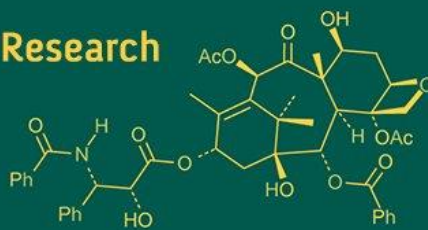


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**Rakshitha MP**  
M.Sc (Agri) Sericulture,  
Department of Sericulture,  
College of Sericulture (UASB),  
Chintamani, Karnataka, India

**Kruthika MS**  
M. Sc (Agri) Sericulture,  
Department of Sericulture,  
College of Sericulture (UASB),  
Chintamani, Karnataka, India

**Bharathi VP**  
Assistant Professor,  
Department of Sericulture,  
College of Sericulture (UASB),  
Chintamani, Karnataka, India

**Bhuvaneshwar Rajesh Naik**  
M.Sc (Agri) Sericulture,  
Department of Sericulture,  
College of Sericulture (UASB),  
Chintamani, Karnataka, India

**Manjunath Basavaraj Helavar**  
M. Sc (Agri) Sericulture,  
Department of Sericulture,  
College of Sericulture (UASB),  
Chintamani, Karnataka, India

**Corresponding Author:**  
**Rakshitha MP**  
M.Sc (Agri) Sericulture,  
Department of Sericulture,  
College of Sericulture (UASB),  
Chintamani, Karnataka, India

## Silk sericin: A versatile material for tissue engineering and drug delivery

**Rakshitha MP, Kruthika MS, Bharathi VP, Bhuvaneshwar Rajesh Naik and Manjunath Basavaraj Helavar**

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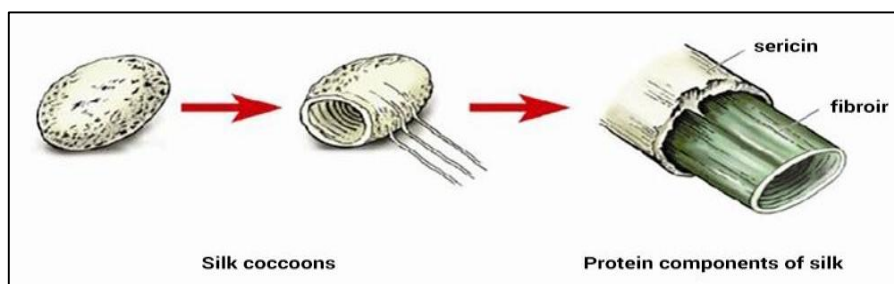
### Abstract

Silk sericin, a natural protein derived from the cocoon of the silkworm (*Bombyx mori*), has emerged as a valuable biomaterial in the fields of tissue engineering and drug delivery. Once considered a by-product of the silk industry, sericin is now recognized for its excellent biocompatibility, biodegradability, and functional versatility. Its inherent ability to support cell growth, stimulate collagen production, and promote wound healing has enabled its application in the development of scaffolds, hydrogels, and skin substitutes. In drug delivery, sericin offers promising features such as pH responsiveness, amphiphilic character, and functional groups that allow for targeted and controlled release of therapeutic agents. Various formulations, including sericin-based nanoparticles and injectable gels, have shown significant potential in treating burns, neurodegenerative diseases, and even diabetes. With its ability to be blended with other polymers and its approval by regulatory bodies, sericin stands out as a sustainable and cost-effective material for biomedical innovation.

**Keywords:** Silk sericin, tissue engineering, drug delivery, biomaterials, wound healing, nanoparticles, hydrogels, biocompatibility, regenerative medicine, controlled release

### 1. Introduction

India is second largest producer of silk in the world with annual production of 34,903 MT (2022/2023). FY23, India produced 36,582 metric tonnes (MT) of silk. Mulberry Silk is the most common among them contributing to nearly 95% of world's silk production. Karnataka is the largest producer of mulberry silk in India. Silk is a natural protein fiber. The protein fiber of silk is composed mainly of fibroin and sericin which is secreted by the silkworm (*B. mori*). Fibroin is a core filament that provides stiffness and strength and makes up more than 70% of the cocoon. Sericin makes up 20-30% of the cocoon and is a glue-like protein that binds fibroin fibers together. In 1865, the chemist Emil Cramer reported that the two main components of silk are the hydrophobic fibroin and the hydrophilic sericin.



The silk gland of the silkworm is anatomically divided into three regions: anterior, middle, and posterior. Fibroin, the core protein of silk, is secreted by the posterior region of the silk gland, especially during the fourth and fifth instar stages. The middle region, which is the largest and features three distinct flexures, serves as a reservoir for the maturation of fibroin and also secretes sericin, the gum-like protein that coats fibroin. This middle region is functionally subdivided into three parts: the posterior section secretes sericin I, which forms the innermost layer around the fibroin; the middle section secretes sericin II, the middle.

layer; and the anterior section secretes sericin III, the outermost layer (Figure.1). Structurally, the middle region starts as a narrow tube, expands at the center, and narrows again towards the posterior end. The anterior region of the silk gland does not produce any silk proteins; rather, it serves as a conduit that transports the silk mixture from the reservoir to the spinneret, where the silk is finally extruded and solidified.

Despite its biological and commercial significance, sericin is often treated as a waste by-product during silk reeling. Globally, it is estimated that around 50,000 tonnes of sericin are discarded annually from an approximate 400,000 tonnes of dry cocoon production. However, increasing research into the biofunctional properties of sericin—such as its antioxidant, antimicrobial, and moisturizing effects—has led to a surge in commercial interest. The global sericin market was valued at USD 314.69 million in 2022 and is projected to grow at a compound annual growth rate (CAGR) of 6.4% in the coming years.

## 2. Structure of sericin

Sericin is a natural, water-soluble glycoprotein composed of 18 amino acids, among which serine is the most predominant, constituting approximately 32% of its total amino acid profile (Zhaorigetu *et al.*, 2003; Padamwar & Pawar, 2004) [27, 17]. The abundance of serine contributes significantly to sericin's adhesive nature due to its capacity to form hydrogen bonds, which give the protein its characteristic glue-like properties. The secondary structure of sericin primarily exists in a random coil configuration, but it can readily transform into a  $\beta$ -sheet structure under certain physical conditions such as repeated hydration and mechanical stretching (Kato *et al.*, 1998) [13]. This structural flexibility enhances sericin's functional adaptability. Advances in molecular biology have led to the sequencing of genes encoding sericin proteins, which revealed that the C-terminal domain is rich in serine-based repetitive sequences, critical for its biochemical activity (Terada *et al.*, 2005) [13]. Sericin has a molecular weight of approximately 10,400 kDa, and its empirical chemical formula is  $C_{30}H_{40}N_{10}O_{16}$ , highlighting its complex polypeptide structure and potential for diverse industrial and biomedical applications (Aramwit *et al.*, 2010) [4].

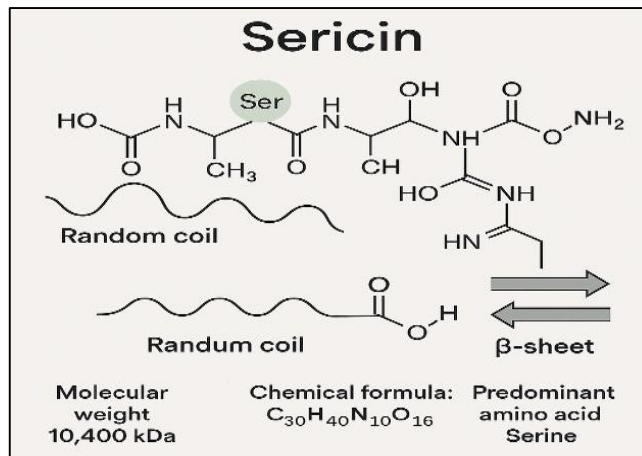
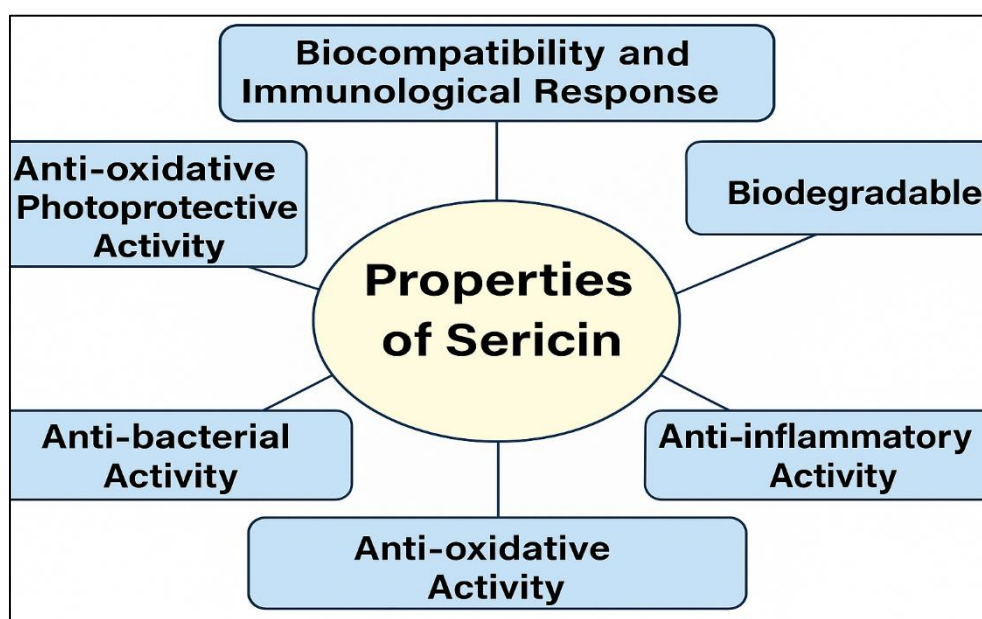


Fig 1: Structure of sericin

## 3. Sericin extraction

Sericin is a group of hydrophilic polypeptides that are typically removed during the degumming of silk. Despite its diverse biological properties including antioxidant, antimicrobial, and moisturizing effects, it is often discarded as a waste by-product in the silk industry (Zhaorigetu *et al.*, 2003; Aramwit *et al.*, 2010) [27, 4]. Sericin can be extracted using three major degumming techniques: chemical, enzymatic, and hot water methods. The chemical method utilizes alkaline or acidic solutions such as sodium carbonate or soap to dissolve sericin, offering high yield but sometimes compromising the bioactivity of the extracted protein (Padamwar & Pawar, 2004) [17]. The enzymatic method employs proteolytic enzymes that selectively hydrolyze sericin while preserving fibroin structure, making it a more environmentally friendly and targeted approach (Aramwit *et al.*, 2012) [3, 4]. The hot water method is a simple and sustainable technique that uses elevated temperatures to extract sericin based on its solubility, often retaining more of its biofunctional characteristics (Kato *et al.*, 1998) [13]. The choice of extraction method significantly influences the molecular characteristics and functional applications of sericin in various biomedical and cosmetic fields.



#### 4. Properties of Sericin

Sericin, a silk-derived protein, exhibits several remarkable properties that make it highly suitable for biomedical and pharmaceutical applications. One of its most significant features is its biocompatibility. Biocompatibility is essential for any biomaterial intended for contact with the human body, as it must not provoke immune responses or cytotoxic effects. Sericin has consistently demonstrated immunological inertness and non-toxicity in various *in vitro* studies, where its addition to culture media did not induce cytotoxicity or inflammatory responses, confirming its safe interaction with mammalian cells (Aramwit *et al.*, 2010) [4]. Another crucial characteristic of sericin is its biodegradability. Biodegradable materials are preferred in medical applications as they naturally decompose in the body without the need for removal. Sericin-based materials have been shown to gradually degrade and be reabsorbed within approximately six weeks post-implantation *in vivo*, reducing patient discomfort and eliminating the need for surgical removal (Aramwit *et al.*, 2012) [3, 4].

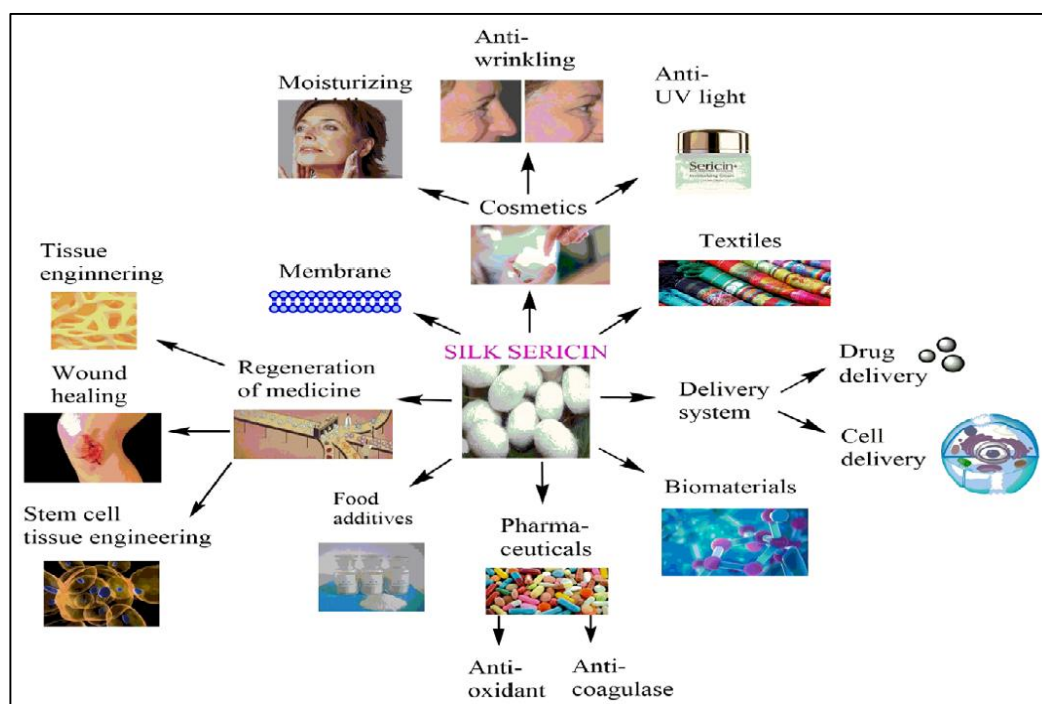
Sericin also demonstrates anti-inflammatory activity, an essential attribute for wound healing applications. During the inflammation phase of healing, sericin can help modulate cytokine production and minimize the excessive activation of metalloproteinases, which otherwise lead to degradation of the extracellular matrix. By regulating this response, sericin promotes an environment favorable for

tissue regeneration (Kundu *et al.*, 2008) [9].

The antibacterial property of sericin has been widely explored, especially due to growing concerns over bacterial infections in wound care. Sericin exhibits significant inhibitory effects against both Gram-positive and Gram-negative bacteria, though it tends to be more effective against Gram-positive strains. This antibacterial activity enhances its potential as a bioactive wound dressing or biomedical coating (Padamwar & Pawar, 2004; Zhaorigetu *et al.*, 2003) [17, 27].

Additionally, sericin possesses strong antioxidative and photoprotective activities. It effectively scavenges reactive oxygen species (ROS), inhibits lipid peroxidation, and demonstrates anti-tyrosinase and anti-elastase activity, largely attributed to its high content of hydroxyl-rich amino acids like serine and threonine (Kato *et al.*, 1998) [13]. These antioxidant properties protect cells from oxidative stress, which is linked to various diseases including cancer and cardiovascular disorders. Moreover, sericin exhibits UV-absorbing capacity, offering photoprotection by maintaining cellular redox balance and absorbing UV radiation, particularly wavelengths under 200 nm, due to the presence of nitrogen-, hydrogen-, and oxygen-containing functional groups (Dash *et al.*, 2008) [9].

#### 5. Silk sericin applications in different industries



(Shahzadi *et al.*, 2022) [22]

Industry	Applications
Biomedical & Pharmaceutical	Supplement in culture media, Antitumor activity-Metabolic effects (gastrointestinal, circulatory, immune systems; lipid metabolism and obesity) Tissue engineering, Wound healing, Drug delivery, Contact lenses, Matrix for implants, Vehicle for cell amplification, Stabilizer in vaccines
Cosmetics & Personal Care	Skincare: improves elasticity, anti-wrinkle/anti-aging effects, UV protection-Nailcare: prevents cracks and brittleness, improves brightness, Haircare: acts as a conditioner, prevents hair damage, Gel formulation: excellent moisturizing properties
Food	Enhances taste and texture of porridge, prevents browning reactions in ingredients, acts as antioxidant and nutrient additive, Improves mineral absorption
Textile	Enhances moisture absorption in fabrics-Provides cleaning properties Improves antibacterial activity, used in fabricated nanofibers-Offeres UV protection: Applied in medical textiles-Nanofibers for wastewater treatment (adsorptive pollutants)-Air filtration products
Others	Anti-frosting agent (roads and roofs), Artificial leather manufacturing Art pigments-Used in road and roof materials



## 6. Sericin in Tissue Engineering

Tissue engineering is a multidisciplinary field within biomedical engineering that integrates principles of biology, materials science, and engineering to develop functional substitutes that restore, maintain, or enhance damaged tissues or organs. This process typically involves the use of living cells combined with a scaffold three-dimensional (3D), biocompatible, and porous structures designed to mimic the extracellular matrix and support cellular attachment, proliferation, and differentiation (O'Brien, 2011). Among various biomaterials explored for scaffold development, sericin, a natural silk protein derived from the silkworm *Bombyx mori*, has emerged as a promising candidate due to its biodegradability, hydrophilicity, and ability to enhance cell adhesion and proliferation (Aramwit *et al.*, 2010) [4]. Studies have demonstrated that sericin-based scaffolds promote the regeneration of skin, bone, and nerve tissues, owing to their antioxidant and immunomodulatory properties (Kundu *et al.*, 2013) [14].



Incorporating sericin into composite scaffolds with polymers like gelatin, chitosan, or alginate has shown to improve the mechanical strength and biological performance of the scaffolds, making them more suitable for load-bearing and complex tissue regeneration applications (Dash *et al.*, 2008) [9]. Moreover, sericin has been reported to support the expression of growth factors such as VEGF and TGF- $\beta$ , which play crucial roles in angiogenesis and tissue remodeling (Sasaki *et al.*, 2005) [21]. Due to its excellent cytocompatibility and ease of processing into films, gels, and sponges, sericin continues to be explored in various experimental and pre-clinical tissue engineering models, especially in wound healing and skin tissue engineering.

## 7. Application of Sericin-Based Biomaterials in Wound Healing and Skin Tissue Engineering

The use of sericin in regenerative medicine, particularly for skin tissue engineering and wound healing, has garnered significant research attention due to its intrinsic bioactivity and compatibility with skin cells. Sericin-based films, hydrogels, and scaffolds have been developed for topical wound applications, owing to the protein's ability to modulate various phases of the wound-healing process (Aramwit *et al.*, 2013; Chen *et al.*, 2018) [2, 8].

One of the primary mechanisms through which sericin enhances wound repair is by promoting the proliferation and activity of skin cells such as keratinocytes and fibroblasts. This regenerative capacity is largely attributed to its amino acid composition, especially methionine, which supports the synthesis of collagen type I and other extracellular matrix (ECM) proteins (Padol *et al.*, 2015) [18]. Furthermore, sericin

has been observed to increase cellular adhesion sites and stimulate mitogenic responses in mammalian cells, accelerating tissue regeneration and reepithelialization (Kato *et al.*, 2005) [12].

In a notable study, Chen *et al.* (2018) [8] fabricated a hydrogel scaffold by integrating sericin with methacrylic anhydride-modified gelatin (GelMA) using 3D printing technology. This bioengineered scaffold demonstrated superior transparency, allowing visual monitoring of wound healing, and showed effective tissue regeneration in skin wound models.

Clinical relevance of sericin has also been substantiated in human trials. Aramwit *et al.* (2013) [2] evaluated the incorporation of sericin into a silver zinc sulfadiazine cream in a study involving 29 patients with 65 second-degree burn wounds. The results indicated that the sericin-enhanced formulation significantly reduced healing time—from an average of  $29.28 \pm 9.27$  days in the control group to  $22.42 \pm 6.33$  days in the treatment group—without inducing any infection or adverse skin reactions. Furthermore, the time required for 50% and 70% reepithelialization was significantly shorter in the sericin-treated group, confirming its therapeutic efficacy.

Although the antibacterial activity of sericin itself was not significantly different from that of the standard cream, its wound-healing benefits stem largely from its ability to stimulate cell migration and cytokine production rather than direct antimicrobial action (Aramwit *et al.*, 2013) [2].

Historically, silk sutures have been employed in wound closures, highlighting the biocompatibility of silk proteins. Modern applications now leverage sericin's capacity to promote cell proliferation and ECM formation, making it a highly promising candidate for advanced wound dressings and skin substitutes (Kundu *et al.*, 2013) [14].

## 8. Sericin as a Functional Oral Gargle Agent

Sericin, known for its hydrophilic nature and film-forming ability, has shown promising potential in oral healthcare, particularly in alleviating symptoms of xerostomia (dry mouth), a condition prevalent among elderly individuals. Its moisturizing properties are well-documented in dermatological applications, where it has been used to enhance skin hydration and reduce transepidermal water loss (Tsukada *et al.*, 1990) [24]. When used in the form of a gel or rinse, sericin increases moisture retention on the mucosal surface, which may contribute to symptomatic relief in xerostomic patients.

Furthermore, sericin exhibits inhibitory effects on tyrosinase, an enzyme involved in melanin synthesis, which accounts for its common use in cosmetic formulations (Kato *et al.*, 2005) [12]. In oral care, however, its utility extends to managing halitosis. A comparative study assessing a sericin-based gargle against a standard commercial mouthwash revealed that the sericin formulation significantly reduced hydrogen sulfide levels, the primary volatile sulfur compound responsible for bad breath. This suggests that sericin not only improves oral hydration but also provides odor control, likely through its antimicrobial and protein-binding properties (Aramwit & Sangcakul, 2007) [1].

At present, the commercial availability of oral care products incorporating silk proteins remains limited, with only one known gargle containing sericin protein available on the market, highlighting a potential niche for future development.

## 9. Sericin-Based Dressings for Burn Wounds

Burn injuries represent a severe form of skin trauma, characterized by extensive tissue damage that disrupts normal physiological repair mechanisms. These wounds progress through four coordinated but overlapping stages: hemostasis, inflammation, proliferation, and remodeling (Guo & DiPietro, 2010) <sup>[11]</sup>. However, factors such as infection, excessive inflammation, and poor vascularization often impair this process, particularly in chronic wounds such as burns, diabetic ulcers, and pressure sores.

Sericin has emerged as a valuable material for developing advanced burn dressings due to its biocompatibility, mitogenic effects, and moisture-retaining properties. When incorporated into hydrogels, films, or composite membranes, sericin supports the migration and proliferation of keratinocytes and fibroblasts key players in reepithelialization and extracellular matrix (ECM) deposition (Kundu *et al.*, 2013) <sup>[14]</sup>. These properties are essential for accelerating epithelial closure, minimizing scar formation, and preventing secondary infections.

In burn management, preventing sepsis is a clinical priority. Therefore, topical dressings often include antimicrobial agents. Sericin has been shown to enhance the activity of such agents and, in some formulations, display mild antimicrobial activity on its own (Aramwit *et al.*, 2012) <sup>[3, 4]</sup>. Its ability to maintain a moist wound environment further supports tissue regeneration and reduces patient discomfort. Additionally, sericin's non-toxic, biodegradable profile makes it a sustainable and safe option for wound care. Studies using sericin-coated or sericin-blended dressing materials have demonstrated shorter healing times, improved granulation tissue formation, and better patient outcomes when compared to standard treatments (Dash *et al.*, 2020) <sup>[10]</sup>.

## 7. Application of Sericin in Drug Delivery

Drug delivery systems play a pivotal role in enhancing the therapeutic efficiency of pharmaceutical agents by ensuring their controlled release and targeted delivery. These systems are crucial for minimizing adverse effects and maximizing the bioavailability of active compounds. Among the biomaterials investigated for drug delivery, silk sericin has emerged as a promising candidate due to its biocompatibility, pH sensitivity, and amphiphilic nature. Sericin contains both polar and non-polar domains, allowing it to interact effectively with a variety of drug molecules, whether hydrophilic or hydrophobic. Its reactive functional groups such as hydroxyl, amino, and carboxyl enable the development of diverse drug carriers, including hydrogels, nanoparticles, and films. These sericin-based structures can be engineered to respond to external pH stimuli, which is advantageous for site-specific and sustained drug release. Wang *et al.* (2014) <sup>[25]</sup> developed an injectable 3D hydrogel from sericin derived from fibroin-deficient silkworm cocoons using glutaraldehyde as a crosslinker. The hydrogel demonstrated properties suitable for long-term drug release, with excellent moldability and compatibility for biomedical use.

### 7.1 Sericin Nanoparticles for Targeted Drug Delivery

Recent advancements have seen sericin integrated into nanoparticle platforms. Bari *et al.* (2023) <sup>[6]</sup> explored a novel formulation combining sericin and crocetin a bioactive carotenoid—to produce nanoparticles aimed at regenerating

intervertebral discs. These sericin-crocetin nanoparticles were dried to form microparticles and assessed for antioxidant, anti-tyrosinase, and anti-elastase activities. Among the formulations, those with crocetin excess (NPMix) demonstrated superior antioxidant properties, while sericin-rich formulations (NPS) showed greater anti-elastase activity.

The particles retained nanometric size before drying (around 250 nm) and expanded to micron-sized structures upon spray drying. These bioactive nanoparticles protected nucleus pulposus cells from oxidative damage, supporting their future application in intervertebral disc therapy.

Similarly, Perteghella *et al.* (2021) <sup>[19, 20]</sup> investigated sericin nanoparticles for nose-to-brain drug delivery. Sericin was crosslinked using crocetin and compared to glutaraldehyde-crosslinked counterparts. The crocetin-based nanoparticles (NPc) not only demonstrated stability and biocompatibility but also showed enhanced ROS-scavenging capabilities. These properties suggest their potential in neuroprotective therapies by bypassing the blood-brain barrier.

In parallel, Biman *et al.* (2009) <sup>[7]</sup> fabricated sericin-based micellar nanoparticles using poloxamers (F-127 and F-87) for dual delivery of hydrophilic (FITC-insulin) and hydrophobic (paclitaxel) drugs. These particles (100-110 nm) showed efficient cellular uptake in MCF-7 breast cancer cells and exhibited cytotoxic effects comparable to free paclitaxel. Their design supports the utility of sericin in self-assembled drug delivery platforms. Additionally, a novel injectable gel using sericin from mulberry and non-mulberry silk was developed by researchers at IIT Guwahati for the delivery of pancreatic islet cells in diabetes management. The hydrogel, loaded with immunosuppressants and tested in rats, supported cell viability and glucose-responsive insulin secretion, offering a promising minimally invasive treatment for type 1 diabetes (Mandal *et al.*, 2021) <sup>[15]</sup>.

## 8. Application of Sericin in Bone Regeneration

Bone regeneration is a critical area of tissue engineering focused on restoring the structural and functional integrity of damaged or diseased bone tissue. An ideal bone substitute must promote osteogenesis, possess mechanical strength, and support the attachment, proliferation, and differentiation of osteoblasts. Silk sericin, with its bioactive amino acids and favorable cell-interaction properties, has recently attracted attention for its potential in bone tissue regeneration.

### 8.1 Osteogenic Potential of Sericin-Based Scaffolds

Sericin contains serine, aspartic acid, and glycine—amino acids known to support cell adhesion and proliferation. These components promote the growth of osteoblasts and enhance extracellular matrix mineralization, which are essential for bone regeneration. Studies have demonstrated that sericin, when used as a scaffold component or a coating material, improves osteoinductive and osteoconductive properties. In a study by Mandal and Kundu (2009) <sup>[14]</sup>, scaffolds made from non-mulberry sericin and fibroin were fabricated using freeze-drying techniques and crosslinked with genipin. These scaffolds showed enhanced mechanical strength and promoted the proliferation and differentiation of MG-63 human osteoblast-like cells. The alkaline phosphatase activity and calcium deposition, key indicators

of osteogenesis, were significantly higher in cells cultured on sericin-based scaffolds compared to controls.

## 8.2 Sericin Composites for Bone Grafts

Combining sericin with inorganic biomaterials such as hydroxyapatite (HA) or bioactive glass has further improved its suitability for bone graft applications. For instance, Zhang *et al.* (2019) <sup>[26]</sup> incorporated nano-hydroxyapatite into sericin-chitosan scaffolds and observed increased porosity, swelling capacity, and mechanical properties. The composite scaffold supported cell viability and showed promising osteogenic differentiation *in vitro*. Similarly, a study by Siritientong *et al.* (2012) <sup>[3]</sup> involved the development of sericin polyvinyl alcohol (PVA) composite films containing HA particles. These films exhibited slow degradation rates and supported osteoblast cell growth, highlighting their potential for guided bone regeneration.

## 8.3 Injectable Gels for Bone Repair

In addition to scaffolds and films, injectable sericin-based hydrogels have emerged as minimally invasive options for bone regeneration. These gels can fill irregular bone defects and conform to complex shapes, making them ideal for clinical applications. The incorporation of osteoinductive agents like bone morphogenetic proteins (BMPs) or growth factors into sericin gels has been explored to further enhance bone repair outcomes.

One such study by Perteghella *et al.* (2021) <sup>[19, 20]</sup> designed an injectable nanocomposite hydrogel containing sericin nanoparticles loaded with crocetin for use in bone and intervertebral disc regeneration. The hydrogel provided antioxidant protection, supported cellular viability, and mimicked the mechanical characteristics of native bone matrix.

## 9. Conclusion

Silk sericin has emerged as a multifunctional biopolymer with significant potential across biomedical and pharmaceutical domains. Its inherent biocompatibility, biodegradability, and ease of processing make it an attractive candidate for developing a wide range of therapeutic materials. Notably, sericin has been successfully incorporated into various drug delivery systems—such as films, nanoparticles, hydrogels, foams, and fibers—demonstrating controlled release profiles and enhanced drug stability.

In the realm of tissue engineering, sericin's ability to support cellular adhesion, proliferation, and differentiation has been particularly valuable, especially in bone regeneration and wound healing applications. Its role in facilitating re-epithelialization and tissue repair underscores its utility in clinical and regenerative medicine.

Economically and environmentally, sericin stands out among natural biomaterials due to its scalable production, potential for functional modification with other polymers, and recognition by regulatory bodies such as the U.S. Food and Drug Administration (FDA). Its integration into biomedical formulations not only aligns with sustainability goals but also adds value to sericulture by converting by-products into high-value therapeutic resources.

With increasing interest in sustainable biopolymers, sericin and other silk-derived substances hold promise as renewable biomaterials for future pharmaceutical innovations and eco-friendly medical technologies.

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