Chapter

# Applications of Silk in Biomedical and Healthcare Textiles

*Edison Omollo Oduor, Lucy Wanjiru Ciera and Edwin Kamalha*

## Abstract

Global trends are shifting towards environmental friendly materials and manufacturing methods. Therefore, natural fiber applications are gaining traction globally. Silk, a natural protein fiber is one of the textile fibers that have recently received more attention due to the new frontiers brought about by technological advancement that has expanded the use of silk fiber beyond the conventional textile industry. The simple and versatile nature of silk fibroin process-ability has made silk appealing in wide range of applications. Silk is biocompatible, biodegradable, easy to functionalize and has excellent mechanical properties, in addition to optical transparency. This review chapter explores the use of silk in biomedical applications and healthcare textiles. Future trends in silk applications are also highlighted.

**Keywords:** Silk, Silk fibroin, Bio-applications, Functional textiles

## 1. Introduction

Silk is a natural fibrous protein biopolymer, spun by arthropods like spiders, mites, fleas and silkworms [1]. The structure, composition and properties of silk differ depending on their specific function and source [2]. Silkworms are one of the silk spinning insects that has been researched in detail and finds wide applications in textiles [3]. Silk production, also known as sericulture, has a long history that is usually closely associated with China. Silk was discovered in 2640 B.C. by Hsi-Ling-Chi, who also found out that silk fiber loosened and unwound in hot water; and twisted to make thread that was used to weave a very strong cloth. Hsi-Ling-Chi later developed a means of raising silkworms and a method of reeling the fibers to make garments [4, 5]. As silk became a very precious commodity, sericulture spread within china and to other countries. Demand for silk products created a trade route that is famously known as Silk Road [6].

Silk filaments from silkworms are classified into two types; mulberry and non-mulberry (also called wild or vanya silk). Mulberry silk are generally produced by *Bombyx mori* which are insects belonging to the Bombycidae family. *Bombyx mori* feeds on mulberry plant leaves. Mulberry silk is further divided into bivoltine and multivoltine, depending on the number of silk cocoon crops harvested annually. Bivoltine is harvested twice a year while multivoltine is harvested throughout the year [7]. Non-mulberry silk on the other hand, is silk from Saturniidae family. Non-mulberry silk includes tasar silk, muga silk and eri silk. Tasar silk is secreted by *Antheraea* silkworms. They have hard and compact cocoons. Tasar silk can either be tropical tasar

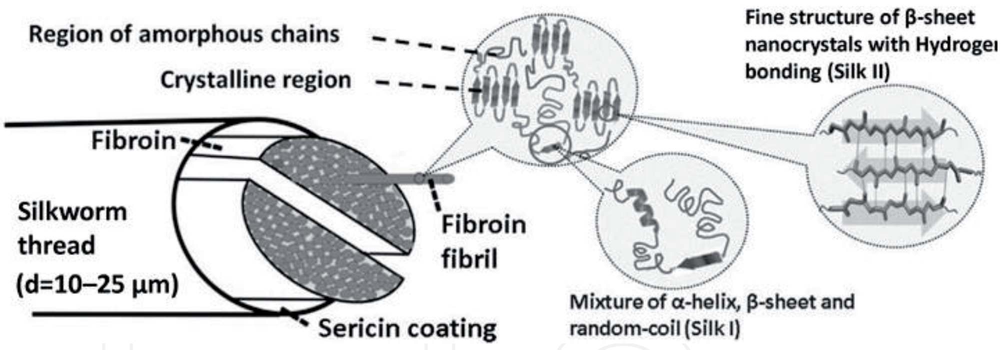


**Figure 1.**
*Schematic presentation of the silk fibroin (SF) structure; d represents the diameter of a single silkworm thread [13]. Reproduced with permission.*

or temperature tasar. Muga silk is produced by *Anteraea assamensis* silkworm; it has a unique natural golden color, with significant luster and durability. Eri silk is produced by *Philosamia synthia ricini (*also called *Samia cynthia)* silkworms, which usually feed on castor or papa plant leaves. Eri silk being in the wild silk category, has however been completely domesticated just like mulberry silkworms. Eri silk cocoons draw shorter silk fibers when compared to other silks which draw continuous filaments [8, 9].

Silk cocoons comprise over 95% proteins and about 5% impurities (mineral salts, waxes, ash). Raw silk consists of two proteins; sericin (gum) and fibroin (fibers). Sericin and fibroin are composed of amino acid chains. The types and composition of these amino acids are different for sericin and fibroin. Non-mulberry silk has lower sericin with higher levels of impurities compared to mulberry silk [10]. After degumming, sericin and other impurities are removed from the raw silk fibers. Therefore, degummed silk is composed of mainly fibroin protein [11, 12].

Several authors have reviewed, described and demonstrated the structure of silk fiber varieties, especially *Bombyx mori* in relation to several performance properties. These include: conformations of silk, heavy chains with possible chain folding and micelle assembly in water, primary structure, 12 repetitive and 11 amorphous regions, amino acid sequences of i, ii, and iii, hierarchal structure among others (**Figure 1**) [13].

Silk fibers are usually used for conventional textile applications after the removal of sericin and other impurities. Recently however, due to excellent mechanical and optical properties, as well as its biocompatibility, biodegradability and implant ability, silk has found increased applications in functional textiles [1, 14, 15]. This has been made possible by the simple and versatile nature of the silk fibroin process ability into various forms such as sponges, gels, strands, blocks, foam, films, and more recently, nanofibers [16–21]. Applications of silk in biomedical materials, drug delivery and in optics and sensing are therefore discussed in this chapter. The chapter underscores the forms and properties of silk making them suitable in these applications.

## 2. Common manufacturing processes for silk-based functional products

More recently, silk fibroin (SF) films with fineness ranging from hundreds nanometers to tens micrometres are obtained from regenerated solutions through liquid processing including: spin coating, inject printing, doctor blade, soft lithography, contact printing or nano- imprinting, among others; that support industrial scale production. Doping, blending and functionalization of SF has also been a route to achieve substrates for advanced technological use in organic electronic sensors based on field effect transistors, and with optically active dyes, particularly for biomedical applications [22–25]. Nano and micro-patterning, through spin coating and lasing, was used to obtain stilbene-doped silk film of significant mechanical performance and optical performance [24].

Innovative attempts during breeding and feeding of silk worms, through incorporation of dopants in the diet, have yielded modified SF substrates of functional value; e.g. silk threads with electrical conductivity through incorporation of silver nanoparticles in mulberry diet, fluorescence introduced in silk fiber through colorant compounds in mulberry feed, among others [26–29]. These approaches save on extra processes and time that would be required as after treatments, and enhance the durability of such functions. Optimization of silk-worm breeding is often required for control and reproducibility of functional substrates. For example, among others, the silkworm survival rates, temperature conditions and duration of the larval cycle are monitored.

Based on different varieties of *B. mori*, in 2019, a silk fibroin based technology was developed in order to optimize and support industrial bio-manufacturing [30]. The evaluation and standardization of extraction, purification, and characterization methods were reported; yielding biocompatible SF substrates with high purity and outstanding chemo-physical performance. The result was a validated bio-diagnostic microfluidic and photonic device (a lab-on-a-chip) (**Figure 2**).

Several conventional textile spinning and construction methods are used for production of functional silk yarns, fabrics; including a variety of finishing technologies through which active functional ingredients may also be introduced. Therefore, such might be applied during fiber spinning (e.g. for sutures) and after fabric construction through a variety of wet and dry finishing processes [31]. Innovative approaches include micropatterning, 3D printing and more nanotechnology based systems (**Figure 3**).

Electrospinning is a common method used in the production of nanofibers and microfibers from SF solutions. The ensuing fibers possess a high specific surface, favoring the use of such scaffolds in tissue regeneration [34, 35]. The mechanism of electrospinning (**Figure 4**) is based on a high electric voltage applied to the fiber polymer solution. The polymer solution is ejected when the electric force overcomes the surface tension of the polymer solution, forming a polymer jet. Electrospinning can be of needle or needleless. The needle electrospinning utilizes a high-voltage

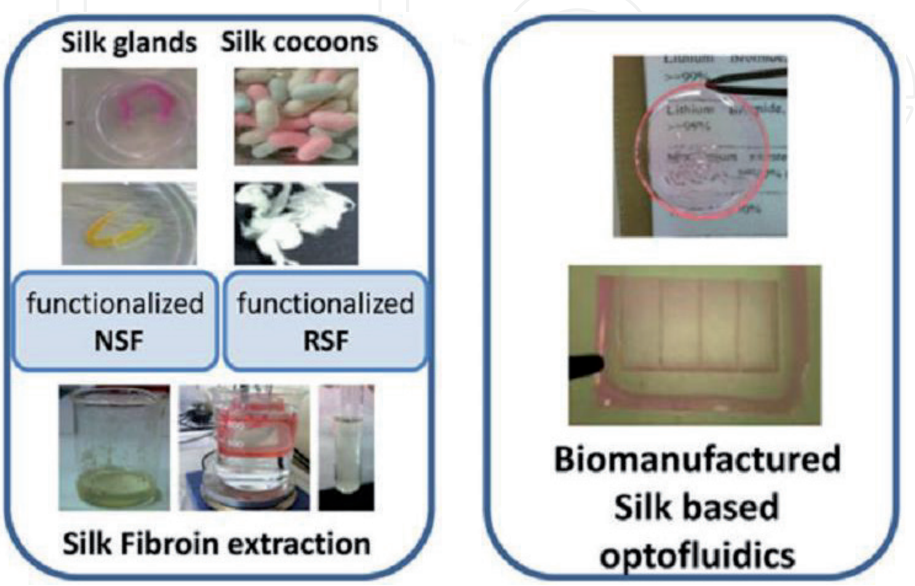


**Figure 2.**
*Schematic picture of the biomanufacturing approach to obtain SF based technological substrates [30]. Reproduced with permission.*

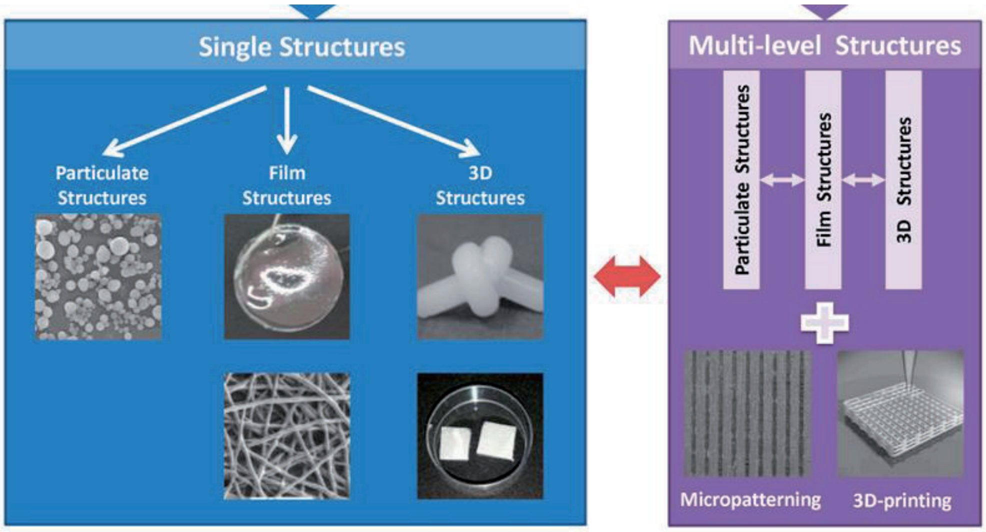


**Figure 3.**
*Structural design of SF-based biomaterials from single structures to multi-level structure [32, 33]. Reproduced with permission.*

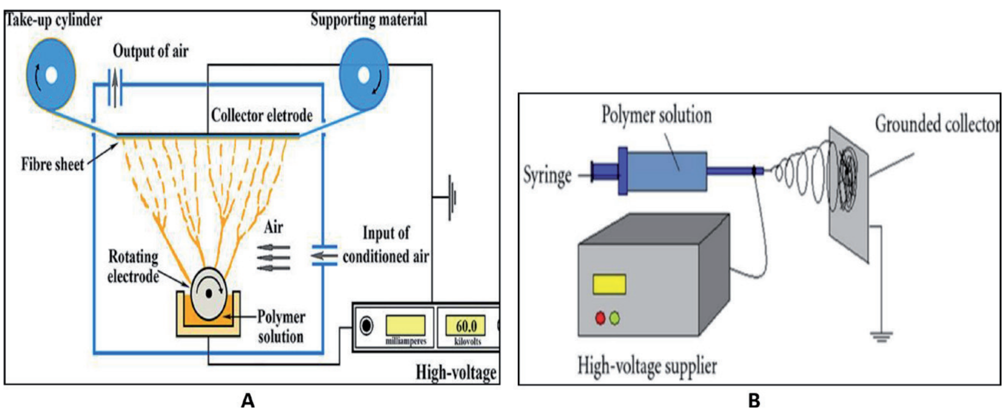


**Figure 4.**
*Schematic images of needle-less (A) and Needle (B) electrospinning processes [40]. Reproduced with permission.*

power supply, and a syringe needle connected to a power supply and pointed towards a collector. Needle electrospinning options pose a demerit of very low productivity, thus, unsuitable for practical commercial value. Needleless electrospinning setups have been innovated recently. In these systems, polymer jets form simultaneously from the surface of polymer solution by self-assembly [36–41].

## 3. Silk in biomedical textiles

Biomedical textiles are composed of fibrous units produced from natural or synthetic materials. These textiles are used in either external or internal environment of living organisms [42]. Biomedical textiles are further used, medically, to improve the medical condition of a patient [43, 44]. Some biomedical textiles include implantable, non-implantable and extracorporeal devices as well as hygiene and health care products [45]. Non-implantable materials/devices include wound dressings materials like bandages and gauzes. While, implantable materials/devices include artificial arteries, heart valves, sutures, and vascular grafts among others. Extracorporeal devices mainly include artificial body organs. Hygiene and health care products include sanitary towels, tissue paper, wipes, hospital gowns and uniforms, hospital bed covers, surgical covers, masks and caps. Other biomedical textiles include polymer sensors and wearable medical implants [46, 47].

Textile materials used in biomedical applications must be non-allergic, non-carcinogenic, non-toxic, biodegradable and biocompatible. Additionally, biomedical textile materials must be able to be stable to handling and use. For example, during sterilization and use, they should not change their physical or chemical properties (e.g. through oxidation or chemical reaction). Other important properties for these textiles include: high tensile strength, elasticity, high burst stream, low permeability and durability [42, 48, 49]. Different synthetic (e.g. polyester, nylon, acrylics, and polyethylene) and natural (e.g. silk and cotton) fibers are used in production of biomedical textiles. Silk fibers possess good toughness and ductility in terms of elongation at break, tensile modulus and tensile strength; suitable for biomedical applications[1, 50]. Additionally, regenerated silk solutions are gaining popularity in producing various biomaterials in form of gels, films, membranes and sponges [51].

### 3.1 Silk in wound dressing

Studies have shown that silk fabricated through non-weaving and electrospinning can be used in wound dressings, and as drug carriers [1, 46, 52, 53]. Xia *et al*. [54] reported that silk fibers functionalized with silver nanoparticles presented special antibacterial properties in a wound dressing material. A two-layered wound dressing developed from a wax-coated silk woven fabric, a sericin sponge and a bioactive layer of glutaraldehyde cross-linked silk fibroin gelatin was reported to reduce the size of the wound, collagen and epithelialization [55–57]. He *et al*. [58] asserts that fibroin hydrogel from *Bombyx mori* cocoons has good healing properties due to its biocompatibility nature, low biodegradability and immunogenic properties. On the other hand, Chouhan *et al*. [59] found that nanofibrous mats of silk, functionalized with Poly Vinyl Alcohol, (as a blend) mat supported diabetic wound healing. The mats were able to promote tissue re-modeling and also regulated extracellular matrix; thus the wound healing.

### 3.2 Silk garments for dermatology treatment

Atopic Dermatitis is a worldwide health concern, with a higher prevalence in developing countries, and occurring in among many age groups. Symptoms for Atopic Dermatitis include redness and itchiness of the skin. These symptoms can be severe leading to a chronically repeating flare characterized by serious eczema (distribution of skin lesions) [60]. Treatment and management of this condition requires skin stabilization, flare prevention, as well as the use of medication that can cure the symptoms [61]. Silk garments have been used as a textile-based therapy for Atopic Dermatitis owing to their hygienic properties including antibacterial properties. Additionally, silk filament fibers are strong and round in shape, and therefore fine and smooth. Wearers experience comfort to the skin as this structure prevents and scratching from friction and irritation to the skin [62]. Moreover, the fine and smooth fibers have no or very little abrasive effect on atopic skin. This enhances the recovery of the irritated skin unlike with rough fibers that irritate the skin. Due to a significant moisture regain, silk fibers are also able to maintain body humidity therefore reducing the sweat circulation and moisture loss that can make xerosis worse [63]. A study by Hung *et al*. [60] further the ability of silk garments to significantly decrease the severity level of dermatitis symptoms. The study emphasized the merits with the smoothness of silk which is friendly to the irritated skin. The fiber enhances collagen synthesis and also reduces inflammation which cures eczematous lesion [63, 64]. Moreover, hygienic properties of silk act as a skin barrier, protecting the skin from bacteria, viruses and other contamination that reduces the inflammation [60, 65]. Of importance is the sensory experience of patients with silk garments as highlighted by these studies; they contribute to the physical and emotional comfort of dermatitis patients which possibly aids the healing process. Therefore, silk garments can be used as a non-pharmacological therapy to impede the severity of Atopic Dermatitis and other related dermatology conditions.

### 3.3 Silk in hygiene and health care products

The good mechanical properties of silk, its softness and antibacterial properties partly account silk's application in producing hygiene and health care products. Some applications of silk in hygiene and health care include: materials used in hospital wards and operating theatre as well as materials used in care and safety of hospital staff and patients. Silk materials used in operating theatre are in form of patient drapes, and surgical gear (as gowns, caps, masks and cover cloths) [46]. Silk, functionalized with titanium dioxide nanoparticles was used to produce a photocatalytic silk mask paper. The mask was found to exhibit special protective functions— degrading volatile organic compounds achieved by combining the unique properties of silk fibers and nano-$TiO_2$ [66–69].

### 3.4 Silk-based tissue engineering

Tissue engineering applies principles of biological sciences and engineering to develop biological substitutes to replace, enhance and maintain damaged or defective tissues such as cartilage, bone, skin and even organs [70, 71]. The choice of the biomaterial and the methods used determines whether the resulting bio-substitute will be functional. Silk has good mechanical properties, has a slow degradation rate and a low inflammatory response which makes it fit for use in tissue engineering. However, Sericin can elicit immune response and must therefore be completely removed before being used [72]. The type of silk that is commonly used in tissue engineering is *Bombyx mori* silk. Other types of silk that are gaining popularity include silk fibers from; *P. ricini*, *A. assama*, A. *pernyi* and *A. mylitta* [71, 73]. Silk-based tissue engineering includes: Scaffolds in form of skin grafts/artificial skin, bone grafts, artificial pancreas, cardiac tissue, artificial liver, artificial Intervertebral Disc Intervertebral disc, among others [74].

#### *3.4.1 Skin grafts/artificial skin*

Skin, the largest body organ protects the body against infections from pathogens and microorganisms [75]. Due to certain illness, the skin may get damaged and may require some replacement in form of grafts. A good graft is supposed to cover and protect the intended place without causing any negative immune response. This promotes fast healing that reduces chances of scarring on the body [46].

In the recent past, different biomaterials like silk fibroin, cellulose alginate, collagen, polycaprolactone (PCL), polylactic acid (PLA), silicone, dextranelastin and polyethylene glycol(PEG) have been explored as possible cellular scaffolds for skin grafts and wound healing [73, 76, 77]. Among these biomaterials, silk has been used to mimic human skin as well as in wound healing. This is because silk has notable properties like low immune response, biodegradability, biocompatibility and is cost-effective [1].

Additionally, studies have proved that silk supports human keratinocytes and fibroblasts which are important in engineering artificial skin [46, 73, 78]. Studies by Chauhan et al. [59, 79] have reported successful use of electrospun silk fibroin from *A. assama* and *P. ricini* silk species in wound dressing. The studies also reported that a blend of electrospun silk fibron with polyvinyl alcohol promotes faster healing of wounds due to granulation during tissue formation. Other studies have demonstrated the use of electrospun silk fibroin from *A. assama* keratinocytes being successfully used in engineering artificial skin.

The therapeutic performance of SERI Surgical Scaffold has been studied; including open label clinical trials and case reports. A few studies have cited side effects such as poor scaffold integration (**Figure 5**), that have required surgical removal of the scaffold [80].

Comparing woven fabric, non-woven fabric and a film foam from silk fibroin in relation to cell culture responses by human oral keratinocytes, studies reported that water vapor-treated non-woven silk fibroin had better cell adhesion and dispersion of human fibroblasts and keratinocytes [46, 81]. This suggests that silk based biomaterials for tissue engineering requires a careful selection of fabrication techniques and material to blend with. Electrospinning is one of the preferred techniques for making non-woven nano-scale fiber mats for engineering artificial skin [51]. More results from electrospinning silk for tissue engineering include: electrospun silk fibroin scaffolds, 3D nonwoven scaffolds made from crosslinking silk fibroin with formic acid, and water vapor-treated silk fibroin nanofiber matrices among others. [46, 81, 82]. Reported blends that have been used successfully with silk for producing artificial skin include alginate, chitin, intermolecular cross-linked recombinant human-like collagen and biomimetic nanostructured collagen [46, 83–85].

### *3.4.2 Bone grafts*

Today, various biomaterials are available for developing scaffold-based bone tissue. One of such material is silk fibroin which has good biological and physic-chemical properties— making it suitable for developing osteoinductive functional

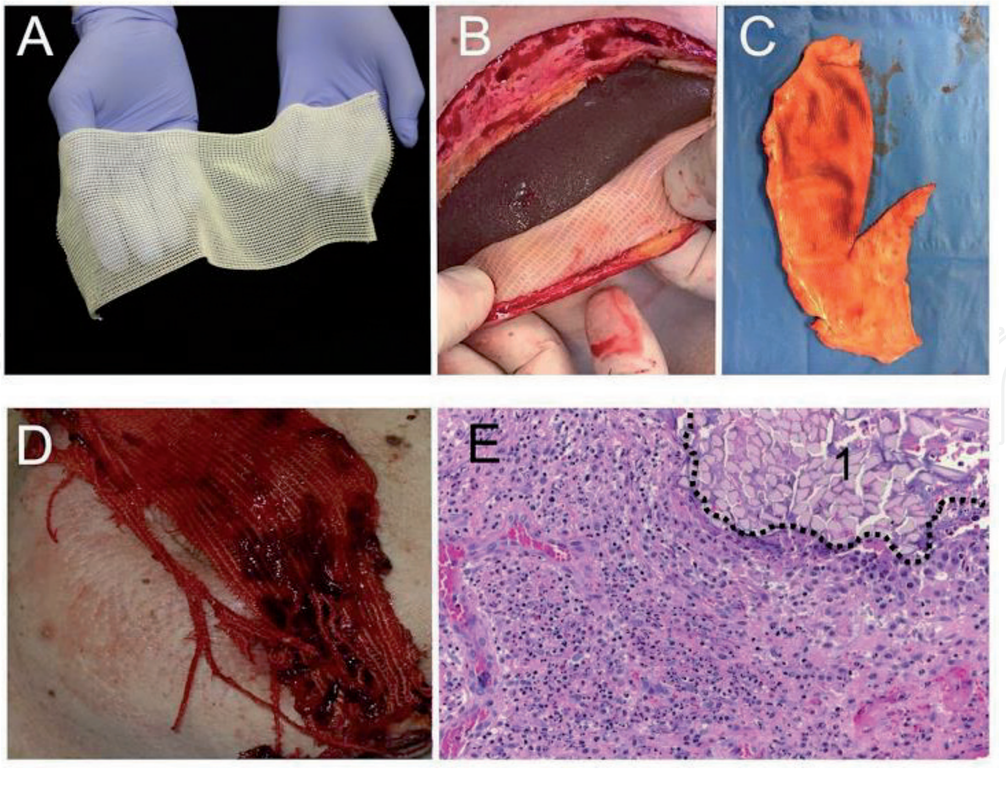


**Figure 5.**
*Examples of SERI Surgical Scaffold implant loss in humans. A) Silk fibroin surgical mesh prior to implantation. B) Intraoperative view showing a free lying scaffold in the breast pocket. C) Retrieved scaffold surrounded with seroma. D) Interaoperative view of surgically removed scaffold with interpenetrated granulation tissue/scar plate (at >5 months), and E) histology of retrieved sample showing granulation tissue with neutrophiles and giant cells at the material (1) interface (dotted line). Reproduced with permission [80]. Copyright 2018, Elsevier.*

bone grafts that resemble collagen [86, 87]. Silk fibroin from *A. mylitta* is reported to make porous scaffolds that mimic borne tissue [88]. Meinel et al. [89] induced osteogenic differentiation of human mesenchymal stromal cells in *B. Mori* silk fibroin to develop a bone graft. Other studies have explored blending *B. Mori* silk fibroin with hydroxyapatite to repair segmental bone defects [90, 91]. Findings by Reardon et al. [92] suggest that electrospun *B. mori* and *A. assama* silk fbroin blended with 70S bioactive glass repairs osteochondral tissue defects. Moreover, a study by Moses et al. [93] reports use of copper-doped bioactive glass silk composite matrices to repair large volume bone defects.

Fixation devices, including bone plates and bone screws have been manufactured from *B. mori* fibroin by casting in hexafluoroisopropanol, and formed into desired shaped (**Figure 6**) [94]. Silk screws tested in rats were well tolerated, showed early resorption and new bone formed around the threads of the screw. Such devices are easily malleable with hydration, allowing shaping for unique anatomical locations during surgery.

### *3.4.3 Artificial ligament and tendon*

Tissue engineering for ligament and tendons requires biomaterials that are biodegradable, have good mechanical properties, good structural integrity,

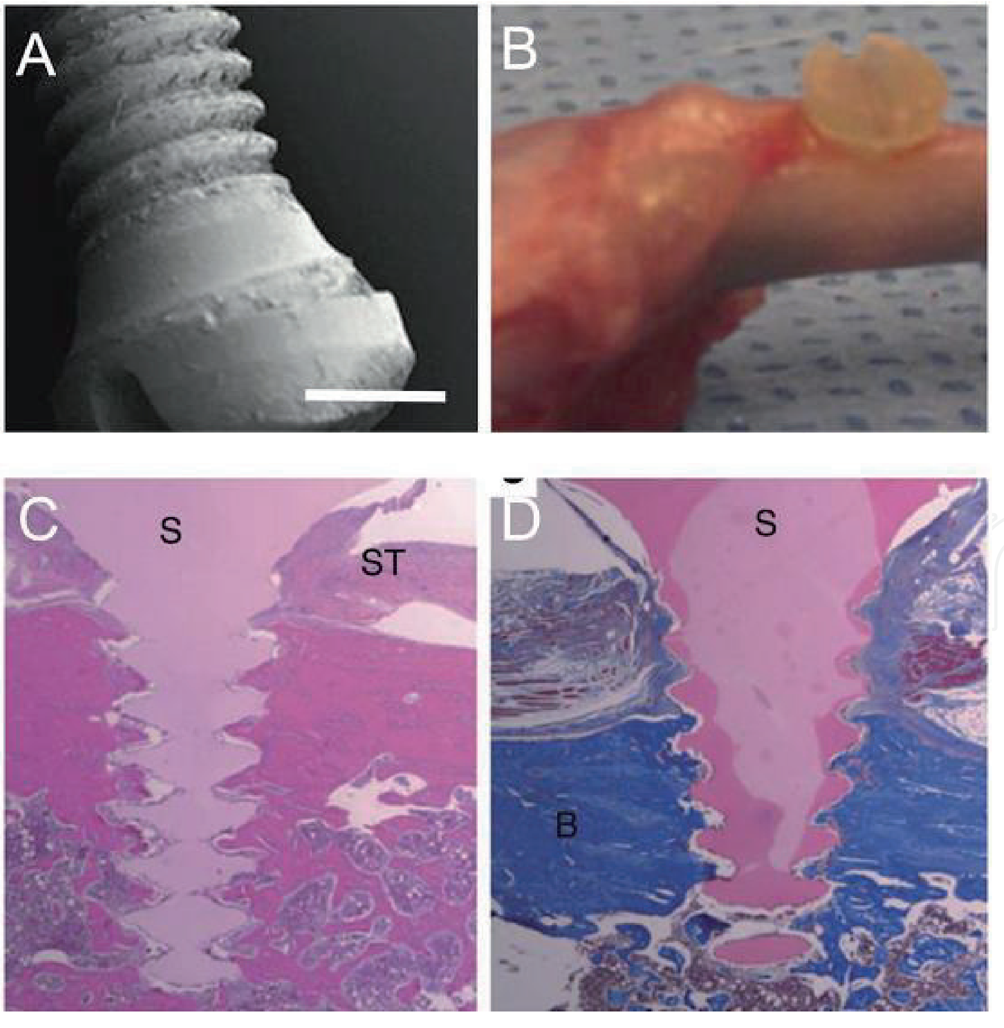


**Figure 6.**
*Silk-based devices for fracture fixation. A) scanning electron microscopy image of a silk fibroin screw. Scale bar is 1 mm. B) Silk fibroin screw inserted into a rat femur at 4 weeks postsurgery. C, D) Cross-sec-tions of the silk fibroin screw inserted into a rat femur at 4 weeks post-surgery; sections stained with H&E and Masson's trichrome, respectively. Adapted with permission [94] Copyright 2014, Macmillan Publishers.*

biocompatible and promote regeneration of new ligament and tendon tissues [46]. Silk is thus a suitable fiber that meets these requirements for performance and function [1, 93]. Weaving and braiding are reported as the most preferred techniques for making silk based ligament and tendon [95–97]. Other studies have reported crosslinking silk fibers with collagen matrix, coating poly(lacticco-glycolic acid) fibers with silk, blending silk fibers with fibroblast growth factor and transforming growth factor-β (TGF-β) in developing artificial ligament and tendon [46, 98–100].

### *3.4.4 Cardiac tissue*

The most difficult part in cardiac tissue engineering is to perfectly mimic the original extracellular matrix. Patra et al. [101] and Stoppel et al. [102] reported to have successfully used scaffolds made *B. mori* and *A. mylitta* silk fibroins to treat myocardial infarction. Moreover, Mehrotra et al. [103] developed a 3-D cardiac construct made from stacking cell-laden silk films; the constructs proved to be good for cardiac tissue regeneration [73].

### *3.4.5 Liver modules*

Different bio-artificial liver and cell therapies to treat liver diseases are available today. Cirillo et al. [104] developed a film from a blend of silk fibroin and collagen. A study by She et al. [105] examined a film made from silk fibroin, chitosan and heparin scaffolds that showed hepatocyte regeneration. Another study [106] reports scaffolds made from a blend of polylactic acid (PLA) and silk fibroin had a higher differentiation and proliferation as compared to scaffolds made from pure PLA alone. Likewise, a study by Janani et al. [107] reports that a functional liver can be fabricated from a blend of mulberry (*B. mori*) and non-mulberry (*A. assama*) silk fibroin.

### *3.4.6 Artificial pancreas*

Different types of microspheres, hydrogels and nanoparticles have been developed to ensure a continuous release of insulin in diabetic patients [108]. In the recent past, islets have been encapsulated with biomaterials before they are transplanted to prevent immune response and to have a continuous insulin release [109]. A study by Davis et al. [110] reports encapsulating islets in silk hydrogel which improved the in vivo functions of the islets after transplanting. In another study, a bio-artificial pancreas was developed using silk alginate to encapsulate insulin secreting cells [73].

### *3.4.7 Artificial intervertebral disc*

A perfect biomaterial for making artificial intervertebral disc must have high tensile strength, be biocompatible and be able to simulate the natural extracellular matrix [111]. A study by Park et al. [112] reports a biphasic hybrid scaffold that was developed from a blend of silk fibroin and hyaluronic acid to simulate the components of an intervertebral disc (nucleus pulposus (NP)) and an annulus fibrosus (AF)). In a related study, Du et al. [113] fabricated a 3-D biphasic silk fibroin scaffold to mimic the AF phase and phase separation technique for the NP phase. Moreover, Bhunia et al. [114] developed a bio-artificial AF construct with directional freezing technique involving concentric rings of lamellar silk scaffolds. The study further reports the proliferation of primary porcine AF cells using a mulberry and a non-mulberry silk combination which helped in cellular maturation, alignment and extracellular matrix deposition.

### 3.5 Silk in sutures

Sutures are an important material in surgical operations for primary wound closure. For this reason, various materials have been used in making sutures. These materials can be classified as either organic or synthetic according to their origin, or absorbable and non-absorbable according to their durability in the body [115]. Important properties for a good suture include: high tensile strength, elasticity, wound safety, knot safety and tissue reactivity [116, 117].

Silk, a natural non-absorbable suture material has been in use as a suture for several decades. However, other degradable synthetic sutures have dominated the market in the recent past. Nonetheless, silk suture is still preferred in cardiovascular, ocular and neural surgery because of its superior properties like good knot strength, ease of processing, minimum propensity to tear through tissue and biocompatibility [117].

Various modifications have been done on silk to improve its weak characteristics such as adding poly vinyl alcohol into silk fibroin to improve the tensile strength, elongation at break and the knot strength [118]. Bloch & Messores [119], reported coating silk filaments with fibroin and bounding them together to reduce the capillarity of silk sutures. Viju & Thilagavathi [120] coated silk-braided sutures with chitosan to improve the antimicrobial activity, tenacity and knot strength. Sudh et al. [121] developed a drug loaded antimicrobial silk suture for use in wound closure and wound healing meant to prevent surgical site infections. Choudhury et al. [122] developed a low-temperature $O_2$ plasma-treated (*Antheraea assama*) silk fibroin (AASF) yarn impregnated with amoxicillin trihydrate. This was aimed at producing a controlled antibiotic-releasing suture (AASF/$O_2$/AMOX) to prevent site bacterial infection and fasten wound healing. This shows the potential of silk in developing suture with special properties.

| Type of Drug Delivery System/material | Associated active ingredient | Key results |
|---|---|---|
| Silk sponges | Erythromycin | Sustained drug release and prolonged antimicrobial activity against Staphilococcus Aureus |
| Silk films | Horseradish peroxidase (HRP) | Enhanced stability |
| | Glucose oxidase (GOx) | Increased enzymatic activity |
| | FITC-dextran | Controlled drug release |
| | Epirubicin | Controlled drug release |
| Silk lyogels | Hydrocortisone IgG | Enhanced efficacy Enhanced stability and sustained release |
| Insertable Silk discs | IgG and HIV inhibitor 5P12-RANTES | Enhanced stability and modified release profile |
| Silk nanoparticles | Curcumin | Modified release profile and enhanced cellular uptake |
| Silk microspheres | Horseradish peroxidase (HRP) | Modified the release profile |
| Silk coated PCL microspheres | Vancomycin | Modified the release profile |
| Silk coated liposomes | Ibuprofen | Enhanced adhesion to human corneal epithelial cells, tunable drug release |
| | Emodin | Selective targeting of keloid cells |

**Table 1.**
*Silk-based drug delivery systems [100].*

### 3.6 Silk in drug delivery

Drug delivery through polymeric systems has gained popularity over the years [51]. These systems serve as reservoirs to active ingredient in drugs and improve the drug's physicochemical properties [123]. Polymeric drug delivery systems are also good in specific targeting, intracellular transport and some are biocompatible which help in improving efficiency of the treatment and the life quality of the patients [123, 124]. A good drug delivery system should be able to stabilize the active ingredient in drugs, be able to modulate the drug's release mechanism, be biocompatible and biodegradable, as well as minimize any side effects of tissue specific targeting of highly toxic drugs [125–127].

Silk fibroin is used in drug delivery systems owing to its properties such as good mechanical properties, mild aqueous processing conditions, biocompatibility, biodegradability and its ability to enhance the stability of active ingredient in drugs; as proteins and small molecules [46, 128]. That notwithstanding, silk fibroin solutions can be processed using various techniques to produce different forms of delivery systems like scaffolds, films, hydrogels, nanoparticles, microspheres, and microcapsules among others [129]. Additionally, silk fibroin has carboxyl and amino groups which allow bio-functionalization with different biomolecules for targeted drug delivery [130]. Silk based drug delivery systems include hydrogels, micro particles, lyophilized sponges, films, nano-fibers and nano-particles.

| Formulation | Gene | Cell line |
|---|---|---|
| Recombinant silk–elastin-like polymer hydrogels (SELPs) | Ad[1]–CMV[2]–LacZ[3] | Head and neck cancer in mice |
| | pDNA[4] (pRL[5]-CMV-luc[6]) | NA |
| | Ad–Luc–HSVtk[7] | Head and neck cancer in mice |
| 3D porous scaffold | Adenovirus Ad-BMP7[8] | Human BMSCs |
| Bioengineered silk films | pDNA (GFP[9]) | Human HEK cells |
| Spermine modified SF | pDNA and VEGF165–Ang-1[10] | In vivo-rat |
| SF-Coated PEI/DNA Complexes | pDNA (GFP) | HEK 293 and HCT 116 cells |
| SF layer-by-layer assembled microcapsules | pDNA-Cy5[11] | NIH/3 T3 fibroblasts |
| Bioengineered silk–polylysine–ppTG1 nanoparticles | pDNA | Human HEK and MDA-MB-435 cells |
| Magnetic-SF/polyethyleneimine core-shell nanoparticles | c-Myc[12] antisense ODNs[13y] | MDA-MB-231 cells |

[1]*Adenovirus.*
[2]*Cytomegalovirus promoter gene.*
[3]*Beta galactosidase reporter gene.*
[4]*Plasmid DNA.*
[5]*Renilla luciferase.*
[6]*Luciferase reporter gene.*
[7]*Herpes simplex virus thymidine kinase gene.*
[8]*Bone morphogenic protein.*
[9]*Green fluorescent protein.*
[10]*Vascular endothelial growth factor and angiopoietin-1.*
[11]*Fluorescent probe.*
[12]*MYC Proto-Oncogene.*
[13]*Oligodeoxynucleotides [100].*

**Table 2.**
*Silk –based gene delivery systems [100].*

Different researches have reported successful use of silk fibroin in delivery systems for different drugs and genes [131–133]. **Tables 1** and **2** below presents some silk based drug and genes delivery systems.

## 4. Silk in protective clothing

Protective clothing are defined as textile structure designed to protect the human body from external threats such as fire, bullets, heat, cold, mechanical, biological, radiological, thermal and chemical hazards. Protective clothing are in different forms e.g. masks, gloves, vests, coats, aprons, hats, hoods or totally encapsulating chemical protective suits [134]. Some general characteristics of good protective clothing include: reliable barrier protection, durability, good fit, flexible, light weight, ease of care, maintenance and repair, ease of disposal and recycling.

Because of the interesting characteristics of silk, various research studies have examined its use in developing protective textiles. Some of these characteristics include hydrophobicity, antimicrobial and antiviral properties [135]. Recently, Parlin et al. [135] examined the potential of silk fabrics as a protective barrier for personal protective equipment and as a functional material for face coverings during the COVID-19 pandemic. Results of this study showed that the use of the commercially available 100% silk material can be used in producing protective coverings that can prolong the lifespan of N95 respirators. The study also found 100% silk fabrics suitable for developing face coverings for the general public to prevent COVID-19 [135]. Additionally, the study suggests that because silk has unique properties such as antimicrobial, antiviral, breathability, and slight hydrophobicity; prevention of penetration of droplets and antibacterial activity can imply potential use in developing respirator inserts [136, 137]. Moreover, other studies had showed that silk could be used as an antimicrobial barrier mask, with better filtration when multiple layers are used [135]. Besides, silk neither irritates the skin nor increases local humidity around the covered face, and prevents accidental stimulation of face touching; making it good for prolonged wear [138].

Another study by Zulan et al. [139] reports use of silk/graphene composite to make flame retardant protective clothing that can be used by fire fighters. Loh et al. [140] reports woven silk fabrics can be used for ballistic protection for aerospace, sports, military, marine and automotives. Mongkholrattanasit et al. [141] studied the ultraviolet (UV) protection properties of silk fabric dyed with eucalyptus leaf extract. Pad-dry and pad-batch techniques together with a metal mordant ($AlK(SO_4)_2$, $CuSO_4$, and $FeSO_4$) were used to apply a natural dye extracted from eucalyptus leaves on silk fabric. Results of his study showed that the UV protection factor of the silk fabric increased with an increase in the dye concentration and a darker shade gave the best UV-protective silk fabrics. Moreover, a study by Zhou et al. [142] also reports silk fabrics treated with red radish extracts provides good UV protection and that such fabrics can be used in making umbrellas, shade structures, awnings, and baby carrier covers among others.

## 5. Silk in optics and sensing

Synthetic biomaterials have been widely used in optics and sensing applications. For ophthalmic applications, which include lens replacement, retina reconstruction, vitreous replacement and ocular surface reconstruction, various materials such as poly-methylmethacrylate (PMMA), silicone, acrylics, poly-tetrafluoroethylene among others have been extensively used due to the biological inert nature of these materials [143, 144]. With technological advances, regenerative medicine strategies have shifted to relying on the ability of the biomaterial scaffolds in supporting human cell adhesion, growth and maintenance of the right cells that encourage tissue replacement as well as integration with adjacent tissues [145]. Since most synthetic biomaterials lacked the aforementioned abilities, emerging technologies attempted the modification of synthetic biomaterial surfaces [146]. However, a major limitation of surface modified synthetic materials was that such materials are not transparent, especially for applications in tissue grafts which need to be optically clear and they are not biodegradable [143]. Materials derived from nature have therefore become popular because they support cell attachment and proliferation. These materials include cross-linked collagen-chitosan hydrogels [147], keratin [148], cross-linked collagen gels [149], silk fibroin [150] etc.

Apart from ophthalmic applications, there has been an increased desire for real-time diagnostics, sensing and deep tissue light delivery, which has led to development of photonic medical devices from materials which are implantable and biocompatible. These devices can therefore be used within the body for therapeutics and long term health monitoring, where they are integrated into the living tissue in the human body [151]. Non-biodegradable inorganic materials such as silicon, gold and compound semiconductors have been traditionally used in photonic devices. However, their biocompatibility have been found to be dependent on the device size, the presence of coatings and mechanical properties [152]. Hydrogel materials from poly-vinylalcohol (PVA) and poly-ethylglycol (PEG), which are biocompatible have also been used in tissue engineering applications because of their ability to retain water and mimic the human body extracellular matrix [153]. However, they have not found extensive application in sensing because of their poor adhesion to substrates and poor mechanical properties [154]. Selection of the right material for implantable photonic devices requires consideration of biocompatibility properties as well as the structural stability, mechanical flexibility and optical clarity [151]; requirements that silk fibroin meet. Silk fibroin is thus gaining traction in optical interfaces and sensor applications in implantable biomedical fields owing to its good mechanical and optical transparency, coupled with its biodegradability and biocompatibility [14]. Silk in film form has a free standing structure with thickness ranging from 20 to 100 μm. The films are very transparent across the visible region of the spectrum and are mechanically robust with smooth surfaces. The films can also be patterned during fabrication to form traverse features that are tens of nanometers, making them attractive in optical device applications [155].

Substratum for corneal limbal epithelial cells has been developed from silk fibroin membranes, by casting dialyzed solutions of silk fibroin protein. The transparent silk membrane was found to support growth of human limbal epithelial (HLE) cell growth, which did not change even when the silk membranes were cast in the presence of fetal bovine serum (FBS) [156]. Such properties are favourable in the development of tissue engineered membranes for restoration of damaged ocular surfaces. Porous silk films have also been fabricated and shown to have potential in use as a carrier of cultivated epithelial sheets during regeneration of corneal epithelium [157].

Diffractive optical elements were fabricated by molding silk fibroin solution on poly-dimethylsiloxane (PDMS) moulds with ruled and holographic diffraction grating, producing nano-patterned silk optical elements of thickness ranging from 30 to 50 μm and a refractive index of n = 1.55. These nano-patterned silk gratings had a diffraction efficiency of 34%, at a wavelength of 633 nm in the first order, which compares to that of transmissive glass gratings. This led to successful formation of silk micro-lens arrays and silk lenses, which couple light into biological substrates [158]. Such silk gratings can also be functionalized, to maintain the biologically active optical elements. Therefore this could allow the use of these silk devices in delivering light to biological matrices and concentrate photons with doped substrates for biological function probes. In another study, silk diffraction gratings with desired patterns were fabricated through photo-induced polymerization of silk conjugates and a photo-initiator, producing good diffraction intensity [159].

Silk micro-prism arrays (MPAs) were prepared by micro-molding technique, resulting into a silk reflector film of 100 μm in thickness. The MPAs provided contrast and optical signal enhancement by retro-reflecting scattered photons through layers of tissue when used in vivo on BALB/c mice. The silk MPAs had no adverse biological effects, degraded slowly and were integrated into the native tissue. Functionalization of silk MPA with doxorubicin (a chemotherapeutic drug), was further reported to allow controlled delivery, storage and imaging of therapeutics, besides improving noninvasive tissue imaging [160].

Optical waveguides, which have the ability to transport and manipulate light in a controlled manner [161], have also been fabricated from silk. Silk fibroin ink, used in direct ink writing technique, has enabled creation of silk optical waveguides. These have been found to easily guide light of wavelength 633 nm. These waveguides were reported to exhibit comparable optical loss measurements to those of thin silk films, an indication that they can be applied in fabrication of functionalized, biocompatible and biodegradable biophotonic elements [155].

Silk fibroin hydrogels have also found use in surface plasmon resonances (SPR) sensors, fabricated by utilizing the principle of metal–insulator–metal (MIM) absorber. Inclusion of a thin insulator layer of 20 nm silk fibroin hydrogel between two 200 nm gold films enables the MIM structure produced to become highly sensitive to changes in thickness and refractive index of the insulating layer. Thus, the hydrogel properties of the silk spacer, which can accommodate water molecules by up to 60% in volume, increases sensitivity to analytes. Sensitivity is dependent on the refractive index and swelling ratio of the silk hydrogel. The silk polymer chains can also act as fluidic channels that facilitate flow of analytes in water, through a nano-sized layer, making silk plasmonic structures suitable for glucose sensor applications [162].

A wearable strain sensor was fabricated by carbonizing pristine silk georgette through high temperature treatment, followed by encapsulation in poly-dimethylsiloxane (PDMS), an elastic polymer. This has shown promising potential for applications in monitoring a wide range of motion based human activities [163]. Silk based wearable sensors utilizes the principle of transformation of silk fibroin through thermal treatment, into an electrically-conductive graphite nano-carbon [164]. Transparent and flexible silk nanofiber-derived carbon membranes have also been fabricated for multifunctional electronic skin with human physiological signal monitoring capabilities [165, 166]. Silk based self-powered pressure sensor films for use in wearable devices have also been fabricated through synthesis of silk and poly-vinylidene fluoride-co-trifluoroethylene [167]. In order to provide a strong interface between a biological surface and a sensor for epidermal electronics, calcium modified silk fibroin has been fabricated and shown to have strong adhesive properties with good stretchability, conductivity and reusability. Therefore calcium modified silk fibroin shows the potential to be applied as an adhesive for epidermal biomedical sensors [168].

Another promising application of silk is in the coating of otherwise non biocompatible optical fibers for bio-sensing inside the human body. Silica exposed core fiber are reported to have been coated with a thin layer of silk and thereafter, doped with fluorophore 5,6-carboxynapthofluorescein (CNF). The doped-silk layer was found to produce fluorescent signals that are coupled into the core of Silica exposed core fiber, allows for remote measurement of pH along the fiber length, when used in mice [169].

## 6. Conclusion

Silk fiber from different varieties has largely been used beyond the traditional textile scope. The widest and earlier use has been noted in biomedical use, especially as sutures, and protective wear due to the enviable properties highlighted for each function. The traditional classification of silk was tagged to luxury. Beyond this, research has been expounded on the functionality of silk. The various forms, including regeneration into nanofibers, nanofilms and nanomembranes provide surfaces for novel functionalization when processed with specific agents. Collagen has been reported the most as a functional material added to silk for, especially biomedical applications. Optics and sensing, present a unique and promising future for functional silk— especially in e-textiles and bio-sensing. However, it is also important to underscore that at different stages of regeneration, the silk structure seems to get altered; especially the loss of considerable strength resulting from altered crystallinity and re-orientation of β-sheets of silk fibroin. Owing to the low proportion of silk production on the market compared to cotton, and synthetic fibers, it is important to explore the annual global demand of silk in regard to future needs for silk in functional textiles. It is also important to explore statistics, on silk processed through novel methods like electrospinning, with respect to commercial viability. For instance, it is often required to strictly control biomaterial properties during processing, owing to the complexity of biomaterial molecules. Of important focus is the standardization of process/manufacturing parameters and equipment in the attempt to commercialize silk functional products. However, with increasing demand for more environmentally sustainable materials and products, more bio-based sectors and economies will emerge; hence, an increased uptake of natural biomaterials such as silk, in higher technology application needs.

## Conflict of interest

The authors have no conflicts of interest to declare.

## Author details

Edison Omollo Oduor[1]*, Lucy Wanjiru Ciera[1] and Edwin Kamalha[2]

1 Technical University of Kenya, Nairobi, Kenya

2 Busitema University, Tororo, Uganda

*Address all correspondence to: edisonomollo@gmail.com

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