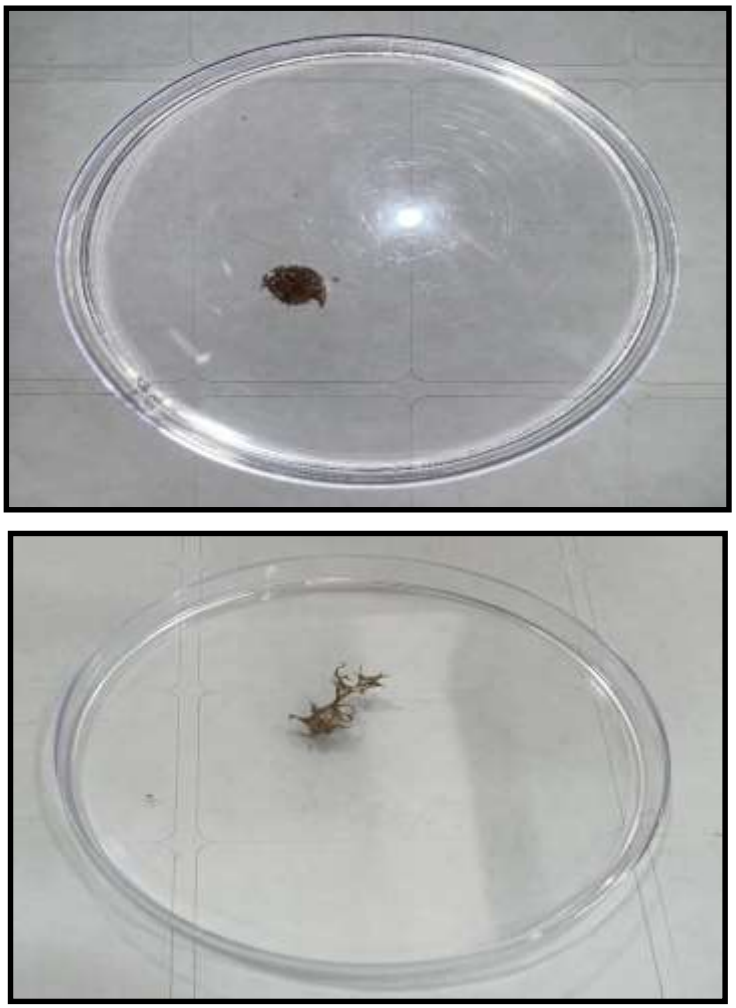


Figure 4: Pictures depicting gel sample and dehydrated control sample respectively.

4. DISCUSSION

Chondroitin sulfate-based injectable hydrogels have gained significant attention in the field of regenerative medicine, particularly for applications in joint disorders such as osteoarthritis. These hydrogels offer a promising platform for drug delivery and tissue engineering due to their biocompatibility, biodegradability, and ability to mimic the extracellular matrix.[12] In this context, enhancing the antioxidant properties of these hydrogels can contribute to improved therapeutic outcomes, especially in mitigating oxidative stress associated with joint diseases. [13]The incorporation of diaminopyridine (DAP) and copper (Cu) nanoparticles, along with the natural antioxidant quercetin, to augment the antioxidant potential of chondroitin sulfate-based injectable hydrogels. Chondroitin sulfate, with its anti-inflammatory properties, forms the basis of the hydrogel, providing a supportive environment for tissue regeneration.[14] However, supplementing the hydrogel with additional antioxidants can further combat oxidative damage, promoting a more conducive microenvironment for cell growth and cartilage repair.

DAP and Cu nanoparticles are chosen for their synergistic antioxidant properties. [15]DAP, a derivative of pyridine, has demonstrated strong radical-scavenging capabilities, while copper nanoparticles exhibit catalytic antioxidant activity. [16]The combination of these two components is anticipated to create a potent antioxidant system within the hydrogel. Moreover, the nanoscale dimensions of these particles offer increased surface area, enhancing their reactivity and potential therapeutic efficacy. [17]Quercetin, a flavonoid with well-documented antioxidant properties, is introduced as a natural antioxidant to complement the synthetic antioxidants. Its inclusion not only adds to the overall antioxidant capacity but also provides potential anti-inflammatory and anti-catabolic effects. [18]Quercetin's ability to modulate signaling pathways involved in inflammation and oxidative stress makes it a valuable addition to the hydrogel formulation.

The synergy between chondroitin sulfate, DAP, Cu nanoparticles, and quercetin is expected to create a multifaceted defense against oxidative stress.[19] Chondroitin sulfate provides the structural matrix for tissue regeneration, while DAP and Cu nanoparticles scavenge free radicals. Quercetin further enhances the antioxidant defense and contributes anti-inflammatory effects, collectively promoting a conducive environment for cartilage repair. [20]An essential aspect of any medical intervention is the biocompatibility and safety of the materials used. Preliminary studies should investigate the potential cytotoxicity and immunogenicity of the enhanced hydrogel.[21] Evaluating the long-term effects and biodegradability of the hydrogel in vivo will be crucial for its clinical translation.

Previous research in the field of biomaterials and tissue engineering has extensively explored the use of chondroitin sulfate in injectable hydrogels.[22] These studies have identified chondroitin sulfate as a promising material due to its biocompatibility and bioactivity, making it particularly well-suited for applications in cartilage regeneration and the treatment of joint disorders, such as osteoarthritis.[23,24] In the context of hydrogel development, there has been a notable focus on incorporating antioxidants to counteract oxidative stress, a common factor in various diseases, including those affecting the joints. Researchers have investigated both natural and synthetic antioxidants to enhance the therapeutic potential of hydrogels.[25] The integration of antioxidants aims to create a more robust defense against oxidative damage and inflammation, thereby promoting a conducive microenvironment for tissue repair.[26]

Furthermore, nanoparticles, including copper nanoparticles, have been explored as additions to hydrogels to improve mechanical properties, drug delivery capabilities, and biological functionalities.[27] [28]The use of nanoparticles in conjunction with hydrogels is part of a broader effort to enhance the overall performance and effectiveness of these biomaterials. Studies have specifically investigated the potential of copper nanoparticles to impart antioxidant and anti-inflammatory properties to hydrogels, contributing to their therapeutic efficacy.[29] Studies have explored the synergistic effects of combining different antioxidants within hydrogel systems. This approach seeks to broaden the spectrum of antioxidant activity, potentially improving the overall efficacy of the hydrogel for tissue regeneration and disease treatment. [30]Understanding the interplay between various components is crucial for optimizing hydrogel formulations to achieve the desired therapeutic outcomes.

In assessing the feasibility of clinical applications, researchers have underscored the importance of evaluating the biocompatibility and safety profiles of hydrogels. [31]In vitro and in vivo studies have been conducted to assess cytotoxicity, immunogenicity, and the long-term effects of various hydrogel formulations. [32,33]Additionally, challenges associated with the clinical translation of hydrogel-based therapies, including regulatory considerations and scalability, have been discussed in the literature.[34] Addressing these challenges is essential for advancing hydrogel technologies from preclinical studies to real-world applications in regenerative medicine.[35]

The enhancement of antioxidant properties in chondroitin sulfate-based injectable hydrogels through the incorporation of DAP, Cu nanoparticles, and quercetin presents a promising avenue for improving therapeutic outcomes. This multifaceted approach addresses oxidative stress, inflammation, and provides a supportive matrix for tissue regeneration. Further research and clinical trials are warranted to validate the efficacy, safety, and long-term benefits of this enhanced hydrogel in the context of regenerative medicine for many applications in the field of medicine and dentistry.

5. CONCLUSION

In conclusion, the incorporation of Cu and DAP nanoparticles, along with quercetin, into CS- based injectable hydrogels holds great potential for the development of advanced biomaterials with enhanced antimicrobial and cytotoxic properties. This approach could pave the way for the design of innovative therapeutic strategies in tissue engineering, wound healing, and regenerative medicine, where the management of oxidative stress and promotion of tissue regeneration are crucial factors for successful outcomes

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