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Biomedical Application of Silk Sericin: Recent Research Trend

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Abstract

Silk sericin, a natural protein from silkworm cocoons, is emerging as a multifunctional biomaterial in biomedicine, particularly in tissue engineering and wound healing. Recent studies have highlighted its biocompatibility, biodegradability, and potential for chemical modification, which allows it to be incorporated into various scaffold architectures. This review article synthesizes current research, including the development of sericin-based hydrogel scaffolds for tissue engineering and sericin's role in enhancing wound healing. Key findings demonstrate sericin's ability to refine scaffold porosity and mechanical strength, expedite tissue healing, and reduce bacterial load in wounds. The integration of sericin into novel bioactive dressings and its use in peripheral nerve injury repair are also discussed, showcasing its adaptability and efficacy. The convergence of these studies illustrates the broad applications of sericin, from scaffold design to clinical interventions, making it a promising material in regenerative medicine and tissue engineering, with the potential to improve patient outcomes significantly.

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Introduction

Silk sericin, a natural protein derived from the cocoon of the *Bombyx mori* silkworm, has long been a subject of fascination due to its biocompatibility, biodegradability, and a host of unique biochemical properties (Kim *et al.*, 2023a, b). Comprising approximately 25-30% of silk by weight, sericin serves as the adhesive that binds fibroin fibers together in the cocoon, contributing to its remarkable strength and durability (Rahul *et al.*, 2023). Historically, sericin was often discarded during the silk production process, considered merely as a waste byproduct (Han *et al.*, 2023). However, with advances in biochemical extraction techniques and a growing recognition of its potential, sericin has gained significant attention in various scientific fields (Lee *et al.*, 2022; Yang *et al.*, 2022).

The importance of sericin in contemporary research cannot be overstated. Its unique properties, such as UV resistance, moisture retention, and the ability to form films, have been leveraged in diverse applications, ranging from textiles to biomedicine (Choi *et al.*, 2023a, b; Yang *et al.*, 2022). Moreover, sericin's ability to promote cell proliferation and modulate immune responses has opened new avenues for research in tissue engineering

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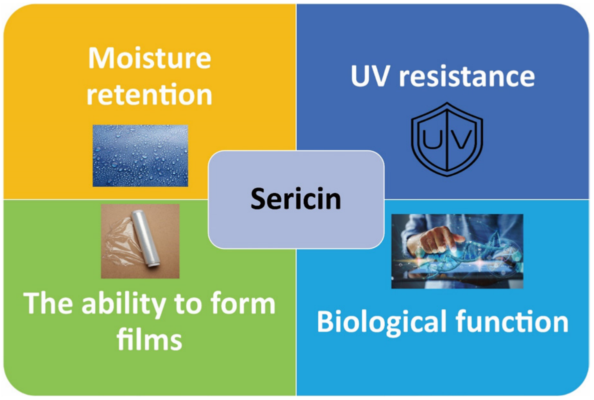

Fig. 1. The versatility of sericin. Sericin, a protein derived from silk cocoons, exhibits a diverse range of properties that make it highly useful for various applications. One key attribute of sericin is its moisture retention capability. This property allows it to effectively bind and retain water molecules, making it an ideal material for skin care products and wound dressings. In addition to moisture retention, sericin also possesses UV resistance properties. This characteristic makes it effective in protecting the skin from harmful UV radiation, thereby reducing the risk of skin damage and premature aging. Another notable feature of sericin is its biological function, particularly its anti-oxidant and anti-inflammatory properties. These attributes make sericin an attractive candidate for applications in the field of biomedicine.

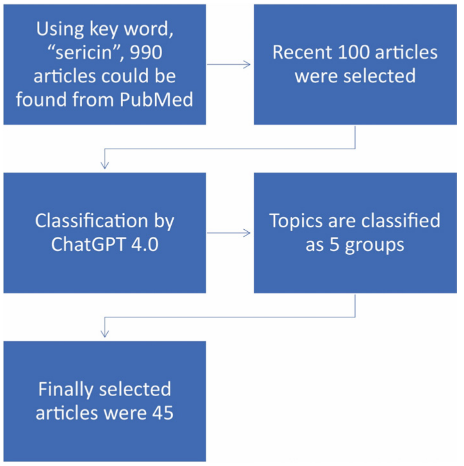

Fig. 2. Flowchart for the article selection.

and regenerative medicine (Yu *et al.*, 2022). The versatility of sericin is further exemplified by its amenability to chemical modifications, which enhances its potential as a multipurpose biomaterial (Fig. 1).

The objective of this review is to provide a comprehensive overview of the recent advances in sericin research, highlighting its evolving applications and the innovative methodologies employed to harness its properties. Using key word, "sericin", 990 articles could be found from PubMed (https://pubmed.ncbi.nlm.nih.gov) at November 11, 2023 (Fig. 2). Among them, recent 100 articles were selected for this review. The classification of each title was done by ChatGPT 4.0 (OpenAI, San Francisco, CA, USA). Based on the title of the articles, topics are classified as 5 groups ("sericin and silk properties", "cellular and molecular interactions", "sericin effects and applications", "drug delivery and biomaterials", and "tissue engineering and wound healing"). Unclassified articles were excluded. The number of finally selected articles were 45 for this review. By scrutinizing the latest trends, this article aims to distill the wealth of available research into a coherent narrative, offering insights into the future trajectory of sericin utilization and its enduring significance in the scientific arena.

Sericin and Silk Properties

Silk sericin, often in the shadow of the more renowned fibroin, has emerged as a versatile material with significant utility. This section explores the structural characteristics and properties of silk sericin as evidenced by recent studies, underscoring its potential in the fabrication of silk-based materials.

Chemical and Physical Properties of Sericin

Advancements in the understanding of sericin's inherent properties are pivotal for its application across various fields. The unique properties of sericin, obtained from fibroin-deficient mutant silkworms, showcase potential in biomedicine and drug delivery systems due to its bioactivity and compatibility (Li *et al.*, 2023b). A novel sericin-based hydrogel designed for enhancing soil moisture content may revolutionize smart agriculture (Jaramillo-Quiceno *et al.*, 2023). The hepatoprotective potential of sericin, along with its antioxidative, anti-aging, and anti-biofilm activities when conjugated with magnesium oxide nanoparticles (Shankar *et al.*, 2023), articulates the material's versatility. Additionally, the synthesis of sericin and caffeic acid composite nanoparticles cloaked with red blood cell membranes (Wang *et al.*, 2023a), and the effects of hydrolyzed sericin as a dietary supplement, highlight its applications ranging from enhancing biocompatibility to serving as a functional food ingredient.

The distinct attributes of sericin, in comparison with other silk proteins, particularly fibroin, are highlighted in studies examining nonwoven silk fabrics from different cocoon layers (Choi *et al.*, 2023a, b). The differential effects of sericin and fibroin on stem cell functions provide insight into their applications in regenerative medicine (Zhang *et al.*, 2023). Comparative evolutionary analyses of silk proteins enhance our understanding of sericin's place in the silk family (Kmet *et al.*, 2023).

Recent Findings on the Structural Characteristics of Sericin:

New insights into the structural aspects of sericin include the non-invasive detection of degumming in historical silk textiles using infrared spectroscopy, indicating sericin's role in textile conservation (Bai *et al.*, 2023). The mesoscale confinement and structural organization of bagworm silk contribute to the understanding of silk's mechanical properties, where sericin plays a crucial part. Additionally, the structural characterization of sericin-based hydrogels for soil water retention focuses on their morphology and implications for moisture management (Jaramillo-Quiceno *et al.*, 2023).

The sericin-poly(vinyl alcohol) biopolymeric matrix demonstrates enhanced thermal stability and cytocompatibility, suggesting its use in tissue engineering (Mandal *et al.*, 2011). The role of sericin in 3D bioprinting points to its promising future in bioprinted implants (Gupta *et al.*, 2021). Its therapeutic potential is further highlighted in treatments for Achilles tendinopathy in rats (Sayin *et al.*, 2023) and in alleviating symptoms of ulcerative colitis (Wang *et al.*, 2023b).

Technological Advances in Sericin Processing:

Autoclaving as a method for silk degumming yields fibers with improved properties, offering a sustainable method for recycling silk waste (Gaviria *et al.*, 2023). The study of the ice recrystallization inhibition activity of *Bombyx mori* silk proteins reveals fibroin's higher activity compared to sericin, suggesting novel applications in cryopreservation (Zhao *et al.*, 2023). The study of the silk gland proteome reveals a complex composition of proteins that contribute to the structural integrity and adhesion of underwater silk structures (Wang *et al.*, 2024). Techniques for improving the storage stability of silk sericin indicate that it can be stored as a dry solid and redissolved to retain its molecular weight and beneficial properties (Lee *et al.*, 2023). Sericin is used as an eco-friendly alternative for food packaging, highlighting its advantageous properties like hydrophilicity, biocompatibility, and antibacterial, antioxidant, anticancer, and anti-tyrosinase activities, and its potential when combined with other biomaterials in the food industry (Seo *et al.*, 2023).

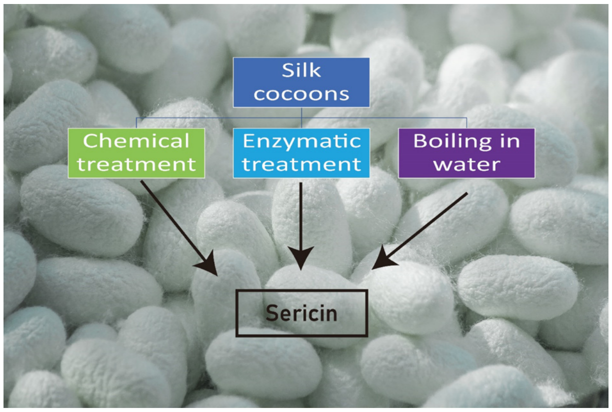

Fig. 3. Sericin, a protein found in silkworm cocoons, holds immense potential for various applications in the fields of medicine, cosmetics, and textiles. To harness its benefits, sericin needs to be extracted from the cocoons using appropriate methods. The extraction process can be classified into three main methods, namely chemical treatment, enzymatic treatment, and boiling in water.

These studies collectively underscore the sophisticated nature of sericin's interactions within silk and its burgeoning potential in material science applications. Sericin emerges not merely as a byproduct but as a vital component in the next generation of silk-based materials (Fig. 3).

The application of cold storage is a traditional method to maintain the quality and extend the shelf life of vegetables. However, the impact of cold-stored food on health has been a subject of debate. Peng *et al.* (2023) conducted a study using silkworms as an animal model to evaluate the effects of cold-stored mulberry leaves on health indicators. The research revealed that cold-stored mulberry leaves (CSML) contained lower levels of vitamin C, soluble sugars, and proteins, and higher levels of hydrogen peroxide, indicating a decrease in both nutritional value and antioxidant capacity (Peng *et al.*, 2023). Although the CSML did not significantly affect the growth and development of silkworm larvae, such as body weight or cocoon characteristics, the initial rates of clustering and cocooning were increased, which implies a reduction in larval lifespan and an enhancement of senescence (Peng *et al.*, 2023). Moreover, the CSML led to upregulation of genes associated with oxidative stress and downregulation of those involved in silk protein synthesis, suggesting a state of oxidative stress and protein deficiency (Peng *et al.*, 2023).

The study's discussion points out that the observed nutritional reductions and increase in ROS are consistent with changes documented in other cold-stored fruits and vegetables, which corroborates the general trend seen across different types of produce. The conclusions drawn from this research indicate that while cold storage of mulberry leaves did not influence the physical growth of silkworms, it adversely affected their health by inducing oxidative stress and reducing protein synthesis, which are essential components for overall well-being.

Cellular and Molecular Interactions

Role of sericin in cellular processes

The inclusion of sericin in cryopreservation media significantly mitigates oxidative stress (Salari *et al.*, 2023) and enhances the survival of ovarian tissues during the freezing and thawing processes (Shu *et al.*, 2023). Sericin at 1% concentration is found to maintain follicular morphology, inhibit apoptosis, and boost levels of endogenous antioxidant enzymes without significantly affecting lactate dehydrogenase (LDH) levels (Shu *et al.*, 2023). These protective effects of sericin are potentially linked to the activation of the PI3K/AKT/mTOR signaling pathway, which is crucial for cell survival and metabolism (Shu *et al.*, 2023).

Ectopically expressed sericin in the posterior silk gland of transgenic silkworms has been shown to affect hemolymph immune melanization responses (Micheal and Subramanyam, 2014). While vitality remained normal, the transgenic silkworms exhibit reduced melanin content and phenoloxidase activity, leading to slower melanization and weaker sterilization abilities (Wang *et al.*, 2023c). This alteration in immune response is traced back to changes in the transcription levels of genes and enzymatic activities in the melanin synthesis pathway, suggesting that sericin 3 impacts both immune response and redox metabolic capacity (Wang *et al.*, 2023c).

The combination therapy of sericin and melatonin offers a significant counteraction to oxidative stress and aids the restoration of spermatogenesis and steroidogenesis in testicular tissues affected by diethylnitrosamine (Habiba *et al.*, 2023). This therapeutic effect is marked by the upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), Wilms' tumor 1 (WT1), and steroidogenic factor 1 (SF-1) expressions (Habiba *et al.*, 2023), which are pivotal signaling pathways for antioxidant defense and cellular function (Singh *et al.*, 2021). The combination therapy also improves semen quality and hormonal balance, underscored by supportive histopathological and ultrastructural analyses (Habiba *et al.*, 2023).

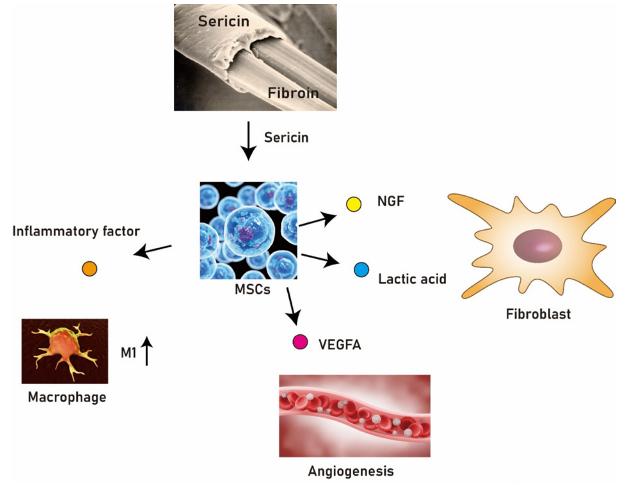

Fig. 4. The influence of sericin on mesenchymal stem cells (MSCs) has been a subject of interest in recent research. MSCs have been shown to secrete various factors such as nerve growth factor (NGF), lactic acid, vascular endothelial growth factor-A (VEGFA), and inflammatory factors when exposed to sericin. These factors have been found to have significant effects on the proliferation of fibroblasts and angiogenesis. The secretion of NGF by MSCs under the influence of sericin suggests that sericin may have the potential to promote neuronal growth and regeneration. Additionally, sericin-stimulated MSCs have been found to secrete lactic acid, which is an important metabolite involved in cellular processes. Lactic acid has been reported to have a positive effect on wound healing and tissue regeneration. The presence of lactic acid in the culture medium of sericin-treated MSCs indicates the potential of sericin to enhance fibroblast proliferation and tissue repair. Furthermore, VEGFA has been shown to promote angiogenesis, the process of forming new blood vessels. The secretion of VEGFA by sericin-stimulated MSCs indicates that sericin may have angiogenic properties and the ability to improve blood circulation in damaged tissues. In addition to the growth-promoting factors, sericin has also been found to induce the secretion of inflammatory factors by MSCs. This suggests that sericin may have the potential to modulate the immune response and promote tissue repair through the activation of M1 type macrophages.

Interaction with cellular receptors and signaling pathways

Through multi-omics analysis, a comprehensive understanding of how silk fibroin and sericin differentially potentiate the paracrine and regenerative functions of mesenchymal stem cells has been obtained (Fig. 4). The cellular responses regulated by these silk proteins include extracellular matrix deposition, angiogenesis, and immunomodulation, which are differentially activated through the integrin/PI3K/Akt and glycolysis signaling pathways. A method to enhance the transdermal delivery of the antioxidant phloretin involves the use of core-shell nanostructures, where a sericin crust is grown around gliadin nanoparticles (Luo *et al.*, 2023). This strategy not only protects phloretin from UV-induced degradation but also facilitates its penetration through the epidermis, improving its bioavailability (Luo *et al.*, 2023). Sericin and crocetin have been combined to create an "active per sé" drug delivery system aimed at regenerating the damaged intervertebral disk. The resulting sericin nanoparticles cross-linked with crocetin have shown antioxidant activity and protective effects against oxidative stress, suggesting their potential in treating or preventing disk degeneration (Bari *et al.*, 2023).

Molecular mechanisms underlying the biological effects of sericin

Sericin's role in suppressing high glucose-induced epithelial-mesenchymal transition in mouse podocytes has been explored, revealing its potential to protect against podocyte damage by modulating related molecular mechanisms, involving miR-30a-5p and its target Snai1 (Liu *et al.*, 2023). The study of alginate/graphene oxide/sericin/nanohydroxyapatite nanocomposite hydrogels have revealed the synergistic effects of immunomodulation and osteogenic induction on bone regeneration (Fu *et al.*, 2023). Sericin's role in macrophage polarization and the combined effects with nano-hydroxyapatite are significant in promoting bone tissue regeneration (Fu *et al.*, 2023). The regulatory effect of sericin protein on inflammatory pathways has been extensively reviewed, highlighting its anti-inflammatory properties and its wide range of uses in pharmaceutical and cosmetic industries, particularly in its potential for treating various conditions (Rahimpour *et al.*, 2023).

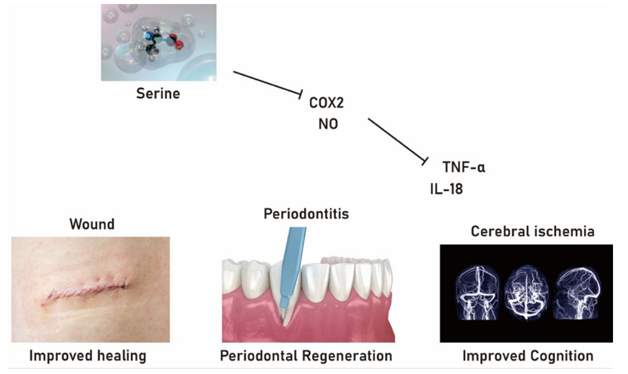

Fig. 5. Sericin, a protein derived from silk cocoons, has garnered attention in the field of medicine due to its promising therapeutic properties. This protein showcases a high concentration of serine amino acids and possesses unique physicochemical characteristics. Serine, one of the amino acids present in sericin, has been found to exert inhibitory effects on cyclooxygenase-2 (COX2) and nitric oxide (NO) production. The inhibition of these molecules can lead to the suppression of tumor necrosis factor-α (TNF-α) and interleukin-18 (IL-18) activity, resulting in various beneficial outcomes. One notable benefit of sericin's inhibitory actions is its potential to enhance wound healing and improve cognitive function after cerebral ischemia. Furthermore, sericin has been investigated for its regenerative properties in the treatment of periodontitis, a common dental disease characterized by the inflammation and destruction of the supporting structures of the teeth. When applied to periodontal tissues, sericin has demonstrated the ability to promote the regeneration of periodontal bone and ligament. This regenerative effect may be attributed to the modulation of inflammatory processes and the promotion of tissue remodeling.

Biological Functions and Applications of Sericin

Therapeutic potential: antioxidant, antimicrobial, and anti-inflammatory effects

Sericin, a protein derived from silk cocoons, has been recognized for its therapeutic potential, leveraging its rich serine amino acid content and unique physicochemical properties (Fig. 5). It has been utilized in various medical applications, ranging from wound healing and collagen production to anti-diabetic and anti-cholesterol treatments (Rahimpour *et al.*, 2023). Research has shown sericin's ability to modulate inflammatory responses by suppressing genes like COX2 and NO, which are instrumental in inflammation (Jeong *et al.*, 2022). This action results in a decrease in pro-inflammatory cytokines such as pe and IL-18, indicating sericin's role as a significant anti-inflammatory agent (Rahimpour *et al.*, 2023). The application of the biomimetic sericin-hydroxyapatite composite graft increases the regeneration of the periodontal tissue in periodontitis (Ming *et al.*, 2023). In addition, sericin treatment in mice with transient global cerebral ischemia/reperfusion improved cognitive functions, reduced oxidative stress and neuronal apoptosis, and modulated inflammatory and apoptotic markers in the hippocampus (Vatandoust *et al.*, 2023).

Sericin also exhibits anti-diabetic effects by enhancing the PI3K/AKT signaling pathway, thereby improving glucose transport and glycogen synthesis in the liver (Rahimpour *et al.*, 2023). Additionally, sericin's antioxidant properties are highlighted in its conjugation with magnesium oxide nanoparticles, which show promise in anti-aging, anti-biofilm, and wound-healing applications (Shankar *et al.*, 2023). The study developed a novel sericin hydrogel that combines the anti-inflammatory and healing properties of sericin with growth factors from injectable platelet-rich fibrin, demonstrating its effectiveness in repairing diabetic wounds, promoting angiogenesis, and reducing inflammation in nude mice (Bai *et al.*, 2023). Silk sericin-based hydrogels, combined with banyan and onion extracts, significantly enhance wound healing in mice with alloxan-induced diabetes, showing greater wound contraction, increased anti-inflammatory cytokines, and decreased pro-inflammatory cytokines and matrix metalloproteinases compared to the control, with the best results from the 4% sericin, banyan, and onion hydrogel (Zahoor *et al*., 2023). The therapeutic efficacy of sericin extends to the realm of metabolic disorders. It contributes to the management of hyperglycemia and type 2 diabetes by enhancing insulin signaling and reducing blood sugar levels (Rahimpour *et al.*, 2023). The antibacterial and antioxidant properties of sericin-enriched formulations have shown potential in wound healing, suggesting its utility in topical applications for skin health (Chuysinuan *et al.*, 2023).

Despite advances in cancer treatment, resistance and side effects remain significant challenges, prompting research into silk protein-based drug delivery systems, like fibroin and sericin, known for their biocompatibility and biodegradability (Kumari *et al*., 2023). In the fight against cancer, sericin has been noted for its ability to induce apoptosis in cancer cells by increasing intracellular ROS and influencing the cell cycle, offering a complementary approach in cancer therapies (Rahimpour *et al.*, 2023). This body of research collectively underscores sericin's significant therapeutic potential, from its antioxidant, antimicrobial, and anti-inflammatory effects to its implications in tissue engineering and regenerative medicine. The scope of sericin's benefits across various health conditions highlights its versatility and potential in contemporary medical applications.

Cosmetic applications: skin hydration, anti-aging, and protection

The cosmetic industry continuously seeks innovative formulations that can deliver multifaceted skin benefits, and sericin-hydrogel formulations have emerged as promising candidates. In a study by Kanpipit *et al.* (2022), hydrogel formulations containing sericin and purple waxy corn cob extract (PWCC) were developed for their potential anti-hyperpigmentation, UV protection, and anti-aging properties. Sericin is known for its wound healing, UV protective, and anti-inflammatory attributes, while PWCC is rich in anthocyanins, which contribute to antioxidant, UV protective, collagen-enhancing, and anti-inflammatory activities. Among several tested formulations, the S4 hydrogel notably inhibited tyrosinase activity, reduced melanin production, and increased cell viability against UV-induced stress in human keratinocytes. Furthermore, it inhibited collagenase and elastase enzymes while boosting collagen type I production, all without exhibiting cytotoxic effects. This study underscores the high potential of sericin-enriched hydrogels as novel skincare products, particularly for anti-hyperpigmentation and anti-aging applications (Kanpipit *et al.* 2022).

Building on the versatility of silk in tissue regeneration, Zhang *et al.* (2022) explored the use of transgenic sericin hydrogels in bone tissue engineering. The study leveraged the properties of sericin and fibroin—main silk components known for their mechanical properties, biocompatibility, and biodegradability. Using transgenic technology to produce bioactive growth factors fused with sericin, they created an injectable hydrogel that effectively promoted osteogenesis in BMP9-stimulated mesenchymal stem cells (MSCs), both in vitro and in vivo. This hydrogel, embedded with platelet-derived growth factor (PDGF)-BB silk sericin, not only augmented bone formation but also inhibited adipogenic differentiation. The synergy between BMP9 and PDGF-BB enhanced osteogenic differentiation through interplay between the Smad and Stat3 signaling pathways in MSCs. This research presents a novel approach for encapsulating osteogenic factors and progenitors in sericin-based hydrogel, proposing a potent strategy for advanced bone tissue engineering (Zhang *et al.,* 2022).

Together, these studies illustrate sericin's significant role in cosmetic applications, where its biological activities can be harnessed for skin health, highlighting its potential for hydration, anti-aging, and protection. The development of sericin-based hydrogels and their integration with natural extracts and growth factors represent a promising frontier in skincare and regenerative medicine.

Drug Delivery and Biomaterials

Development of sericin-based drug delivery systems

Silk sericin is versatile in biomedical applications due to its unique properties, including moisturizing, antioxidant, and anti-inflammatory effects, and is utilized in various forms like hydrogels and nano-materials for tissue engineering, skin restoration, and drug delivery (Saad *et al.*, 2023). Recent advancements in drug delivery systems have been significantly bolstered by the introduction of sericin-based nanoparticles and hydrogels, which serve as an efficient means of encapsulating and releasing therapeutic agents. One study by Bari *et al.* (2023) has innovatively utilized sericin's bioactive properties by combining it with crocetin to create microparticles with antioxidant, anti-inflammatory, immunomodulant, and regenerative properties. These sericin-based particles are shown to be potent in preventing oxidative stress damage and exhibit intrinsic activities such as anti-tyrosinase and anti-elastase, which may be instrumental in treatments targeting intervertebral disk degeneration (Bari *et al.,* 2023).

In another groundbreaking effort, Ullah *et al.* (2023) have reported the first hydrogel system encapsulating PETase for colonic delivery, aiming to address microplastic pollution. This system, made from sericin, chitosan, and acrylic acid, showcases an impressive 61% encapsulation efficiency with a 96% PETase release at pH 7.4, indicating its potential as a stimulus-sensitive carrier for targeted drug delivery (Ullah *et al.,* 2023). The hydrogel's response to pH variations and its ability to release encapsulated molecules in a controlled fashion make it particularly suitable for applications where environmental pH changes can be utilized to trigger the release of therapeutic agents (Ullah *et al.,* 2023).

The innovative aspect of these sericin-based systems is their ability to enhance crosslinking and subsequently develop elastic polymeric chains in response to pH changes. This responsiveness is crucial for ensuring the release of active molecules like PETase in a sustained manner, particularly in the gastrointestinal tract where pH varies significantly (Ullah *et al.,* 2023). With the development of these sericin-infused materials, the field of drug delivery is poised to become more efficient, environmentally conscious, and capable of targeting specific areas within the body for treatment. The results from these studies demonstrate a promising future for sericin in advanced drug delivery applications, underlining its role not just as a mere biomaterial, but as a dynamic component in the development of sophisticated medical treatments.

Design of sericin biomaterials for various medical applications

In the design of sericin biomaterials for medical applications, there is a compelling convergence of research focused on its therapeutic potential across various domains. On one hand, we have findings from the study by Bakr *et al.* (2023), which underscore the hepatoprotective effects of sericin. This study demonstrates sericin's efficacy in mitigating hepatic damages such as inflammation and histopathological changes induced by diethylnitrosamine, a known carcinogen (Bakr *et al.* 2023). The therapeutic potential of sericin is further emphasized through its synergistic use with melatonin, indicating a broader scope of application in counteracting liver damage and potentially inhibiting tumor growth (Bakr *et al.,* 2023).

On the other hand, the work by Li *et al.* (2023a), introduces a novel silk protein wound dressing (SPD) that exploits the unique double network structure of silk fiber and sericin hydrogel for skin wound healing applications. The SPD not only possesses favorable physicochemical properties such as porosity and mechanical strength but also exhibits biological activities that are conducive to wound healing (Li *et al.,* 2023a). These activities include pH-responsive degradability, antioxidative properties, and cell compatibility. Moreover, SPD's ability to facilitate sustained drug release and enhance wound healing, as evidenced in the full-thickness skin wound model in mice, signifies a major stride in the development of bioactive dressings (Li *et al.,* 2023a). Silk sericin-based hydrogels also help the rapid wound healing in acute wound (Munir *et al.*, 2023). A heparin-based sericin hydrogel encapsulating basic fibroblast growth factor significantly enhances vascularization, re-epithelialization, and collagen deposition, thereby accelerating wound healing in mice (Du *et al*., 2023).

Combining the insights from these studies, it is evident that sericin holds great promise in the biomedical field, not just confined to liver protection or skin regeneration individually, but as a versatile biomaterial with multifaceted medical applications. Its inherent biological properties can be harnessed to develop next-generation biomaterials for tissue engineering, regenerative medicine, and protective therapies against organ-specific toxicities. The ongoing research and development into sericin biomaterials are thus a testament to their potential in ushering in innovative treatments that could revolutionize medical practices and improve patient outcomes in a variety of contexts.

Tissue Engineering and Wound Healing

Sericin in scaffold design for tissue engineering

The burgeoning field of tissue engineering is witnessing a transformative phase with the integration of silk sericin into scaffold design, heralding new prospects for the repair and regeneration of damaged tissues. The research by Tuancharoensri *et al.* (2023) explores the impact of silk sericin concentration and crosslinking systems on the characteristics of poly(2-hydroxyethyl methacrylate) hydrogel scaffolds. Their findings highlight how sericin, with its exceptional biocompatibility, refines the scaffolds' porosity and mechanical integrity, essential for replicating the extracellular matrix, thus enhancing the overall functionality of the engineered tissues (Tuancharoensri *et al.,* 2023).

Baptista-Silva *et al.* (2022) extends the application spectrum of sericin to the development of an in situ-forming hydrogel, specifically targeting the oxidative stress prevalent in diabetic wound environments. The sericin-infused hydrogel, through enzymatic crosslinking, embodies a dual therapeutic strategy, demonstrating antioxidant prowess and angiogenic promotion (Baptista-Silva *et al.,* 2022). This sericin hydrogel not only expedites tissue healing but also signifies a leap forward in the treatment of chronic wounds, advocating for sericin's pivotal role in diabetic wound care (Baptista-Silva *et al.,* 2022). The use of scaffolds made from a blend of sericin and human placenta-derived extracellular matrix for cutaneous wound treatment, highlighting their successful fabrication via freeze-drying, and confirming their potential in tissue regeneration through various analyses including morphology, functional groups, mechanical strength, antibacterial activity, in vitro and in vivo assays, which demonstrated non-toxicity, wound-healing efficacy, angiogenic potency, and significant reduction in wound size with collagen deposition in animal models (Bhoopathy *et al.*, 2023).

The comprehensive review by Liu *et al.* (2022) underscores sericin's biocompatibility and cell-adhesive properties, which are instrumental in fabricating a range of biomedical constructs, including bulk materials and micro-nano structures. Sericin's abundant functional groups, owing to its diverse amino acid composition, empower it to be chemically modified and cross-linked, thus offering a malleable platform for various tissue engineering and regenerative medicine applications (Liu *et al.,* 2022). The review elaborates on sericin's capacity to support cell growth, its antioxidant activity, and its potential to enhance the functionality of tissue engineering scaffolds, ranging from bone to skin tissue repair (Liu *et al.,* 2022). An automated gel aspiration-ejection method to create collagen-fibrin hybrid gel scaffolds, enhanced with silk sericin, which closely mimic native bone extracellular matrix in terms of structure and function, aids in cell proliferation and osteoblastic differentiation for bone tissue engineering (Griffanti *et al.*, 2023).

In synthesis, these studies cumulatively affirm the versatility and effectiveness of silk sericin in scaffold design for tissue engineering. Sericin's modifiable nature facilitates its incorporation into diverse scaffold configurations, promoting cellular interactions and fostering tissue regeneration (Liu *et al.,* 2022). It stands out for its customizability, conferred by distinct crosslinking methods and concentrations, directing the evolution of bespoke tissue engineering solutions (Tuancharoensri *et al.,* 2023). The convergence of these research endeavors underscores sericin's emerging role as a cornerstone material in the next wave of biomaterials, poised to invigorate regenerative medicine and ameliorate clinical outcomes on a broad scale.

Role in wound healing: mechanisms and clinical evidence

The role of sericin in wound healing is multifaceted, offering promising clinical evidence for its use in various therapeutic interventions. The novel synthesis of amoxicillin-loaded sericin biopolymeric nanoparticles, as reported by Diab *et al.* (2022), illustrates sericin's capacity for enhancing antibacterial activities and wound healing efficiency. This study found that sericin/propolis/amoxicillin nanoparticles significantly reduced bacterial load and accelerated complete wound healing in both normal and diabetic rats. Histological examinations revealed better-organized dermis and mature collagen fiber formation in treated wounds, underscoring sericin's potential as an effective agent against bacterial wound infections (Diab *et al.,* 2022).

In the realm of nerve injury, Li *et al.* (2020) demonstrated the efficacy of a carbon nanotube (CNT)/sericin conductive nerve guidance conduit in promoting functional recovery in a rat model with transected peripheral nerve injury. The CNT/sericin conduit, characterized by its biocompatibility, biodegradability, and porous structure, proved to be a viable alternative to autografts, particularly when combined with electrical stimulation, indicating sericin's potential in neural tissue engineering (Li *et al.,* 2020).

Moreover, Li *et al.* (2023a) developed a silk protein wound dressing (SPD) with a natural silk fiber-sericin hydrogel double interpenetrating network. This innovative dressing, with its high porosity and mechanical strength, has shown to effectively enhance wound healing in a mouse full-thickness wound model (Li *et al.,* 2023a). The inclusion of resveratrol in the SPD further amplified its antioxidative and anti-inflammatory properties, leading to the regeneration of hair follicles and sebaceous glands, increased vascular endothelial growth factor expression, and reduced inflammation, thereby significantly accelerating the wound healing process (Li *et al.,* 2023a).

Together, these studies provide compelling evidence of sericin's role in wound healing. Its mechanisms of action, including enhanced antibacterial properties, support for cellular growth and matrix organization, and improved tissue regeneration, make it an asset in the development of new bioactive dressings and scaffolds for clinical use. These advancements in sericin-based therapies not only offer potential for more effective wound care but also open avenues for innovative treatments in regenerative medicine and tissue engineering.

Conclusion

In concluding this review on the recent research trends of silk sericin, this versatile protein holds significant promise across multiple domains of biomedicine. From the meticulous design of scaffolds for tissue engineering to the innovative approaches in wound healing, sericin has proven to be a cornerstone in the development of biomaterials. The promising outcomes of these studies, such as the accelerated wound healing in diabetic rats and the functional recovery of transected peripheral nerve injuries in rat models, underscore sericin's role as an effective agent in clinical applications. Furthermore, the inclusion of sericin in advanced dressings and its ability to enhance the functionality of engineered tissues highlight its pivotal role in regenerative medicine.

On the cusp of a new era of biomaterials science, silk sericin emerges as a key player, offering novel solutions and hope for patients suffering from a variety of conditions. With ongoing research and development, sericin-based materials are set to revolutionize medical practices and improve patient outcomes, redefining the landscape of regenerative medicine and tissue engineering. The convergence of sericin's multifaceted applications, from tissue scaffolding and nerve regeneration to its wound healing and antibacterial properties, reflects its unparalleled potential as a bioactive material. As the full capabilities of sericin continue to be unlocked, it is anticipated that future innovations will further solidify its status as an indispensable resource in the biomedical field.

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