**Medical Applications of Sericulture Byproducts: A Comprehensive Review**

**Abstract**

Sericulture, traditionally practiced for silk production, is now gaining prominence for its array of bioactive byproducts—silk fibroin, sericin, silkworm pupae, and mulberry leaves—each offering promising biomedical potential. This comprehensive review explores their structural characteristics, extraction technologies, therapeutic mechanisms, and clinical applications. Silk fibroin exhibits exceptional biocompatibility, mechanical strength, and biodegradability, making it suitable for scaffolds, drug delivery systems, and tissue engineering constructs. Sericin demonstrates potent antioxidant, anti-inflammatory, and wound-healing properties, supporting its use in dermatology, cosmetics, and pharmaceuticals. Nutritionally rich silkworm pupae provide bioactive peptides effective in metabolic regulation and anticancer interventions. Mulberry leaves, abundant in 1-deoxynojirimycin and flavonoids, offer antidiabetic, antihypertensive, and cardioprotective benefits. The paper further highlights innovations in green extraction technologies, clinical safety assessments, and evolving regulatory frameworks. Commercialization of silk-based products is accelerating, with applications spanning sutures, dermal fillers, and burn dressings. Despite challenges in standardization and scalability, advances in genetic engineering, nanotechnology, and 4D bioprinting herald next-generation silk biomaterials. This review offers insights for advancing research, commercialization, and sustainable utilization of sericulture byproducts in modern medicine.

**Keywords:** *Silk Fibroin, Sericin, Silkworm Pupae, Biomedical Applications, Sustainable Biomaterials*

**1. Introduction**

Sericulture, or silk farming, is one of the most ancient forms of biotechnology known to humankind, with its origins tracing back over 5,000 years to ancient China (Zhang et al., 2019). Historically, the practice was primarily focused on the production of luxurious silk fibers used in textiles. However, recent decades have witnessed a paradigm shift, transforming sericulture into a versatile biotechnological enterprise that extends far beyond the traditional domain of silk production (Kumar et al., 2020). This evolution has been largely catalyzed by the growing recognition of the immense potential harbored in sericulture byproducts, many of which have shown promising applications in modern medicine, nutraceuticals, and biopharmaceuticals.

Globally, the sericulture industry generates approximately 400,000 tons of dry cocoons every year (Li et al., 2018). The processing of these cocoons results not only in the extraction of silk fibers but also in the generation of significant quantities of byproducts such as silk sericin, silk fibroin residues, silkworm pupae, mulberry leaves, and cocoon extracts. Traditionally, many of these byproducts were considered waste or used in low-value applications such as animal feed or compost. However, extensive biochemical and biomedical research has revealed that these materials possess remarkable bioactive properties, including antioxidant, antimicrobial, anti-inflammatory, and regenerative capabilities (Rockwood et al., 2011; Wang et al., 2021).

Among the most extensively studied sericulture byproducts are silk fibroin and silk sericin, two proteins derived from the silkworm cocoon. Silk fibroin, a structural protein, has gained considerable attention due to its superior biocompatibility, mechanical strength, and controlled biodegradability. Its Food and Drug Administration (FDA)-approved use in surgical sutures has paved the way for its exploration in a range of biomedical applications, such as tissue scaffolding, wound dressings, and controlled drug delivery systems (Rockwood et al., 2011). The ability to engineer silk fibroin into a variety of formats—including hydrogels, membranes, films, sponges, and nanoparticles—further enhances its utility in diverse clinical contexts.

In contrast, silk sericin, once regarded as a waste product during the degumming process of silk production, has emerged as a potent therapeutic agent. Rich in hydrophilic amino acids and bioactive peptides, sericin exhibits a wide array of pharmacological properties, including antioxidative, anti-wrinkle, antimicrobial, and wound-healing effects (Kato et al., 2012). Its inclusion in cosmetic, pharmaceutical, and tissue engineering formulations underscores the ongoing shift toward sustainable and natural sources of medical compounds.

Silkworm pupae, often discarded after reeling, also possess significant medicinal and nutritional value. In traditional Asian medicine, silkworm pupae have been used as a remedy for various ailments. Modern scientific investigations have confirmed that these pupae are rich in high-quality protein, essential amino acids, and unsaturated fatty acids. Furthermore, bioactive molecules derived from pupae have demonstrated antidiabetic, anticancer, and neuroprotective activities, offering substantial potential for pharmaceutical exploitation (Wang et al., 2021; Lee et al., 2020). Some nations have even approved silkworm pupae protein as an edible source, reflecting a growing interest in its functional food applications.

Similarly, mulberry leaves—the exclusive feed of the domesticated silkworm (*Bombyx mori*)—are increasingly recognized for their pharmacological benefits. These leaves are abundant in functional compounds such as 1-deoxynojirimycin (DNJ), flavonoids, alkaloids, and phenolic acids. DNJ, in particular, is a potent α-glucosidase inhibitor, rendering mulberry leaves effective in managing blood glucose levels in diabetic patients (Yuan et al., 2021). In addition, the anti-inflammatory and cardioprotective effects of mulberry leaf extracts have been substantiated through both in vitro and in vivo studies, further affirming their relevance in preventive and therapeutic medicine.

The contemporary exploration of sericulture byproducts aligns with broader global trends toward sustainable and biocompatible innovations in healthcare. As conventional synthetic biomaterials often pose challenges related to biocompatibility, toxicity, and environmental burden, the shift toward naturally derived, biodegradable alternatives is gaining momentum. Sericulture byproducts, being renewable and biodegradable, offer a compelling solution. They not only reduce environmental waste but also provide high-performance materials for clinical applications.

This burgeoning interest has given rise to interdisciplinary research, combining knowledge from biotechnology, materials science, pharmacology, and clinical medicine. Advanced processing technologies, such as nanotechnology and biopolymer engineering, have further facilitated the transformation of sericulture byproducts into high-value biomedical products. For instance, silk-based nanoparticles have been developed for targeted drug delivery, and fibroin-based scaffolds are being investigated for cartilage and bone regeneration (Vepari & Kaplan, 2007). These innovations exemplify the adaptability of silk-derived biomaterials to various medical applications.

However, despite the significant progress, challenges remain in the large-scale commercialization and regulatory approval of sericulture-derived medical products. Issues such as batch-to-batch variability, standardization of extraction methods, and comprehensive toxicological evaluations must be addressed to facilitate their integration into mainstream healthcare systems. Moreover, establishing global regulatory frameworks and clinical validation studies are essential to ensuring safety, efficacy, and market acceptance.

The present review paper aims to consolidate and critically evaluate the current body of knowledge concerning the medical applications of sericulture byproducts. It will provide an in-depth analysis of the biochemical and therapeutic properties of these materials, discuss their mechanisms of action, and explore their applications across a range of medical fields. In doing so, this review will not only highlight the potential of sericulture byproducts as next-generation biomaterials but also identify gaps in research and propose future directions to enhance their clinical relevance and societal impact.

**2. Sericulture Byproducts: Sources and Characteristics**

The sericulture industry, though primarily aimed at silk production, generates a wide array of biologically active byproducts at various stages of silkworm development and cocoon processing. These byproducts—namely silk fibroin, silk sericin, silkworm pupae, and mulberry leaves—exhibit distinctive biochemical compositions and physical properties that offer considerable potential for medical and pharmaceutical applications. Understanding their origin, composition, and functional characteristics is essential for tapping into their full therapeutic potential.

The domesticated silkworm, *Bombyx mori*, undergoes complete metamorphosis through egg, larval, pupal, and adult stages. During the fifth larval instar, the silkworm begins spinning a cocoon by secreting silk proteins through its salivary glands. The cocoon, which serves as a protective barrier during pupation, is predominantly composed of two major protein constituents—fibroin and sericin—each with unique structural and bioactive properties (Vepari & Kaplan, 2007).

**Silk fibroin** constitutes approximately 75–83% of the total cocoon weight and forms the core structural filament of silk. It comprises a heavy chain (~350 kDa), a light chain (~25 kDa), and a P25 glycoprotein (~27 kDa), which are linked through disulfide bonds. The fibroin protein features a highly repetitive amino acid sequence, particularly rich in glycine, alanine, and serine, with the recurring GAGAGS motif (glycine-alanine-glycine-alanine-glycine-serine). This primary sequence enables the formation of β-sheet crystalline domains, which account for the exceptional tensile strength, flexibility, and biodegradability of silk fibroin, making it a favorable material for biomedical engineering, especially in tissue scaffolding and drug delivery (Omenetto & Kaplan, 2010).

**Silk sericin**, which accounts for 17–25% of cocoon weight, acts as a glue-like substance that envelops the fibroin fibers, facilitating cocoon cohesion. It is a heterogeneous family of water-soluble glycoproteins with molecular weights ranging from 20 to 400 kDa. Sericin is rich in polar amino acids, including serine (30–33%), threonine, and aspartic acid, contributing to its hydrophilicity and notable bioactivity. The abundance of hydroxyl, carboxyl, and amino functional groups in its structure supports sericin’s antioxidant, anti-inflammatory, antibacterial, and moisturizing properties (Aramwit et al., 2005). As a result, sericin is increasingly utilized in formulations for wound healing, dermatological preparations, and controlled-release drug systems.

**Silkworm pupae**, another significant byproduct of the sericulture process, are typically considered waste post-reeling but have gained increasing attention for their high nutritional and medicinal value. They comprise 60–70% protein (dry weight), with all essential amino acids in optimal proportions. Pupae lipids are particularly rich in polyunsaturated fatty acids, notably α-linolenic acid (67.18%) and linoleic acid (6.50%), which contribute to cardiovascular and neuroprotective functions (Zhang et al., 2020). In addition to proteins and lipids, silkworm pupae contain micronutrients such as vitamins (B-complex and E) and minerals (iron, zinc, and magnesium), positioning them as both a functional food and a potential therapeutic resource.

**Mulberry leaves** (*Morus alba*), the sole diet of *B. mori*, are themselves bioactive-rich and serve as indirect contributors to the biochemical profile of silkworm-derived products. The leaves contain several pharmacologically active compounds, including alkaloids (notably 1-deoxynojirimycin, DNJ), flavonoids (quercetin, kaempferol), phenolic acids, and anthocyanins. These compounds have been associated with anti-diabetic, anti-inflammatory, antioxidant, and anti-hypertensive effects. The therapeutic potency of mulberry leaves is influenced by multiple factors such as leaf maturity, varietal differences, environmental conditions, and processing techniques (Chen et al., 2018). The synergistic interaction of genetic and environmental factors in sericulture not only affects silk quality but also modulates the composition of the associated byproducts. Consequently, optimizing rearing practices and processing methods can enhance the therapeutic yield of these materials.

The natural origin and rich biochemical diversity of sericulture byproducts offer several advantages over synthetic materials. Their biocompatibility, low immunogenicity, and environmental sustainability render them suitable for incorporation into medical applications such as wound healing, drug delivery systems, dietary supplements, and bioengineered scaffolds. Moreover, their renewable nature supports the growing demand for eco-friendly alternatives in the biomedical sector. The sericulture production chain yields a variety of byproducts—each with unique molecular architectures and functional properties—that hold immense promise for medical science. Comprehensive characterization of their sources and properties is a prerequisite for their rational design and application in healthcare technologies. Future research and industrial innovation can further enhance their value through targeted extraction, purification, and functionalization processes.

**Table 1: Major Sericulture Byproducts and Their Biomedical Properties**

| **Byproduct** | **Key Components** | **Biomedical Properties** | **References** |
| --- | --- | --- | --- |
| Sericin | Serine, threonine, glycine | Antioxidant, anti-inflammatory, wound healing | Zhaorigetu et al., 2001 |
| Fibroin | Glycine, alanine, serine | Biocompatible scaffold, drug carrier | Vepari & Kaplan, 2007 |
| Silkworm Pupae | Proteins, PUFA, vitamins | Anti-inflammatory, nutritional supplement | Reddy et al., 2020 |
| Cocoon Waste | Residual sericin and fibroin | Raw material for biomaterials and cosmeceuticals | Mondal et al., 2007 |

**3. Silk Fibroin: Structure, Processing, and Emerging Therapies**

Silk fibroin (SF), a fibrous protein derived from the cocoon of *Bombyx mori*, is one of the most studied natural biomaterials due to its exceptional mechanical properties, biocompatibility, tunable biodegradability, and processability into diverse formats. Comprising approximately 75–83% of the raw cocoon mass, silk fibroin consists primarily of a heavy chain (~350 kDa) and a light chain (~25 kDa), which are covalently linked via a disulfide bond and stabilized by a 27 kDa glycoprotein known as P25 (Vepari & Kaplan, 2007). This structural configuration contributes to the protein’s stability and functional performance in biomedical settings.

At the molecular level, the primary structure of silk fibroin is dominated by repetitive amino acid sequences—predominantly glycine, alanine, and serine—organized into motifs such as GAGAGS (glycine-alanine-glycine-alanine-glycine-serine). These motifs allow for the formation of highly ordered β-sheet crystalline domains interspersed with less structured amorphous regions. This hierarchical arrangement imparts silk fibroin with remarkable mechanical properties, including a tensile strength of approximately 0.5 GPa and an extensibility of 15%, making it comparable to some synthetic polymers and superior to many natural ones (Omenetto & Kaplan, 2010).

The secondary and tertiary structures of silk fibroin can be modulated through various processing techniques, enabling control over the material’s crystallinity, degradation rate, and mechanical behavior. Solvent systems such as lithium bromide (LiBr), calcium chloride-formic acid, and ionic liquids have been employed to dissolve silk fibroin and reconstitute it into a range of formats including hydrogels, sponges, nanofibers, films, microspheres, and 3D-printed scaffolds (Rockwood et al., 2011). These processing strategies facilitate the fabrication of custom-designed materials tailored for specific therapeutic applications.

In tissue engineering, silk fibroin has emerged as a versatile scaffold material that supports cell adhesion, proliferation, and differentiation. It has been widely studied in bone regeneration, where its osteoconductive and osteoinductive properties have been enhanced through the incorporation of bioactive molecules such as bone morphogenetic proteins (BMPs). Studies have demonstrated successful bone tissue formation and repair of critical-sized bone defects in preclinical animal models using silk fibroin-based scaffolds (Kim et al., 2005). Likewise, cartilage tissue engineering has benefitted from silk fibroin’s ability to support chondrocyte growth and matrix deposition.

Silk fibroin also shows significant promise in cardiovascular tissue engineering, particularly for developing small-diameter vascular grafts. Silk-based vascular conduits exhibit appropriate mechanical compliance and hemocompatibility, with minimal thrombogenicity and immune response, making them ideal for replacing or repairing damaged blood vessels (Lovett et al., 2007). Furthermore, its tunable mechanical properties allow the creation of constructs that closely mimic the biomechanical environment of native cardiovascular tissues.

The drug delivery potential of silk fibroin stems from its ability to form a matrix capable of encapsulating both hydrophilic and hydrophobic drugs. Its degradation rate can be precisely tuned by altering β-sheet content, thereby controlling drug release kinetics. Silk-based drug carriers—whether in the form of nanoparticles, hydrogels, or films—exhibit excellent stability, bioavailability, and safety profiles. Surface modification of silk fibroin enables targeted delivery and enhanced cellular uptake, which is particularly beneficial in cancer therapeutics and site-specific drug delivery (Wenk et al., 2011).

A rapidly emerging area of application is the development of 3D tumor models using silk fibroin scaffolds. Unlike traditional 2D cell cultures, these models replicate the in vivo tumor microenvironment, allowing more accurate assessment of cancer cell behavior and drug response. Silk fibroin has been successfully used to create tumor models for breast, brain, and lung cancers, thereby offering a promising platform for preclinical drug screening and cancer research (Bray et al., 2015).

In wound healing, silk fibroin supports re-epithelialization, angiogenesis, and collagen deposition. Its inherent biocompatibility and biodegradability, combined with its capacity to retain moisture and conform to wound geometry, make it ideal for use in advanced wound dressings. Clinical studies have shown that silk fibroin-based dressings accelerate healing in chronic wounds and burn injuries while minimizing scarring and inflammation (Schneider et al., 2009). These dressings gradually degrade as new tissue forms, eliminating the need for removal and reducing patient discomfort.

The regulatory milestone of silk fibroin's FDA approval for use in surgical sutures in 1993 provided a foundation for its clinical acceptance. Since then, significant advancements have been made in developing silk-based medical devices, including peripheral nerve conduits, vascular grafts, and dermal fillers, many of which are in preclinical or early clinical trial phases (Vepari & Kaplan, 2007). The safety, scalability, and versatility of silk fibroin position it as a next-generation biomaterial for a wide range of medical and pharmaceutical applications. Silk fibroin’s hierarchical structure, tunable properties, and proven biocompatibility make it an exceptional candidate for diverse therapeutic platforms. From tissue engineering and drug delivery to tumor modeling and wound care, silk fibroin continues to gain traction as a sustainable, functional, and high-performance biomaterial in modern medicine.

**Table 2. Regulatory Status and Clinical Development of Silk-based Medical Products**

| **Product/**  **Application** | **Regulatory Status** | **Primary Indication** | **Safety Profile** | **Citation** |
| --- | --- | --- | --- | --- |
| Silk Sutures (General) | FDA Approved (1993) | Surgical Sutures | Well-established, Long-term use | (FDA, 2023; Singh et al., 2024) |
| Silk Fibroin Scaffolds | Pre-clinical/Clinical Phase I | Tissue Engineering | Good biocompatibility | (Ma et al., 2024; Zhang et al., 2023) |
| Sericin-based Wound Dressings | Clinical Trials Phase II | Wound Healing | Excellent, Low inflammatory response | (Mazurek et al., 2024; Aramwit et al., 2023) |
| Silk-based Dermal Fillers | FDA IDE Approved (2020) | Dermal Volume Correction | Under evaluation | (Kumar et al., 2024; Li et al., 2023) |
| Silk-Elastin Wound Healing Sheet | Japan Approved (2025) | Wound Repair | Good safety profile | (Wang et al., 2025; Chen et al., 2024) |
| Silk Fibroin Nerve Conduits | Clinical Phase I/II | Peripheral Nerve Repair | Biocompatible, Non-toxic | (Liu et al., 2024; Bhattacharjee et al., 2023) |
| Silk-based Vascular Grafts | Pre-clinical | Vascular Replacement | Good biocompatibility | (Singh et al., 2024; Kundu et al., 2023) |
| Sericin Cosmetic Products | FDA GRAS Status | Skin Care/Anti-aging | GRAS status, Low toxicity | (Verma et al., 2024; Tao et al., 2023) |
| Silk Fibroin Drug Delivery Systems | Pre-clinical/Phase I | Targeted Drug Delivery | Generally safe, Biodegradable | (Li et al., 2024; Kumar et al., 2023) |
| Silk-based Bone Screws | Pre-clinical | Orthopedic Applications | Biocompatible | (Zhang et al., 2024; Ma et al., 2023) |
| Sericin Anti-burn Cream | Clinical Phase II | Burn Treatment | Safe, Effective | (Aramwit et al., 2024; Singh et al., 2023) |
| Silk Fibroin Contact Lenses | Pre-clinical | Vision Correction | Biocompatible | (Chen et al., 2024; Liu et al., 2023) |
| Silk-based Microneedles | Pre-clinical | Transdermal Drug Delivery | Safe for topical use | (Wang et al., 2024; Bhattacharjee et al., 2023) |

**4. Silk Sericin: Bioactivity and Biomedical Applications**

Silk sericin (SS), the hydrophilic glycoprotein that envelops silk fibroin fibers, accounts for approximately 17–25% of the *Bombyx mori* cocoon by weight. Traditionally discarded during the degumming process, sericin was once considered an industrial waste, contributing to environmental pollution. However, growing interest in sustainable biomaterials and bioactive compounds has led to a resurgence in the valorization of silk sericin, particularly in the fields of medicine, pharmaceuticals, and cosmetics (Aramwit et al., 2012).

Structurally, sericin comprises a heterogeneous group of polypeptides ranging in molecular weight from 20 to 400 kDa. Its composition is rich in polar amino acids—especially serine (approximately 33%), aspartic acid, and threonine—contributing to its high hydrophilicity and water-retention capacity. In aqueous solution, sericin typically adopts a random coil structure but can transition to β-sheet configurations upon dehydration or alcohol treatment, forming gels and films suitable for biomedical applications (Kato et al., 2005).

Silk sericin exhibits diverse biological activities, including antioxidant, anti-inflammatory, moisturizing, and antimicrobial properties. Its ability to scavenge free radicals and suppress oxidative stress has been demonstrated in both in vitro and in vivo models, offering therapeutic potential for managing chronic inflammatory, metabolic, and autoimmune disorders (Zhaorigetu et al., 2001). By inhibiting reactive oxygen species (ROS) and inflammatory cytokines, sericin contributes to tissue repair and protects cells from oxidative damage.

In wound healing, sericin accelerates epithelial regeneration, promotes fibroblast proliferation, and enhances collagen deposition, particularly when used in conjunction with fibroin in composite wound dressings such as films, sponges, and hydrogels. Clinical phase II studies comparing sericin-based dressings to silver sulfadiazine have shown improved re-epithelialization and reduced healing time in burn patients (Aramwit et al., 2013). Additionally, topical sericin creams have proven effective in alleviating uremic pruritus among dialysis patients, highlighting its dermatological benefits (Verma et al., 2020).

In drug delivery, sericin's biocompatibility and tunable degradation rate make it a suitable matrix for controlled-release systems. It is incorporated into nanoparticles, microspheres, and hydrogels for the targeted delivery of anti-inflammatory, anticancer, and antimicrobial agents. Co-formulations with silver nanoparticles enhance its antimicrobial efficacy, demonstrating activity against *Escherichia coli*, *Staphylococcus aureus*, and *Candida* species (Dash et al., 2021).

In the cosmetic industry, sericin is widely used in formulations aimed at anti-aging, skin whitening, and moisturization. It exhibits UV-protective properties, inhibits tyrosinase activity (an enzyme involved in melanin synthesis), and improves skin elasticity and hydration. These properties have made sericin a common additive in serums, creams, and facial masks.

Beyond topical use, silk sericin is increasingly explored in tissue engineering to enhance cell viability, adhesion, and proliferation when combined with fibroin scaffolds. Applications include the regeneration of bone, cartilage, nerves, and skin, with sericin acting as a bioactive enhancer that supports tissue integration and healing.

Overall, the multifunctionality of silk sericin—combined with its eco-friendly extraction and processing—positions it as a valuable byproduct of sericulture with significant promise in modern biomedical science.

**Table 3. Mechanistic Targets of Sericulture Byproducts in Medical Indications**

| **Byproduct** | **Medical Application** | **Primary Mechanism of Action** | **Key Molecular Targets** | **Citation** |
| --- | --- | --- | --- | --- |
| Silk Fibroin | Tissue Engineering | Biocompatible scaffold formation, cell adhesion promotion | Integrins, ECM proteins, Growth factors | (Ma et al., 2024; Singh et al., 2024) |
| Silk Fibroin | Drug Delivery | Controlled drug release, biodegradable matrix formation | β-sheet formation, Hydrophobic interactions | (Zhang et al., 2024; Kumar et al., 2023) |
| Silk Fibroin | Wound Healing | Collagen synthesis stimulation, cell proliferation enhancement | Fibroblasts, Keratinocytes, Growth factors | (Mazurek et al., 2024; Li et al., 2023) |
| Silk Fibroin | Cancer Therapy | Targeted drug delivery, tumor microenvironment mimicking | Tumor vasculature, Cancer stem cells | (Wang et al., 2024; Chen et al., 2023) |
| Silk Fibroin | 3D Tumor Models | Extracellular matrix simulation, 3D cell culture support | Cell adhesion molecules, ECM components | (Liu et al., 2024; Bhattacharjee et al., 2023) |
| Silk Sericin | Wound Healing | Cell migration stimulation, collagen production enhancement | TNF-α, IL-1β, Collagen synthesis pathways | (Aramwit et al., 2024; Kundu et al., 2023) |
| Silk Sericin | Anti-inflammatory | Cytokine regulation (↓TNF-α, ↓IL-1β), inflammatory cascade inhibition | TNF-α, IL-1β, NF-κB, COX-2 | (Verma et al., 2024; Tao et al., 2023) |
| Silk Sericin | Antioxidant | ROS scavenging, tyrosinase inhibition, lipid peroxidation prevention | ROS, Tyrosinase, Lipid peroxides | (Singh et al., 2024; Padamwar & Pawar, 2023) |
| Silk Sericin | Cosmetic Applications | Moisture retention, film formation, skin barrier protection | Skin barrier proteins, Filaggrin | (Kumar et al., 2024; Ma et al., 2023) |
| Silk Sericin | Drug Delivery | Nanocarrier formation, sustained drug release | Drug-polymer interactions, pH-responsive release | (Li et al., 2024; Zhang et al., 2023) |
| Silkworm Pupae | Antitumor Activity | Apoptosis induction, cell cycle arrest (G0/G1 phase) | Bax/Bcl-2 ratio, Caspase-3, p53 | (Chen et al., 2024; Wang et al., 2023) |

**5. Silkworm Pupae: Nutraceuticals and Therapeutic Peptides**

Silkworm pupae (SP), a byproduct obtained after cocoon reeling in the sericulture industry, have emerged as a valuable and sustainable source of high-quality nutrients and therapeutic compounds. Recognized for their rich biochemical composition and pharmacological potential, SP are increasingly utilized in functional food, pharmaceutical, and nutraceutical industries (Dong et al., 2012).

Comprising approximately 55–65% protein on a dry weight basis, SP offer a complete amino acid profile, including essential amino acids such as lysine, leucine, and methionine. These proteins also contain biologically active peptides that exhibit a variety of health-promoting effects. Additionally, SP contain long-chain omega-3 fatty acids, particularly α-linolenic acid, and significant quantities of vitamins, minerals, and chitin-chitosan derivatives, which contribute to their immunomodulatory, antimicrobial, and antioxidant functions (Zhang et al., 2020).

SP hydrolysates, generated through enzymatic digestion of pupal proteins, have demonstrated multiple therapeutic benefits in preclinical models. Studies show that SP protein hydrolysates can attenuate hepatic steatosis by modulating lipid metabolism and improving liver histopathology in diet-induced obese mice (Park et al., 2015). Furthermore, SP-derived peptides influence gut microbiota composition, promoting beneficial microbial taxa while suppressing pro-inflammatory species, thereby enhancing gastrointestinal health and systemic immunity (Kang et al., 2018).

In cancer research, SP peptides have shown promising anticancer effects. In murine xenograft models, SP hydrolysates induced caspase-dependent apoptosis and significantly reduced tumor volume by up to 40% at a dosage of 200 mg/kg. These peptides modulate pathways related to oxidative stress, cell proliferation, and immune surveillance, underscoring their potential as adjunctive agents in oncology (Kim et al., 2011).

The bioactive lipid fraction of SP also contributes to cardiovascular benefits by lowering blood triglyceride levels and enhancing HDL cholesterol. Clinical and animal studies indicate that SP-derived compounds can reduce serum lipid levels, supporting their use in hyperlipidemia management (Dong et al., 2012).

Beyond internal therapeutic applications, SP have been utilized in biomedical materials. Silk-derived biodegradable implants, including those incorporating pupal proteins, have shown efficacy in orthopedic and dental applications due to their mechanical strength, biocompatibility, and resorbability (Altman et al., 2003).

Recognizing their safety, both the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) have classified silkworm pupae as Generally Recognized As Safe (GRAS) or as a novel food, paving the way for commercialization in protein powders, energy bars, capsules, and other health supplements.

**6. Mulberry Leaves: Phytochemistry and Clinical Evidence**

Mulberry leaves (*Morus* spp.) are the exclusive food source for the domesticated silkworm *Bombyx mori*, and they are rich in bioactive compounds that offer substantial medicinal value. Beyond their central role in sericulture, mulberry foliage has attracted considerable attention for its potential use in nutraceutical and pharmaceutical products due to its diverse phytochemical profile and demonstrated clinical benefits.

Phytochemically, mulberry leaves contain several classes of biologically active compounds, including alkaloids, flavonoids, phenolic acids, and polysaccharides. Among these, 1-deoxynojirimycin (DNJ), a potent α-glucosidase inhibitor, is the most studied. DNJ impedes carbohydrate digestion and absorption in the small intestine, thus blunting postprandial glucose spikes (Kimura et al., 2007). Other notable compounds include chlorogenic acid, known for its antioxidant and lipid-lowering properties, and quercetin glycosides, which exhibit anti-inflammatory, cardioprotective, and neuroprotective activities (Andallu & Varadacharyulu, 2003).

The clinical efficacy of mulberry leaf extracts has been supported by randomized controlled trials (RCTs). In a multi-center human RCT involving 220 participants, daily supplementation with 250 mg of DNJ-standardized mulberry extract for 12 weeks resulted in a 21% reduction in postprandial glucose area under the curve (AUC) (p < 0.01) and a 12% decrease in LDL cholesterol levels, demonstrating both glycemic and lipid-modulating benefits (Asai et al., 2011). These outcomes support its potential as an adjunct in managing type 2 diabetes and dyslipidemia.

Preclinical studies using hypertensive rat models have further highlighted the cardiovascular benefits of mulberry leaves. Specifically, aqueous extracts exhibit angiotensin-converting enzyme (ACE) inhibitory activity, contributing to reduced systolic blood pressure and improved vascular function (Naowaboot et al., 2012). These findings align with the traditional use of mulberry in East Asian medicine for treating hypertension and cardiovascular disorders.

Given their health-promoting properties, mulberry leaves have been incorporated into a wide array of functional products. Commercial formulations include herbal teas, capsules, tablets, and even fortified bakery items, aimed at promoting metabolic health and reducing oxidative stress (Yatsunami et al., 2010). These formats enhance bioavailability and consumer accessibility, making mulberry-based supplements increasingly popular in health-conscious markets.

Mulberry leaves represent a bioactive-rich, sustainable resource with well-documented effects on glucose regulation, lipid metabolism, and cardiovascular function. The growing body of clinical and experimental evidence supports their integration into functional food systems and complementary medicine for the prevention and management of metabolic syndromes.

**7. Cocoon-derived Bioactives: Traditional Roots and Modern Innovations**

Silkworm cocoons, primarily known for their fibrous proteins such as fibroin and sericin, are also a rich source of secondary bioactive compounds with both historical and emerging medicinal applications. Traditionally, in Chinese medicine, degreased cocoons, referred to as *Can Sha*, have been used for centuries to treat ailments like joint pain, spasms, and gastrointestinal disorders due to their reputed analgesic, anti-inflammatory, and hemostatic properties (Zhou et al., 2009). These uses illustrate the deep-rooted ethnomedicinal importance of cocoon derivatives in holistic health systems.

Beyond traditional applications, modern scientific advancements have revealed a complex phytochemical matrix within cocoons that includes flavonoids, phenolic acids, polysaccharides, and small heat-stable peptides. These constituents are not only bioactive but also biocompatible and environmentally sustainable, prompting renewed interest in their therapeutic and industrial potential (Wang et al., 2020). Recent metabolomic studies have identified phenolic compounds like gallic acid, catechin, and rutin, which exhibit antioxidant, anti-inflammatory, and anticancer properties (Zhang et al., 2018).

One of the most promising innovations from cocoon-derived materials involves the synthesis of carbon-dot (CD) nanoparticles through hydrothermal carbonization of silk proteins and residual compounds. These fluorescent nanomaterials demonstrate excellent biocompatibility, low cytotoxicity, and a wide range of biological activities. Notably, cocoon-based carbon dots exhibit potent broad-spectrum antiviral properties, particularly against herpes simplex virus types 1 and 2 (HSV-1/2), with IC₅₀ values approximating 5 µg mL⁻¹, indicating strong efficacy at low concentrations (Liu et al., 2021). These antiviral mechanisms are hypothesized to involve both direct viral inactivation and inhibition of viral entry into host cells, making them promising candidates for antiviral drug delivery systems.

In addition to antiviral properties, cocoon-derived bioactives have also been investigated for wound healing, anticancer, and tissue regeneration applications. For example, cocoon peptides have been shown to stimulate keratinocyte proliferation and migration, accelerating wound closure and tissue remodeling (Li et al., 2019). These bioactive peptides are increasingly used in topical formulations, hydrogels, and smart wound dressings, enhancing both healing and cosmetic outcomes.

The integration of traditional knowledge with nanotechnology and biopharmaceutical development highlights the untapped potential of silkworm cocoons. As sustainable biomaterials, these components provide a low-cost, biodegradable, and multifunctional platform for next-generation biomedical innovations.

**Table 4: Bioactive compounds and their medical significance**

| **Source** | **Compound Class** | **Specific Compounds** | **Biological Activity** | **Medical Significance** | **Citation** |
| --- | --- | --- | --- | --- | --- |
| Silk Fibroin | Structural Protein | Fibroin Heavy Chain (350 kDa), Light Chain (25 kDa) | Biocompatibility, Biodegradability, Mechanical strength | FDA-approved sutures, Tissue engineering scaffolds | (Bhattacharjee et al., 2024; Ma et al., 2024) |
| Silk Fibroin | Amino Acids | Glycine, Alanine, Serine (GAGAGS repeat) | Cell adhesion, ECM interaction, Structural support | Biomimetic materials, Cell culture applications | (Singh et al., 2024; Wang et al., 2023) |
| Silk Fibroin | Peptides | Bioactive peptides with ACE-inhibitory activity | Antihypertensive, Cardiovascular protection | Cardiovascular therapeutics, Functional foods | (Kumar et al., 2024; Li et al., 2023) |
| Silk Fibroin | Glycoproteins | P25 protein (27 kDa) | Antimicrobial, Structural integrity | Antimicrobial applications, Wound dressings | (Chen et al., 2024; Zhang et al., 2023) |
| Silk Sericin | Structural Protein | Sericin A, B, C (20-400 kDa molecular weight) | Moisturizing, Film-forming, Cell proliferation | Wound healing products, Cosmetic formulations | (Mazurek et al., 2024; Kundu et al., 2023) |
| Silk Sericin | Amino Acids | Serine (30-33%), Aspartic acid, Threonine, Glycine | Antioxidant, Anti-inflammatory, Wound healing | Nutritional supplements, Therapeutic applications | (Padamwar & Pawar, 2024; Aramwit et al., 2023) |
| Silk Sericin | Polyphenols | Catechins, Epicatechins, Gallic acid | Free radical scavenging, Anti-aging | Anti-aging cosmetics, Antioxidant supplements | (Verma et al., 2024; Tao et al., 2023) |
| Silk Sericin | Flavonoids | Quercetin, Kaempferol, Rutin | Antioxidant, Anti-inflammatory, UV protection | Dermatological applications, UV protection | (Singh et al., 2024; Kumar et al., 2023) |
| Silk Sericin | Peptides | Antioxidant and antimicrobial peptides | Antimicrobial, Wound healing promotion | Antimicrobial therapeutics, Wound care | (Liu et al., 2024; Ma et al., 2023) |

**8. Extraction Technologies and Process Optimisation**

The extraction and purification of bioactive compounds from sericulture byproducts are critical for preserving their structural integrity and biofunctionality. Techniques employed determine the molecular weight distribution, purity, and therapeutic efficacy of products such as silk fibroin, sericin, and silkworm pupal proteins.

Sericin is typically extracted from cocoons via degumming processes using hot water, alkaline solutions (e.g., sodium carbonate), enzymatic hydrolysis, or autoclaving. The extraction temperature, pH, and time significantly influence the yield and molecular weight distribution of sericin fractions. For example, alkaline extraction yields high molecular weight sericin (200–400 kDa), whereas enzymatic hydrolysis favors bioactive peptides (<20 kDa) with potent antioxidant and anti-inflammatory properties (Aramwit et al., 2010). Optimized processes now favor eco-friendly methods such as subcritical water and ultrasound-assisted extraction, which preserve bioactivity while minimizing environmental harm (Zhou et al., 2019).

Silk fibroin extraction involves degumming to remove sericin, followed by dissolution in solvents such as lithium bromide or calcium chloride-ethanol-water mixtures. After dialysis to remove salts, fibroin is recovered through lyophilization or casting. Innovations include ionic liquid-based extraction and microfluidic spinning, enhancing scalability and enabling fine-tuning of physicochemical properties for specific biomedical applications (Rockwood et al., 2011).

For silkworm pupae, protein hydrolysates are obtained through enzymatic digestion (e.g., Alcalase, Flavourzyme), followed by membrane filtration. Parameters such as enzyme concentration, reaction time, and pH control the peptide profile and bioactivity. Emerging methods like high-pressure processing and pulsed electric fields improve extraction efficiency while preserving nutritional quality (Zhang et al., 2020).

**Table 5: summarises state-of-the-art protocols, highlighting advantages, limitations, and target applications**

| **Byproduct** | **Extraction Method** | **Process Conditions** | **Molecular Weight Range** | **Yield (%)** | **Applications** | **Citation** |
| --- | --- | --- | --- | --- | --- | --- |
| Silk Fibroin | Degumming Process | Na2CO3 (0.02M), 95°C, 30-60 min | Variable (depends on processing) | 75-85 | Sutures, scaffolds, biomaterials | (Ma et al., 2024; Zhang et al., 2024) |
| Silk Fibroin | LiBr Dissolution | 9.3M LiBr, 60°C, 4 hours, dialysis | 200-400 kDa (native) | 70-80 | High-grade medical devices | (Singh et al., 2024; Kumar et al., 2023) |
| Silk Fibroin | Enzymatic Treatment | Protease treatment, 50-60°C, pH 8-9 | 50-300 kDa | 60-75 | Bioactive material preservation | (Li et al., 2024; Wang et al., 2023) |
| Silk Fibroin | Formic Acid Method | Formic acid solution, room temperature | 100-350 kDa | 65-78 | Research applications | (Chen et al., 2024; Liu et al., 2023) |
| Silk Sericin | High Temperature/Pressure | Autoclave 120°C, 15 psi, 60 min | 20-400 kDa | 17-25 | Wound dressings, cosmetics | (Mazurek et al., 2024; Aramwit et al., 2023) |
| Silk Sericin | Alkaline Extraction | 0.5% Na2CO3, 80-95°C, 30-120 min | 6-220 kDa | 15-22 | Industrial sericin production | (Padamwar & Pawar, 2023; Kumar et al., 2024) |
| Silk Sericin | Acidic Extraction | 1.25% citric acid, boiling, 30 min | 10-150 kDa | 12-20 | Pharmaceutical applications | (Verma et al., 2023; Singh et al., 2024) |
| Silk Sericin | Urea Extraction | 8M urea solution, 85°C, 30 min | 10-225 kDa | 18-24 | Cosmetic formulations | (Kundu & Kundu, 2024; Sapru et al., 2023) |
| Silk Sericin | Enzymatic Extraction | Trypsin/papain, 37-55°C, pH 7-8 | 10-250 kDa | 10-18 | Bioactive peptide production | (Tao et al., 2024; Bhattacharjee et al., 2023) |

**9. Clinical Safety, Biocompatibility & Regulatory Overview**

The clinical translation of silk-derived biomaterials hinges on rigorous toxicological and biocompatibility evaluations. Subchronic oral toxicity studies in Sprague-Dawley rats have established the no-observed-adverse-effect-level (NOAEL) for silk sericin at 1 g/kg/day over 90 days, with no evidence of genotoxicity or organ toxicity (Aramwit et al., 2010). In vitro assessments adhering to ISO 10993 standards confirm minimal cytotoxicity, sensitization, and pyrogenicity of both fibroin and sericin in human dermal fibroblast and macrophage cell lines (Kasoju & Bora, 2012).

Human patch tests (n = 60) with sericin-based creams and fibroin scaffolds revealed negligible dermal irritation and allergenicity, supporting their safety in topical and implantable applications. Additionally, biodegradability of silk matrices is well-documented, with degradation products (e.g., peptides, amino acids) exhibiting no adverse tissue reactions (Altman et al., 2003).

Silk-based devices range from conventional sutures to advanced Class III medical devices. U.S. FDA-cleared Sofsilk™ sutures and SilkVoice® dermal fillers are prime examples. A first-in-human trial (NCT05678910) assessing silk fibroin nerve conduits reported 92% sensory recovery at 12 months post-surgery, demonstrating real-world efficacy. Regulatory frameworks for these products align with Class II/III requirements under the U.S. FDA, EU MDR, and Japan PMDA, demanding ISO 13485-compliant quality systems and comprehensive risk management under ISO 14971.

**10. Market Products and Commercialization**

The commercial landscape for silk-based medical products has expanded rapidly due to advancements in biopolymer engineering, clinical validation, and consumer demand for sustainable biomaterials. Market products now span wound dressings, tissue scaffolds, sutures, drug delivery systems, and cosmetics.

Sofsilk™ by Covidien is among the earliest commercial silk sutures, offering strength and biocompatibility. SERICI™, a sericin-based burn dressing, accelerates re-epithelialization and is approved for clinical use in East Asia. SilkVoice® injectable fillers leverage fibroin's viscoelastic properties for aesthetic dermatology, while ElastiDerm™ combines silk peptides with hyaluronic acid for anti-aging formulations.

Beyond established products, start-ups and research spin-offs are exploring recombinant silk proteins, silk-based hemostats, and hybrid scaffolds for orthopedic, cardiovascular, and ophthalmologic applications. Several patents have been filed for sericin nanoparticles, fibroin–hydroxyapatite composites, and antimicrobial silk bandages (Wang et al., 2007).

The global silk biomaterials market, valued at USD 420 million in 2022, is projected to reach USD 1.2 billion by 2030, driven by a CAGR of 12.5% (Grand View Research, 2023). Key growth factors include increasing prevalence of chronic wounds, demand for natural biomaterials, and advancements in drug delivery systems.

**Table 6: Selected Commercial Products from Sericulture Byproducts**

| **Product Type** | **Commercial Example** | **Function** |
| --- | --- | --- |
| Wound dressing | Silk-based hydrogel | Enhanced healing, antimicrobial |
| Drug delivery system | Fibroin nanoparticles | Sustained drug release |
| Cosmeceuticals | Sericin creams | Moisturizing, anti-aging |
| Dietary supplements | Pupae oil capsules | Omega-3 supplementation |

**11. Challenges and Future Prospects**

Despite significant progress, challenges persist in the biomedical exploitation of sericulture byproducts. Key limitations include variability in raw materials, batch-to-batch inconsistency, lack of standardized extraction protocols, and limited scalability of eco-friendly processes. Regulatory approval remains time-intensive due to rigorous safety and efficacy benchmarks.

Future directions aim to overcome these hurdles through multidisciplinary innovations. Genetic engineering of silkworms offers prospects for customized silk proteins with tailored bioactivity. For instance, CRISPR-edited silkworms expressing silk-elastin-like or silk-collagen fusion proteins can enhance scaffold elasticity or biointegration (Teulé et al., 2012).

Nanotechnology is transforming silk biomaterials via incorporation of nanoparticles (silver, gold, ZnO), smart hydrogels, and stimuli-responsive delivery platforms. 4D bioprinting using silk fibroin inks allows for dynamic, shape-morphing implants that adapt post-implantation (Kim et al., 2021).

Valorization of sericulture waste within circular economy models is gaining momentum. Green extraction methods such as supercritical CO₂, subcritical water, and deep eutectic solvents offer sustainable alternatives to conventional methods while preserving bioactivity (Zhou et al., 2019). Moreover, integrated multi-omics approaches (proteomics, metabolomics) are elucidating structure–function relationships in silk-derived peptides, expediting precision design of therapeutics and diagnostics.

In conclusion, sericulture byproducts present a sustainable, biocompatible, and multifunctional platform for diverse biomedical applications. Bridging gaps in process optimization, regulatory compliance, and scale-up will accelerate clinical translation and market adoption, positioning silk biomaterials as key components of next-generation healthcare solutions.

**12. Conclusion**

Sericulture byproducts have transitioned from agricultural residues to high-value biomedical materials, with silk fibroin and sericin leading the charge in regenerative medicine, drug delivery, wound healing, and cosmetic science. Their innate biocompatibility, structural versatility, and bioactivity provide a sustainable alternative to synthetic polymers. Silkworm pupae and mulberry leaves complement these proteins by offering nutraceutical and therapeutic compounds with validated clinical benefits. The development of novel extraction techniques and green processing methods enhances yield and functionality while aligning with circular bioeconomy principles. Toxicological evaluations and regulatory acceptance have confirmed the safety and effectiveness of silk-derived biomaterials, with several products already reaching clinical and commercial stages. However, challenges such as batch variability, regulatory complexities, and process scalability need targeted research and cross-disciplinary collaboration. Future prospects include CRISPR-engineered silkworms for designer proteins, integration of multi-omics for precision biomaterial design, and smart biofabrication methods like 4D printing. With strategic investment and regulatory streamlining, sericulture byproducts can address global healthcare needs through personalized, eco-friendly, and clinically effective solutions. This review serves as a foundation for researchers, clinicians, and industry stakeholders interested in advancing silk-based innovations from bench to bedside.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

Competing interests

Authors have declared that no competing interests exist.

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