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# A Review of The Use of Silk Fibroin in Sports Medicine/Injury

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**Abstract.** Due to the increased promotion of sports and life span in many countries, sports medicine has become an important area for further research and investigation. With the advancement of technologies, tissue engineering is a prevalent topic for future development. Silk has been used for therapeutic strategies in many different areas since the Neolithic Age. Silk fibroin is a protein extracted from silk with a special structure with many potentials. This article will focus on the use of silk fibroin in common Musculoskeletal injuries which is divided into three areas: open wound injuries, fracture, and tissue engineering. However, traditional therapies for these three areas present limitations such as graft rejection and requiring a second surgery. Hence the article aims to explore the application of silk and how silk overcomes these limitations in medical applications when combined with other materials. SF demonstrates many potentials in medical applications based on the properties of excellent biocompatibility, causing a mild immune response, and supporting cell proliferation and tissue regeneration.

**Keywords:** Silk fibroin; Sports injury; fracture; Wound healing; tissue engineering.

## 1. Introduction

One of the major problems in the healthcare system especially sports medicine is damaged tissues. Sports injury is defined as various types of injuries that occur during exercise or movement [1]. Even though most musculoskeletal injuries involving sports occur mostly in adolescents and athletes. Due to the increased population of older people and the increase in life span. It is suggested that the average life expectancy of the human population will increase from 73.6 years in 2022 to 78.1 years in 2050 [2]. This also increases the prevalence of musculoskeletal injuries due to the natural aging process. Musculoskeletal injury often has long-term effects if mistreated and hence affects the older population that may gradually develop. This article will focus on the 3 main types of sports injuries: Fracture, open wound healing and tissue regeneration. Current treatments include joint preservation surgery, palliative surgery, and arthroplasty. However, these procedures have good short-term outcomes, but the long-term outcomes are still not clear.

A new biomaterial from silk cocoons can be utilised as a potential treatment to overcome these limitations. Silk has been used as a therapeutic material since the Neolithic Age[3]. It is known for its mechanical strength and adaptability and was approved by the FDA in 2019 [4]. For medical applications, the commonly used silk fibroin (SF) is from silk cocoons and spiders [5]. Spiders produce a silk protein known as spidroins in their silk gland and store as a liquid. However, as they come in contact with air, it solidifies and make it harder to produce a larger quantity. In addition, spiders have a wide food chain, therefore causing allergies. In comparison, silk from the silk cocoons is easier to get as they are easier to breed and maintain and have one type of food source from mulberry leaves. Silk fibroin is a biomaterial that is highly biocompatible, and well tolerated by the human body. It has the potential to be used as a medical application. This report will discuss the use of silk fibroin in 3 types of common sports injury and applications, open wound healing, fracture fixation and tissue regeneration along with examples.

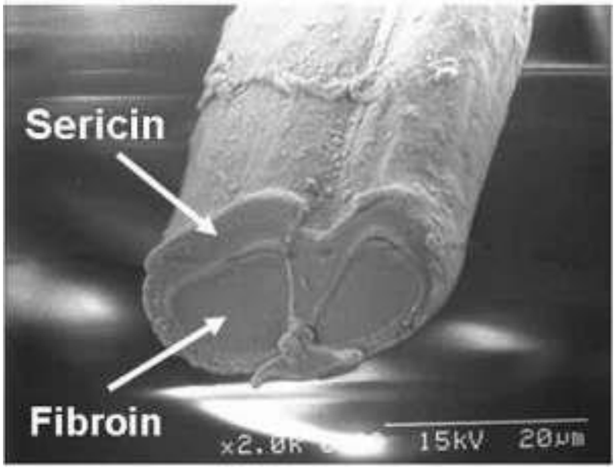

**Figure 1.** The structure of SF [6]

Through natural selection, the features of silk from the silk cocoon present significant properties to enhance their survival conditions. SF consists of a sequence of amino acids with the majority of glycine, alanine and serine. The sequence of amino acids is one of the most significant properties of SF which is significant for its biocompatibility and strength. This formation allows SF to be used as an important material supporting cell proliferation and growth. The advantages of silk fibroin such less chance of graft rejection and does not cause an inflammatory response from the body (4). The B sheet formation determines the biodegradability and mechanical strength. Once the SF is arranged in a fibrous form, it consists of a heavy chain and a light chain covalently linked together as shown in **Figure 1**. In addition, another 30 percent of the material that holds the fibroin together is secretin. It is also a material that allows shows anti-inflammatory response and helps to create an environment for cell proliferation [7].

## 2. Main body

### 2.1. Fracture

Current technologies for fracture using absorbable screws made of materials such as poly-L lactic acids present limitations such as graft rejection and causing inflammatory response. SFS nails have similar density and elasticity to human bones, are biodegradable and do not require secondary surgery. Another advantage is that the researcher can modify the rate of degradation by combining it with gentamicin, hence further enhancing the recovery of fracture for personalized cases. For large bone tissue engineering, modify hydrogels with silk fibroin to create an ideal bone tissue engineering. The study by Perrone introduced an alternative method using SF for fracture fixation injecting SF screws into the left limb of 28 rats and mechanically fixing the femurs of rats. The results suggest that the SF screw does not cause complications or inflammatory response for fracture fixation and all rats gained full mobility. This provided evidence that SF can effectively fix fractures (8). After a 4 and 8-week period, the absorption of the SF screws is also assessed. As a result, they present comparable mechanical strength resisting the shear forces compared to the polylactic-co-glycolic acid screws, which have the potential to be used as an alternative. However, future studies are required to investigate the mechanical strength of the silk screw [8].

Another example by Shi assessed the SF skews with 4 different amounts of gentamicin per 1 g of silk is evaluated compared to the pure silk screws fixing femurs in a rabbit’s model. The group with treatment of 16mg of gentamicin per 1g of silk was the most effective overall controlling the rate of bacterial growth and preventing infection. From the results of the study, the degradation rate is the highest with 16mg of gentamicin per 1 g of silk compared to lower concentrations of gentamicin, this finding suggests that gentamicin might affect the structural integrity of Sf and hence affect the stability of SF [9].

Furthermore, a study by Bottagisio assesses the vancomycin-enriched SF sponges treating bone infection. The study divided rats into 2 groups to stimulate 2 conditions: osteomyelitis and septic nonunion. The key findings of the study suggest that the vancomycin-enriched sponges (AFN-PSF) present full bone healing in most cases and also had new bone formation in the remodeling phase. From 7 and 14 days after treatment, rats who received pure SF sponges had an increase in neutrophils, suggesting an inflammatory response. In comparison to the rats that received AFN.PSF sponges. The AFN-PSF group demonstrated better healing results and less inflammation in a clinical setting. Hence, this finding can be applied to patients going through arthroplasty to prevent infection. This further suggests that silk is more effective while combing with other materials than using pure SF independently [10].

## 2.2. Wound healing

Skin is one of the biggest organs of the human body protecting all the internal organs. An open wound injury is a common injury in many areas of sports. Wound healing includes 4 phases hemostasis, inflammation, proliferation, and remodeling [11]. Applying silk on wounds has been a tool since ancient times. Hence, modern technologies are now exploring the scientific reasons and applications behind this method as many properties of SF suggest that it has the potential to accelerate the wound-healing process and prevent infection.

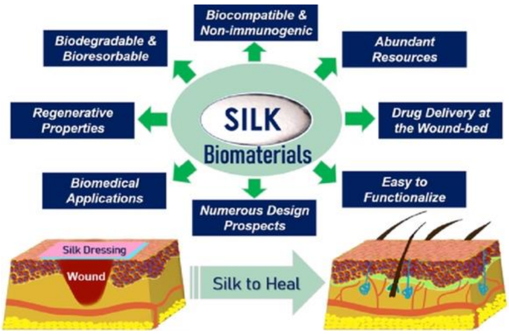

**Figure 2.** The main properties of SF in wound healing [4]

The first example by Chouhan suggests that one of the main reasons for enhancing the wound healing properties is that the cross-linking modalities of SF allow it to be used as a biomaterial for wound repair, stimulating cell proliferation and increasing wound healing, especially for deep wound and burned wounds [4]. The main functions and properties are analysed in **Figure 2.**

One example that uses the SF on burnt wounds, which is one of the worst forms of wounds, suggests that covering the wounds in an early stage of the trauma can effectively reduce the possibilities of infection and scar reduction. Recovering from a burnt wound requires the secretion of the growth factor and collagen. This study by Shan conducted animal studies on Sprague Dawley rats using nanofibrils made of 25 percent SF and 75 percent gelatin. They were divided into 4 groups assessing the SF nanofibrils dressing on wound healing. The healing process of the wound was assessed by measuring wound closure percentage. The result of this study suggests that SF nanofibrils allow effective gas exchange for the wound as well as bacterial prevention. The combination of SF and gelatin allows the nanofibril to keep structural integrity for up to two days and effectively prevents further scar formation [12].

Another example by Chouhan suggested that silk demonstrates accelerated wound healing properties. It provides a favorable environment supporting cell proliferation. This study explored the application of SF not only in accelerating the healing process but also act on the extracellular matrix deposition to reduce the chances of scars. The non-mulberry SF created the ECM environment and properties to accelerate wound healing. By combining epidemiological growth factor with SF protein, skin regeneration can achieve pleasant outcomes without scars formation[13].

### 2.3. Tissue regeneration

Repairing damaged tissues that have a low capacity to regenerate. SF has the potential to provide a niche for cell regeneration, preventing the need for secondary surgery to take out the material as it can be gradually degraded into the body without rejection. A big part of a successful transplant of the biomaterial for tissue regeneration is cell attachment and interactions, effectively using the surrounding nutrients for the regeneration of the regrowth of the tissue (14). The first example is the use of SF in cartilage regeneration. The composition of cartilage lacking nerves, blood vessels and lymphatics makes it a big concern in tissue regeneration. A common medical condition requiring cartilage degeneration is osteoarthritis, which is often due to overuse and aging. The property of SF makes it a promising biomaterial for cartilage regeneration. It is required to be carefully modified into SF hydrogels, having the unique properties of mechanical strength, flexibility and high-water content, which shows the potential for this application. It can also be used as a non-invasive treatment as it can be injected into the target tissue[14].

Then, another application that uses SF skews used for Anterior cruciate ligament (ACL) repair is also a promising area with great potential. ACL recovery is a challenging area as it provides knee support. Current treatment for ACL fixation uses metallic skews; however, limitations include the requirement of second removal surgery. ACL injuries are one of the biggest challenges in sports medicine. In this example by Seo, researchers utilised a silk scaffold consisting of SF with collagen hyaluronan (HA) substrate conducted on dogs weighing around 12 kg. The ACL was incised and removed completely. The dogs were divided into groups that received the composite silk scaffold with collagen HA, pure silk, and a group that only received HA. They were examined after 6 weeks. The researchers analysed the T cell growth and the immune response. The group of dogs that received SF scaffolds increased T cell growth by 1.5 to 2 times compared to the control group. This shows a significance in tissue engineering. In addition, there is a rise in interferon-gamma levels suggesting a mild immune response in the pure SF group and the composite SF scaffolds group. This indicates that SF as a material did not cause an excessive adverse effect on the body [15].

## 3. Discussion and analysis

This article discusses the use of SF in 3 common injury areas in sports. Based on the examples above, the example used in this article represents some of the most utilised areas for SF. The studies discussed suggested that SF as a material can stimulate a mild immune response which is required for all fracture, wound healing and tissue regeneration. Proving evidence that SF is safe and support cell proliferation which is required for all three injuries without having an adverse effect on the body. This makes it a successful candidate for medical application. It is also a material with great biocompatibility and excellent mechanical strength. The results from studies also suggest that SF alone might not have presented the advantages but combined with other materials that enhance the significance of the results. it is a flexible material that can be modified and customized with other materials when required, making it an ideal candidate for both soft and hard tissue engineering. The biodegradability of SF is also worth mentioning as it can be modified depending on the situation, providing mechanical support when needed and no waste will be produced. In addition, the material is environmentally sustainable. Silkworm farming has a low energy input and causes less environmental pollution. The processing method is nontoxic, which minimizes the pollution compared to other alternatives.

Although SF has the potential in many medical applications, it presents several limitations. Firstly, some patients with personal beliefs might have contradictions in using this product. For example, vegans avoid using all animal products and hence this material contradicts their principles of harming animals. Secondly, SF originates from China, so it is hard for other countries to maintain silkworm farming. Silkworm farming also hard to achieve consistent quality and mass production. Finally, maintaining the quality of silk is complicated, factors such as temperature, light and humidity might affect the storage of SF, and hence affect the quality and effectiveness.

## 4. Conclusion

In conclusion, SF demonstrates many potentials in medical applications based on the properties of excellent biocompatibility, causing a mild immune response, and supporting cell proliferation and tissue regeneration. Creating an environment for cells and tissues and reacting with the body environment *invivo* having a positive immune response which shows a promising biomaterial for future innovations. It is also flexible to modify and combine with another biomaterial, presenting features of a promising biomaterial for fracture fixation, wound healing and tissue regeneration.

Furthermore, this presents its versatility in drug delivery, preventing bacterial infection which favours healing and reduces infection risks. With more research and clinical trials, SF can be used as a promising treatment in the sports medicine area and common injuries in athletes. Future research and indications of SF can be further explored for areas such as oral application and fixing the damaged nervous system.

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