

## **Supercritical Fluid Technology-based Decellularized Extracellular Matrix for Biomedical Applications**

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### **ABSTRACT**

Recently, decellularized extracellular matrix (dECM) has garnered enormous interest in the fields of tissue regeneration due to its exceptional conservation of biological cues for tissue repair. However, the traditional decellularization methods, including chemical and enzymatic approaches, still face challenges, such as residual chemical reagents, damage to active components, and high costs, limiting the broad applicability of dECM. Therefore, developing a mild and efficient decellularization method is crucial for expanding the applications of dECM materials and developing new products. Herein, we propose the utilization of supercritical fluid (SCF)-based technology to prepare dECM and optimize various process parameters for the construction of drug carriers and tissue regeneration applications. Firstly, we investigate the impact of temperature, pressure, and processing time on the decellularization of porcine skin to determine the optimal process conditions. Under these conditions, immunogenic components can be effectively removed, and the biological components of dECM, such as total proteins, collagen, and glycosaminoglycans, can be maximally preserved. Further, we utilize the supercritical antisolvent (SAS) process to prepare uniformly distributed dECM nanoparticles loaded with the antibacterial drug tobramycin, aimed at promoting the repair of infected skin wounds, which is the first related work on dECM nanoparticles. Next, we use electrostatic spinning technology to make the dECM into a fiber membrane and uniformly loaded with stem cell secretome (Sec) to construct a composite artificial skin. This composite artificial skin avoids the current issues of insufficient nutrient supply and slow cell proliferation in the wound areas of artificial skins, achieves effective loading of Sec, and ultimately promotes skin wound repair and collagen regeneration effectively. In addition, we further enzymatically dissociate the dECM prepared by SCF technology to obtain a water-soluble dECM pre-gel. An injectable microsphere-hydrogel composite system is constructed by combining the pre-gel with PLLA microspheres containing Sec. This system proves to be effective for long-term soft tissue augmentation and promoting collagen deposition and tissue regeneration, offering promising new products and methods for cosmetic and reconstructive surgery with excellent clinical application prospects. In summary, the use of green and efficient SCF technology has significant economic implications in preparing dECM and developing various biomaterials, which offer promising alternatives for tissue repair and regeneration applications.