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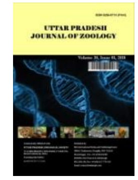

# ANTIMICROBIAL ACTIVITIES OF NATURAL AND RECOMBINANT SPIDER SILK – A REVIEW

**ANITHA ABRAHAM[1,2*], MATHEW M. JOSEPH[2] AND M. MINU[2,3]**

[1]Department of Zoology, Maharajas College, Ernakulam, Kerala-682011, India.
[2]Department of Zoology, Sacred Heart College (Autonomous), Thevara, Kochi, Kerala-682013, India.
[3]Department of Zoology, SNM College, Maliankara, Kerala-683516, India.

**AUTHORS' CONTRIBUTIONS**

This work was carried out in collaboration among all authors. Author AA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors MMJ and MM managed the analyses of the study and literature searches. All authors read and approved the final manuscript.

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## ABSTRACT

Spider silk is a protein fibre spun by spiders and they use their silk for a variety of purposes such as for making webs or other structures, which function as sticky nets to catch their prey, or as nets or cocoons to protect their offspring, or for depositing sperms etc. It has a variety of properties that make them useful in a range of potential industrial and medical applications. Spider silk has been used for making fishing gears and lures, weaving ceremonial and bullet- proof garments and also used clinically as surgical sutures for centuries due to its biocompatibility, slow degradability and high tensile strength. Research on its antibacterial activity is important for humans as they are facing novel and harmful pathogens day by day. Most of the microorganisms are becoming resistant to many antibacterial agents. This review is an attempt to discuss the antimicrobial activities of natural and recombinant spider silk. Our studies revealed that antibacterial activities are exhibited by the silk of some specific species of spiders. (*Pardosa brevivulva*, *Eriovixia excelsa, Stegodyphus sarasinorum, Cyclosa confraga, Nephila pilipes, Pholcus phalangioides, Tegenaria domestica, Pityohyphantes phrygianus, Parawixia dehaani, Crossopriza lyoni, Neoscona theisi and Argiope trifasciata).* The silk of some spider species (*Linothele fallax, Linothele megatheloides, Argiope aurantia and Latrodectus hesperus*) do not show such activity. It was observed that gram positive bacteria are more susceptible to spider silk than gram negative bacteria. Recombinant spider silk also possesses a high potential for biomedical applications because of its anti-microbial property, biocompatibility and biodegradability. Antimicrobial properties of spider silk can also be influenced by the diet and environmental conditions. Further future studies in this regard may lead to the discovery of novel biomaterials and new therapeutic drugs against microbes which will be of great significance especially in this pandemic situation.

**Corresponding author: Email: anithaabraham@maharajas.ac.in;*

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## 1. INTRODUCTION

Ranging from the construction of orb web to adhesives and cocoons, the chemistry arrangement and functions of spider silks are distinguished by extraordinary diversity [1]. It is secreted formerly inside the spider in a liquid state, and once exposed to the sunlight, it becomes solidified. Spiders spin dragline silk from the main ampullate gland, which has a long tail and a larger sac region. The sac leads to a funnel and a tapering duct within a sheath and attains the shape of three loops, where the fibre is formed. In the narrow tubular area, which is specialised for rapid water recovery, the fibre is further processed [2]. The silk then passes out of the spigots.

Spiders are armed anatomically with 5-7 different types of glands specialized for the secretion of silk. Each of the glands synthesizes its own type of silk to be utilized for a specific purpose. The glands are named major &minor ampullate glands, tubuliform, flagelliform, aciniform, aggregate, and the pyriform glands [3].

Spider silk threads are made up of various silk proteins termed spidroins. The heterogeneity of spider silk is caused by various arrangements of spidroins, and in total there are seven different types of spider silk. Spidroin proteins entail amino acids such as alanine, glycine, leucine, proline, tyrosine and phenylalanine. Tandemly repeated amino acid sequences and antiparallel crystalline β-sheet segments produced by polyalanine motifs constitute for the exceptional strength and extensibility of natural spider silk fibre [4]. The hydrophilic regions of spider silk are characterized by an abundance of glycine which gives elasticity to the silk fibre [5].

Spider silk is a sturdy fibre that is very thin and has amazing ductile strength as well. Pyrrolidin, potassium hydrogen phosphate and potassium nitrate are responsible for the longevity of spider silk. Pyrrolidins resist the drying out of the thread. Potassium hydrogen phosphate makes the thread acidic and inhibits the growth of fungi as well as bacteria. Potassium nitrate avoids protein denaturation and thus it also contributes to the inhibition of bacterial and fungal growth [6].

Spider silk is a natural material which, in its strength as well as elastic properties, outperforms almost every synthetic material. The significant prerequisite for the production of synthetic as well as recombinant spider web-based polymers is the novel ampullate silk spidroin-1 from *Nephila* spiders [7]. The advancement in recombinant DNA methodologies in order to clone the genes of spider silk for the expression in transgenic organisms is necessary, because it is difficult to domesticate spiders for collection of silk in large-scale. *Latrodectus hesperus,* the cob weaver black widow spider as well as the orb weaver *Nephila clavipes* are becoming model species for expression study experiments to retrieve the genetic blueprints from family members possessing spider silk gene [8].

Spider silk can be considered as a suitable material for dressing of wounds as it is biodegradable, non-antigenic and non-inflammatory [9]. The use of recombinant spidroins in wound dressings, gene delivery systems, cancer treatments, pharmaceutical fabrics, polymers and also as clothing materials is being studied. Recombinant spider silk was publicized to have noble cyto- as well as biocompatibility in studies regarding subcutaneous implantation and as wound dressers [10,11]. The key objective of this review is to discuss the antimicrobial activities of natural and recombinant spider silk.

## 2. PRACTICAL APPLICATIONS OF SPIDER SILK

Ancient Greeks used spider silk to elude bleeding in addition to cure wounds. Due to its longevity and tolerance to extremes in temperature and moisture spider silk is used as cross-hairs in optical instruments. It is also used to manufacture rust-free panels on motor vehicles, bullet-proof fabric, light weight clothing that is wear-resistant, cables, nets, seat belts, parachutes, bottles that are biodegradable, band aids, surgical suturing threads etc. Spider silk's biodegradability and biocompatibility make it possible to use as artificial tendons and ligaments, tissue repair materials, surgical sutures, scaffolds that support the growth of various cells, including fibroblasts, neural stem cells and chondrocytes etc [12]. To render clothes like silk, natural spider silk can be used, and clothes made of spider silk have good breathability, can withstand moisture caused by sweat and are more resistant to wear and tear. By attaching $TiO_2$ particles to PA6, a composite nano cobweb fibre mat with antibacterial property was developed. The material's waterproof, moisture-permeable, breathable, and heat-transfer characteristics can be adjusted to suit the needs of various protective clothing by changing the cobweb pore size and the amount of micropores. A new form of artificial blood vessel created using natural spider silk as a supporting matrix has intense biocompatibility and mechanical properties similar to those of natural blood vessels and is capable of making cells to adhere, discriminate, and proliferate [13]. A suture coating was developed by altering chimeric spider silk proteins with antibacterial properties that can effectively prevent infections in wound [14].

## 3. ANTIMICROBIAL ACTIVITIES OF NATURAL SPIDER SILK

Spider silk web metabolites demonstrated strong antibacterial property against seven multi-drug resistant bacteria including three gram negative bacteria (*E. coli, A. baumannii and S. typhi*) and four gram positive bacteria (*S. aureus, Bacillus, E. faecalis and S. pneumoniae*) [15]. The silk of *Pardosa brevivulva* has reported to exhibit strong bactericidal as well as fungicidal potential as it effectively inhibited the growth of *S. typhi, K. pneumoniae, A. flavus, C. albicans, U. maydis,* and *A. solani* [16]. The growth of *Streptococcus* sp.*, Acinetobacter* sp., *Pasteurella* sp.*,* as well as *Staphylococcus* sp. was inhibited by the silk of *Eriovixia excelsa*. [17] The web of *Stegodyphus sarasinorum* sp showed antibacterial activity by inhibiting *E. coli* and *S. aureus* [18]. At the same time none of the spider silk with inhibitory action against *Pencillium digitatum* and *Aspergillus flavus* was observed till the date [19].

Several studies proved that the spider web extract has effective antibacterial activity against *Enterobacter cloacae*, *Escherichia coli*, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis, Bacillus subtilis, Staphylococcus aureus*, and *Streptococcus* sp. [20]. Inhibition in the growth of *Streptococcus* sp. and *Acinetobacter* sp. was exhibited on treatment with silk recovered from *Cyclosa confraga* [21]. Dragline silk from *Nephila pilipes* is reported to inhibit the growth of *Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* [22, 23]. The recovered silk from *Pholcus phalangioides,* the cellar spider (Fuesslin, 1775) revealed antibacterial activity against two gram positive bacterial strains namely, *Staphylococcus aureus* and *Streptococcus pneumoniae* [24]. *Pholcus phalangioides* spider silk has a stronger inhibitory effect on gram-positive bacteria *Listeria monocytogenes* than on gram-negative bacteria *Escherichia coli* [25].

The growth of the gram-positive bacterium *Bacillus subtilis* can be inhibited by the web silk of *Tegenaria domestica* , at the same time no substantial inhibition was detected against the gram-negative bacterium *Escherichia coli* [26]. Spider webs in acetone solvent exhibit antibacterial behaviour with an inhibition zone diameter of 10 mm against *Bacillus subtilis* and an inhibition zone diameter of 9 mm against *Escherichia coli* [27]. It was shown that the web silk of *Tegenaria domestica* and the egg silk of *Pityohyphantes phrygianus* greatly inhibited bacterial growth [28]. Silk from webs and retreats of social spider *Stegodyphus dumicola* (Pocock 1898) hindered to a limited degree the development of *Bacillus thuringiensis* [29]. *Parawixia dehaani* egg sac silk is found to be even more antibacterial than *Pholcus phalangioides* drag-line silk [30]. *Crossopriza lyoni* silk (Family Pholcidae) showed strong bacteriostatic activity against *Acinetobacter* sp. as well as *Streptococcus* sp. [31]. Silk obtained from *Neoscona theisi*, an Araneidae family orb-weaver spider, was found to inhibit bread fungal growth [32]. Silk-treated apricots harvested from spider, *Argiope trifasciata* (Araneae, Araneidae) have an improved shelf life up to 14 days under normal conditions compared to untreated apricot that is rotten and becomes unpalatable within four days [33].

When tested on *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Enterococcus faecalis,* the spider silk of *Linothele fallax* (Mello-Leitao, 1926) and Linothele megatheloides (Paz& Raven, 1990) did not exhibit any antibacterial properties [34]. Against both gram positive (*B. subtilis*) and gram negative bacteria (*E. coli and P. aeruginosa)*, *Argiope aurantia* silk also did not demonstrate antibacterial activity) [35]. No antibacterial potential was revealed by two species of common Pholcidan spider's web against either *E. coli* or *Staphylococcus* and also cobwebs which were more than 24 hours old showed no effect on the growth of bacteria [36].

While studying the antibacterial properties on *Pseudomonas fluorescens*, spider silk did not demonstrate strong antibacterial properties [37]. The gumfoot capture threads of the western black widow spider, *Latrodectus Hesperus* (Chamberlin & Ivie 1935)cause a rise in the growth of *Escherichia coli* for the whole gumfoot thread treatment, but had no impact on the strong and water-soluble components individually [38]. Absence of zone of inhibition revealed the absence of antibacterial properties in the silk of three spider species. When nitrogen is unavailable, the resistance of spider silk to bacterial degradation is possibly due to bacteriostatic mechanisms [39].

## 4. ANTIMICROBIAL ACTIVITIES OF RECOMBINANT SPIDER SILK

Spider silk has been fused with the human antimicrobial peptides HNP-2, HNP-4 and hepcidin, and these new functional silk proteins can inhibit the growth of *Escherichia coli* and *Staphylococcus aureus*

[40]. Spider silk proteins were bioengineered with AMP (6mer-HNP1) and developed an antibacterial drug-free coating which showed exceptional antibacterial properties for commercial silk sutures [41]. By fusing spider dragline consensus sequences (6mer) and the antimicrobial peptide hepcidin with bactericidal action, a new chimeric protein, named 6mer+hepcidin was developed [42]. Different spider silk domains originating from the spider Nephila clavipes dragline sequence were combined with two antimicrobial peptides, Hepcidin (Hep) and Human Neutrophil peptide 1 (HNP1) and these 6mer-HNP1 silk-based films and various silk fibroin (SF) content significantly decreased bacterial adhesion and biofilm formation, although higher bacterial counts were observed on the prepared films [43]. Recombinant spider silk functionalized with endolysin SAL-1 that degrade peptidoglycan and the biofilm matrix degrading enzyme Disperin B have been shown to have a bacteriolytic effect and to inhibit the formation of biofilm [44].

The bacteriostatic as well as fungistatic properties of the recombinant spider silk are distinctive, whereas recombinant materials prepared from *B. mori* regenerated fibroin, which resemble to the composition and properties spider silk proteins, do not exhibited antimicrobial behavior [45]. Hybrid materials from the spider silk of *Linothele fallax* and nanoparticles of tungsten as well as molybdenum oxides had a superior impact on the gram-positive bacteria [46]. Linking enzymes that are bactericidal in nature and four other natural antimicrobial peptides resulting in a silk material A-4RepCT on treating with *Escherichia coli*, showed to decrease the viable bacteria in solution, in contrary to wild-type 4RepCT on which bacterial proliferation continued [47]. Antimicrobial composite materials with enhanced properties are designed by linking the eADF4 (C16), the engineered spider silk protein and antimicrobials loaded MSN which revealed long-term inhibitory properties against *Escherichia coli* and *Pichia pastoris* [48]. By reducing the adhesion of bacterial strains, the antimicrobial peptides (AMPs) added to the recombinant spider silk 4RepCT has improved its antimicrobial effect [49]. MaSp1, the A recombinant spider silk protein extracted from *N. clavipes* showed significant antimicrobial activity on fusing with silver ions [50]. The recombinant spider silk membrane protein stimulates the wound skin recovery by increasing the expression as well as secretion of the growth factor bFGF and hydroxyproline [51]. Nanofibrous mats made of natural silkworm SF are used as a bulk material that are top-coated with the spider silk recombinant protein (4RepCT) in meld with a cell-binding motif, peptides that are antimicrobial in nature, and a growth factor in order to synthesize a bioactive SF- spider silk- based biomaterial for wound-healing and skin replacement application [52,53].

Biotechnological production of recombinant spider silk is the solely practicable resolution to reap silks on a bigger scale and to satisfy growing desires of medication and biotechnology because the spiders cannot be farmed because of their aggressive behavior and territorial nature and also the collection of silk from webs is a long task. Recombinant spidroins are cloned and expressed in bacteria, yeast, insects, plants, class cell lines and transgenic animals. Sequences from *Nephila clavipes* and *Araneus diadematus* are mostly used for producing recombinant spider silk. Recombinantly made spider silk proteins possess a high potential for medicinal applications [54].

## 5. CONCLUSION

Antimicrobial potential are unveiled by the silk of specific spider species namely, *Pardosa brevivulva*, *Eriovixia excelsa, Stegodyphus sarasinorum, Cyclosa confraga, Nephila pilipes, Pholcus phalangioides, Tegenaria domestica, Pityohyphante sphrygianus, Parawixia dehaani, Crossopriza lyoni and Neoscona theisi, Argiope trifasciata,* whereas some spider species (*Linothele fallax, Linothele megatheloides, Argiope aurantia, Latrodectus hesperus*) do not show any inhibitory activity. It was observed that comparatively, gram positive bacteria are highly susceptible to spider silk than gram negative bacteria. The range of spider silk proteins and their biocompatibility and biodegradability make them important tools for future applications in producing new biomaterials and new medicines. Recombinant spider silk possesses a high potential for biomedical applications because of its biocompatibility and biodegradability.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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