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Review on Medical Application of Spider Silk

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Abstract

The natural world is the source of many therapeutic products. Spiders evolve about 374-380 million years ago and *Attercopus fimbriamguis* is known to be the oldest spider species. Spiders produce several types of silk. Spider silk is important because of its maximum mechanical strength, biocompatibility and biodegradability, pore filling ability and very low immunogenicity. Spider silk has fascinating combination of properties that makes it an extremely attractive candidate for numerous applications in medicine. Spider silk fibers possess two small coating peptides SCP-1 and SCP-2. These two peptides involved in anti-microbial role of silk. Anti-fungal and anti-microbial compounds such as bisphosphonates peptides, phospholipids hydrate and potassium nitrate were also observed in silk fibers. Spider silk contains peptides and biomolecules that able to stimulate and improve conditions of wound healing.

Keywords: Antifungal, Antimicrobial, Silk, Spider, Wound Healing

Introduction

Spiders evolve about 374-380 million years ago and *Attercopus fimbriamguis* is known to be the oldest spider species [1]. At present, spiders constitute a diverse group of 114 families, 3935 genera and 44,906 species occurring worldwide [2]. Spiders have six or seven sets of glands spun having different fibers. Spiders are well-known for their silk-using skills. More than 40,000 species of spiders have been identified to produce silk [3], most of which catch prey by using silks. They have evolved to be able to produce a variety of task-specific silks for activities such as catching prey, escaping from predators, and protecting egg sacs [4]. Spider silk refers to a wide range of continuous filaments spun by the several species of Arthropoda[5]. Silks are critical for the survival and success of all species of spiders [6].

All most all spiders produce silk throughout their lives, and most are capable of spinning multiple types of silk threads. Spider silk threads are extruded from discrete glands through individual spigots located on their abdominal spinnerets. The silk threads are assembled nearly instantaneously from liquid feed stocks, or ‘‘dopes’’, of protein at ambient temperatures and without caustic chemicals [7]. The substantial interest in spider silk is therefore primarily motivated by the potential to exploit spider silks’ incredible mechanical properties for applications ranging from high performance textiles to medical devices [8, 9]. The web of spider or silk get with respect to nature of spider, Ground spiders construct their webs on grounds and predate on crawling insects. While the other spiders have Ariel traps specifically designed to capture flying insects. Apart from capturing prey the web of spiders is also a place of retreat that saves them from predators and external influences [10].

Spider silk has fascinating combination of properties that makes it an extremely attractive candidate for numerous applications in medicine and industry [11] such as conduits in repair of peripheral nerve injury [12] and pharmacological activities like inflammatory and wound healing activity [13], An Antibacterial Activity [14, 15] also mixture of spider dust with different medicinal plant can cure various types of diseases. Spider silk useful in drug delivery and release [16] and Human bone marrow stromal cell and ligament fibroblast responses on Rat Genome Database modified silk fibers [17]. Spider silk is an innovative material in a biocompatible [18]. The silk's morphologies and its biocompatibility are much of desire for it elicits less or no immune response in hosts [19].

Applications of spider silk in medical field and life-sciences are increasing nowadays [8]. Spider silk possess outstanding and valuable therapeutic, wound healing and regenerative properties [20]. This makes spider silk a remarkable and extraordinary biomaterial [21, 22]. The growing need for new therapeutics in wound healing has fuelled the initiative to explore the potential of spider silk in medicine [23]. Intensive efforts are underway to discover natural biochemical agents that can promote wound healing. On account of its fine sized fiber, spider webs are thought to have great clotting potential [24]. Silk is rich in vitamin K, which plays a direct role in clotting of the blood [25]. Silk-derived biomaterials being biocompatible to the human tissues are usually used in surgery including Bandages and surgical threads [18]. Therefore, the objective of this seminar paper is to review on medical application of spider silk.

2. Spider silk production and structure

2.1. Spider Silk Production

Spiders are unique in their reliance on silk throughout their lives, their diverse uses of silk, and their production of toolkits of as many as seven or eight different types of silks, each of which have a unique chemical composition and come from its own discrete gland(s) and associated spigot(s) [26, 27]. Specifically, web building spiders can produce six types of silks each exhibiting different function [28]. Ampullate glands produce fibers that are used in dragline, frame and radii thread; piriform glands produce fibers used in attachment disks; aciniform glands produce fibers used in swathing silk, silk decorations, male sperm web and soft inner layer of the egg sac; tubuliform glands produce fibers used in egg sac silk; aggregate glands produce the glue of sticky spirals; flagelliform glands produce the axial thread of sticky spiral fibers[4,29]. Aciniform silk is remarkable for its extreme toughness, and the dragline silk that is major ampullate silk is the strongest fiber [26].

Silk proteins are initially secreted in the tail of the major ampullate silk gland and stored as a liquid dope in the lumen of the gland at high concentration, up to 50% wt/vol [24].Shear forces, water uptake, and ion exchange in the funnel and duct cause a phase shift so that new secondary structures form in the spidroins. These structures interlink individual molecules, causing the silk to solidify. A muscled valve provides a final draw down as the fiber exits the spigot, influencing the alignment of the molecules along the axis [30]. With fibroins packed together in micelles that isolate the central repetitive modules of the fibroins in the interior [31, 32].

Solidification of the fiber occurs when the structure of these micelles is disrupted such that the termini can dimerize, and the crystal forming motifs in the central repetitive regions of the proteins are no longer isolated so that their hydrophobic nature instead leads to the formation of b-sheets that stack together and interlock individual fibroins [32, 33]. This process is mediated by a combination of water resorption, ion exchange, drop in pH, and shear flow as the dope passes through an elongated ‘‘S’’- shaped duct [33]. A final draw-down of now solid, but still wet fiber occurs at the narrow distal end of the duct, which is mediated in part by a muscled valve in orb spiders [34].

2.2. Spider Silk Structure

The fundamental building blocks of the spider silk biopolymer are amino acids (43). Amino acids prevent the silk fibers from drying by tending to absorb moisture from the air. All spider silk threads are mainly composed of one or more proteins, called spidroins, which tend to be large up to 350 kDa per monomer. All spidroins share a common primary structure pattern comprising a large central core of repeated modular units, accounting for approximately 90 % of the amino acids of the protein, flanked by non-repetitive domains. These non-repetitive terminal domains have a folded globular structure and are comprised of approximately 100 – 140 amino acids [35, 36].

Amino acids sequences are highly conserved throughout different spider species and silk types [37]. Silk fibers have a core shell type structure and are typically composite materials formed of silk protein(s) and other associated molecules such as glycoproteins and lipids [38]. The fibrous silk protein is mainly composed of fibroin and sericin. Silk Fibroin consists of layers of antiparallel ß crystalline or pleated structures which rich in amino acid Alanine and Glycine. The ß crystalline structure contributes to its high mechanical strength and had much influence on the degradability property of silk as the biomaterial [39].

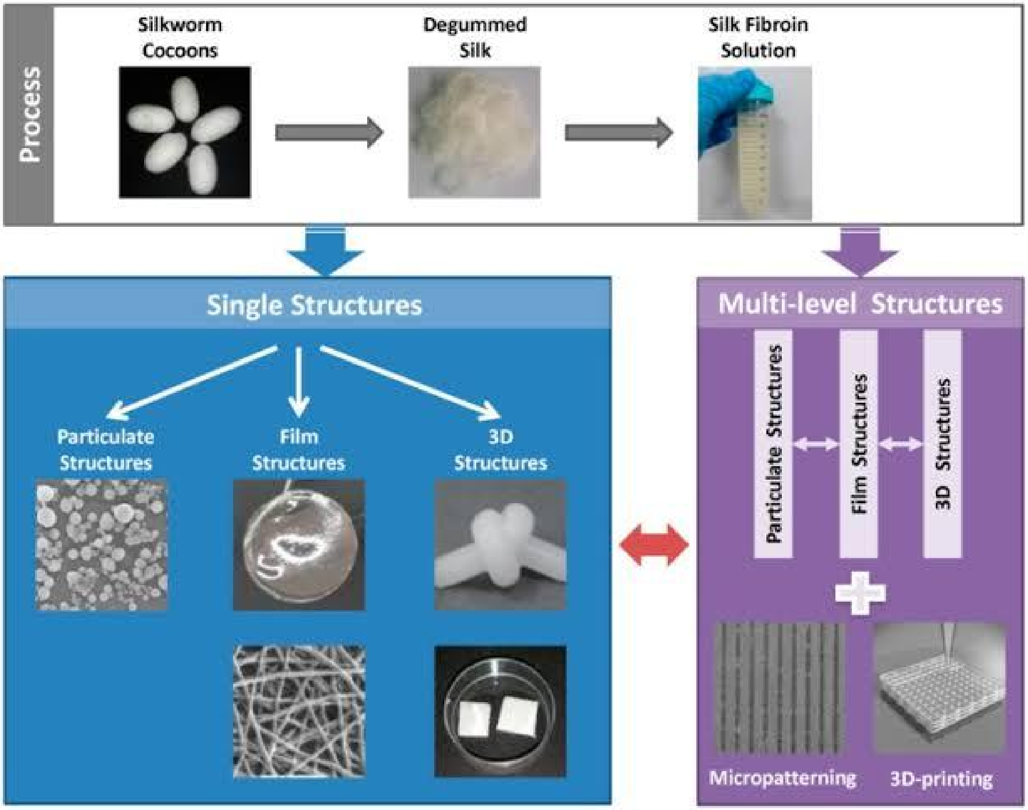

Fig 1. Structural design of SF based material from single structure to multi level structures reproduced from [40]

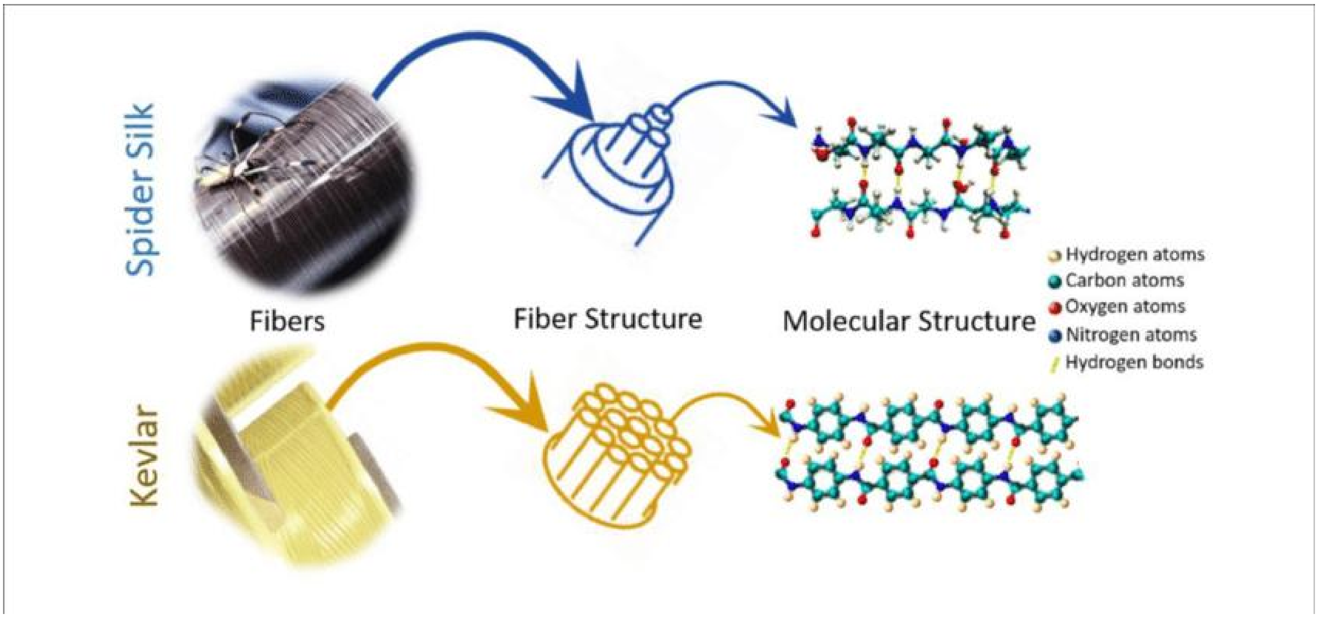

Fig 2. Comparison between spider silk and Kevlar fiber [41]

3. Properties of spider silk

Spider silk exhibit different physical and biological characters due to their different amino acid sequences, spinning conditions, and hierarchical structures. The hierarchical structures of spider silk proteins vary among silk types. Spider silk is very large molecular weight; hydrophobic, thermally stable at very high or low temperature are some of the properties of silk which depend on the sources, conditions for instance climate and ambience apart from how they are produced. Silks obtained from the forced silking have different features and properties when compared with the silks obtained from freely walking spider [42,43].

The mechanical properties of silk fibers spun by spiders vary depending on many extrinsic and intrinsic factors. Spider major ampullate (MA) silks vary in mechanical properties in response to various environmental stimuli, such as humidity, ambient temperature, wind, and solar radiation [43]. The factors involved in determining strength and load tolerance response of silk fibers mainly include heat, and exit rate. Mechanical properties of spider silk also depend upon the way of spinning as well as chemistry of constituent amino acids [24].

The total number of ‘small’ amino acids (serine, alanine and glycine) is taken to be an indication of crystal forming potential. However, different types of silk and even the same silk can show different amino acid make up [29] and furthermore it is believed that the large differences in silk‟s mechanical properties are the result of the way in which it is spun [24] rather than simply a product of the amino acid composition.

Table 1. total no. of amino acid from spider

Amino Acid	Spider frame	Viscid Silk
Glycine	372	442
Alanine	176	83
Serine	74	31
Proline	158	205
Acidic	58	30
Basic	11	31
Aromatic	45	37

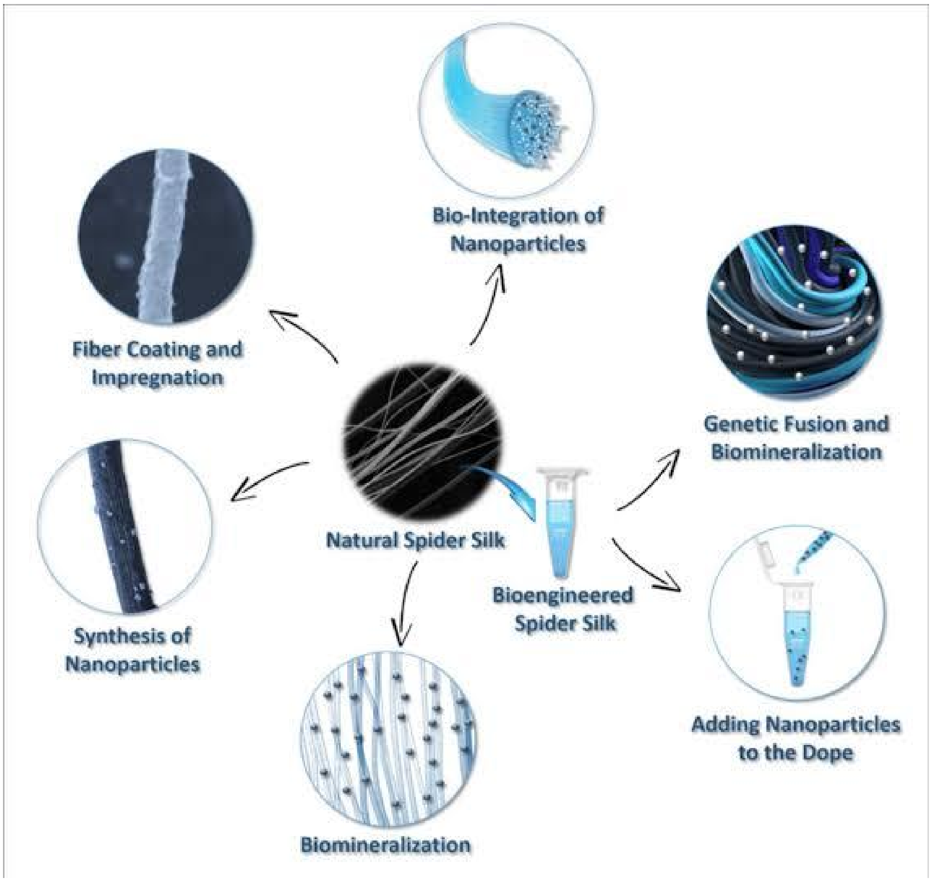

Fig 3. Summary of techniques for creating spider silk-based hybrid materials [44]

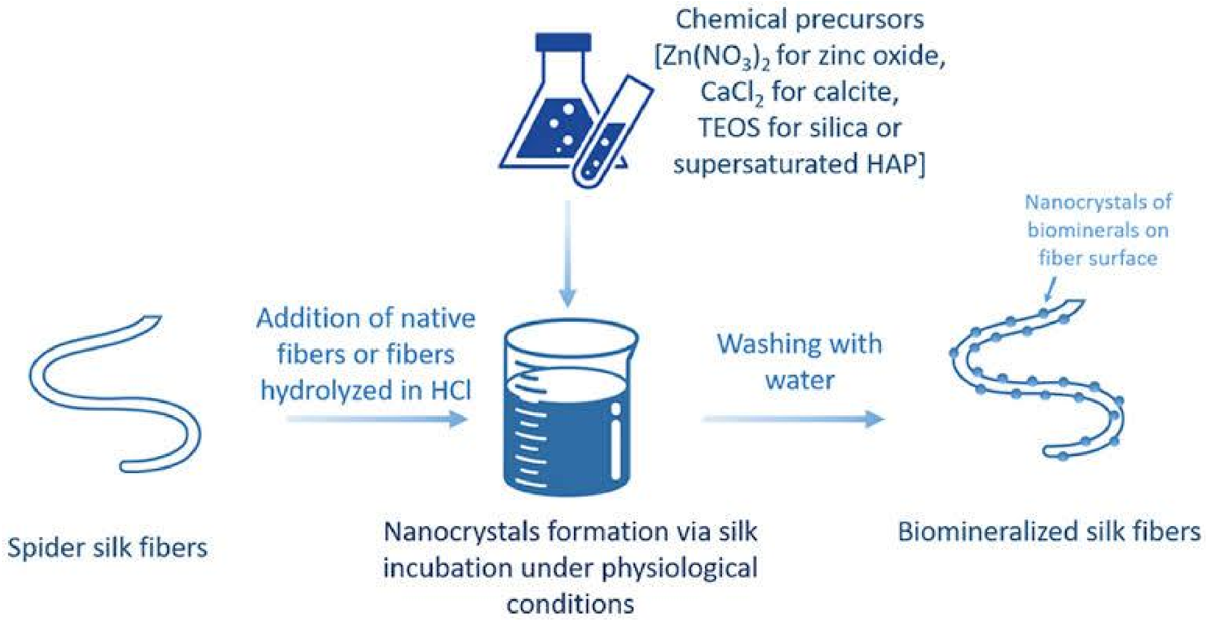

Fig 4. Schematic illustration of using natural spider silk for the synthesis of nanoparticles in hybrid material formation [45].

4. Medical applications of spider silk

Spider silk fibers possess two small coating peptides SCP-1 and SCP-2. These two peptides involved in anti-microbial role of silk [46]. Anti-fungal and anti-microbial compounds such as bisphosphonates peptides, phospholipids hydrate and potassium nitrate were also observed in silk fibers [36]. Micro-organisms are unable to grow on spider silk because of its acidic nature. Antimicrobial activity of spider silk is because of soluble/ non-soluble growth restraining factors in silk [46] or surface or structural property of a material [47]. Silk of Neoscona inhibit the growth of fungus on bread. These all chemical elements present in silk are very important in enhancing the economy of country because these kill those microbes that are damaging crops, fruits, decomposing food above threshold level and also dispersing many epidemic disorders [48].

4.1. Antimicrobial Activity of Spider Silk

At present age of alarming health concerns that spider silk could prove a miraculous substance having potent antibacterial activity. The lipids present in spider silk contain 12 methyltetradecanoic acid and 14-methylhexadecanoic acid that inhibit growth of microbes. Many studies have also exposed that 12-methyltetradecanoic acid prevent the growth of rice pathogen, Magnaporthe oryzae. These anti-microbial compounds are amino acids such as glycine, alanine and huge quantity of pyrrolidine in silk fiber [35, 49].

Wright and Goodacre [15] reported that spider silk has anti-microbial activity against Bacillus subtilis (Gram negative bacteria) but no bacteriostatic action was observed for Gram negative bacteria (Escherichia coli). These anti-microbial compounds basically induce growth inhibition zone in both gram positive and gram-negative bacteria i.e., Listeria monocytogenes and Escherichia coli [50]. Gram positive bacteria are more susceptible than gram negative bacteria by spider silk when its growth inhibition effect was seen [51].

Acidic conditions are not suitable for growth of fungus and many pathogenic and silk protein digesting bacteria therefore this silk is protected from bacterial attack. Potassium nitrate in spider silk also inhibits bacterial growth and hence protects silk from degradation [52]. Spider silk proteins have strong antimicrobial action against a broad spectrum of pathogenic bacteria and are capable of sustaining the proliferation of mammalian cells[53]. There is also possible evidence that the web silks of Zilladiodia and Linyphiidae spiders have an inhibitory effect on the growth of *B. subtilis* bacteria. Furthermore, silk of *Lasiodora parahybana* is also shown to possess some antimicrobial activity [54].

Antimicrobial properties of spider silk can also be influenced by spider diet and environmental conditions. Contamination of the spider silk by the ground had negative effect on its antibacterial properties [54]. The spider silk extract in formic acid was employed for membrane dialysis and re-dissolved in in dimethyl sulfoxide. The DMSO fraction of *Pardosa brevivulva* silk was able to inhibit the growth of gram-positive B. megaterium and two gram-negative bacteria S. typhi and K. pneumoniae. The activity of spider silk showed a dose-dependent response; with increasing concentration of silk the activity was increased [48].

Roozbahani *et al.* [48] reported that silk of Pholcus phalangioides against two bacterial foodborne pathogens viz. Listeria monocytogenes and *Escherichia coli* and greater inhibitory effect on gram-positive bacteria L. monocytogenes than gram-negative bacteria *E. coli* [51]. Antibacterial potential of silk of Nephila pilipes and reported that has ability to inhibit the growth of Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa [48].

Gomes *et al.* [53] assessed for antimicrobial activity of genetically engineered spider silk against gram-negative Escherichia coli and gram-positive Staphylococcus aureus and reported prominent activity against E. coli as compared to S. aureus. Al-Kalifawi and Kadem [55] reported the antimicrobial activity of *Tegenaria domestica* silk against both gram-negative and gram-positive bacteria.

The *T. domestica* silk was tested to see if it had an effect on the growth of mammal cells. The data suggest there is no evidence that the presence of spider silk inhibits the growth of mammal cells. As spider silk is not naturally exposed to mammal cells there would not be an advantage conferred on the spider if its silk inhibited mammal cells. Snail slime which has been found to be antimicrobial has also been found to not affect mammal cells. But many antimicrobial compounds also have a negative effect on mammal cells so are not useful for medical applications. If the antimicrobial properties of spider silk were used in mammal cells it appears that the mammal cells would not be negatively 105 affected. While it is not known how much of the antimicrobial agent was introduced to the mammal cells it is known that it was at concentrations that are able to affect bacteria [53].

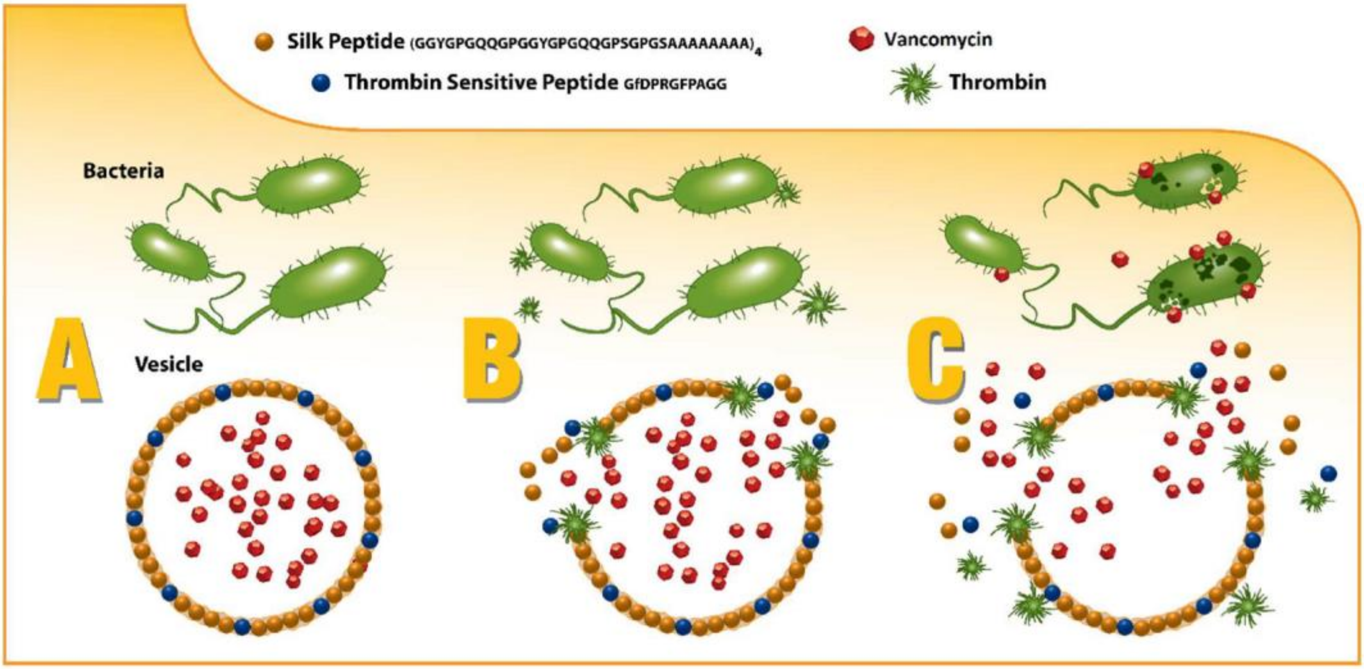

Fig 5. Graphical representation of the infection responsive release of the drug triggered by bacterial enzyme [56].

4.2. Anti-Fungal Activity of Spider Silk

Spider silk is not readily decomposed by microorganisms due to its acidic property. Another compound potassium nitrate is believed to prevent the protein from denaturing in the acidic milieu. These properties of spider silk make it a good candidate for preservative and acts as antifungal agent [49]. Spider silk against fungal strains does not give similar results as compared to the bacterial strains. Antimicrobial peptides create an acidic environment above pH of 4 which is not suitable for fungal growth [56, 57]. *P. brevivulva* silk showed activity against Aspergillus flavus, Candida albicans, Ustilago maydis, and Alternaria solani[12].

4.3. Wound Repairing and Nerve Regenerating Potential

Spider silk play important role in the regeneration of many tissues and body cells such as skin, nerve, bone, and cartilage [58,59]. Many damaged connective tissues such as tendons and ligaments can also be repaired [60]. Spider silk films supply structural support and induce regeneration in the tissues [59].

The growing need for new therapeutics in wound healing has fueled the initiative to explore the potential of spider silk in medicine [23]. Intensive efforts are underway to discover natural biochemical agents that can promote wound healing. On account of its fine sized fiber, spider webs are thought to have great clotting potential in addition to bactericidal properties [24]. Silk is rich in vitamin K, which plays a direct role in clotting of the blood [25]. Silk-derived biomaterials being biocompatible to the human tissues are usually used in surgery [18].

Silk of P. phalangiodes and C. lyoni web caused a higher rate of wound healing and reduced the epithelialization period significantly than the natural untreated healing. Both of the species turned out to be functional in improving the overall wound conditions and epidermal cell proliferation due to blood clotting and antibacterial action of silk proteins [53]. Native spider silk is biologically active and do not require further modification for wound healing application [61]. Spider silk antimicrobial peptides and bioactive molecules have shown stimulations of specific cells such as monocytes and T-cell which are beneficial for wound healing [62] and on nerve regeneration application [63]. These antimicrobial peptide functions as chemotactic agent to stimulate wound healing process by activation the acquired immune response system [64, 65]. The positive stimulation on fibroblasts and epithelial cells proliferation [66] to induce neo-vascularization and cytokines mobilization [67] is important for skin regeneration. Cell migration is fundamental prerequisite for wound healing [68].

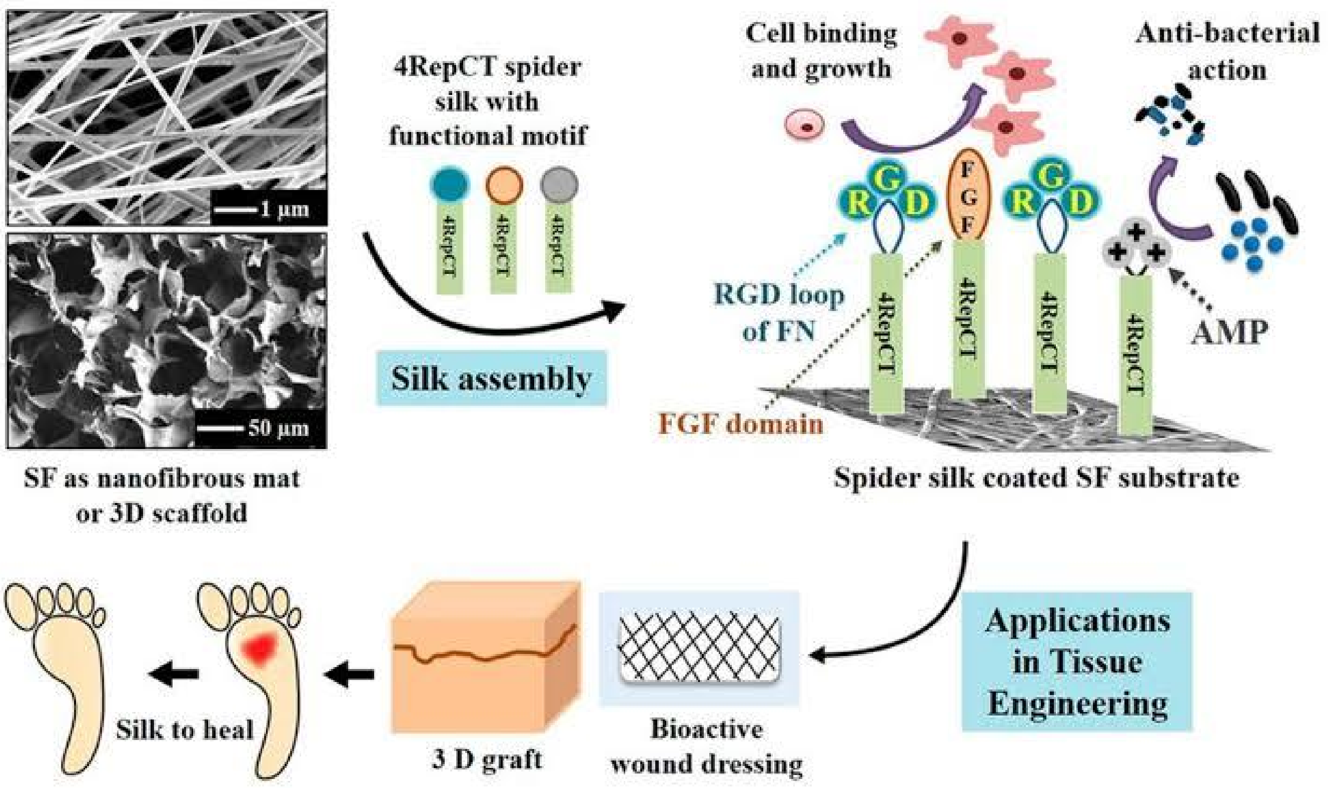

Fig 6. Schematic representation showing the development of functionalized silk substrates for wound healing and skin tissue engineering applications [69]

Spider silk fibers promote myelin formation, axonal regrowth and Schwann cells migration in nerve, which leads to better nerve conduction [70]. It also shows increased adherence and proliferation of fibroblast and keratinocytes, cells involved in structural framework of skin [71]. This elaborate study also showed formation of bilayer structure of epidermis and dermis by spider silk treated cell lines when cultured at air-liquid interface to induce cell differentiation [71]. It is interesting how a single silk fiber works at various microscopic levels of healing mechanism. Spider silk promotes synchronized nerve and skin cell regeneration, which is one of the key factors for the faster wound healing process.

4.4. Bone and Cartilage Tissue Regeneration

Tissue Regeneration Bone is naturally composed of both inorganic and organic materials being predominately calcium phosphate as an inorganic phase and collagen as an organic substrate. Various biodegradable polymer-based materials have been introduced as components in manufacturing bone replacement implants. Collagen is of particular interest as biomaterial for bone tissue engineering, but it generally suffers from lack of mechanical stability when processed in vitro, and it loses integrity over time. Silks, therefore, have also been in the focus of research, due to their good mechanical properties. Materials made of recombinant spider silk proteins in the work presented by Bhushan [47]. Could be biomineralized, and those materials induced an enhanced level of alkaline phosphatase activity of human mesenchymal stem cells which were cultured on the substrates. As the employed spider silk contained multiple carboxylic acid moieties, the calcium ions were able to bind and facilitate the mineralization. When the composite polymer solution of eADF4 (C16) and poly (butylene terephthalate) (PBT) or poly (butylene terephthalate-co-poly(alkylene glycol) terephthalate) (PBTAT) was processed into films, calcium carbonate was preferentially deposited on eADF4(C16), but not on the synthetic polymer phase[63].

Gomes *et al.* [53] further showed the potential of spider silk proteins for bone regeneration. They used a major ampullate spidroin (MaSp1) of Nephila clavipes functionalized with bone sialoprotein (BSP) fusion protein to induce cell attachment, differentiation and deposition of calcium phosphate on the surface of a film yielding an accelerated calcification in vitro after 6 h at 37 °C. Films made of this fusion protein not only induced the deposition of CaP, but also allowed good adhesion of human mesenchymal stem cells and significant improvement of their differentiation.

4.5. Vascularization of Spider Silk

Vascularization of Spider Silk Scaffolds reported a similar behavior of cells in contact with spider silk foams in a co-culture of endothelial cells and cells from connective tissue. The fraction of endothelial cells in the mixture with mesenchymal stem cells was 2–10%. After two weeks of culture, endothelial cells had gathered and formed millimeter-long branched sprouts. Vessel-like structures could be seen with prominent rings of endothelial cells in the foam, and the diameter of the lumen of these vessels was about 10–20 µm [62].

Conclusion and Recommendations

Spider silk is a collection of diverse antimicrobial compounds including amino acids and different antimicrobial peptides. Potassium hydrogen phosphate is an antimicrobial peptide that releases protons in aqueous solution, resulting in a pH of about 4, making the silk acidic. This low pH inhibits the growth of fungi and bacteria that would otherwise digest the protein. Therefore, spider silk is not readily decomposed by microorganisms due to its acidic property. Another compound potassium nitrate is believed to prevent the protein from denaturing in the acidic milieu. Spider silk of studied species has significant inhibitory effect on microbes i.e., fungus. The antimicrobial compounds present in the spider silk induce the formation of growth inhibition zone in both gram positive and gram-negative bacteria i.e. Listeria monocytogenes and Escherichia coli. Inhibitory effect of spider silk was found to be higher on gram positive bacteria than gram negative bacteria. These properties of spider silk make it a good candidate for medical application.

List of abbreviations

AMP	Antimicrobial Properties
BSP	Bone Sialoprotein
DMSO	Dimethyl Sulfoxide
FGF	Fibroblast Grow Factor
KDA	Kamfgruen Der ARbeiterklasse
MaSP	Major Ampullate Spidroin
PBT	Polybutylene Terephthalate
SCP	Secure Contain Protect
SF	Silk Fibroin
VE	Vascular Endothelial

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