Minireview Article

Extraction and Biological application of Silk Sericin: an over view

Abstract

The sericin is a byproduct which is obtained from silk industries. Mainly *Bombyx mori* is responsible for the synthesis of sericin. Sericin is proteinaceous in nature and is biodegradable. The two major components of silk i.e., fibroin and sericin have to be removed from raw silk to give it a luster or shine by degumming process. Silk sericin and its nutritive value has now been known to everyone in China and Japan. Many uses of sericin like pharmaceutical uses, textile -based uses, use in cosmetics has now been explored in India but the use of sericin as dietary supplement is not still discovered. Tons of silk has been produced in India and the degummed water goes as waste which can be used. Nanotechnological discoveriss of sericin have given foremost advances in the field of biomedicine and tissue engineering, with special consideration the applications of a natural product for the enhancement of new pharmaceutical formulations and biomaterials. Sericin conjugated nanoformulations are a vast example of nanotechnological tools applied to the blueprint of an biocompatible ,economically viable, and biodegradable compound as well as its use as nanomedicine. The aim of this review is to highlight the application of sericin in different fields like in biomedical, food additives and the nanoformulation of silk sericin.

Keywords: *B. mori*, Silk gland, Sericin, Fibroin, Nanoformulation

Introduction

Silks are assemblance of polypeptides and protein subunits, which are generally proteinaceous in nature and are divided into fibrous proteins. Silk constituted of a wide range of protein based high molecular weight polymers analogous with insects, weaving spider and silk worms [1]. Sericulture is vitally a cottage_industry producing four different types of silk. A large micro economy is supported by sericulture in rural areas. The classification of waste silk can be like cocoon waste, rearing waste and thread waste. The extraction of fibroin and sericin makes sericulture a feasible platform for industry. Silk fibres are formed by the natural process of silk worms. Silk is very much appreciated and adapted in the fashion industry because of its uncommon nature like tensile strength, thin fibre and various mechanical properties. Silk fibres are having importance in medical, pharmaceuticals and textile industries due its peculiar characteristics.

Sericulture is the technique of cultivation of silkworms and extracting silk from them. Silk consists of 70-80% of fibrous protein called fibroin and 20-30% of globular protein called sericin. The presence of sericin makes the fibres rigid and the removal makes it squishy. Sericin has non-filamentous while fibroin has filamentous character [2]. Silk fibroin makes the filament of silk worm and gives its distinct physical and chemical properties [3], [4]. Silk adapts a range of secondary structures, including α-helix, β-sheet, and crossed β-sheet, but mainly sericin occurs in an amorphous random coil and to a lesser extent, in a β-sheet organized structure.

Sericin is a macromolecular protein having molecular weight ranging from 10 to 310 kDa [5]. This is made up of 18 aminoacids among which serine, histidine, glycine, threonine, tyrosine, aspartic acid and glutamic acids are main [6] and also having strongly polar side groups such as carboxyl, hydroxyl, and amino groups. The main components of silk sericin are aspartic acid and serine, which are 19% and 33% respectively. Sericin has been recognized with several important properties [7] like UV resistance [8], anticoagulant and antioxidant activities [9] and inhibitory action of tyrosinase [10]. Due to non- immunogenic response sericin application has been assorted, in the pharmaceuticals, biomedical, cosmetics and food industries [11]. It has been studied that the functional properties of sericin could have vary according to their molecular weight. Sericin having higher molecular weight is generally used in biomedical applications [12], enzyme immobilization [12], and wound dressing [13] whereas sericin having lower molecular weight is used in cosmetics application due to its well anti-oxidant, anti-tyrosinase and anti-elastase activities [14]. In addition, sericin was also found to have anti-cancerous, anti-coagulant [15], cryoprotective activities [16]. These findings indicate that sericin has promising position in pharmaceuticals industry. Sericin is the second most major silk protein that has excellent moisture absorbing capacity which makes it more likely to be used as an additive in cosmetics. Recovering sericin from waste water brings down the environmental impact of silk processing and at the same time yields a valuable ingredient for food [17], pharma and cosmetic industry [18].

Sericulture

Silk is a natural protein polymer, some forms of which can be woven in to textiles. Sericulture is the pocess of cultivation of silk worms and the extraction of silk from them. For this purpose *Bombyx mori* plays a very unique and vital role. Production of silk is a seasonal activity and it does not need much investment, because it is a process starting with providing of mulberry leaf as it is the only nutrient source of silkworm and progressing until the production of silk. Generally, one cocoon produces 300- 600 m of silk filament, which made essentially of 2 elements. The fibre, called fibroin makes up between 75 % and 90%, and sericin the gummy substance secreted by the caterpillar to glue the fibre in to cocoon comprises up to 10 to 25% of silk. Fibroin is insoluble whereas sericin is soluble in water. To make approximately 1 meter of silk material, about 3000 cocoons are used.

Silk worm Life Cycle - *Bombyx mori*

Bombyx mori has been tamed for more than seven thousand years which is known to be a lepidopteran insect. Due to the wide importance of silk production throughout the centuries the physiology of these species has been extensively studied [19]. Egg, larva, pupa or chrysalis, and adult moths are the four different stages of metamorphosis of silk worm life cycle. Larval stage consists of five stages or ages [18]. The first stage of the metamorphosis is the production of eggs. About 300-400 numbers of eggs are being laid by the female silk worm and after laying she dies and the male silk worm is supposed to live a longer life [20]. The second stage of metamorphosis includes the incubation of eggs for 10 subsequent days for their hatching into larvae or caterpillar. The larvae are able to outhouse their skin five times during their life span and accumulate enough nutrition by eating the mulberry leaves. The pupa or chrysalis stage begins after the nutritional phase and the cocoons are formed [21]. The cocoon protects the pupa from unnatural death and microbial degradation [22].

The cocoons are being intertwined around the caterpillars by moving its head as 8 or S shaped which is done by stretching. The length of cocoons is 700-1500 cm which are of several grams, compact and have a single filament of silk. The cocoons are ellipsoidal in shape and are hard to break which gives it a rigid structure to get rid of various environmental hazards. An alkaline substance is secreted from the two thickened sides of the cocoons which emerges moth to finish its metamorphosis [20, 21].

Varieties of silk and their importance:

There are 5 important types of silk with mercantile importance, which are obtained from different species of silkworms and nourishes on a number of food plants. Excluding mulberry, other varieties of silks are generally termed as non-mulberry silks. In india all these varieties of silk are cultivated.

a. Mulberry silk:

Mulberry silk produced from the silkworm *Bombyx mori* which nourishes on the leaves of mulberry plant. The amount of silk produced in the world comes from this variety. The average length of this silk fiber is 520 m [23]. Silk generally refers to mulberry silk. These silk worms reared indoors and completely domestic. The major silk producing states of india are Karnataka, West Bengal, Andhra Pradesh, Tamil Nadu, Jammu and Kashmir. Around 92% of total mulberry raw silk production of country occurs by these states [23].

b. Tasar:

The word tasar derived from Sanskrit word trasar that means "shuttle". There are 2 types of tasar silk such as temperate tasar also known as oak tasar and another one is tropical tasar [23]. *A. mylitta* produces tropical tasar where as oak tasar is produced by the silk worm *A. Proylei* [24]. It is copper colour, coarse silk which produced from the silkworm, *Antheraea mylitta* which mainly eat foods from plant Asan and Arjun [25]. The cocoon shape is oval and its colour is brown. The thickness of the wall is 0.38±0.02mm and the density is 804±34kg/m [26]. The average length is 700m. According to Sen and Babu the dye uptake of tasar silk is higher than both eri and muga which are the wild type of silk but lower than the mulberry silk fiber for disperse dye and acid dye [27]. The rearing is conducted on the tree in open. In India tasar silk is produced on the states of Odisha, Chhattisgarh and Jharkhand, Maharastra, West Bengal and Andhra Pradesh .

c. Oak tasar:

This type of tasar is produced by the hybrid of Chinese silkworm *Antheraea proyeli* [28]. Oak silk is a finer variety of tasar. This is feeds on natural food plants of oak. In male insect the density of silk fiber is 1.345g/cm^3 and in female it is 1.344g/cm^3 where as the crystallinity percentages of fiber in male and female are 44.6 and 41.8 respectively [29]. This variety of oak tassar is generally found in the sub-

Himalayan region of india which including the states of Meghalaya, Himanchal Pradesh, Manipur, Assam, Jammu and Kashmir, Uttar Pradesh. China is the leading manufacturer of oak tasar in the world.

d. Eri:

Eri silk also recognized as errand or endi. This is the only silk fiber reeled without harming the pupa and is known as "peace silk" or "vegan silk" [30]. Unlike other varieties this eri silk is a multivoltine silk arises from open-ended cocoons. The price of eri silk is lower than both muga and tasar silk and according to survey it is most produced wild silk fiber with 6661 tonnes in india [31]. The shape of the coccon is oval and having creamish white in coloration. The average filament length of the cocoon is 450 approximately and the density of the variety is 1.28g/cm^3-1.29g/cm^3[27]. According to kumar and Ramachandran this fiber can be suitable for thermal wear and inner garments [32]. Eri silk fiber with cotton blend produces woven fabrics and ring-spun yarn and also it is stated that blended eri silk fiber with is stronger and longer than cotton [33]. This silk is generated from the domestic silkworm *Philosamia ricini* that mainly nourishes on castor leaves. This eri silk is mostly used for the preparation of chaddars by the tribals for their own use. This culture is practiced in Assam, Bihar, Odisha, West Bengal but the Northern states of India is considered as this silk worms homeland**.**

e. Muga:

This is a golden yellow colour silk mainly found in Assam. This is generated from silkworm *Antheraea asamensis* and is semi domesticated silk worm [31]. Muga is the word derived from Sanskrit word which means "amber" and also referred as "pride of india" [28]. The thickness of the wall is 277±29mm. The average length is 450 m and the fibr density is 1,332-1.338g/cm3. It is much finer than tasar silk and coarser than mulberry silk. As compared to both tasar and mulberry silk the dyeing of this muga silk fiber is much higher [34]. Muga culture is very specific and an integral part of the tradition and culture of the state Assam. This silk is used in sarees, chadars and considered as high value product.

Silk and its chemical composition:

Silk fiber is mainly composed of two main proteins: fibroin (70-80%) and sericin (20-30%), and other minor components such as carbohydrates, waxes and ash (1.0-2.0%) [35, 36]. Silk comprises of some impurities like fat, wax, inorganic salt and colouring matter. Fibroin is a fibrillar protein, having semi-crystalline structure that provides stiffness and resistance to fiber, while sericin is an amorphous protein and operates as a binding agent for the maintenance of structural integrity of the cocoon [37, 38, 39]. Silk is the only natural fiber existing as a continuous filament. Silk has a wide range of textile properties that have made it to be used in industries. Some examples are its fineness, strength, elasticity, dyeability, softness, flexibility, gloss, elegance, and high properties [40, 20]. Silk comprises of some impurities like fat, wax, inorganic salt and colouring matter.

Table 1. Composition of sericin

Silk Composition	**Percentages**
Pigment	0.2%
Wax matter	0.4-0.8%
Inorganic matter	0.7%
Carbohydrates	1.2-1.6%
Sericin	20-30%
Fibroin	70-80%
Total	100%

Sericin and its Amino acid composition:

Chemically sericin and fibroin together have amino acids. Table 2 contains the amino acid percentages in sericin [41,7]. Fibroin is rich in glycine and alanine whereas sericin is rich in serine and aspartic acids.

Out of 18 kind of amino acids present in sericin, serine accounts for 27.3% which is high. serine having strong polar hydroxyl groups and is related to physiochemical and functional properties of sericin. Aspartic acid and glycine account for 18.8% and 10.7% respectively which indicates that both aspartic and glycine are important amino acids.

Sericin contains 18 amino acids with essential amino acids which is identified by the presence of 32% of serine and is also a silk protein. About 45.8% of total sericin is made up of amino acids where non polar amino acids constitute about 12.2% and polar amino acid constitute about 12.2% residues. About 20-30 % of cocoon weight is made up of sericin. The important feature of sericin is to cover fibroin. Sericin mainly found in an amorphous coil and less in a β sheet form. The randomly coiled structure easily changes to β-sheet structure, as a consequence of recurrent moisture absorption and mechanical stretching [42, 43].

Table 2: Amino acids composition of sericin

Symbol	Amino acid	Sericin
G	Glycine (Gly)	10.7
A	Alanine (Ala)	4.3
S	Serine (Ser)	27.3
Y	Tyrosine (Tyr)	4.6
V	Valine (Val)	3.8
D	Aspartic acid (Asp)	18.8
R	Arginine (Arg)	4.9
E	Glutamicacid (Glu)	7.2
I	Isoleucine (Ile)	1.3
L	Leucine (Leu)	1.7
F	Phenylalanine (Phe)	1.6
T	Threonine (Thr)	7.5
C	Cystine (Cys)	0.3
H	Histidine (HiS)	1.7
K	Lysine (Lys)	2.1
M	Methionine (Met)	0.5
P	Proline (Pro)	1.2
W	Tryptophan (Trp)	0.4

Sources of Sericin:

For generating sericin silkworm is the only source, hence sericin is recovered from cocoons, silk waste or from the degumming waste water of silk industry. Overall yearly cocoon production is around 400,000 metric tons across the world and from the degumming process only, 50,000 metric tons of sericin is junked in sewage every year [44]. Now a days sericin is retrieved by silk degumming process [45]. Large amount of sericin can be recovered from silk waste as compared to silk degumming liquor.

Morphology of Silk gland and Sericin synthesis

Silk gland which is the labial gland of *B. mori* produces sericin. The silk glands are the set of tubular organs which begins from the digestive tract and hold forth to the caudal portion. According to the complexion and work silk gland is categorised into the anterior silk gland called as ASG, which shapes the excretory duct and is having 200 cells, the posterior silk gland known as PSG which secrets fibroin and have 500 secreting cells, middle silk gland called as MSG producing 3 types of sericin and have 300 secreting cells [36]. The middle portion is subdivided into 4 parts anterior, posterior, anterior middle, posterior middle [46].

Silk Sericin and its forms:

Depending on solubility, sericin can be classified into three types, such as:

(i)sericin A: Sericin A is the outer most layer which is Insoluble in hot water. it accounts for 17.2% of nitrogen and amino acids like, serine, glycine, threonine and aspartic acid.

(ii)sericin B: Sericin B is the middle layer which on acid hydrolysis produces same amino acid of sericin A with tryptophan. It contains 16.8% of nitrogen.

(iii)sericin C: Sericin C is the inner most layer, which is adjacent to fibroin as it is insoluble in warm water. it can be separated by treatment with hot dilute acid or alkali from fibroin. It yields proline on acid hydrolysis in addition to amino acids present in sericin B. It also contains sulphur and 16.6% of nitrogen [47, 17].

The three-layer structure of sericin can be studied through ϒ- ray. The outer layer shows some fibre direction filaments, middle contained layer cross fibre filaments, and the inner layer displays longitudinal filaments. The structure of sericin also depends on the casting temperature. Lower the casting temperature more the sericin molecules assume β- sheet rather than random.

On the basis of colour of cocoons, sericin can also be classified. Low viscosity sericin is the white sericin, medium viscosity sericin is the yellow sericin which is usually used in salad dressing and the high viscosity sericin is the yellow- green in colour which contains flavanol pigments having antioxidative properties and is mostly incorporated in baking of bread [17].

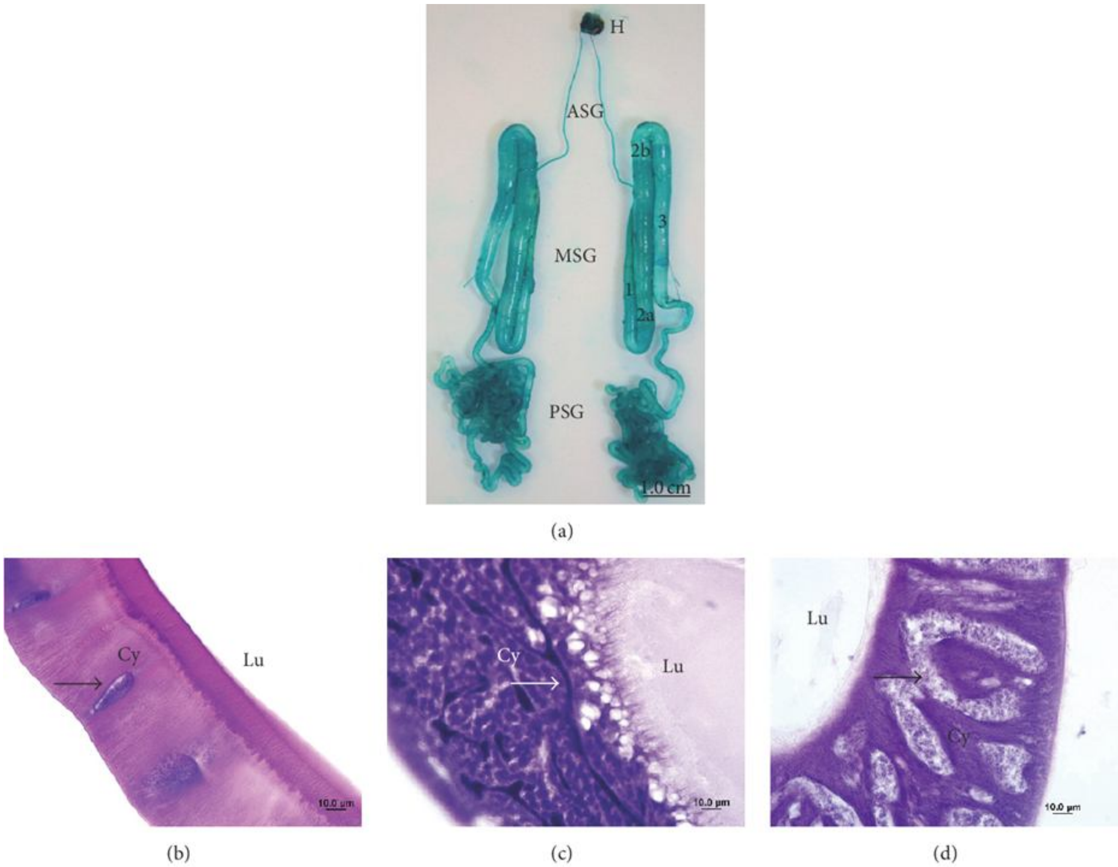

Figure 1: Photography of Bombyx mori silk gland (a), stained with light green 1%. Anterior (ASG), middle (MSG), and posterior silk gland (PSG). MSG and its areas: anterior (1), anterior-middle(2a), posterior-middle(2b), and posterior (3). Head (H). In (b), (c), and (d), photomicrographs of different regions anterior, middle, and posterior, respectively, stained with haematoxylin and eosin. Cytoplasm (Cy), nucleus (arrows), and lumen (Lu).

(Source: Silkworm sericin: properties and biomedical application.)

Sericin Extraction:

Sericin can be extracted from silk by detaching it from the fibroin part. Only Fibroin part is demanded in silk industry so removal of sericin is needed and is done by degumming process which later discarded. The load in effluents can be lighten by the refurbishment of sericin from the degumming water by making us to get a biopolymer having various important properties. Different methods are available for extraction of sericin. Sericin can be extracted from fibroin by boiling [48], use of soap [49], alkali [50], organic solvents like tartaric and citric acid [40], enzymatic methods based on proteolytic enzymes [51]. Another method is the use of high temperature and high pressure to remove sericin from silk.

Presently several methods are adopted by researchers to extract sericin. Separation of sericin established looking upon its solubility in hot aqueous solutions. The solubility escalates significantly in the augmented alkaline or acidic solutions [52]. Effective degumming process using soap and alkali were preferably used for the complete withdrawal of sericin [18, 40]. When sericin is of more significance this method is not generally used because separation of soap from sericin is very complex process and after all if small traces of soap are left application of sericin becomes complicated. It can also be extracted using certain acids like citric, tartaric, and succinic acid etc. temperature should be kept at boiling while using acidic conditions [35, 51]. Acids and alkalis have degrading effect on proteins and sericin being proteinous nature can get damaged while extraction. So, extraction in urea solution with 2-mercaptoethanol becomes useful having lesser degrading effect on sericin and damage can be downplayed. Using this process around 95% of the total sericin present can be separated out without any damage [53]. But this is costly and time consuming because before application, purification of sericin is required and is done by dialysis procedure.

Extraction of sericin is done by using alkylase or with2-2.5g/L alkaline protease at 60□ for 90 mins, at pH 10. Hydrolysis with trypsin at different concentrations, temperatures and treatment times is employed for extraction of sericin. For 1% of trypsin solution the hydrolysis is almost complete in 10 and 34 h at 37 and 20□, respectively. The amount of sericin obtained by 4 h treatment with 1 and 8% of trypsin solution is 26.4 and 28.7%, respectively [17]. But the huge expances and sensitivity to working condition of enzyme confines the use of this method for extraction purpose [48].

Hot water extraction is the most widely used method due to above constraints for extraction of sericin. In this method silk is heated in hot distilled water without adding any chemical. Time and temperature play an important role in the amount of sericin extracted. Though this method causes the degradation of sericin but yet degradation is to an extent that sericin still retains its important properties. It has been reported that temperature can be applied to the system either by boiling at atmospheric pressure [47], HTHP (high temperature high pressure [54, 55], IR (infrared radiations) [49] or microwaves [53]. However sericin extraction by HTHP method is free of chemicals but produces fumes, is messy, time consuming and may damage fibroin [47].

After extraction sericin is refined to powder form. In different studies researchers have tried various processes like membrane filtration [56, 57], ethanol precipitation [45, 7], freeze drying/tray drying [58] and spray drying [7] to isolate sericin.

Table 3: Degumming process of silk Sericin

Sl no.	Degumming procedures	Limitations	Advantages	References
1	Boiling	Time consuming, damages fibroin and time consuming	Simple process	[48]
2	Enzymes	Degrades sericin majorly and costly	Saves chemicals, water and energy	[53]
3	Soap and Alkali	Difficult in sericin recovering, effluent problems	Mostly used and simple process	[59]
4	Organic acid (Tartaric acid, citric acid)	Non efficient and effluent problem	Compassionate as compared to alkali	[60]
5	High temperature high pressure (HTHP)	Causes bad smell, fumes and degrade fibroin	Impurities are not produced	[53]

Sericin based nanoformulation and molecular mechanism

Sericin is widely used in medical and cosmetics formulation but their molecular formulation persists ambiguous concerning differential properties, these are the property responsible for nanoformulation and therapeutic effectiveness. Chemical structure is the essential factor for the nanoformulation of sericin. The bioactive molecule which is to be conjugated with sericin, their molecular mechanism and biodegradability is accountable for laboratory formulation in nanotoxicological aspects and therapeutics that is immunogenicity and biocompatibility. The oxygen scavenging effects which is also reactive of sericin based nanomaterial are imputed to primary structure of sericin amino acids [61, 62, 63]. On mitochondrial structure conservation elaborates the antioxidant properties of sericin. By controlling the NADH- ubiquinone oxidoreductase (which is a respiratory complex), the prohibitin-2 and mitochondrial elongation factor 2, intracellular proteins which generally controls the death of cell by apoptosis and process of necrosis. Apart from this, sericin also modulate other enzymatic activity such as beta-hydroxybutyrate dehydrogenase and acyl-CoA synthase, carnitine palmitoyltrasferase 2, and aconitate hydratase by controlling the metabolism lipids into hepatocytes [64]. All those factors contain a major outcome in momentous nanoformulations, which is used for clinical trials in place of traditional therapeutics.

Several methods are reported for the preparation of sericin conjugated nanoparticle, which are mainly based on decreasing of hydrophobic interactions and protein unfolding in linking the chemical groups and protein structure. For manufacture of silk conjugated nanoparticles several basic methods such as self-assembly, desolvation, and salting-out are generally used, these techniques use light processing conditions and very simple to achieve [65,66]. Different methodologies are used for the manufacture of nanoparticle conjugated sericin, which include supercritical fluid techniques, electro spraying, capillary microdot printing,electric filed and microemulsion. Dessolvation, self- assembly and cross-linking are the most used techniques for the synthesis of sericin based nanoparticle [67]. Out of these, the frequently used technique to produce protein-based nanoparticles is desolvation. Double desolvation method followed by some researchers To get condensed and thin size nanoparticles, several researchers follow the double desolvation method [68].

Application of sericin conjugated nanomaterials:

Different perspectives have been studied for sericin. Taking into consideration for numerous biological applications such as anti-aging, antimicrobial, anti-inflammatory, hepato-protective, UV-protectant, antioxidant, anti- cancer, antiviral, wound healing, in association with engineered nanoparticles Sericin has potential use for cutting-edge therapeutics.

Tahir *et al*. (2020), estimated the antibacterial activity of sericin based silver nanoparticles [69]. The growth of *Escherichia coli, Klebsiella pneumonia* and *Staphylococcus* *aureus*, is reduced due to the biogenic engineered nanoparticle(synthesized using biological organism). Besides, sericin conjugated nanoparticles were very much stable at different pH and temperature and also most effectual against bacteria. So, it is concluded that sericn based silver nanoparticles holds a pronounced antibacterial activity, which suggests that a wide range of applications with a cheap-priced and established antimicrobial agent. Pankongadisak *et al.,* (2018), invented gentamicin sulfate-based Poly (L-lactic acid) sericn fusion scaffolds. These engineered nanomaterials contains strong potential against the *S. aureus* TISTR 1466and *E. coli* TISTR 780 [70]. Sericin, chitosan, and glycerophosphate combined with the longan seed extracts were also used for the antibacterial study [70]. Several biomedical applications are demonstrated such as wound dressing, artificial skin, and tissue engineering was also studied for the dialdehyde carboxymethyl cellulose and silk sericin [71,54]. Therapeutic nature of sericin for epithelial corneal regeneration in mice using the mixture of sericin and hard magnesium hydroxide engineered nanoparticle described by Nagai *et al.,* (2019) [72]. Shah *et al.,* (2019), prepared a Chitosan-sericin- silver nanocomposite films [73]. For wound care applications these findings recommended strongly the use of chitosan sericin silver nanocomposite and the trials have been done for wound dressings using sericin composites clinically. The silk sericin conjugated nanofibrous mats using poly vinyl alcohol-sericin blended mats studied by (Gilotra *et al.,* 2018) for wound healing applications [74]. Sericin-based dressing is a potential engineered nanomaterial is effective for the curing of chronic wounds like diabetic foot ulcers. There are several compounds, such as silver nanoparticles/ Agar Film Sericin/ [75], poly (ethylene terephthalate) fibers associated with sericin-capped silver nanoparticles, poly-L-lysine-conjugated sericin nanoparticles [76], Sericin and Glycerol Films conjugated with silver nanoparticles [77]. Sericin in bionanomaterials contains antibacterial characteristics. Liu *et al.,* (2018), developed a silver nanoparticle to control *S. aureus* and *E. coli* and polyelectrolyte membrane (PEM) modified sericin/Agar films [78]. However,other nanoformulations which contains sericin, have been used in medical applications like ZnO nanoparticles on Sericin/Polyvinyl Alcohol Composite Film [79] and sericin-capped gold nanoparticles [80].

Different sericin formulation

The biological activities which are connected with its simple functionalization shaped more possibilities for designing varieties of materials which includes hydrogels, films, and sponges, particularly, for skin tissue regeneration. Sericin traditionally transplant polymers like alginate, chitosan, methacrylate and gelatin which open direction for improvement of resourceful materials for dermal sealant, and human skin artificial equivalents. Hydrogels, planned for regeneration of skin shows favorable result on wounded skin recommending the additional practical revitalization which is the most well-described matrices [81], He reported the use of a UV photo-cross linked hydrogel nanoformulation formed of sericin- methacrylate. Due to various molecular mechanisms, the skin regeneration index is enhanced and decrease in swelling is seen, which includes angiogenesis stimulation. β3 and TGF-β1, which are known to be growth regulator improve the curing process. Various sericin conjugated systems have been emerged as innovative ideas. For example, sericin-polyvinyl alcohol combines and forms a film act as a foundation for silver nanoparticle formation in laboratory having significant antibacterial activity towards the culture of *Staphylococcus aureus* and *Escherichia coli* [82].

Biological Applications of Sericin

Biomedical Uses

Silk fibers are used in medical field because of its compatibility [83]. The instigation of immune system is due to silk proteins. Sericin accredit hypersensitivity reaction [84]. Sericin both have anticoagulant and antioxidant properties [18]. The antioxidant nature of sericin is due to serine and threonine content [85]. This protein reduces the oxidative stress in the colon of human and also is responsible for the reduction of cancerous cells. Sericin effectively supress the amount of 1,2- dimethylhydrazine which is a colorectal cancer-causing agent and it is noticed that when sericin is taken orally by rats and mice it eliminates the cancer-causing agent thus by reducing the chances of cancer [86, 87]. Sericin is considered to be a best component in cosmetics and food industries. It has been shown that sericin activates the apoptosis factor and decline the growth of tumour cells. Sericin upgrade proliferation and attachment of keratinocytes and fibroblast in the human skin [88].

Vehicle for drug delivery

For the chemical nature of sericin, it can be used for drug delivery. Various molecular size and concentration of sericin is used to produce gel and sponge and the sericin can be used for the release of drug protein which is charged [89]. When a drug's release profile is reliable as well as controlled, with a delivery system being compatible and presenting an adaptable morphology, as the silk proteins, then only its distinguished effect is obtained. The chemical reactivity of Sericin permits easy binding of other molecules and pH receptivity which helps in fabrication of small materials and is used for drug delivery.

Wang *et al* (2014) manufactured a pure 3D sericin gel which is covalently crosslinked. This gel becomes an injectable material and allows long term survival and cell adhesion and it possesses different chemical and physical properties and which provides the drug release capacity providing multi- purpose stage for cell therapy [90]. The properties of alginate hydrogels can be improved by sericin and this has different edges particularly in migration, photoluminescent property, degradation, and cell adhesion. It is investigated from the above theory that the sericin may serve as a versatile platform for delivering drugs and cells. The sericin may be used pure or conjugated with others polymers to form particles, matrices, and hydrogels which improve the drug delivery capacity.

Metabolic effects

The antioxidant property of sericin makes it to be used in the gastrointestinal tract. Sericin is used as a supplementation in animal for constipation [91]. As it encourages the health of colon by harmonizing the defencing capacity of the body and it also can be contemplated as prebiotic.

Okazaki *et al*. (2011) to appraise the effect of sericin on the intestinal lumen of mice, supplemented the rats with 40 g/kg of sericin for 3 weeks [92]. This study revealed that sericin increases the quantity of immunoglobulin A (IgA) faecal in the colon, which lesser the risk of ulcerative colitis and colon cancer [93], and increased the presence of faecal mucins and wet weight of faecal matter, which is responsible for the reduction of lipoproteins having low-density. Therefore, sericin can be scrutinized as a prebiotic, as the colon health is improved or upgraded because of sericin which harmonize the immune response and the intestinal barrier function. The potential of anticoagulation of sericin was observed. The serine residue extracted from cocoons of *B. mori* is sulphated using chlorosulfonic acid by the scientists. It was observed that higher the molecular fractions higher will be the anticoagulant activity, estimated to be 1/10 to 1/20 of heparin.

Use in Cosmetics

Sericin used in cosmetic formulation, such as creams and shampoos, leads to an increase in cleaning with minimum irritation, hydration, antiwrinkle and antiaging effects [94] and protects nails from cracking and being fragile. Specifically, these applications are for the existence of amino acids with hydrophilic side groups (80%), for instance serine (30 to 33%), which has water absorbing capability. The sericin form a smooth and soft film on the skin surface which prevents the deprivation of water [95].

The study in the laboratory disclosed the action of sericin to lessen the resistance and increase in the hydration level and hydroxyproline of the epidermal cells and the moisturizing nature of sericin on human skin and [96]. The occlusive effect of sericin was accredited due to increase in hydration, which averted the trans epidermal water loss, accountable for dehydration of skin. It is still argued by the authors that sericin has same amino acid configuration like filaggrin which exist in the stratum corneum of the skin and is natura, hydrator of skin; and, thus, sericin is a vital moisturizing agent.

Diseases of skin such as ictiosis and atopic dermatitis is because of the dryness of skin which is responsible for the degradation of free amino acid in the stratum corneum. The utilization of sericin resulted in the increase of filaggrin and free amino acids, also increase of caspase-14, peptidylarginine deiminase-3 (PAD3) and peroxisome proliferator-activated receptor (PPARγ) molecules which are responsible for the recovery of dry skin by increasing the profilaggrin and filaggrin degradation of free amino acid. Therefore, sericin is useful and an ultimate way for the treatment of atopic dermatitis.

Sericin for tissue engineering

Burn dressing

The healing of wound is a complex process including an automatic series of events which combinedly referred as "cascade of healing" in order to restore the wounded tissue. The cascade of healing is classified into 4 overlapping stages that is hemostasis, inflammation, proliferation and remodeling [97, 98]. Burn is characterized by changes in erythema to whole damage of the affected part. Multiple surgeries, disability and mortality, long duration of hospitalization and rehabilitation with expansive medical costs are the result of burn injury [99]. To prevent infection the burn need to be treated as early as possible so the epithelialization can be induced [100] and the Antimicrobial agents are always prepared to avoid the infection related to sepsis caused by the burn [99].

In the wound healing process the sericin has been used in regenerative medicine to maintain the rapid multiplication of keratinocytes and fibroblasts [101]. According to aramwit et al, This sericin can reduce the growth of fibroblasts and collagen production without any activation of pro- inflammatory cytokines. It can be used to treat burns, prevent infection and reduced scars and also employed as wound dressing cream to control the infection [97, 73].

Oral gargling

According to Kurioka *et al*, Sericin inhibits the tyrosinase activity and it is studied that tyrosinase has high impact on skin pigmentation. The skin treated with sericin having high level of hydroxylproline as compared to the skin treated with distilled water. The hydration level increased when sericin gel applied to the skin [96]. Xerostomia, also known as dry mouth, which is associated with hypofunction of the salivary glands or don't make enough saliva to keep the mouth wet. Generally this condition is seen in elderly people. Sericin increases the hydration rate and can be used for gargling which is beneficial for those people suffering from xerostomia. In addition to it is proved that sericin stabilize wound healing [88]. According to kumar and team, mulberry leaves is used for oral gargling and silk worm eat mulberry leaves and 70% of mulberry proteins are used for the production of cocoon. Besides this wound healing and increase hydration properties are enough to support the use of sericin as an oral gargling agent [102]. Taking in to consideration, the beneficial effect of sericin regarding wound healing and increasing hydration, the manufacture of oral gargles containing sericin will increase probably.

Bone regeneration

In severe bone defects self-healing is very infrequent and need non- natural bone replacement for therapy [103]. In tissue engineering sericin has been used, for example renovate of connective and epithelial tissue [104]. Deficiency of mechanical strength in sericin makes itself less applicable for bone regeneration however also the mechanical properties of sericin are appropriate for soft tissue engineering [105, 103]. Yet, the novel silk sericin with some alternation can be applied as an unnatural bone replacement for severe bone damage as it improves both mechanical and bone inducing properties.

For bone tissue engineering sericin is not applied as scaffold because of poor mechanical properties. According to Zhang and team, the composite of hydroxyapatite and sericin films could balance the feasibility of osteosarcoma MG-63 cells in human because of the deposition of hydroxyapatite; hence, the these films can be applied for bone regeneration [106]. Hydroxyapatite and sericin nanocomposite increases the cell viability and is nontoxic [107]. For the repair of bone tissue, Qi , designed a graphene oxide/sericin methacyloyl hydrogel as a scaffold with mechanical strength and osteoinductive capability and this scaffold had good cell adhesion properties, cell proliferation and migration ability, biocompatibility and osteogenic induction properties.After implantation , this scaffold fruitfully build up new bone regeneration and persuade autologous bone marrow- derived mesenchymal cell differentiation, and the entire process of functional and structural repair occur within 12 weeks. So sericin conjugated biomaterials can be employed in bone tissue engineering [103].

For other tissues regeneration

Previously it is mentioned that sericin has been used for nerve or cartilage regeneration. Dinescu studied that with improved hyaluronic acid and chodroitin sulfate collagen sericin scaffold can be used as a non permanent physical support for human adipose – derived stem cells for cartilage tissue engineering. In cartilage tissue engineering hyluronic acid and chondroitin sulfate are the 2 mainly valuable factors used in the design of biomaterials where as the adipose – derived stem cells show high chondrogenic potential [108].when the chondrocyte- laden sericin methacryloyl hydrogel injected to the rat model, it takes 8 weeks to form artificial cartilage; and this cartilage showed molecular, histological and mechanical resemblances to natural cartilage.

The pure sericin channel used for peripheral nerve reconstruction in a rat injury model is reported 1st time and for the reconstruction of injured peripheral nerves, the sericin nerve guidance channel can be used as an substitute to autologous nerve graft [109]. It is reported a carbon nanotube and sericin nerve channel can help successfully the structural and functional healing of nerves as compared to the autograft.

Conclusion

Sericin with its several valuable properties has emerged as a commercial resources in many industries like cosmetics, pharmaceuticals, food and biomaterials. Sericin becomes precious biopolymer due to its environment friendly properties and numerous valuable applications. Sericin has wide application in the field of pharmaceuticals, biomedical and textile industries. It is used as anti aging agent in cosmetics. Properties such as antibacterial, anticancer, anticoagulant, hydrophilic, moisture absorption, antioxidant ,biodegradability and cell compatibility as well as UV-protection have enabled its for cosmetic as well as biomedical applications. In 21st century, nanoscience has gained more attention from researcher due to its unique properties. Nanotechnological innovation offer interesting biological as well as physiochemical properties which are significantly promising in biomedical and tissue engineering due to its small size, ability to interact with concerned tissue and large surface area. These are widely applied in a variety of fields such as drug delivery, cancer therapy, bio detection of pathogens, electronics etc. However due to lack of awareness sericin is discarded as effluent by the industries. So far some major studies have been performed still more detailed clinical trials and studies of sericin need to be carried out for their possible applications in the area of cosmetics and pharmaceutical. Sericin-based nanoformulations can be an excellent example of biocompatible, biodegradable compound and economically viable, as well as its used as nanomedicine. As we know the future of sericin will be promising. So, further research is though required. Considering, sericin which is a by product of silk manufacture, this protein has potential value from both ecological and economic viewpoint with promising food and biological application and will support silk industry to make value added products.

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