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Sericin coats of silk fibres, a degumming waste or future material?

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ABSTRACT

Silk is a fibrous biopolymer with a recorded history in the textile industries for centuries. This fibre is constituted of two different proteins: fibroin and sericin, of which the latter accounting for approximately 20–30 % of the silk mass. Silk sericin (SSER) was previously considered as a waste by-product in silk fibroin extraction. SSER has recently garnered significant scientific interest due to its extensive biological and pharmacological properties. These include antioxidant effects, biocompatibility, low immunogenicity, controlled biodegradability, and the ability to induce cell proliferation. This review covers studies about various aspects of this emerging material, namely, its general morphology, specific structure, molecular weight, features of different layers, and gene sequences. The impact of different extraction methods and the application of extracted SSER based on molecular weight are discussed. Additionally, the characteristic functional groups in the amino acids of sericin facilitate its applications in regenerative medicine, wound healing, drug delivery, textile, environment, and energy, in various forms like hydrogels, films, scaffolds, and conduits. SSER-based materials offer great potentials for multi-functional applications in the upcoming decades, showcasing adaptability for various functional uses and promising future technological advancements.

1. Introduction

Silk, a natural protein fibre, is produced by insects, such as silkworms, spiders, flies, mites, scorpions, and bees [1–3]. These silk fibres have various functions, such as forming cocoons, capturing prey, and constructing webs. The varying amino acid sequences in silk proteins dictate the fibre's structure and function [4]. Among the various forms of silk, cocoon is the most widely utilized. Silk cocoons are produced by either mulberry silkworm, *Bombyx mori* (Bombycidae), or non-mulberry silkworm, *Antheraea assamensis* (Saturniidae) [5]. Silk cocoons are primarily composed of fibroin (70–80 %), and sericin (20–30 %), along with other minor constituents. Generally, the majority of silk cocoons are white, as shown in Fig. 1 (a), and some cocoons present colourful surfaces because of a mixture of impurities [6]. Silk fibroin (SF) is a fibrous protein in the form of a delicate twin threads, linked by disulphide bonds and enveloped by three successive sticky layers of sericin, as shown in Fig. 1 (b), and has been applied for a variety of areas [7–9].

In silk textile industry, cocoons are processed in aqueous solutions to remove the sericin or gum from the silk yarn to improve the sheen, colour, and texture of the silk, which is generally known as degumming. During the degumming process, the insoluble SF is retained while the soluble silk sericin (SSER) and other soluble ingredients are discarded as wastes. However, SSER has recently been utilized in various applications owing to its unique properties. SSER is a water-soluble, glue-like protein with strong polar functional groups, such as carboxyl, hydroxyl, and amino groups, which make SSER readily soluble in water [5,10]. Besides, SSER molecule holds free radical scavenging potential, anti-tyrosinase and antioxidant activities [11]. It has been employed for multiple applications, such as bio-imaging, drug delivery, wound healing, osteogenic differentiation, cartilage regeneration, gut repair, sperm cryopreservation, nonwoven fabric, adsorption of toxic ions, biosensing, and flexible micro-optics.

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Table 1 provides an overview of various applications of SSER, showing the molecular weight (MW) and the associated extraction methods. The extraction conditions, such as temperature and solution acidity significantly affect the MW of SSER. Moreover, SSER has multiple functional groups, which allow it to be modified with other functional groups, such as methacrylic group, making it 3D printable [12]. Recent research has explored the use of SSER for bioprinting via volumetric additive manufacturing methods, making SSER-based materials suitable for expanded applications in biomedicine [13].

SF has been discussed in great detail in previous reviews [1,9,171,172]. In contrast, SSER, a by-product of SF extraction from silk cocoon, has gradually attracted researchers' interest due to its unique characteristics that are absent in SF. The number of research papers on the SSER published over the past 23 years is shown in Fig. 2 (a). It shows a steady increase in publications from 2021 onwards, with an approximate annual increase of 25 %. The research output on SSER is comparable to other commonly used biomaterials, namely, SF, polyethylene glycol diacrylate (PEGDA), and gelatine methacrylate (GelMA) (Fig. 2 (b)) [173–176]. Although some recent reviews on SSER have been published, they primarily focus on its biomedical applications [6,12,177–181]. As a macromolecule, SSER has a variety of applications beyond biomedicine. Hence, this review aims to provide a comprehensive overview to cover all aspects of SSER and its utilizations.

In this review, major databases (PubMed, Web of Science, Scopus, and ClinicalTrials.gov) were searched using keywords of silk sericin and sericin to find relevant articles published from 2015 to 2023. To filter all relevant articles, we first remove duplicates from database. Furthermore, we excluded review articles, patents, conference abstracts, dissertations, articles in non-English languages, containing low-quality data or from inaccessible sources, papers not peer-reviewed, and those outside the scope of this review. Initially 2697 studies have been found. After applying the criteria, as shown in Scheme 1, we refined the selection to 226 studies. In the first step, we summarized the extraction of sericin, its composition and characteristics. Then we discussed its applications in tissue regeneration, wound healing, drug delivery, adsorption, energy, and other non-medical areas. Finally, we discussed the future directions and our perspectives on this emerging material.

2. Extraction of SSER

A single fibre of silk is composed of fibroin (the inner layer) and a cover of sericin (the outer layer), as shown in Fig. 1 (b). The general degumming process to isolate SSER from silk cocoons comprising the following steps as illustrated in Fig. 1 (c). First, the silk cocoons are cut into pieces. Next, they are boiled in hot water or alkaline solution to separate SSER and insoluble SF with continuous stirring. Then, the SSER solution is centrifuged to remove impurities. Lastly, the solution is dialyzed against deionised water and lyophilized to get SSER powder [5,183].

There are also other methods to extract SSER, for example, alkaline extraction, boiling in aqueous urea solution, acid extraction, and genetically engineered self-degumming cocoons [184–186]. Among the SSER extraction methods, boiling in water is the simplest and most cost effective. This approach avoids the introduction of impurities, hence obtaining high purity SSER, and preserving its biological properties. However, this method is limited to extracting only the outermost layer of SSER. To extract the second layer of SSER, increasing the temperature and pressure via autoclave is needed. For the extraction of the innermost layer, weak acid and alkali solutions are employed. While these solutions can quickly extract all three layers of SSER, the limitation is that they will damage the molecular chain of SSER, leading to degradation and potential alteration of its physiochemical properties. Alternatively, extracting SSER in a neutral salt solution (e.g., BrLi) at low temperature can preserve the molecular chain of SSER, which may maintain the original properties of the SSER protein. However, this method is costly and requires proper waste liquid treatment to prevent environmental pollution. The advantages and disadvantages of different methods of SSER extraction have been summarized in Table 2. SSER can also be recovered from wastewater of the textile processing. Through neutralization of the degumming solution with acids, calcium ions in the degumming solution can be precipitated, which can be used as a fertilizer to avert environmental pollution [187,188].

3. Molecular structure of SSER

SSER is composed of three layers, namely, inner layer, middle layer, and outer layer, as shown in Fig. 1 (b) [3,182]. The outer layer of SSER is produced by the anterior cells of the middle silk gland of the silkworm,

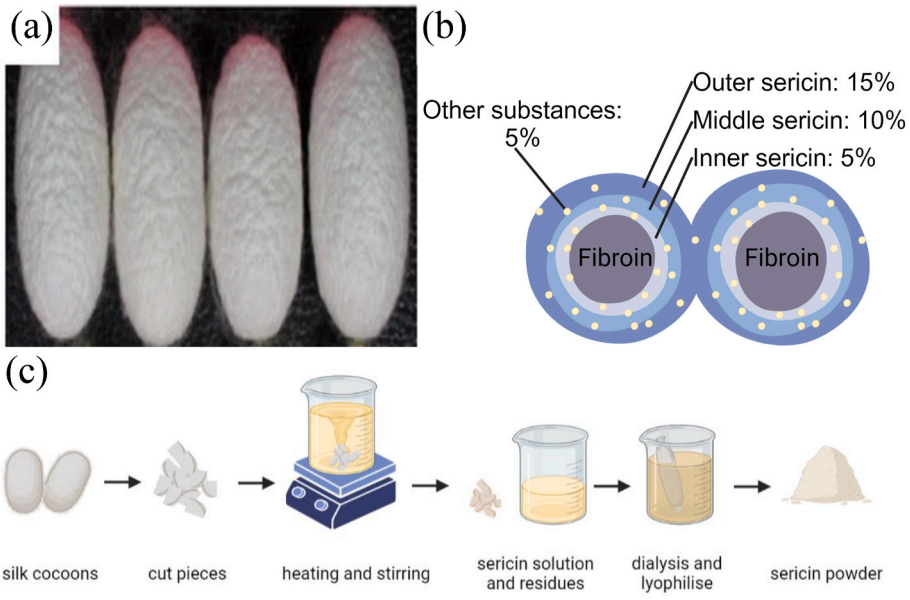


Fig. 1. (a) The physical morphology of a typical silk cocoon. Reproduced with permission [6] Copyright 2015, Elsevier B.V.; (b) The weight percentage of 3 SSER layers [6,182]; (c) A schematic diagram to show the common methods to extract SSER from silk cocoons in the lab [5].

Table 1
Applications of SSER with different extraction methods and MW.

MW (kDa)	Extraction Method	Applications	References
Antheraea pernyi			
>10	Water at 120 °C	Skin regeneration	[14,15]
		Osteogenic differentiation	[16,17]
>5	0.02 M Na_2CO_3	Antibacterial	[18]
Antheraea mylitta			
–	1 % ascorbic acid	Skin carcinoma therapy	[19]
Bombyx mori			
>10	Water at 120 °C	Wound healing	[11, 20–29]
		Antioxidant	[25,30,31]
		Biocomposites and fibres	[32,33]
		Drug carrier	[25, 34–41]
		Drug discovery	[42]
		UV protection	[43,44]
		Antibacterial	[43, 45–49]
		Cosmetics	[50,51]
		Angiogenesis	[52]
		Intervertebral disk regeneration	[53]
		Heavy ions absorption	[54–60]
		Electrode modification	[61]
		Bone regeneration	[62,63]
		Cell proliferation	[64]
		Surfactants	[65]
>30	Water at 100 °C	Seed cover	[66]
		Biocomposites	[67–72]
		Myocardial infarction therapy	[73]
		Bone repair	[74,75]
		Bio-absorption	[76]
		Electrode modification	[77,78]
		Textile	[79]
>30	Water at 80 °C	Osteogenic differentiation	[80]
		Drug carrier	[81]
		Sensors	[82]
>5	0.02 M Na_2CO_3	Cartilage repair	[83,84]
		Biocomposites	[85–87]
		Wound healing	[88–90]
		Drug delivery	[91]
		Haemostasis	[92]
		Cell Proliferation	[93,94]
		Antibacterial	[95]
		Electrodes modification	[96]
		Bioink	[13]
		Cryopreservation	[97]
>5	0.1 M Na_2CO_3	Drug carrier	[98]
>5	0.5 M Na_2CO_3	UV protection	[99]
		Wound healing	[100]
		Antioxidant	[101]
>5	0.2 % Na_2CO_3	Biocomposites	[102,103]
		Bone regeneration	[104]
–	0.5 % $NaHCO_3$	Carbon dots	[105]
		Wound healing	[106]
>5	1 % K_2CO_3	Flexible electronics	[107]
>100	LiBr at 35 °C	Regenerate nerve	[108,109]
		Antiviral	[110]
		Myocardial repair	[111]
		Electrodes	[112]
–	0.04 M citric acid	UV photodetectors	[113]
>5	3 wt% citric acid	Bioimaging	[114]
>10	8M urea 50 mM Tris	Drug carrier	[115]
≤20	0.025 % Ca $(OH)_2$	Antioxidant	[116–119]
Commercial SSER powder			
250	–	Small drug particle absorption	[120]
>200	–	Cryopreservation	[121]
130	–	Biocomposites	[122–124]
15–70	–	Electrodes modification	[125]
		Drug carrier	[126–129]
20–30	–	Anode materials	[130,131]
8–20	–	Antioxidant	[132–134]
–	–	Food cover	[135,136]
		Cryopreservation	[137]
		Biocomposites	[138–144]

Table 1 (*continued*)

MW (kDa)	Extraction Method	Applications	References
		Bone regeneration	[145]
		Wound healing	[146]
		Antioxidant	[147]
		Drugs carrier	[148–151]
		Haemodialysis	[152]
		Advanced textiles	[153]
		Ion absorption	[154–157]
		Biosorption	[158]
		Electrocatalysts	[159,160]
		Electrodes modification	[161,162]
		Microwave absorption	[163]
		Flexible biosensors	[164–167]
		Flexible electronics	[168]
		Probiotic coating	[169]
		Angiotensin enzyme inhibitor	[170]

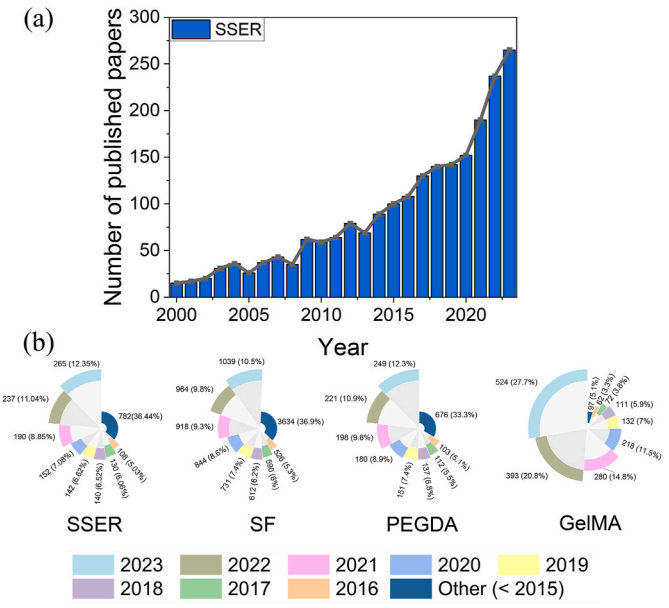
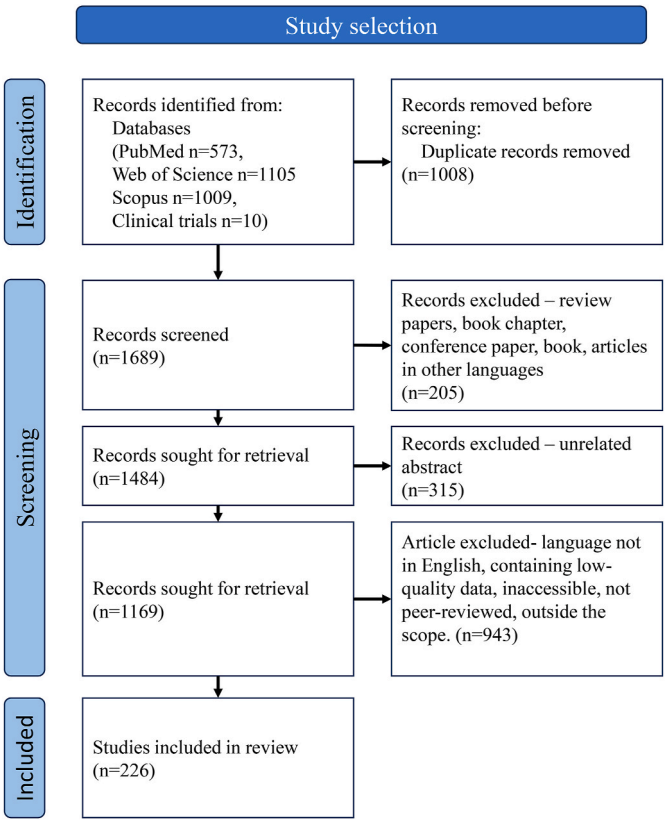


Fig. 2. (a) The publication trend of SSER research from year 2000–2023. (b) The number and percentage of published papers of four representative biomaterials: SSER, SF, PEGDA and GelMA. The data were obtained by searching in Scopus from 2000 to 2023.

while the inner layer is secreted by the posterior cells of the gland [6]. The inner, middle and outer layers approximately account for 15 %, 10.5 %, and 4.5 % of the total silk fibre mass, respectively [6,184]. The outer layer, as the most water-soluble layer, has a higher MW (>30 kDa). It can be extracted by boiling in sufficient water at 100 °C for 1 h. The resulting solution is then frozen at −20 °C overnight and lyophilized to obtain the outer layer SER powder. The remaining insoluble residue can be placed in a high-pressure boiler at 120 °C for 1 h to extract the middle layer into the water, which has a relatively lower MW than the outer layer. The SSER powder from the middle layer can be obtained using the same method above. The inner layer, adjacent to the silk fibroin filament, has a higher β-sheet structural content and exhibits greater thermal stability. After the degumming process, this layer can be extracted in a sodium carbonate solution by boiling at 100 °C for 30 min [184,189,190].

The MW of SSER can be affected by the extraction methods, which dictate its characteristics [185]. As presented in Fig. 3 (a), the range of MW values of SSER was broadened, and the peak value gradually decreased due to the hydrolytic decomposition of SSER in the longer boiling process. Fig. 3 (b) shows that, with increasing MW, the viscosity of sericin solution, gel-sol transition temperature, mechanical strength,



Scheme 1. Flow chart of retrieved and selected articles during this review.

Table 2
The advantages of different extraction methods of SSER.

Extraction Method	Advantages	Disadvantage	Reference
Water at 120 °C	• High purity • Minimize contamination • Sterilization • No chemical residue	• 3rd layer not removed • Autoclave required	[25,30,31]
Water at 80 °C or 100 °C	• Easy to perform • Preserve the bioactivity • Cost effective • No chemical residue	• 2nd and 3rd layers unremoved	[74,75,81]
Weak alkaline solution (e.g. Na_2CO_3)	• High yield • Efficient removal	• Cause SSER degraded • Chemical residue	[13,88–91]
Strong alkaline solution (e.g. Ca $(OH)_2$)	• High yield • Efficient removal • Short extraction time	• Significant degradation • Chemical residue	[116–119]
Weak acidic solution (e.g. citric acid)	• Environmentally friendly • High yield	• Chemical residue	[114]
Salt solution (e.g. LiBr)	• Mild condition • Maintain native properties • Selectively extraction	• Some irons might cause water pollution • Expensive	[108,109, 111]

and extension rate of the sericin film increase, while the porosity and swelling ratio decrease [191,192]. Although the MW values of SSER extracted via different methods vary, their amino acid sequences show no significant differences.

The main components of SSER have been tested using gas chromatography-mass spectrometry (GS-MS) as illustrated in Fig. 4 (a) acetamide (15.5 %); oxime-, methoxy-phenyl- (40.8 %); 2-piperidinone (9.8 %); 3-aminopiperidin-2-one (3.5 %); phenol, -4-(2-aminoethyl)- (10.4 %) and pyrrolo [1,2-a]pyrazine-1,4-dione, and hexahydro-(3.5 %). The components with different proportions contribute to colour, smell, and mechanical properties of SSER [11]. In the Fourier transform infrared (FTIR) spectrum, the random coils were represented by the amide II and amide I peaks at 1512–1519 and 1633-1639 cm^{-1}, respectively. Amide I absorption primarily represents the C=O stretching vibration. Amide II absorption contains N-H bending and C-N stretching vibrations; amide III arises mainly from the C-N stretching vibration coupled with N-H in-plane bending vibration, presenting β-sheets structure at 1236-1240 cm^{-1}, as shown in Fig. 4 (b) [20,68, 193].

4. Biosynthesis of sericin

Typically, cocoons of *B. mori* and *A. yamamai* are the most used. Five sericin genes have been identified in *B. mori*, among which Ser1 and Ser3 mainly code sericin protein in cocoon silks, while Ser2, Ser4 and Ser5 largely regulate sericin synthesis in non-cocoon silks [194–196]. The non-cocoon silk normally has more β-sheet structure than that in cocoon silk, which provides better mechanical properties [196]. Additionally, five sericin genes have been identified in *A. yamamai*. However, the function of these genes has not been studied in detail [197]. A typical *B. mori* SSER gene sequence is shown in Fig. 5 (a). The blue and red letters represent hydrophilic and hydrophobic amino acids, respectively, with a ratio of about 70 %–30 % confirming the high hydrophilicity of the SSER [107]. The amount of hydrophobic amino acids gradually decreases from the inner to the outer layer, making the outer layer more water-soluble than the other two layers. Representative amino acids with different functional groups in their side chains are shown in Fig. 5 (b). The sequence of amino acids determines the function of the protein. For example, Ser4-rp1 is hydrophilic and rich in charged amino acids, while Ser4-rp2 is relatively hydrophobic and rich in alanine and glycine [196]. Moreover, carbon, nitrogen, and oxygen elements in SSER account for 55 %, 16 %, and 28 % of the mass, respectively [105].

To acquire non-contaminated SSER, the deoxyribonucleic acid (DNA) of SSER can be amplified and ligated with other protein sequences, like cecropin B in a plasmid. The plasmid can be transfected into bacterial cells such as *Escherichia coli*, and both SSER and SSER-cecropin proteins are expressed and properly folded in these bacterial cells. The proteins can be refined by using resin to obtain pure SSER or SSER-cecropin B protein. Compared with SSER extracted from cocoons, the recombinant SSER is purer and free from heavy metal contaminations [198].

5. Molecular modification of SSER

5.1. SSER hydrophilicity

SSER has poor mechanical strength and is highly hydrophilic because of its high content of hydrophilic amino acids such as serine (35 %) and threonine (10 %) [199]. The hydrophilicity of sericin has limited its applications in biomedical fields; therefore sericin has been modified to achieve higher hydrophobicity. For example, sericin was bound to the hydroxyl group of cholesterol to form amphiphilic macromolecular conjugation. The conjugates can form micelles in aqueous solutions to encapsulate drug molecules [200]. In another example, SSER was covalently bound with phenolic compounds, which increased its thermal stability and surface hydrophobicity [201].

To improve the mechanical strength of SSER, Hidetoshi and colleagues [193] tested SSER films in ethanol as shown in Fig. 6 (a). When immersed in ethanol, sericin aggregated into an oriented structure owing to the strong hydrogen bonds among extended polymer chains [199,202]. The aggregated SSER became less hydrophilic, which

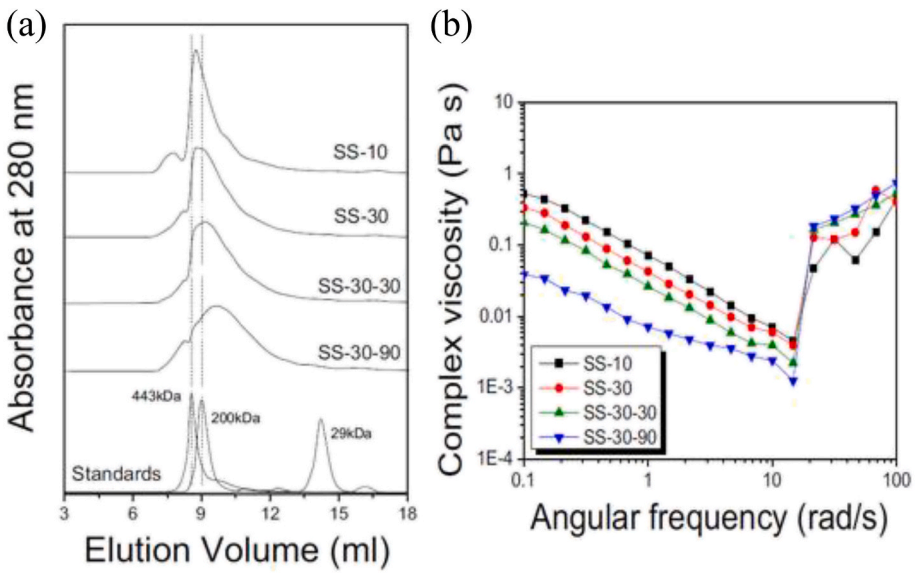


Fig. 3. (a) MW of SSER obtained by different extraction conditions via gel permeation chromatography; (b) The complex viscosities of 0.3 % (w/w) SSER solutions in formic acid. The numbers following the SSER denotes the durations of treating the silk cocoons with hot water (120 °C) in minutes and in one and two steps extraction processes. Reproduced with permission [191]. Copyright 2018, Elsevier B.V.

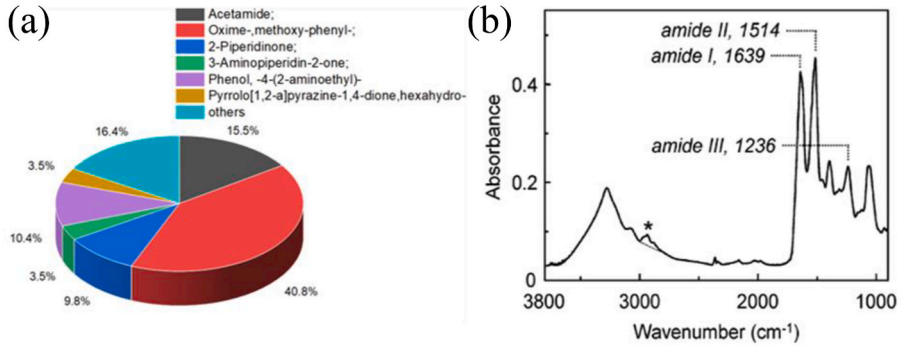


Fig. 4. (a) Proportion of each component in sericin. Reproduced with permission [11]. Copyright 2019, SAGE Publications; (b) Fourier transform infrared spectroscopy – attenuated total reflectance (FTIR–ATR) spectrum of SSER. Reproduced with permission [193]. Copyright 2005, American Chemical Society.

prevents it from dissolving quickly in water.

5.2. SSER biocomposites

SSER can be combined with other materials to create biocomposites, thereby enhancing its poor mechanical strength, functionality, and cell attachment properties [32,33,139,140,203,204]. For example, incorporating SF with SSER to fabricate scaffolds can impart good shape recovery and fatigue resistance properties [204]. During the fabrication of SSER-SF biocomposites, water induces the amorphous molecules to form a β-sheet structure, improving their mechanical properties [87]. Increasing the concentration of SSER in these scaffolds enhances Young's modulus, compressive strength, and degradation rate [205]. Additionally, self-healing properties of the SSER-based biocomposites can be achieved via evaporation induction (Fig. 6 (b)) [139]. Besides, SSER has been copolymerized with various monomers to form new biocomposites for biomedical applications. These include copolymerization with lactide monomer [206], vinyl monomer [102], and cellulose [207,208]. However, it is important to note that the introduction of SSER into biocomposites may cause inflammation potentially.

6. SSER hydrogels

SSER hydrogel is a 3D porosity structure that can swell in the water and support cell matrix by providing a suitable microenvironment [111]. SSER hydrogels are renowned for their biocompatibility, biodegradability, excellent moisturizing properties, and unique physicochemical properties, offering remarkable potential across biomedical applications such as wound healing, tissue engineering, and drug delivery systems. Sericin is a water-soluble material since it has a large amount of polar functional groups in its molecular structure, but it is challenging to make sericin hydrogel without using additional materials or molecular modifications [37].

For instance, Xie et al. used pristine SSER and SF as bioink to form 3D structures via volumetric additive manufacturing, as shown in Fig. 7 (a) [193]. Hydrogels made from SSER with chemical crosslinking agents can cause side effects related to the toxicity of chemical residues in the scaffold. To address the issue, a physical method for preparing sericin hydrogel using ultrasonication was reported, which can enhance the mechanical properties of sericin by β-sheet crystallisation and maintain both the transparency and flexibility of SSER [209].

Due to the presence of several hydroxyl and amino groups, SSER molecules can be modified into a photocrosslinkable macromer using methacrylic anhydride, as illustrated in Fig. 7 (b) [83,142,210]. SerMA

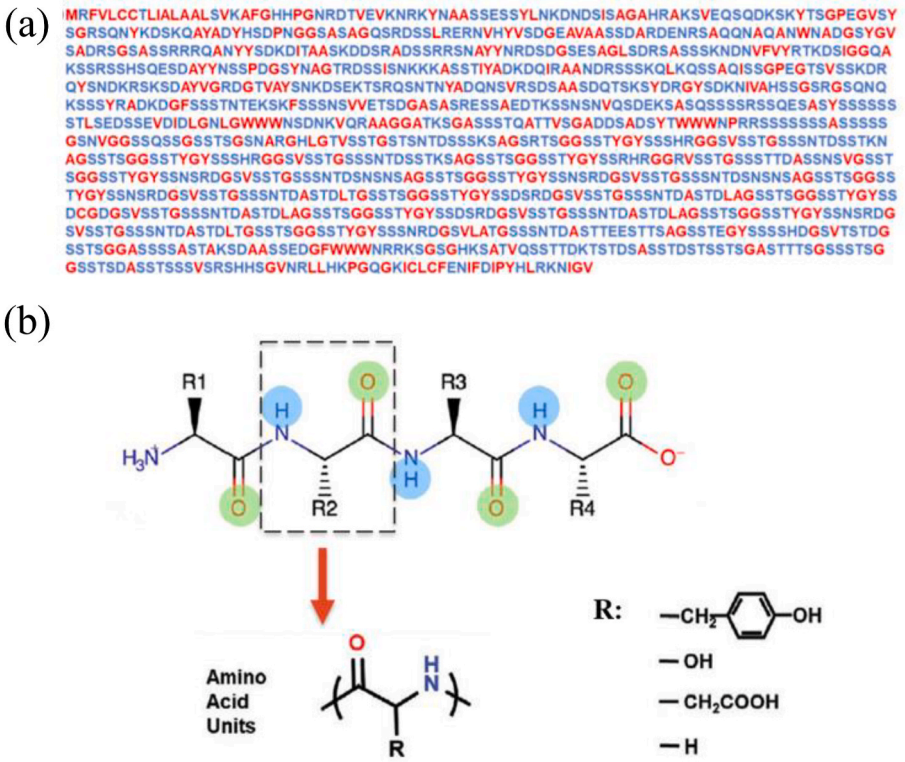


Fig. 5. (a) The sequence of a typical kind of the sericin gene (SER1). Blue and red letters refer to the hydrophilic and hydrophobic amino acids, respectively. Reproduced with permission [107]. Copyright 2020, WILEY-VCH Verlag GmbH & Co.; (b) The molecular chain of SSER and representative functional groups in repeated amino acid units. Reproduced with permission [66,107]. Copyright 2020, WILEY-VCH Verlag GmbH & Co and Springer Science Business Media. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

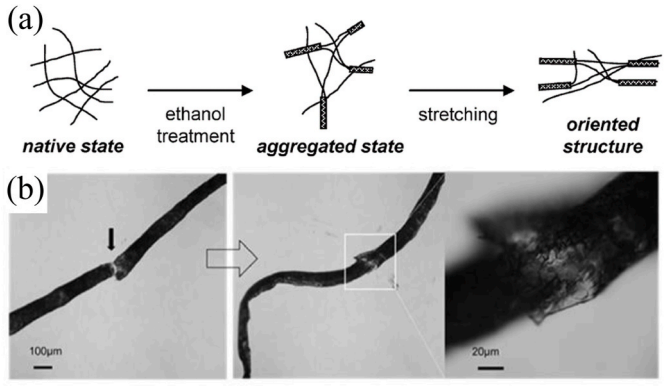


Fig. 6. (a) Schematic representation of the SSER molecular chain getting aggregated and then oriented upon treatment with ethanol. Reproduced with permission [193] Copyright 2005 American Chemical Society.; (b) Self-healing properties of cyclo-FF/SSER composite fibres. Reproduced with permission [139]. Copyright 2021, American Chemical Society.

can be rapidly photo-polymerized to form a hydrogel with negligible immunogenicity while keeping its antibacterial ability. Network density and mechanical properties of the hydrogel can be tuned by optimizing methacrylic substitution degree to accommodate various requirements of tissue engineering [83,90,142]. An injectable hydrogel based on SerMA was formulated to deliver human umbilical cord mesenchymal stem cells to promote angiogenesis and recover fertility [94]. Compared to polyethylene glycol (PEG) hydrogel, SerMA hydrogel caused fewer foreign-body responses [142,143].

Most of the hydrogels are not trackable *in vivo,* which poses challenges to monitor them after implantation. A standard method to detect a hydrogel is to introduce fluorescence dyes, which bring cytotoxicity and other potential impairments [211]. Sericin has intrinsic photoluminescent property in 280–600 nm, which makes it trackable without using fluorescence dyes [212,213]. The stable fluorescence and biocompatibility of SSER enable *in vivo* tracking besides controlled drug release for site-specific cancer therapy [91]. In a recent study, an injectable sericin scaffold was developed to repair stroke-affected brain in an animal model. The fluorescent sericin material allows for real-time monitoring of the scaffold [214].

7. Protective effect of SSER for skin

SS can induce the paracrine production of cells, including vascular endothelial growth factor A (VEGFA), nerve growth factor (NGF), lactic acid, pro- and anti-inflammatory factors to regulate the biological process by promoting the metabolic switch of cells to glycolysis. These paracrine productions can enhance cell proliferation, migration, vascularisation, and mild inflammatory activation for wound healing and skin regeneration [215]. As a result, it can offer protective effect over skin.

Traditional wound dressings provide antioxidant, haemostatic, and antimicrobial functions, but the visualization of wounds is rarely studied. Fig. 7 (c) illustrated an SSER methacrylic gelatine (SSER-GelMA) based transparent film [216]. Using the film, wound healing process can be observed without disturbing the tissue.

SerMA hydrogel was also employed for the full-thickness skin injuries promoting scarless wound healing with regeneration of hair follicles and sebaceous glands. The underlying repair mechanisms include inflammatory inhibition, angiogenesis stimulation, growth factor regulation, and recruitment of mesenchymal cells for skin appendage regeneration [217]. For example, a newly developed SerMA-based hydrogel incorporated silver ions was utilized for wound healing [92].

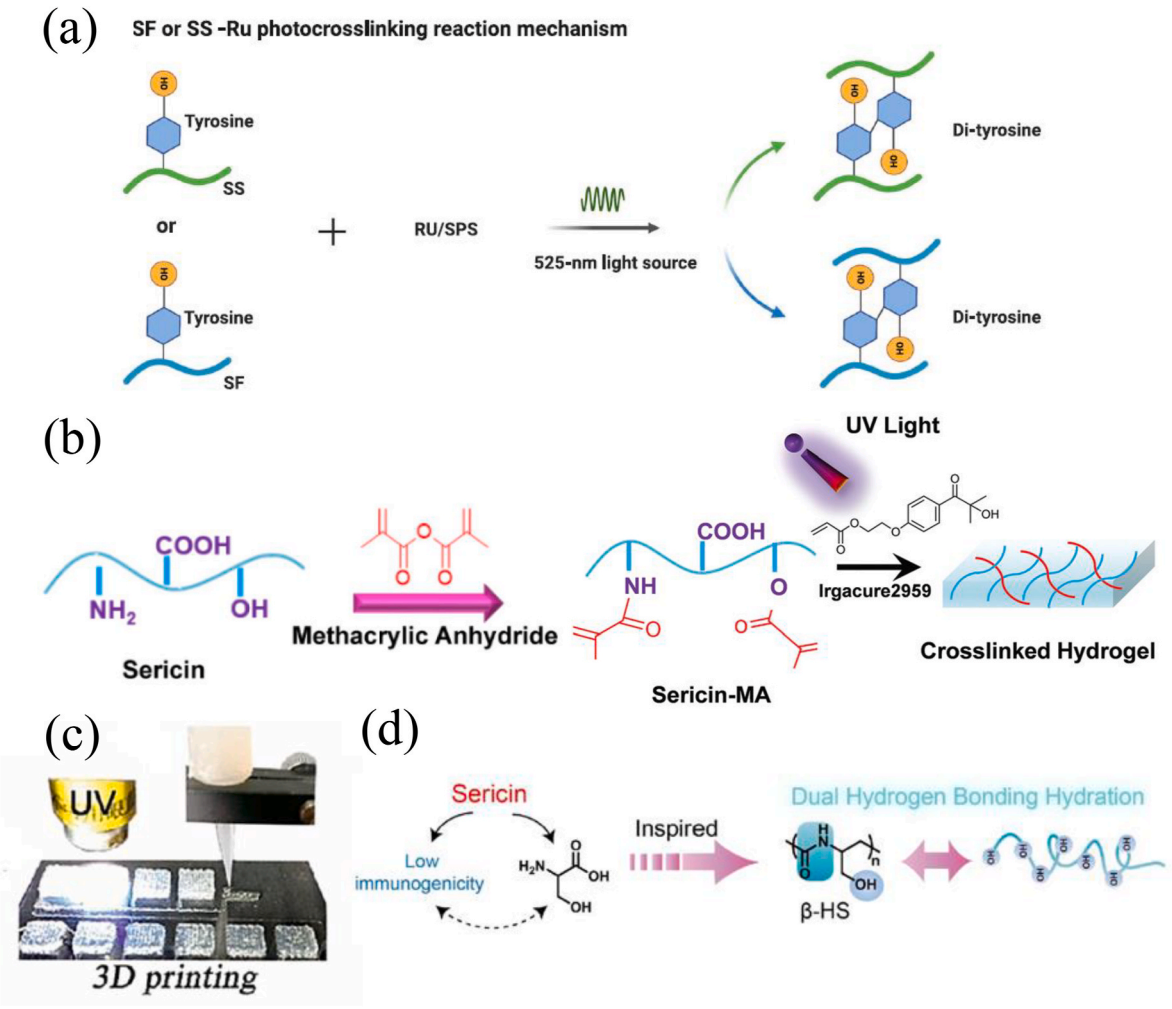


Fig. 7. (a) Photocrosslinking mechanism of silk-based materials (SSER or SF)/Ru-SPS system. Reproduced with permission [13] under CC 4.0 license http://creativecommons.org/licenses/by/4.0/; (b) The process to synthesise SerMA and develop hydrogel. Reproduced with permission [83]. Copyright 2018, Elsevier Ltd. (c) The 3D printed transparent SSER/GelMA hydrogel was photo-cross-linked under UV light. Reproduced with permission [216]. Copyright 2018, American Chemical Society; (d) SSER inspired Synthesis of β-HS composed of racemic β-homoserine. Reproduced with permission [141]. Copyright 2020, Wiley-VCH Verlag GmbH & Co.

The bleeding time for liver injury, rat tail amputation, and femoral artery injury were significantly shortened when the SerMA hydrogel was used instead of the commercial gelatin sponge. Additionally, the presence of silver ions in the dressing enhanced the hydrogel's antibacterial function [92].

Poly ethylene glycol (PEG) was previously considered as an ideal material for clinical applications [218]. However, PEG showed both immunogenicity and antigenicity [219]. In contrast, SSER has abundant hydrophilic amino such as serine, and owns low immunogenicity and foreign body response properties, which inspired the fabrication of poly-β-homoserine (β-HS) (Fig. 7 (d)) [141]. The β-HS based hydrogel was repellent to the adhesion of cells, platelets, bacteria, and fungi, which resulted in a lower foreign-body response and immunogenicity.

In other studies, it was found that the density of blood vessels in the wrapped tissue has been improved by using SSER hydrogels, when compared with PEG hydrogels. The methionine amino acid of sericin plays an essential role in activating collagen synthesis and facilitating wound size reduction. Additionally, high water absorption of sericin accelerates epithelisation rate of the wound [220,221].

Long-term exposure to ultraviolet (UV) light can lead endogenous antioxidant imbalance and result in inflammation, immunosuppression, photoaging, erythema, edema, and skin cancer [222]. SSER may serve as an exogenous antioxidant against UV-induced skin damage and anti-melanogenesis [51,99,147,223].

Human keratinocytes were used as a cell model to study the protective effects of SSER. In the cell cycle analysis, UVB (280–320 nm) can cause cell arrest in the G1 phase and lead to cell death. However, SSER can scavenge the reactive oxygen species (ROS) and melanin induced by UV irradiation, and maintain the redox balance [44]. Besides, the SSER can induce expression of p53 in the cells, which can repair DNA damage and decrease risks of skin cancer [99].

Bacterial cellulose (BC) is a biomaterial useful for tissue engineering [224]. Lamboni and colleagues used SSER to accelerate the wound healing effect of BC [20]. BC was functionalized with SSER through molecular hydrogen binding. The functionalization of the BC with SSER improved cell migration and proliferation [138,178]. The synthesised composites showed suitable porosity for gas exchange and wound effluent absorption. Besides, SSER enhanced the oxygen permeability of the composites, which optimizes the microenvironment to accelerate wound healing [225]. Additionally, mixing SSER with gelatine can accelerate the healing process of diabetic ulcers, as SSER has the potential to promote cell proliferation and to kill bacteria (Fig. 8 (a)) [26,29,146].

Mixing with other antimicrobial agents can further enhance antimicrobial ability of SSER hydrogel [49]. Silver and gold ions have been widely used to inhibit bacteria [19,46,95,226–230]. Previous studies have shown that SSER-poly (vinyl alcohol) (PVA) hydrogel can improve cellular viability and proliferation [22,28,231–234]. Tao and colleagues

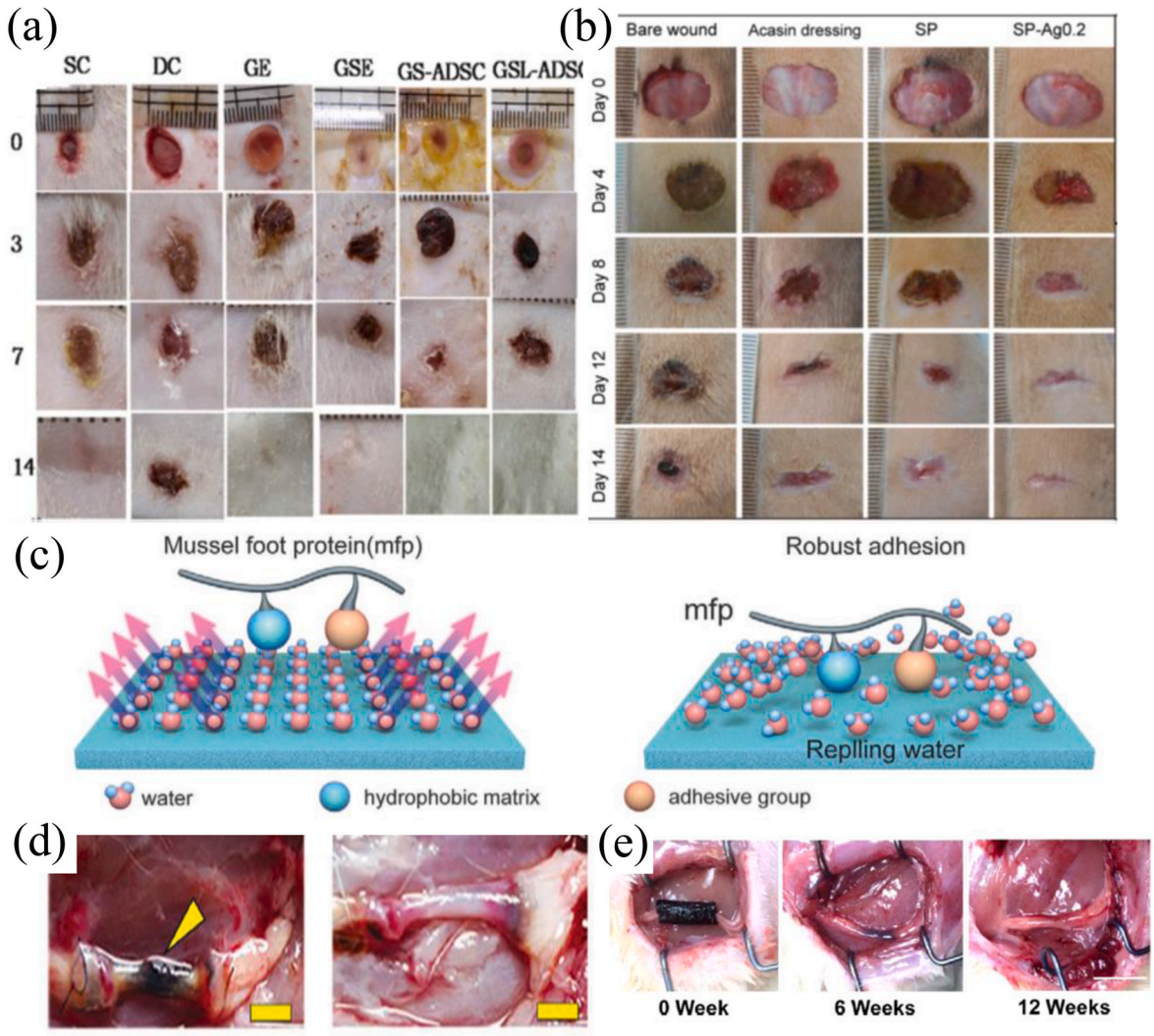


Fig. 8. (a) The wound healing effect of gelatine with SSER dressing. Reproduced with permission [26] under CC BY-NC-ND 4.0 license. https://creativecommons.org/licenses/by-nc-nd/4.0/; (b) The wound healing effect of SP-Ag dressing. Reproduced with permission [24] under CC BY-NC-ND 4.0 license. https://creativecommons.org/licenses/by-nc-nd/4.0/; (c) The mechanism of underwater adhesion of synthesised hydrophobic SSER decorated with hydrophilic tannic acid. Reproduced with permission [89]. Copyright 2022, Wiley-VCH GmbH; (d) 5 mm sericin conduits were observed after the implantation for sciatic nerve. Reproduced with permission [108]. Copyright 2015, WILEY-VCH Verlag GmbH & Co.; (e) Sciatic nerve regeneration and conduit degradation. Reproduced with permission [109]. Copyright 2020, American Chemical Society.

[24] synthesised silver nanoparticles with sericin/PVA hydrogel to promote wound healing (Fig. 8 (b)). Moreover, SSER-based hydrogel exhibited synergistic effect in enhancing the antibacterial property of silver [24,27]. Similarly, SSER with silver nanoparticles-based polyethylene terephthalate fibres [122,123] has been used to functionalize polyglactin sutures.

Many biomaterials have limited adhesive capacity to wound tissues due to the presence of water, which can impair bonding between biomaterials and tissue surfaces. SSER has ~30 % hydrophobic amino acids, which are useful in hydrophobic environments [107]. Self-aggregated hydrophobic SSER co-assembled with hydrophilic tannic acid has been proposed for long lasting adhesion on tissue surfaces [89]. As shown in Fig. 8 (c), the hydrophobic SSER respells water from the tissue surface, allowing the hydrophilic tannic acid to adhere effectively.

8. Bone and cartilage regeneration

To assist bone regeneration, external aids are needed as a damaged bone could not regenerate without a supporting scaffold [70]. The materials used in bone repair should be biocompatible, osteogenic, osteoinductive, and osteoconductive, and should not induce bone damage, inflammation, nor should interfere with natural healing and regeneration process of bones [235]. SSER has been shown to induce cell regeneration with negligible inflammation [236]. Hence, SSER has great potential for use in the osteogenic cell differentiation and proliferation, promoting bone and cartilage regeneration [75,83,237].

For example, SerMA hydrogel has been used as a biomimetic extracellular matrix to support the growth of chondrocytes and promote *in situ* cartilage repair due to the biological and mechanical similarity to the native cartilage [83]. In another example, Yang and colleagues reported that silk sericin could assist in osteogenic cell differentiation. They collected the sericin from *A. pernyi* silkworm and treated it with $CaCl_2$ and Na_2HPO_4 solutions to induce biomineralization. During this biomineralization process, the sericin structure self-transformed from random coil to the β-sheet, which enhanced the mechanical strength of SSER. Increasing the concentration and time of solution mineralization contributed to the formation of surface nano-needle structure. The bone marrow derived mesenchymal stem cells (BMSCs) proliferated faster in biomineralized sericin compared to non-biomineralized sericin [16].

Moreover, osteogenic cell differentiation and proliferation were more rapid in the SSER with higher MW rather than lower MW SSER [74,189]. Conductivity between BMSCs can be improved by incorporating graphene oxide into SSER [84,145,238]. SSER retained the differentiation ability and proliferation capacity of cryopreserved osteoblasts for up to 30 days [137]. Besides calcium ions, zinc and magnesium ions can also promote SSER crystallisation, changing from random coils to β-sheet [239]. The copper ions can further improve tissue regeneration and the mechanical property of scaffolds [240].

Additionally, Kweon et al. [241] divided the whole silk cocoon into three layers, demonstrating that the middle layer exhibited the best performance for *in vivo* bone regeneration. This capability is owing to the abundance of β-sheet structure in the middle layer, which increases bone morphogenic protein-2/4 (BMPs) expression [74]. However, the ratio of SSER and SF in this middle layer has not been investigated. To enhance β-sheet formation, SSER can be pre-treated with 4-hexylresorcinol to further increase BMPs expression [242,243].

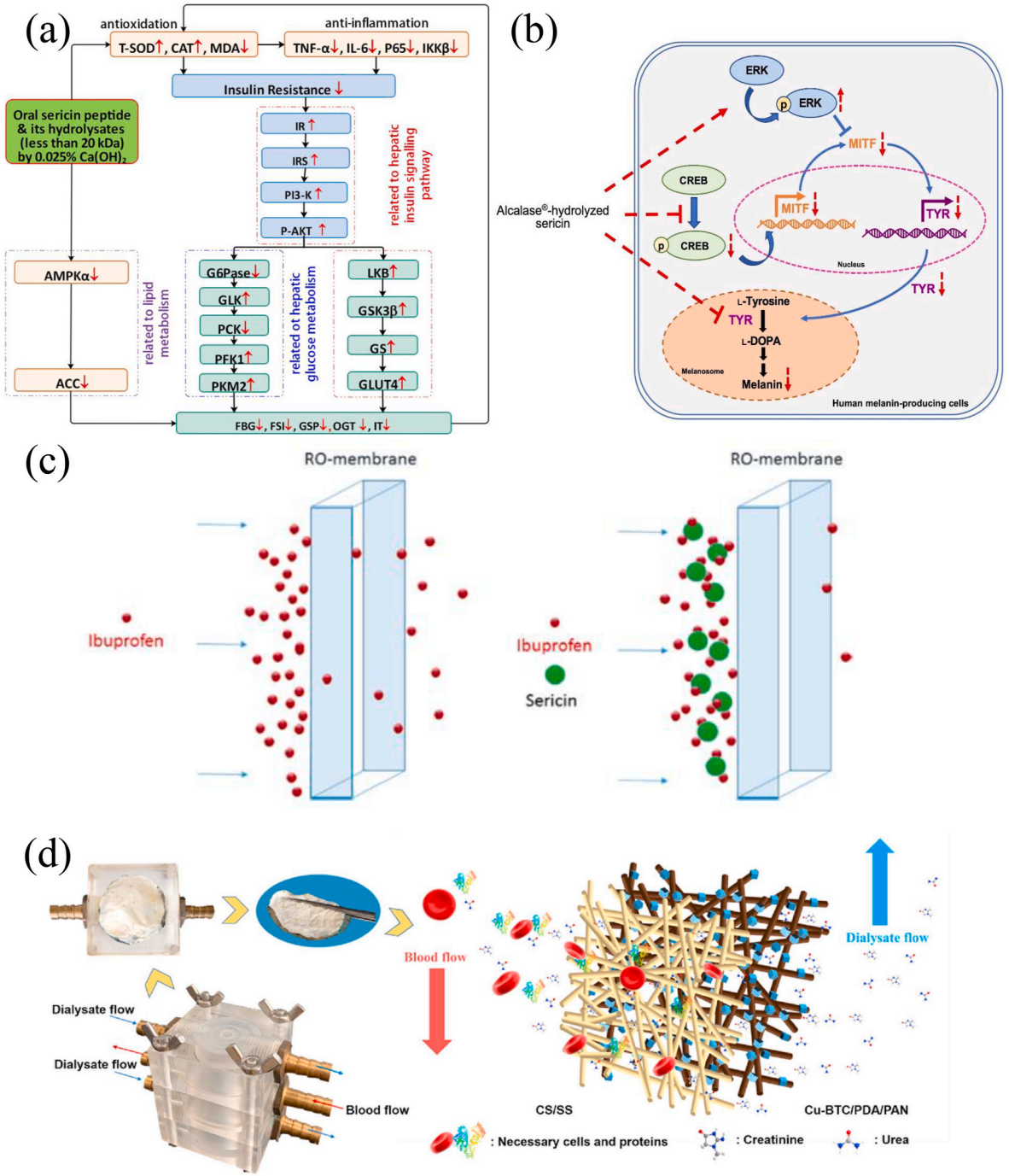


Fig. 9. (a) Schematic of the sericin mechanism of influence on a significant decrease in blood glucose levels. Reproduced with permission [116]. Copyright 2019, Elsevier B.V.; (b) A schematic illustration of the role of hydrolysed sericin in the treatment of hyperpigmentation disorders. Reproduced with permission [50] under CC 4.0 license.http://creativecommons.org/licenses/by/4.0/.; (c) Principal scheme to separate ibuprofen after its attachment to SSER, based on the particle sizes. Reproduced with permission [120]. Copyright 2017, American Chemical Society. (d) Diagram of dialysis process of the uremic toxins. Reproduced with permission [152]. Copyright 2021, Elsevier B.V.

9. SSER in regeneration of nerves

A gap defect in peripheral nerves is a major cause for sensory or motor function loss [244]. In this context, SSER has shown potential in aiding the recovery of peripheral nerve damage. SSER conduit for peripheral nerve regeneration was first reported by Xie et al. [108]. The efficacy of 5 mm pure silicone conduit, pure sericin conduit, sericin-silicone coated conduit, and autologous nerve graft were compared *in vivo*. The pure silicone conduit showed minor recovery effects. The sericin-silicone coated conduit demonstrated superior performance compared to the pure sericin group, and its efficacy approaching that of the autologous nerve graft group (Fig. 8 (d)). However, according to the author, the gastrocnemius muscle's atrophy in the sericin-silicone coated conduit group should be noted. Further optimisation of this engineered conduit could be implemented in the future and applied to repair more significant nerve gap defects. Adding carbon nanotubes (CNTs) could further enhance the mechanical properties and electrical conductivity of the injured nerves during conduit regeneration (Fig. 8 (e)). The electric stimulation can induce growth factors activation and be beneficial to conduit regeneration [109].

10. Pharmacological applications of SSER

While SSER is mainly used as a material, it has been explored as a therapeutic agent for lowering blood sugar level, reducing skin hyperpigmentation and treating inflammatory bowel diseases.

Oral administration of SSER can significantly decrease the blood glucose level, probably due to its ability to reduce oxidative stress in a high glucose environment (Fig. 9 (a)) [116,117,119]. The indicators in the type 2 diabetic model in mice were evaluated after SSER oral ingestion. The results showed that malondialdehyde (MDA) decreased in the liver while the total superoxide dismutase (T-SOD) and catalase (CAT) content increased in the treated mice. Inflammatory factors including tumour necrosis factor (TNF-α), interleukin-6 (IL-6), P65 and IKKβ and protein expressions of these factors decreased in these experiments. The lipid metabolism related indicators such as activated protein kinase (AMPKα) and acetyl-CoA carboxylase (ACC) were also reduced. Other factors like glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PCK) decreased, while the levels of glucose kinase (GLK), insulin resistance (IR), insulin receptor substrate-1 (IRS-1), phosphorylated AKT (p-AKT), hepatic kinase B (LKB), and glucose transporter 4 (GLUT4) increased [116,118]. Therefore, SSER can lower blood glucose levels by improving antioxidant capacity, enhancement of insulin sensitivity, glycogen synthesis, and lipid synthesis.

In another study, it was found that SSER can be applied in the treatment of hyperpigmentation disorders [50]. The alcalase-hydrolysed sericin can inhibit the expression of microphthalmia-associated transcription factor (MITF) while enhancing the expression of phosphorylated extracellular signal-regulated kinase (ERK) in human melanocytes. This process leads to decrease in tyrosinase (TYR) levels and melanin content, as illustrated in Fig. 9 (b) [50].

In addition, Ma and colleagues investigated the effect of SSER in dextran sulphate sodium (DSS)-induced ulcerative colitis in mice to understand the underlying mechanism. Body weight, colon length and weight, spleen weight, and TNF-α value have been assessed in the treated mice. The parameters in the treated animals with hydrogel (chitosan/alginate)-embedding SSER molecules were close to the healthy control group. In vitro studies showed that purified SSER can enhance the healing process of mucus and secretion of anti-inflammatory factors, suppress the production of pro-inflammatory factors, and eradicate intracellular reactive oxygen species [100].

The SSER derived carbon nanosheets exhibit fluorescence, which facilitates the labelling of stem cells without impairing their viability and proliferation [114]. Also, SSER can deoxygenate graphene oxide, thereby reducing the cytotoxicity of graphene [245]. The material demonstrated strong photothermal ability under near-infrared laser irradiation (808 nm), making it suitable for cancer cell elimination.

11. SSER in drug delivery systems

When used as an excipient in drug delivery systems, SSER can enhance drug stability and improve its targeting capability [36,42,128,129]. Environmental factors such as salinity, temperature, and pH values, all have impacts on SSER structure and properties [68,171,246,247]. Moreover, non-covalent interaction occurs between SSER and drug molecules. These factors affect the solubility, absorbability, decomposition, and self-assembly of the SSER-based drug delivery systems [40,41,106,171,248–250].

For example, hydrophobic drugs tend to recrystallize during storage, which alter their bioavailability and therapeutic efficacy [251]. A method to stabilize the hydrophobic molecules is to add polymers to them to facilitate intermolecular interactions between drugs and polymers through hydrogen bonding and/or electrostatic interactions [252]. SSER as a polymer can inhibit the crystallisation of amorphous drugs via anti-plasticizing effect [253].

Drug targeting is an effective strategy directly delivering medicine to the target sites. It has been reported that modified SSER can be conjugated with a tumour-targeting agent and a florescent dye to specifically target tumoral cells [127,254]. For controlled drug release, SSER-based nanoparticles have been used to deliver doxorubicin, leading to extensive DNA damage in cancerous cells [35,149]. When doxorubicin is loaded in SSER-PLA micelles, its effectiveness is significantly enhanced at higher concentrations. Although free doxorubicin diffused rapidly into cells, SSER-PLA micelles released the drug slowly for sustained cancer therapy [35].

Regarding its pH sensitivity applications, SSER has been used as a nanoscale drug carrier of rifampicin and pyrazinamide to treat tuberculosis [255]. The nanocomposites exhibited high sensitivity to pH values during drug release. The protonation in acidic environments could accelerate the degradation of the SSER composites, which ascertained specific release in tuberculosis-infected areas. In another study, Xu and colleagues genetically engineered pH-responsive SSER nanospheres with recombinant human lactoferrin to treat ulcerative colitis [81]. The negatively charged SSER was able to release lactoferrin at colonic sites at pH $>$ 5.5. The effect of the low-dose lactoferrin nanosphere was found to be comparable to the high-dose free lactoferrin in a solution form.

Owing to its biocompatibility and biodegradability, SSER can be used as a material to coat nanoparticles to enhance their performance *in vivo*. For example, superparamagnetic iron oxide can be designed to apply for both therapeutic and diagnostic purposes. Despite its favourable features, the compound is unstable and can lead to reactive oxygen species (ROS) generation. Elevated ROS levels can cause oxidative stress and severe damage to cells. To reduce ROS, SSER can be used to coat the iron oxide nanocarriers, due to its high biocompatibility, biodegradability, and *in vivo* stability [98].

12. SSER for removal of toxins

The SSER owns strong absorption ability and sericin coated membranes were used for removal of the different classes of drugs like non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. The absorption mechanism is based on ionic interaction and hydrogen binding, hence charged medicines are more effectively removed than uncharged drugs [256,257]. As shown in Fig. 9 (c), ibuprofen molecules could be adsorbed by sericin particles, which making them available for physical removal by a size separation membrane [120]. The key factors on the capacity of binding medicines to SSER were temperature and pH. Because the binding process is endothermic, high temperature can accelerate the reaction. By adjusting pH of the solution, we can control desorption of molecules from the membrane's surface [256].

Li and colleagues used an electro-spun method to fabricate a SSER-bilayer nanofiber membrane to dialyse creatinine and urea from the blood in haemodialysis, as shown in Fig. 9 (d). The polar groups in the SSER chain facilitate absorption of the uremic toxins. After 4 h of dialysis, the clearance rates for both creatinine and urea exceeded 80 % [152].

13. SSER in clinical trials

Using 'sericin' as the keyword, ten clinical trials were found on clinicaltrials.gov, as shown in Table 3. The first clinical trial of SSER based products was conducted in 2012 and 70 % of the trials have occurred in the past 5 years. This indicates that after comprehensive research, SSER products have progressed into the clinical trial stages. However, it is worth noting that all the clinical trials were sponsored by Chulalongkorn University, Thailand. No other countries or institutes are currently involved in the SSER based products in clinical trials, registered on clinicaltrials.gov.

Among the trials, 40 % were in Phase II or completed, while the remaining 60 % were still listed as unknown status or yet to recruit. All the clinical trials are focused on skin-related applications, such as wounding healing and skin disorders, with 40 % of the products being wound dressings, 40 % creams, 10 % pads, and 10 % hydrogels. Clinical trials in 2020 and 2021 highlighted combination of sericin with chitosan, indicating a trend towards synergistic effects in skin treatment. Trials in 2023 and 2024, are focused on sericin and turmeric creams, suggesting an exploration of SSER potential into anti-inflammatory and antioxidant benefits for skin disorders and psoriasis. The combination of sericin with other biomaterials suggests a trend towards more sophisticated and potentially more effective treatments. Ongoing trials indicate a future of continued innovation in wound healing, expanding into broader skin disorders.

14. Textile

Silk, due to its low thermal conductivity, helps to keep the body cool in warm weather [258]. The proportion of SSER in silkworm cocoons varies depending on their varieties, ranging from 15 % to 35 %, with bioengineered silk cocoons containing more than 40 % SSER or even up to 90 % [259,260]. Controlling the SSER content significantly influenced the electro-spinnability of SF fibres due to the viscosity of SSER. Pure fibroin lacks favourable electro-spinnability, but this characteristic improves remarkably when SSER exceeds 0.6 wt%. At this concentration, the fibre elongation and breaking strength are also improved [261]. As SSER content in the fibre increased, the strength of silk yarn decreased after hot-press treatment, while elongation considerably increased [259]. Considering the vast verities of recognized silkworm to be used for degumming process, and different characteristics and concentrations of sericin in the different verities, more studies are needed to evaluate the effects of sericin amounts on the mechanical and tensile characteristics of silk fibroin after hot-press treatment. Further experiments should be conducted concerning the range of crystallinity index, mechanical properties, and thermal stability of the electro-spun silk. However, increasing the SSER concentration can decelerate the gelation and β-sheet formation of fibres [262].

Table 3
SSER clinical trials on clinicaltrials.gov website.

No.	Year	Phase	Type	Application	Status
1.	2012	I, II	Sericin scaffold	Wound healing	Completed
2.	2014	I, II	Bioactive coating layer dressing	Wound healing	Completed
3.	2015	II	Sericin wound dressing	Wound healing	Completed
4.	2020	N/A	Sericin and chitosan cream	Skin ulcer	Completed
5.	2020	N/A	Absorption pad for blood and pus	Skin disorder	Unknown
6.	2021	N/A	Sericin and chitosan cream	Skin ulcer	Unknown
7.	2021	N/A	Wound dressing	Wound healing	Unknown
8.	2021	N/A	Drug laden sericin hydrogel sheet	Wound healing	To recruit
9.	2023	N/A	Sericin and turmeric cream	Skin disorder	To recruit
10.	2024	N/A	Sericin and turmeric cream	Psoriasis	To recruit

By adding thioflavin T, a benzo-thiazole extrinsic fluorescent dye, the formation of β-sheet can be monitored by ATR-FTIR. The results suggested that SSER can form hydrogen bonding with SF and slow down the transformation of β-sheet structure. These findings offered new insights into the storage and processing of fibroin and any biomimetic technological applications in which it is essential to control the conversion and solidification of fibroin.

The advanced heat-managing textile is designed to meet the requirements of diverse environmental conditions. SSER can shield transition metal carbide/nitride from oxidation, enhancing the textile's durability and thermal management capability [101]. The combination of graphene and SSER (GS) in a brick-and-mortar structure achieves variable thermal conductivity at different humidity levels. The maximum switching ratio of thermal conductivity between dry and humid conditions could reach 14 times, making it well suited for applications in weather-responsive textiles [153].

As mentioned previously, SSER as an exogenous antioxidant material can be applied against UV [262]. Metal oxides and noble metal nanoparticles are widely used for UV protection. However, washing fastness and cost have limited the application of these metal additives. Synthesised SSER-Cu nanoparticles can enhance the UV protection and antibacterial properties of silk fabrics [43,48]. SSER serves as a stabilizer and binder for Cu nanoparticles, with the optimal mixing weight ratio between SSER and CuSO4 being 4:1 to balance UV protection and antibacterial activity.

The removal of unpleasant smells caused by bacteria is essential in sportswear. If sweat is not removed from the clothing, bacteria can rapidly multiply and release many metabolic products. The Ag nanoparticle combined with SSER can create a temperature-responsive interpenetrating polymer network, which resists the proliferation of *S. aureus* and *E. coli* by more than 95 % [263]. SSER can also increase the anti-static ability of synthetic polymer fibres, enhance dyeability with sufficient washing and light fastness, while maintaning breathability and water vapor permeability [79]. It also reduces the release of microfibres to control the potential pollution caused by microfibres [264].

Silk is an ideal raw material for textile manufacturing, and SSER plays a crucial role in enhancing mechanical properties, antibacterial function, essential binding elements, and temperature response for everyday needs [265,266]. Understanding and optimizing the ratio of the silk fibre, sericin, and other functional components will be beneficial for producing objected functional and high-quality products based on silk.

15. Water decontamination

The release of heavy metal ions and oil spills into water sources poses significant threats to both human health and the environment. Physical absorption can be considered as an economical method to remove these contaminants [155]. To this end, SSER can be used to absorb heavy metal ions [10,54–60,154,156,157,267]. For instance, SSER cross-linked with alginate can absorb gold ions [154]. In addition, the sericin-alginate particles can reduce Cr (VI) to Cr (III) ions for chromium ion removal [54]. In another example, Koely and colleagues [10] designed organic-inorganic hybrid flowers via the combination of SSER

and copper (II) phosphate. These flowers have large surface area and porosity to absorb several metal ions. By increasing SSER concentration, which expanded the absorption area of a single hybrid flower, the absorption of Pb (II) ions can be significantly enhanced. Besides, this SSER-based flowers can also absorb heavy metals such as Cd (II) and Hg (II) ions. Moreover, organic dyes like methylene blue can also be removed using SSER-based materials [158].

Apart from heavy metals, oil leakage is another threat to environment. The difficulties in cleaning up spills without generating toxic by-products continue to present a challenge. To address this challenge, SSER-based carbon aerogel has been used to improve the absorption efficiency of oils [76]. In another study, polypropylene membrane coated with a layer of sericin was used to purify household wastewater [256]. The results showed that more than 90 % turbidity in water can be removed.

16. SSER based electrodes

To combat energy crisis, researchers are constantly looking for eco-friendly resources to replace carbon-based fuels [268]. Hydrogen is one of the largest reserve elements on the earth, with a high energy density. The most common method to produce hydrogen is through water electrolysis [269]. However, slow kinetics and high overpotential of oxygen evolution reaction limited the electrocatalytic efficiency. Unstable interfaces between electrode and electrolyte affected performance of the ions-based batteries [270,271].

SSER is made up of 18 types of amino acids, which are abundant in nitrogen and carbon elements [96]. It can therefore be used to cover the electrodes to protect the cathode from oxidation induced corrosion [61,131,132,163,272–274]. As a precursor, it can be hydrothermally calcined to modify the cathode surface to achieve high discharge capacity [78,130,161]. Compared with the conventional polyvinylidene fluoride-based electrodes, SSER-based electrodes have lower energy barrier, hence enhance ionic conductivity [125,272].

17. SSER based flexible biosensors

SF and SSER have been used as feedstocks in flexible micro-optic

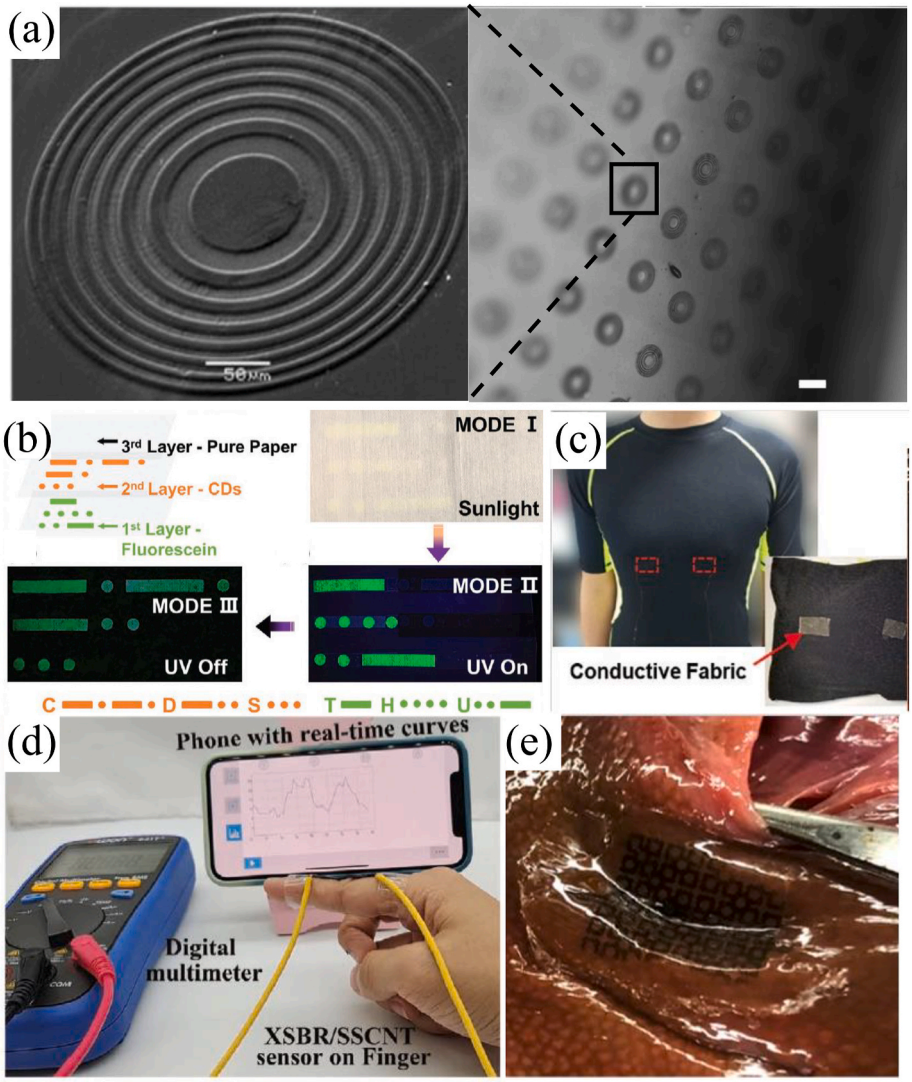


Fig. 10. (a) SSER/SF based Fresnel lenses integrated on a flexible film (scale bar = 100 μm). Reproduced with permission [275]. Copyright 2015, American Chemical Society; (b) Morse codes for information encryption under different states. Reproduced with permission [105]. Copyright 2021, Wiley-VCH GmbH; (c) Printed SSER-CNTs (carbon nanotubes) textile electrodes. Reproduced with permission [107]. Copyright 2020, WILEY-VCH Verlag GmbH & Co. KGaA; (d) Optical image of the external connections of the carboxylic styrene butadiene rubber (XSBR) and SSER modified carbon nanotubes (CNTs) sensors with wireless detection. Reproduced with permission [165]. Copyright 2021, Wiley-VCH GmbH; (e) SSER based biomarkers at tissue surface. Reproduced with permission [164]. Copyright 2019, American Chemical Society.

manufacturing [275], as shown in Fig. 10 (a). The optical microstructure can be integrated onto both rigid substrates and flexible films. Besides, the optical system can be stably stored for months and controllably biodegraded in less than 4 weeks.

In another example, SSER-derived carbon dots (CDs) were fabricated using SSER (Fig. 10 (b)) [105]. CDs have unique luminescent properties and potential applications in many fields. However, several issues, including aggregation-caused quenching and unsustainable preparation, limited their applications. To address the challenges, sericin was used, as a silk-derived sustainable material, to prepare CDs using a household microwave oven. The sericin-derived CDs are potentially useful for white-light-emitting diodes, information encryption, anti-counterfeiting, and wearable visual humidity sensing.

Flexible biosensors can be applied in wearable and implantable systems to monitor human health [166,172,276,277]. Carbon nanomaterials, such as carbon nanotubes (CNTs), are commonly used in flexible electronics [168,278]. However, their toxicity for living systems and low dispersity in solvents limited their applications. The different aromatic amino acids of SSER can form strong π–π interactions with CNTs, which can stabilize the SSER and CNTs hybrid materials. SSER can reduce the surface energy of CNTs, to improve the dispersibility of CNTs in water [107]. These SSER-CNTs materials have been successfully used in inkjet-printing, direct writing, stencil-printing, and printing in various flexible substrates, such as paper, polyethylene terephthalate (PET) films, and textiles (Fig. 10 (c)) [107].

Additionally, SSER-CNTs can be mixed with carboxylic styrene butadiene rubber (XSBR) via noncovalent bonds to make multifunctional sensors for detecting stress and temperature evolution [165]. The XSBR/SSER-CNTs sensors can be stretched to 400 % without breaking and preserved at 12.58 MPa high elongation strength. The thermal detection capacity of this sensor ranged from 30 to 100 °C and it was highly sensitive between 40 and 70 °C. The response time for thermal or strain change was only 10 s. The flexible sensors can be used for remote detection and recording the patients' behavior, as shown in Fig. 10 (d) [165].

Xu and colleagues [164] fabricated a flexible SSER-based biosensor to monitor vascular endothelial growth factor (VEGF), as shown in Fig. 10 (e). The biosensor was fabricated by photolithography with a material consisting of a photoreactive silk sericin coupled with a conducting polymer. To calibrate the sensor, Ag/AgCl and Pt electrodes were used. Three types of solution were used to test the sensor's reaction and different bending angles in response to mechanical challenges.

18. Food additive and seed protection

Recently, SSER has been studied as a gelling agent in the food industry to provide low-calorie options for desserts [279,280]. On the other hand, SSER can also help to preserve seeds [135,136]. Sonjan and colleagues [66] prepared a crosslinked PVA-SSER film for seed coating, which consisted of 20 % w/w dimethylurea, 10 % w/w PVA and 2 % w/w SSER. The coated seeds showed 15 % higher germination than the non-coated ones, and fewer fungi were found in them due to the antibacterial activity of SSER. Apiwattanasiri and colleagues investigated the effect of SSER coating on the survival rate of the probiotic *Lactobacillus casei* [169]. The SSER-coated probiotic cells could be effectively protected and stored for an extended period. Besides, the heat resistance of the SSER-coated probiotic cells increased to 65 °C compared to the untreated group.

19. Discussions and future perspectives

SSER is a distinctive biopolymer derived from various species, typically from silk cocoons. Historically, it was considered as a by-product of silk fibroin (SF) degumming process. However, it has recently garnered significant research interest due to its biocompatibility, antioxidant properties, low-inflammatory response, and its capacity to promote cell viability and proliferation [6,9]. Additionally, SSER's inherent photoluminescent properties enable tracking without the need for external agents [212]. The silk cocoons contain approximately 20–30 % SSER, but genetically engineered variants can have up to 90 % w/w [259,260]. These genetically engineered SSER can be secreted with exogenous protein, offering potential for new molecular designs and functionalities of SSER. The structure of the genetically engineered SSER can be predicted using the artificial intelligence tools like AlphaFold and validated via cryo-electron microscopy [281,282]. The data obtained from these genetically engineered SSER structures can further serve as a database to train the simulation models for predicting protein configurations.

Research on SSER-based materials has explored their mechanical properties, effect on cell differentiation, wound healing, pharmaceutical applications, textile, energy, and other eco-friendly uses [87,193,205,261]. SSER's versatility and potential applications are amplified by its ease of functionalization with both natural and synthetic materials [139,204,205,207,208].

On the other hand, this biopolymer has some limitations, including the need for sustainable and scalable extraction methods, suboptimal mechanical properties, and its animal origin, which may limit its applicability in certain biomedical fields [283]. The degradation of SSER during extraction processes is also an obstacle. Nonetheless, SSER with various MW can be used across diverse fields, including pharmaceuticals, energy, textiles, and environmental applications (Table 1). Mild extraction methods, such as extraction using LiBr, can preserve the complete structure and maintain the biological properties of SSER [108,109]. It is worth noting that different MW of SSER exhibits varying characteristics. For instance, high MW SSER excels in antioxidant capacity, antibacterial properties, higher viscosity of aqueous solution, higher gel-sol transition temperature, higher amount of β-sheet structure, mechanical strength, and extension rate of the sericin film when being compared with lower MW SSER [18,184,191]. Higher MW SSER also exhibits stronger osteogenic activity due to its high β-sheet structure ratio [189]. In contrast, low MW SSER can be used to treat hyperpigmentation disorders by inhibiting melanin-producing cells and enhancing phosphorylated extracellular signal-regulated kinase expression. High MW SSER is suitable for drug carriers and biocomposites, while low MW SSER is used as an antioxidant agent [122,123,127–129,132,134,198]. The antioxidant properties of SSER have made it a popular choice for food preservation, drug preservation, and UV protection [3]. A thorough understanding of SSER's molecular mechanism, and extraction methods can enhance its applications and selecting the appropriate MW can result in more effective products and therapies.

The antimicrobial properties of SSER remain a subject of debate. Some studies attribute these properties to the impurities introduced during degumming [284], while others suggest the properties are dictated by SSER's MW [18]. In addition, SSER exhibits a stronger antibacterial property against Gram-positive bacteria (*S. aureus*) compared to Gram-negative bacteria (*E. coli*) [18,285].

SSER's high content of hydrophilic amino acids (approximately 70 %) makes it a highly hydrophilic protein. This characteristic can be modified by decorating SSER with hydrophobic chains to acquire specific functionalities [83,102,206,286]. Moreover, physical or chemical treatment can convert SSER's random coil into β-sheet structures, thereby enhancing its mechanical properties [193]. Additionally, combining SSER with other materials can further improve strength and related properties [32,33,139,140,203,204], which is a useful approach to adjusting the properties of proteinaeous materials [287,288].

Furthermore, the amino acids in the molecular chain of SSER facilitate self-crosslinking and modification with other molecules, making it a promising candidate for hydrogel formation through 3D printing [286]. The printed SSER hydrogels can offer customized formulations and structures that replicate *in vivo* microenvironments for various cells and tissues, influencing their biological behaviours and functions. Besides, SSER hydrogels, when combined with conductive materials, have

the potential to broaden their applications in flexible electronic devices, such as real-time wearable monitoring systems or implantable indicators [105,107,164,165].

The clinical trials of SSER are primarily conducted in Thailand, with the focus on skin-related applications. The geographical limitation of studies may stem from the fact that silk is originally sourced from South and East Asia, and SSER is extracted from silkworm cocoons. Concerns over biological invasion from silkworm larvae restrict its availability and use in regions, such as Europe and the United States. However, modern techniques for detecting and removing of silkworm larvae along with advancement in air transport and hermetic storage, are making it easier to access this material. This advancement is driving global research effots in SSER.

Currently, SSER-based biomedical applications include cartilage and nerve regenerations, drug delivery systems, or biosensors [12]. The expansion of clinical trials and the industrialization of SSER products are expected to accelerate their market entry. Further investigation into SSER is warranted to realize its full potential as a multifunctional material. With its abundance and wide range of applications, SSER-based materials show significant potential for future development.

CRediT authorship contribution statement

Yunong Yuan: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Mohammad Nasri:** Writing – review & editing, Methodology, Investigation. **Azadeh Manayi:** Writing – review & editing, Investigation. **Junying Zhang:** Writing – review & editing, Investigation. **Chunyong Wu:** Writing – review & editing, Investigation. **Tae-Joon Jeon:** Writing – review & editing, Investigation. **Lifeng Kang:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data were used for the research described in the article.

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