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Silk-based biomaterial scaffolds for dental tissue regeneration

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Being a natural biomaterial with exceptional biological features, silk-based biomaterial offers an attractive option for fabricating biomimetic scaffolds that provide excellent physicochemical and biomechanical support and induce several physiological signaling pathways to facilitate tissue regeneration. Recent advancements in various biofabrication strategies enable the creation of silk-derived cell-instructive scaffolds that accelerate the regeneration of dental tissue, which is a complex, multicellular, and polymorphic structure. This review highlights recent innovations in silk-based biomaterial scaffolds and comprehensively explores current shortcomings in developing them as ideal dental biomaterials for therapeutic delivery and regeneration. We discussed various structural-property relationships and their ability to induce pro-regenerative and immune-signaling pathways for the regeneration of different dental-associated soft and hard tissues. We further conclude by providing a perspective on the potential of silk-based multifunctional regenerative platforms in revolutionizing tooth regeneration.

Silk-based scaffolds have emerged as promising biomaterials in tissue engineering, particularly for the regeneration of dental and oral soft tissues. Derived from silk fibroin (SF), a protein obtained from silkworm cocoons, these scaffolds provide a three-dimensional framework that closely mimics the natural extracellular matrix. Their unique combination of tensile strength, biocompatibility, and biodegradability makes them well-suited for supporting cell growth and tissue repair[1]. Dental and associated soft tissues possess limited regenerative capacity, making effective biomaterials essential for clinical restoration. Silk-based scaffolds have demonstrated the ability to promote cell adhesion, proliferation, and differentiation, processes that are critical for tissue regeneration. For example, mineralized SF scaffolds can replicate both the architecture and chemical composition of bone, thereby enhancing bioactivity and cell proliferation[2].

In dental applications, silk scaffolds have shown particular promise in supporting human dental pulp stromal cells (hDPSCs), which play a central role in dental tissue repair and regeneration[3,4]. Studies have reported encouraging outcomes in areas such as periodontal regeneration, pulp repair, and root canal therapy, highlighting their translational potential. Beyond hard tissues, SF-based scaffolds have also been applied to regenerate gingiva, periodontal ligaments, and oral mucosa[5,6]. Their biocompatibility, biodegradability, and adaptability make them suitable for both hard and soft tissue engineering. Recent advancements in fabrication techniques, especially 3D printing, have further expanded the potential of silk scaffolds by enabling the design of complex, tissue-mimicking structures[7].

Additionally, silk can be functionalized with bioactive molecules to enhance regenerative outcomes. Studies have shown that silk-based scaffolds exhibit osteogenic and chondrogenic properties, making them valuable for alveolar bone regeneration and other implantable applications[8]. Importantly, silk also demonstrates anti-inflammatory and pro-angiogenic effects, which support healing and vascularization, which are key factors in successful tissue regeneration[9,10]. Overall, silk-based scaffolds represent a versatile and practical approach for dental and oral tissue engineering. Their ability to combine structural support with biological activity positions them as a promising class of biomaterials for improving clinical outcomes in regenerative dentistry[10–12] (Fig. 1a).

Need for new materials in dental applications

Dental tissues are highly complex organs composed of both hard and soft tissue components, each characterized by distinct physicochemical microenvironments. Recent advances in bio-nanotechnology, materials science, and additive manufacturing have created new opportunities for designing biomaterials and delivery platforms across multiple tissue types, including bone, cartilage, tendons, and neurons. However, the regeneration of dental tissues remains particularly challenging due to their structural and functional complexity. Unlike many other organs, dental tissues exhibit a

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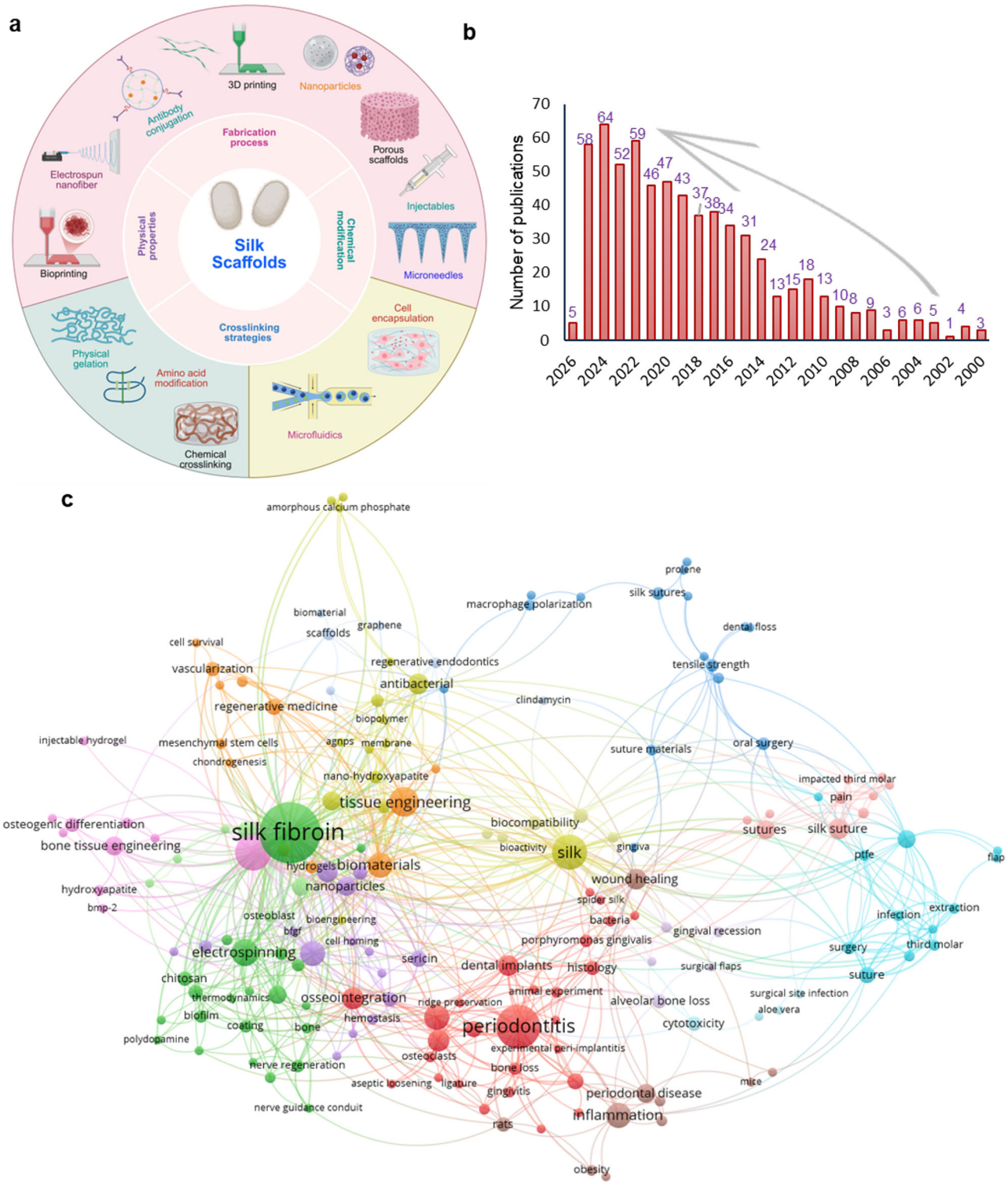

Fig. 1 | Application of silk-based biomaterials in dental tissue application. **a** Schematic illustration of various applications of silk-derived biomaterial scaffolds for dental tissue regeneration. **b** A quantitative bibliometric analysis was conducted to map the growth of research interest in silk-based scaffolds for dental applications. Publication data were extracted from PubMed using the search terms *'silk'* and '*dental*' for the period 2000–2026. After excluding systematic analyses, book chapters, observational studies, meta-reviews, case studies, and literature reviews, a total of 552 primary research articles were identified. The annual number of these publications is presented as a bar graph, illustrating a pronounced upward trend in research output over the past two and a half decades. **c** The research landscape was further analyzed using VOSviewer software to perform a bibliographic coupling analysis based on co-occurring author keywords. The network map visualizes the interrelated themes within the field of silk scaffolds for dental tissue repair and regeneration. Each distinct color cluster represents a primary research focus or application area. The size of an individual node corresponds to the frequency of a keyword's occurrence, while the thickness of connecting lines indicates the strength of co-occurrence links between terms. The analysis was configured with a minimum keyword co-occurrence threshold of three, generating a network from 208 significant keywords. This visualization elucidates the dominant thematic concentrations and their interconnections within the extant literature.

remarkable diversity in composition and architecture. Enamel, for instance, consists almost entirely of highly mineralized inorganic material organized into sophisticated micro- and nano-scale architectures, yet it is accelerated and utterly incapable of self-regeneration. In contrast, the odontogenic zone and pulp tissue present a confined, nutrient-rich environment that is especially susceptible to microbial colonization.

The challenges are compounded by heterogeneity in the inorganic-to-organic ratio across different regions of the tooth, which directly influences mechanical strength, surface chemistry, and local immunity. Furthermore, the surface topography of dental tissues serves as the initial point of interaction with biomaterials, making it critical in determining adhesion, integration, and long-term functionality. Anatomical variation among individuals further complicates the development of universal restorative strategies, as differences in tooth morphology, including crown and root dimensions, significantly influence treatment outcomes. Additionally, the oral cavity is a highly dynamic environment due to the continuous flow of saliva enriched with proteolytic enzymes, which can compromise the stability and longevity of biomaterials.

Given these complexities, the regenerative potential of different dental tissues is inherently limited. Dentin, the periodontal ligament, and pulp tissue possess restricted regenerative capacity, mainly due to insufficient populations of dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs). The dentin–pulp interface is especially difficult to restore, as it consists of a highly specialized organic matrix interwoven with spatially organized odontoblasts. These limitations underscore the pressing need for the development of advanced biomaterials that can overcome the structural, biological, and environmental challenges specific to dental tissues.

To address these challenges, new generations of dental materials must meet multiple criteria with improved mechanical performance, such as enhanced strength, durability, and wear resistance, which can extend the lifespan of restorations and reduce patient discomfort. Equally important is biocompatibility, with materials designed to mimic the properties of native dental tissue and avoid adverse reactions. Aesthetic qualities, including translucency and color stability, are also increasingly prioritized by patients seeking natural-looking restorations. Advances in minimally invasive techniques, enabled by tooth-colored composites and adhesive bonding, preserve natural structures and offer conservative treatment options.

Moreover, the integration of digital dentistry, such as computer-aided design and manufacturing (CAD/CAM), necessitates the use of materials compatible with these workflows, ensuring precision and efficiency. Finally, sustainability considerations are gaining importance, driving the development of eco-friendly, biodegradable, and recyclable dental materials that minimize environmental impact. Taken together, these innovations reflect a paradigm shift in restorative dentistry, where materials science addresses not only functional and aesthetic needs but also aims to overcome the unique biological and structural challenges inherent in dental tissue regeneration.

Recent trends in research further underscore the importance of such innovations. The number of publications related to silk and dental tissue has steadily increased over the past two decades. Notably, until 2025, a surge in research output is expected, reflecting heightened interest in this field, particularly with the silk-based biomaterial platform (Fig. 1b). This rise in scientific activity underscores the increasing recognition of silk-based biomaterials and other advanced materials as viable solutions to the challenges of dental tissue regeneration, thereby further reinforcing the urgency of continued material innovation.

How the silk structure helps with regeneration

Naturally, silk is primarily comprised of two main proteins, named as fibroin and sericin. Fibroin, constituting about 70% of the cocoon weight, is a fibrous protein with a semi-crystalline structure, comprised of amino acids such as l-alanine, glycine, and l-serine in a sequence linked by peptide bonds. The heavy chain of SF contains hydrophobic domains with repeating hexapeptide patterns, forming stable antiparallel β-sheet crystallites, which contribute to the mechanical strength of silk fibers[13]. On the other hand, sericin, making up about 25% of silk, possesses high defensive abilities against ultraviolet light and oxidation, providing lubrication, protection, and adhesion in cocoon silk. Sericin is a water-soluble protein with a loose and disordered spatial structure, acting as the outer glue-like coating on silk fibers, and can be removed through thermo-chemical treatment. Owing to their distinct molecular architectures, separation of sericin and fibroin is essential, as removal of amorphous, hydrophilic sericin yields β-sheet-rich fibroin with defined crystallinity, mechanical robustness, reduced immunogenicity, and controlled biodegradation, while enabling independent exploitation of sericin's bioactivity[14,15].

The interaction between fibroin and sericin, with fibroin providing mechanical strength as the inner core and sericin acting as a protective and adhesive layer, contributes to the unique structure and properties of silk. Hierarchical nanofibril structure refers to the multilevel assembly of SF into β-sheet nanocrystals that organize into nanofibrils and higher-order bundles, enabling efficient load transfer and high mechanical strength comprising nanofibrils that can be easily processed into films with high strength, further enhancing the mechanical properties of silk, making it a versatile material with applications in textiles and biomedicine[16,17]. Nonetheless, the molecular structure of natural and synthetic silk differs significantly. Synthetic silk refers to recombinantly produced or silk-mimetic polymers with molecular architectures distinct from those of native SF, resulting in differences in mechanical behavior, degradation kinetics, and regenerative performance. Natural silk is composed of fibroin, which forms a complex hierarchical structure comprising crystalline and amorphous domains[18,19]. In contrast, synthetic silk is typically produced through recombinant DNA technology, resulting in a simpler, more uniform structure, the simpler and more uniform molecular architecture of synthetic silk enables precise control over composition, mechanical properties, and degradation behavior, thereby improving reproducibility and tunability for targeted regenerative applications[20,21].

The differences in molecular structure contribute to variations in mechanical properties, biodegradability, and biocompatibility between natural and synthetic silk, making each type of silk better suited for different applications. Natural silk can be sourced from a variety of organisms, including silkworms, spiders, and mussels[22]. Silkworms, particularly those of the species *Bombyx mori*, are the most common source of natural silk for biomedical applications. The advantages of natural silk for regeneration include its biocompatibility, biodegradability, and ability to support cell adhesion and proliferation[23]. However, natural silk also has some disadvantages, including batch-to-batch variability and the potential for allergic reactions in some individuals. Synthetic silk, on the other hand, can be produced in a more controlled manner, with consistent properties and fewer potential immune reactions. However, synthetic silk may not be as biocompatible or biodegradable as natural silk, which limits its possible applications for regeneration[24,25]. Figure 2a illustrates the dependence of scaffold–cell interactions and degradation behavior on silk architecture, while Fig. 2b highlights how variations in amino-acid composition and bioactive motifs in natural silk underpin its superior biological performance.

In summary, the choice between natural and synthetic silk for regeneration depends on the specific application and desired properties. Natural silk has unique advantages, including biocompatibility and biodegradability, but also has some limitations, such as batch-to-batch variability. Synthetic silk can be produced with more consistent properties but may not be as biocompatible or biodegradable as natural silk[26]. Moreover, while natural silk can exhibit variability between batches due to differences in biological source and processing conditions, reproducible clinical performance can be achieved by implementing standardized purification and fabrication protocols alongside rigorous physicochemical characterization, which together minimize inter-batch differences in structure and mechanics and support translation into reproducible clinical applications. Regardless of the type of silk used, the macroporous structure of silk sponges can be tailored to promote tissue regeneration, making silk scaffolds a promising biomaterial for tissue engineering[27].

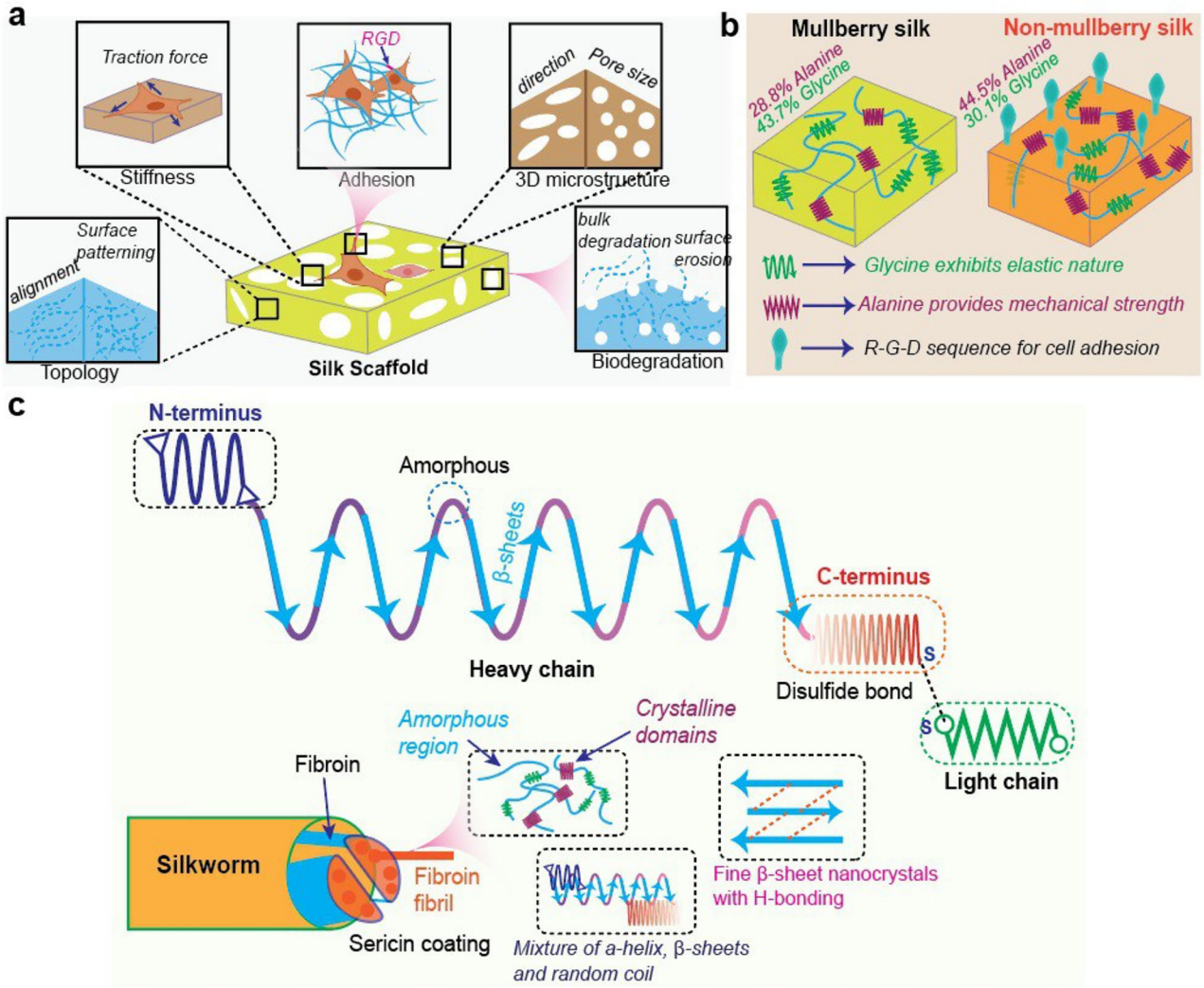

Fig. 2 | The molecular structure of silk. a Illustration of silk scaffolds exhibit tunable physicochemical properties, including mechanical strength, biocompatibility, topography, biochemical functionality, and controlled degradability, which can be engineered to regulate cell adhesion, mechanotransduction, and stem-cell differentiation for dental tissue regeneration. **b** Chemical composition of mulberry and non-mulberry silk, the presence of cell-adhesive motifs, such as RGD sequences, varies among non-mulberry silks and is shown here schematically for representative cases rather than as a universal feature. **c** Molecular configuration of a single silk fiber.

The SF sequence typically encompasses distinct motifs, such as Gly-Ser-Gly-Ala-Gly-Ala, which fosters β-sheet structures formation, which is critical for the robustness and stability of silk fibers[28]. Additionally, repetitions of Gly-Ala-Gly-Ala dipeptides further reinforce the structural integrity of silk by facilitating β-sheet assembly (Fig. 2c). Furthermore, glycine-rich domains interspersed within the fibroin sequence confer elasticity and flexibility to silk fibers, enabling them to endure stretching without fracturing and to recover their original shape post-deformation[29]. Nevertheless, not all non-mulberry silks inherently possess RGD (Arg-Gly-Asp) sequences; their presence is species-dependent[30]. For instance, fibroin from certain non-mulberry silkworms (e.g., *Antheraea mylitta*, tasar silk) contains natural RGD motifs, whereas other sources may not[30]. Spider silk proteins, such as those from *Nephila clavipes*, also frequently contain RGD sequences. Critically, synthetic or recombinant silk is a distinct category where the amino acid sequence is engineered, which allows to deliberately incorporate or omission of RGD sequences to precisely control cell-adhesive properties for specific applications[31,32]. SF sequences often exhibit tandem repeats of specific motifs, fostering a hierarchical structure characterized by stable crystalline regions intermingled with flexible amorphous segments[33]. This unique arrangement governs the mechanical properties of silk materials, including stiffness, toughness, and elasticity. Manipulating the fibroin sequence through genetic engineering or chemical modification enables the customization of silk-based materials to suit diverse biomedical applications, including tooth regeneration Fig. 3.

The versatile processability of SFs into various forms, such as gels, films, and scaffolds, contributes to their suitability for tissue engineering applications, allowing for tailored solutions based on specific tissue regeneration needs[34,35]. Additionally, silk proteins consist of both reactive and non-reactive amino acids, providing active sites for chemical modifications that enable control over protein structure and function, thereby supporting dental and/or orofacial tissue regeneration.[18,36]. Furthermore, the mechanical strength of SF, along with its tunable biodegradation properties, makes it an advantageous material for bone regeneration, as it can mimic the mechanical properties of native tissue and promote osteogenesis[29]. The structure of SF fibers, with β-sheet crystallites embedded in an amorphous matrix, has the potential to enhance tissue regeneration properties, including promoting cell proliferation and extracellular matrix production. Moreover, SF scaffolds with micron-sized fibers can influence cell morphology, affecting cell adhesion and migration genes during tissue regeneration processes, showcasing the importance of silk structure in guiding cellular behavior for successful regeneration[37]. The ability to tailor silk structure and composition for specific tissue regeneration applications

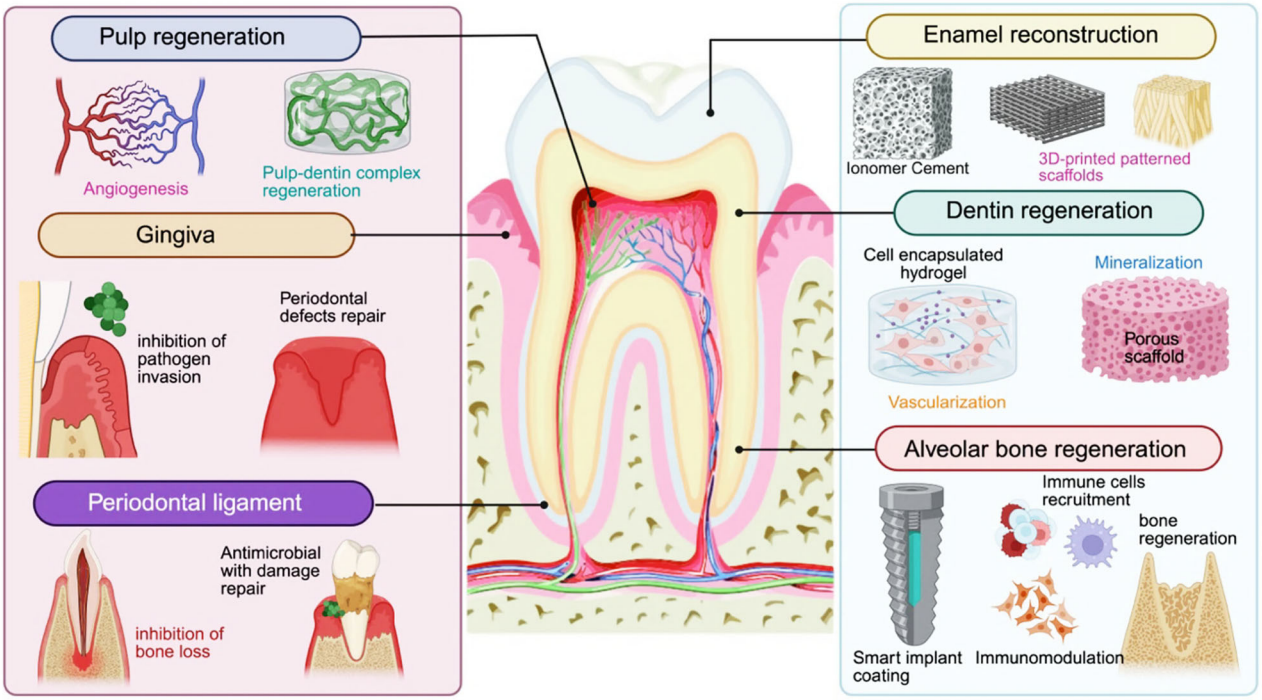

Fig. 3 | Overview of silk-derived biomaterial platforms and associated biological functions in dental and orofacial tissue repair and regeneration. The figure depicts representative silk-based material formats, including scaffolds, hydrogels, and surface coatings, together with the biological responses they enable, such as angiogenesis, mineralization, immunomodulation, antimicrobial activity, and tissue-specific regeneration of pulp, dentin, enamel, periodontal ligament, gingiva, and alveolar bone. Not all illustrated elements represent standalone scaffold architecture; some denote functional or biological outcomes mediated by silk-based biomaterials.

highlights its potential as a promising material in the dental application. Additionally, silk scaffolds can be functionalized with various substances, such as growth factors, peptides and targeted ligands, to further enhance the regeneration process, showcasing the adaptability and customization capabilities of silk-based materials. Overall, the unique properties and functionalization possibilities of silk-based scaffolds make them a valuable asset in enhancing the regeneration process across various tissue engineering applications[4].

Silk as a biopolymer: effect of silk fibroin in various dental tissues

The ultimate goal of modern dentistry is shifting from the replacement of damaged tissues to their true regeneration. This paradigm shift necessitates biomaterials that can actively participate in the healing process by providing a scaffold that mimics the native ECM. Among natural polymers, SF has garnered significant attention. Derived from the cocoon of the silkworm *Bombyx mori*, SF is an FDA-approved biomaterial with a unique combination of properties: excellent mechanical strength, tunable degradation rates, minimal immunogenicity, and the ability to be processed into various formats like films, sponges, hydrogels, and nanofibers[38,39]. These attributes make SF an ideal candidate for addressing the complex challenges in dental tissue regeneration.

In dentistry, SF has been used to regenerate various dental tissues, including dentin, pulp, gingiva, periodontal pockets, and enamel. SF scaffolds have also been used to support the growth of DPSCs, which can differentiate into various dental tissues. The use of SF in dental tissue engineering has shown promising results in terms of regenerating damaged or lost dental tissues, making it a potential alternative to traditional dental restoration materials.

Over the years, SF has been studied for its potential use in various dental tissues, including periodontal tissues. Periodontal disease is a common condition that affects the gums and bone surrounding teeth, and current treatment options are limited. However, SF has been shown to have potential in promoting periodontal tissue regeneration[40]. In a study examining the effects of SF on periodontal tissues, researchers discovered that SF scaffolds stimulated the growth and differentiation of periodontal ligament stem cells, suggesting its potential as a regenerative therapy[41]. Additionally, SF has been shown to possess excellent biocompatibility and natural properties, such as strength and resistance to temperature and humidity[42]. SF has also been investigated for its potential use in dental pulp tissues, which play a crucial role in tooth development and repair. In a study exploring the effects of SF-RGD-stem cell factor scaffold on dental pulp stromal cells, it was observed that the scaffold promoted cell migration, proliferation, and attachment, indicating its potential for use in dental pulp tissue engineering[43,44].

SF has also been studied for its use in dental implants and as a component of restorative materials. In a study evaluating the effects of different aperture-sized collagen/SF scaffolds on the attachment and proliferation of DPSCs, researchers found that the scaffolds promoted cell growth and attachment, indicating their potential for use in dental implant materials. SF has been investigated across multiple dental tissues, reflecting its adaptability as a biopolymer for dental regenerative applications.

Additionally, SF has been shown to have minimal immunogenicity, making it a promising material for use in dental pulp regeneration[45]. SF has also been studied for its use in dental implants and as a component of restorative materials. Multiple studies evaluating the effects of different aperture-sized collagen/SF scaffolds on the attachment and proliferation of dental pulp stem cells, researchers found that the scaffolds promoted cell growth and attachment, indicating their potential for use in dental implant materials[46,47]. In addition, SF has been demonstrated to exhibit excellent mechanical properties and biological interactions, rendering it a promising biomaterial for use in dental implants and restorative materials[48]. The use of SF across multiple dental tissue models reflects its adaptability as a biopolymer for dental regenerative applications.

Modification of silk for enhanced regeneration

Despite its considerable promise, the clinical translation of silk scaffolds for dental applications is constrained by several material science and biological challenges. The mechanical environment of the oral cavity is exceptionally dynamic. While SF exhibits superior toughness compared to many biopolymers, however its intrinsic properties are insufficient for direct replacement of load-bearing tissues. Native human dental enamel exhibits a Vickers hardness of 3–4 GPa and a modulus of elasticity of 70–90 GPa, which pure SF scaffolds cannot match[49,50]. Even dentin which has a lower modulus (15–25 GPa), significantly exceeds the mechanical capacity of most SF scaffolds[51,52]. For instance, pure regenerated SF films typically exhibits a tensile modulus in the range of 2–10 GPa, and other restorative composites based on SF reported the hardness values as low as 0.25 GPa and a modulus of ~6 GPa, making it unsuitable for non-occlusal applications[53,54]. This fundamental mismatch necessitates the discovery of composite materials with silk, such as integration with hydroxyapatite (HA) or bioactive glass, to approach the stiffness and wear resistance required for posterior restorations or implant coatings[55].

Furthermore, the tunable degradation of SF is a key parameter, yet achieving predictable in vivo resorption rates in the oral cavity remains complex. Typically, the bio-degradation process is affected by initial β-sheet crystallinity, scaffold topology, and the local proteolytic microenvironment[56]. For example, low-crystallinity porous sponges designed for periodontal regeneration can undergo rapid dissolution, with 60–80% enzymatic degradation within 4–8 weeks[57]. Concurrently, highly crystalline, dense SF films can persist for over 12 months in vivo[56]. Moreover, the clinical challenge lies in precisely matching the scaffold's degradation timeline with the native dental tissue regeneration process (e.g., ~6 weeks for gingival healing vs. 4–6 months for alveolar bone fill)[56,58]. Furthermore, the dynamic oral environment, which is characterized by pH fluctuations, complex enzymatic activity, and cyclic masticatory loading, which can accelerate degradation in unpredictable ways, potentially leading to premature structural failure[59].

Finally, the biological performance of SF is exquisitely sensitive to processing parameters, leading to challenges in reproducibility, scalability and sterilization[60]. Batch-to-batch variability can arise from the silk source, extraction method (e.g., LiBr vs. Ajisawa's reagent), and processing parameters, affecting molecular weight and ultimately mechanical properties[61,62]. For instance, Wang et al. explored the effect of various degumming and dissolution procedures on the molecular weight of native SF[63]. Similarly, sterilization process of SF also presents additional challenges, for example autoclaving can induce excessive β-sheet formation, increasing brittleness; alternatively gamma-ray irradiation at standard doses (>25 kGy) can cause peptide chain scission, reducing tensile strength by up to 30%. Other procedures like gaseous sterilizations by ethylene oxide requires lengthy outgassing to remove cytotoxic residues[64,65]. Moreover, these factors complicate the manufacturing of standardized, off-the-shelf medical devices.

Over the decades, various methods have been explored to modify the chemical nature of SF, enhancing the versatility of silk materials. Aqueous-based processing techniques have enabled the fabrication of silk into a broad range of material formats, making it a highly versatile biopolymer for various dental tissues[47,66]. Tailoring the surface chemistry of silk through controlled processing provides a versatile strategy to fine-tune cell–material interactions and regenerative outcomes in dental and associated soft tissues[67–69]. For instance, for periodontal and alveolar bone regeneration, recent studies indicated that porous SF scaffolds exhibited interconnected pore sizes in the range of ~200–500 μm, which facilitate vascular ingrowth and osteogenic cell infiltration, while maintaining mechanical stability and suitable for load-bearing environments. Additionally, most of the crosslinking strategies were based on β-sheet induction or enzymatic/photo-crosslinking, which can stabilize printed architectures, enabling tunable stiffness, controlled degradation, and improved osteogenic outcomes[57]. Structurally, SF is characterized by repetitive (Gly–Ala–Gly–Ala–Gly–Ser) motifs that assemble into antiparallel β-sheet nanocrystals, conferring mechanical strength and structural stability[69]. Nonetheless, not only the chemical structure, but also the silk chain length or molecular weights have been a great interest to tune the physical characteristics of silk-based scaffolds[70].

Moreover, building on this native architecture, SF networks can be formed through physical β-sheet–mediated crosslinking or further tailored via chemical and supramolecular strategies, including click chemistry, host–guest interactions, and dityrosine linkages. Therefore, many studies exploit reactive functional groups of native silk fiber along the protein backbone to modulate material properties (Fig. 4a). For instance, Boni et al. revealed that tailoring the exposure of hydrophobic regions at the silk scaffold surface should represent an alternative strategy to modulate the immune response. This can be achieved by coating SS–SF composites with SS or other hydrophilic polymers, to take advantage of their antibiofouling properties[71]. Nevertheless, self-healing and injectable SF hydrogel has also been developed based on supramolecular host-guest interaction[72]. Herein, we have also listed various design parameters and reaction variables to tune the overall properties of silk scaffold (Fig. 4b). In the list below, we have highlighted the most commonly used physical and chemical modifications that have been made on the silk backbone to induce various biological attributes:

1) *Cyanuric chloride-activated coupling*: Molecules with hydroxyl or amino groups are conjugated to cyanuric chloride, then react with tyrosine residues in SF under basic conditions. Highly compatible with SF due to stability at basic pH and availability of tyrosine residues. Results in the formation of modified silks. This coupling strategy is particularly attractive for silk modification because cyanuric chloride enables site-selective conjugation through tyrosine residues under mild basic conditions, permitting efficient incorporation of functional or bioactive moieties while preserving the native β-sheet architecture and mechanical integrity of SF[73] (Fig. 4c).
2) *Carbodiimide (EDC-NHS) coupling*: Activation of carboxyl groups in SF with carbodiimide, followed by reaction with amine-containing molecules. Facilitates the covalent bonding of various molecules to SF, thereby enhancing its functionality and resulting in the creation of stable amide bonds between SF and molecules[74] (Fig. 4d).
3) *Arginine masking*: Masking of arginine residues in SF using 1,2-cyclohexanedione to prevent unwanted reactions. Allows selective modification of other amino acid residues in SF without interference from arginine, results in the protection of arginine residues during chemical modification processes[75].
4) *Reaction with chlorosulfonic acid*: Sulfation of tyrosine and serine residues in SF using chlorosulfonic acid in pyridine at 70 °C. This modification introduces negatively charged sulfate groups onto the SF backbone, increasing hydrophilicity and surface charge and enhancing electrostatic interactions with proteins, growth factors, and cells, thereby modulating bioactivity, degradation behavior, and cell–material interactions. Enables the incorporation of sulfate groups into SF, thereby altering its properties and interactions[76].
5) *Diazonium coupling*: This reaction enables dissolved SF with diazonium salt of aniline derivative in borate buffer (pH 9.0)[77], which allows for tailored modification levels by adjusting the molar ratio of diazonium salt to tyrosine, resulting in the incorporation of small molecules with various functional groups into SF, creating both hydrophobic and hydrophilic derivatives[78] (Fig. 4e).
6) *Tyrosinase-catalyzed grafting*: Enzyme-catalyzed grafting of other biopolymers to silk fiber using tyrosinase enzymes. In this process, tyrosinase hydroxylates and oxidizes the tyrosine residues in the native silk, enabling grafting reactions. This results in the formation of pH-sensitive Schiff-base or Michael addition products when primary amines in glucosamine react with o-quinones in SF[79].
7) *Poly(methacrylate) grafting*: Attachment of acrylate monomers to the native silk chain, followed by radical polymerization was explored to modify the SF fibers. Amino acids of Silk fibers react with 2-methacryloyloxyethyl isocyanate to introduce covalent bonds for polymerization. This reaction results in graft polymerization of

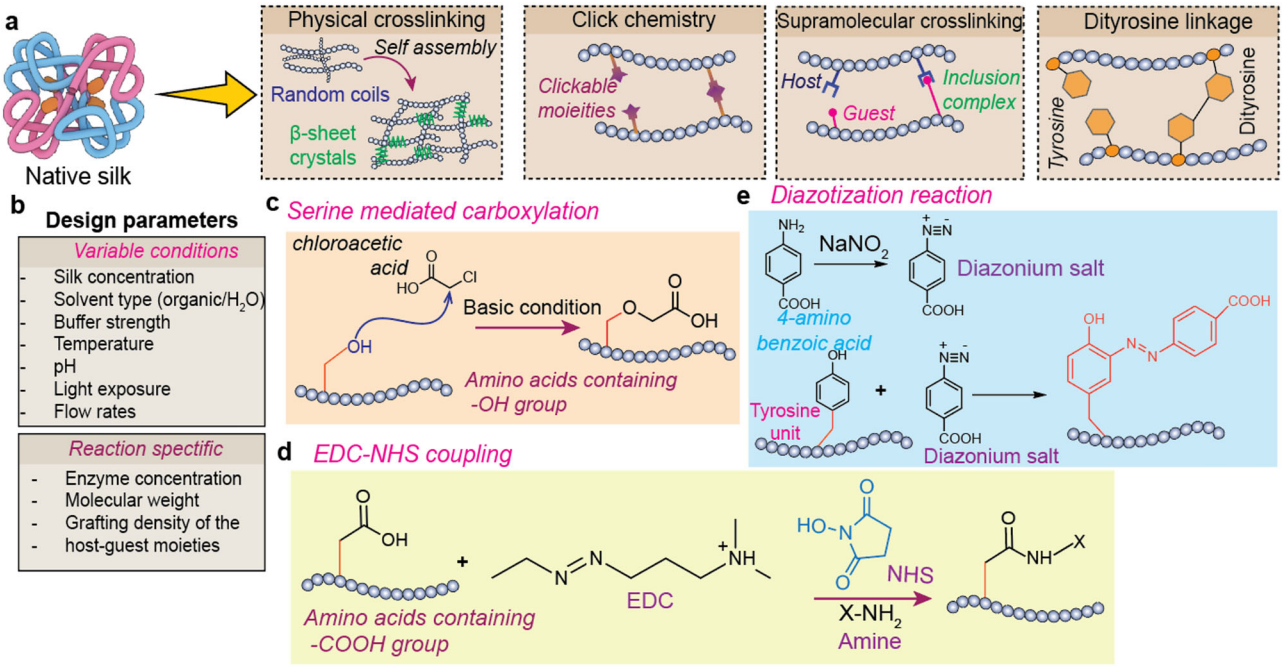

Fig. 4 | Physical and mechanical modifications of silk. a Schematic representation of various gelation and chemical crosslinking strategies employed for the fabrication of silk-based scaffolds intended for dental tissue regeneration. **b** Summarization of different design parameters and reaction-specific aspects that can be controlled to obtain tunable biomedical properties[171]. **c** Under alkaline conditions, serine residues in SF undergo nucleophilic substitution with chloroacetic acid, resulting in site-specific carboxylation of hydroxyl groups[171]. **d** Illustrates diazonium coupling, in which aromatic amines are converted into diazonium salts and subsequently react with tyrosine residues along the SF backbone to form covalent azo linkages. **e** *Carbodiimide coupling*: Amino acids bearing carboxyl (-COOH) or amine ($-NH_2$) groups (e.g., aspartic acid, glutamic acid, and lysine) can be crosslinked with complementary amine- or carboxyl-containing ligands in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxy succinimide (NHS) under mildly acidic conditions (pH ~6).

2-methacryloyloxyethyl phosphorylcholine onto modified silk, leading to the addition of phosphate or quaternary amine functional groups. Further addition of this group enhanced the SF hydrophilicity, antifouling behavior, and protein resistance, while improving cytocompatibility and stability in physiological environments[80].

Beyond cataloguing chemical modification methods, understanding their structure–activity relationships are critical for rational design of functional silk scaffolds. For example, carbodiimide-mediated coupling, such as EDC/NHS, activates carboxyl groups for amide bond formation, which can influence the orientation and stability of tethered peptides like RGD by establishing robust covalent linkages without extensive disruption of the protein backbone, thereby supporting sustained integrin engagement. In contrast, enzymatic or oxidative grafting approaches that target phenolic residues (e.g., tyrosinase-mediated coupling) can lead to distinct spatial presentation and potentially preserve local secondary structure, which may modulate the bioactivity and accessibility of conjugates in complex physiological environments such as the oral cavity. Recent advances in silk chemistry highlight the importance of aligning conjugation strategy with desired functional outcomes and scaffold mechanics to optimize biological performance.

Besides chemical techniques, different physical and biological approaches have also been explored to modify the functionality of the silk. Techniques such as stretching and calendaring can be utilized for this purpose. Stretching silk can orient the fibers, enhance tensile strength, and result in a more radiant appearance. Calendaring is a process that involves running silk over hot rollers to provide a smoother and shinier finish on the nanofiber[81]. For instance, heat treatment is exploit for modifying the physical and mechanical properties of silk[82]. Typically, the tensile strength of spider silk is stronger and more rigid than silkworm-derived silk fiber, make it a suitable choice for developing ultra strong, thermostable biomaterials. Alternatively, electrospinning is another technique used to produce nanofibers with high mechanical strength or other special properties by spinning a polymer in the gel state viscoelasticity[39]. Additionally, covalent crosslinking and plasticization are emerging approaches for physiologically stabilizing SF[83]. Blending silk with other polymers is an alternative way to expand the range of applications for silk-based platforms[84,85]. Modifying the processing conditions during the blending results in particles with varying profiles, including size, shape, charge, and lipophilicity, which in turn affect the biological properties of the composites[86]. As discussed above, the processability of SF enables its fabrication into diverse kind of scaffold with tunable morphologies, including 3D porous sponges, electrospun fibrous mats, and films, thereby supporting a wide range of dental regenerative applications[87,88].

Genetic engineering of silk-producing organisms, such as silkworms and spiders, has paved the way to produce novel silk materials with tailored properties. Techniques such as gene splicing enable the production of synthetic spider silk proteins in heterologous systems including bacteria, transgenic goats, and plants[89]. These bioengineered silk proteins can be further modified by incorporating specific amino acids, peptides, or protein domains, resulting in functionalized silk fibers with unique mechanical properties and cytocompatibility[36,90]. For example, genetically-engineered bacteria have been utilized to produce spider silk protein variants composed of elastic domains with other biological properties[91].

As previously discussed, enzymatic modification of SF provides a controllable strategy to modulate the particle size distribution, surface charge, and physicochemical behavior relevant to application-specific design. One notable example is the methacrylate modification of silk, which has enabled precise fabrication approaches and a plethora of new applications for silk materials[67]. Furthermore, these enzymatic modifications can tune the biological properties of native silk to overcome some inherent limitations and expand the uses of silk-based materials in reconstructive surgery, pulp, and dentin-pulp complex regeneration[67,92]. Moreover, recent advances in various biofabrication techniques have significantly accelerated the clinical translation of silk-derived scaffolds. Several of these silk-based biomaterials have demonstrated clinical success in oro-dental tissue

regeneration and are now commercially available. The currently available silk-derived products for oral-dental applications are summarized in Table 1. Despite these advances, the translation of silk-based biomaterials into routine clinical practice remains limited. Herein, we have listed the ongoing and completed clinical trials investigating silk-based scaffolds for various dental and associated soft tissue repair or regeneration in Table 2, compiled from publicly available databases.

Recent advancement in SF-based scaffolds for dental applications

Dental Pulp Stem Cells (DPSCs) differentiation

The crucial role of DPSCs in the native dental tissue, making it a promising avenue for dental tissue engineering. Native DPSCs can differentiate into various cell types that are crucial for the repair and regeneration of damaged dental tissues. These cells play a vital role in pulp regeneration, contributing to the recovery of odontogenic and osteogenic tissues, thereby facilitating the healing process of dental structures. Their inherent properties make them ideal candidates for regenerative dentistry applications, including the repair of damaged dental tissues and the regeneration of dental pulp[93]. The potential of DPSCs in dental tissue regeneration underscores the necessity for effective scaffolds that can support their proliferation, differentiation, and integration into the host tissue.

Together with biomaterials DPSCs controlled various cellular responses, which are essential for coordinated dental tissue repair and regeneration. Silk scaffolds facilitate the attachment and migration of DPSCc, which is essential for the formation of new tissue[94]. Furthermore, the structural and biochemical properties of silk scaffolds can be tailored to mimic the natural extracellular matrix, thereby promoting better interactions between DPSCs and the scaffold. Combining DPSCs with silk scaffolds have shown promising results in improving dental tissue regeneration outcomes. Studies have demonstrated that SF blended scaffolds, when combined with basic fibroblast growth factor (bFGF), can effectively drive the reconstruction process of pulp-like tissues in dental applications by fostering DPSCs differentiation. Such scaffolds not only support the structural requirements for tissue regeneration but also provide biochemical cues that enhance the functionality of DPSCs in terms of their proliferation, differentiation, and migration abilities. SF-RGD-stem cell factor (SF-RGD-SCF) scaffolds have also been explored for their effects on DPSCs, showing significant improvements in cell migration, proliferation, and attachment (Fig. 5a)[95]. These advancements highlight the potential of combining DPSCs with spatio-temporally designed silk scaffolds, paving the way for more effective strategies in dental tissue regeneration[5].

Guided bone regeneration using silk-based scaffolds

Guided Bone Regeneration (GBR) has emerged as a crucial technique in dentistry for restoring bone defects and augmenting alveolar ridge volume. GBR not only promotes bone regeneration but also provide conducive microenvironment for dental implantation and restoration. The introduction of silk scaffolds into GBR procedures brings several advantages. Over the years various silk-based scaffolds have been developed with exceptional physicochemical characteristics, including remarkable tensile strength, biocompatibility, and the ability to be engineered into various forms suitable for bone regeneration[96,97]. Likewise, silk-based scaffolds can be modified to release bioactive substances that further stimulate bone regeneration, offering a next-level approach to GBR[98,99].

Clinical applications of silk scaffolds in bone regeneration have shown promising results, underscoring the potential of silk as a superior biomaterial in regenerative medicine[100]. Success stories of silk scaffolds in bone regeneration include their use in accelerated healing processes, particularly in the GBR. One study highlighted the effectiveness of an SF membrane in promoting osseous healing in peri-implant defects, showcasing the scaffold's capacity to support bone growth and stability around dental implants[101]. Similarly, antimicrobial agents, such as metronidazole-loaded SF methacrylated/SilkMA electrospun scaffolds, can be used to control infection in root-end resected periapical lesions while supporting bone regeneration[102] (Fig. 5b). Furthermore, the combined antibacterial and osteogenic functions are also achieved with electrospun SF-based barrier membrane loaded with epigallocatechin gallate (EGCG) and polydopamine (PDA)[103]. Moreover, all these studies not only demonstrate the practical viability of silk scaffolds in dental applications but also pave the way for further innovation in scaffold design and application.

Osteo/odontogenic differentiation is a pivotal aspect of dental tissue engineering, focusing on the differentiation of DPSCs into bone-forming (osteogenic) or tooth-forming (odontogenic) cells. Studies have shown that DPSCs, when provided with the appropriate scaffold and biochemical cues, can differentiate into cells capable of regenerating bone or dental tissues[104]. These scaffolds can be engineered to release growth factors that specifically promote osteo and odontogenic differentiation, further enhancing the regenerative potential of DPSCs. This approach not only holds promise for regenerating dental tissues but also represents a significant step forward in the development of regenerative therapies for dental and periodontal diseases.

Pulp regeneration with silk dental floss and scaffolds

The importance of pulp regeneration in dental tissue directly impacts the restoration of the physiological function of the pulp-dentin complex. Pulp regeneration involves reconstructing this complex to restore its vital functions, which are crucial for maintaining the overall health and longevity of teeth. This process is essential not only for the structural integrity of teeth but also for preventing further dental issues that could arise from damaged or diseased pulp. The ability of the pulp to recover and regenerate is fundamental to dental health, highlighting the need for effective regeneration techniques[105].

Recent innovations in using silk dental floss and scaffolds for pulp regeneration have shown promising results, primarily due to the unique properties of silk-based biomaterials. These attributes have enabled the widespread integration of silk-based scaffolds across soft and hard tissue engineering strategies[106,107]. Specifically, silk dental floss and scaffolds have been explored for their potential in enhancing the regeneration of dental pulp tissue[108]. Several studies have demonstrated that silk scaffolds enhance dental pulp stem-cell proliferation, differentiation, adhesion, and migration, thereby supporting effective pulp tissue repair and regeneration[94,109–111]. For instance, the SF-based hydrogel desensitizer achieves 660 μm dentin tubule occlusion for dentin hypersensitivity treatment[112], (Fig. 5c). This innovative approach leverages the odontogenic potential of DPSCs, further boosted by the silk's conducive environment for tissue regeneration[113].

Silk-based scaffolds not only offer a physically supportive structure but also actively participate in the regeneration process by enhancing cell functions necessary for tissue repair[114]. SF/hyaluronic acid/demineralized dentin matrix hybrid hydrogel was developed as an alveolar bone graft substitute[115] (Fig. 5d). Studies also highlight the efficacy of silk scaffolds in promoting bone and neural regeneration, demonstrating their versatility and advances in bone regeneration and formation in maxillofacial bone defects[116]. A comparative study highlights the innovative edge of silk-based scaffolds and dental floss in pulp regeneration, providing a more effective and biologically conducive approach to dental tissue engineering[117].

In summary, the use of silk-based scaffolds in pulp tissue regeneration has shown promising results on various occasions. DPSCs have played a significant role in dental pulp regeneration, and advancements in combining them with silk scaffolds have improved outcomes[118]. Additionally, innovations in using silk dental floss and scaffolds for pulp regeneration have shown comparative advantages over traditional techniques. Overall, the use of silk-based scaffolds in dental tissue regeneration has the potential to revolutionize the field of dentistry and improve patient outcomes[119].

Dental implant, composite resins, and coating

Due to its inherent biocompatibility, lower immune rejection, and long-term stability, silk-based scaffolds are gaining significant attention as implant materials or for implant coating techniques. Over the years, clinical

Table 1 | Commercially available silk products for oro-dental tissue regeneration

Product Name	Company	Silk Source	Form	Application	Key Features
Silk Voice®	Serica Technologies	Bombyx mori (Bm)	Silk fiber scaffold	Vocal cord repair	Biocompatible, customizable porosity promotes tissue integration
SeriScaffold®	Allergan	Bm	Mesh scaffold	Soft tissue repair	High tensile strength, biocompatible, long-term durability
SilkGro™	TissueGen	Bm	Electrospun fiber	Nerve regeneration	Sustained drug delivery and customizable fiber diameter promote nerve growth.
BioSilk™	Silk Therapeutics	Bm	Aqueous silk solution	Skin regeneration	Biocompatible, versatile, supports cell proliferation
FibroSilk™	Silk Fibro, Inc.	Bm	Nanofiber mat	Wound healing, tissue engineering	High surface area promotes cell adhesion and proliferation
PureSilk®	Sofregen Medical	Bm	Injectable gel	Soft tissue augmentation	Injectable, biocompatible, resorbable
PureSilk® Sutures	Sofregen Medical	Bm	Suture	Surgical sutures	High tensile strength, minimal tissue reaction, biodegradable
RegenerSil™	Orthox Ltd.	Bm	Fiber matrix	Cartilage repair	High strength, biocompatible, promotes cartilage formation
SericaFlex®	Serica Technologies	Bm	Silk fiber scaffold	Tendon and ligament repair	Flexible, high tensile strength, promotes tissue regeneration
SF Sponge	EMD Millipore	Bm	Sponge	Cell culture, tissue engineering	High surface area, customizable pore size, excellent cell adhesion
SilkBone®	Orthox Ltd.	Bm	Scaffold	Bone regeneration	Osteoconductive, high mechanical strength, promotes bone growth
SilkBone™	SilkBone Regeneration	Bm	Composite scaffold	Bone regeneration	High mechanical strength, osteoconductive, and biodegradable
SilkBone™ Matrix	Bone Biologics Corp.	Bm	Composite scaffold	Bone grafting, bone repair	Osteoconductive, high compressive strength, promotes bone growth
SilkDerm®	Silk Therapeutics	Bm	SF solution	Dermal fillers, skin care	Biocompatible, promotes collagen synthesis, supports skin regeneration
SilkGel®	FibroSilk Inc.	Bm	Hydrogel	Soft tissue regeneration	Injectable, high-water content, customizable mechanical properties
SilkHance™	Silk Biomaterials Corp.	Bm	Scaffold	Cartilage regeneration	High porosity, supports chondrocyte growth and is biocompatible
SilkMATRIX™	AMSilk	Recombinant Bm	Hydrogel	Wound care, tissue engineering	Biocompatible, high moisture content, promotes healing
SilkMed®	RegenMed	Bm	SF film	Drug delivery, wound healing	Controlled drug release, biocompatible, flexible
SilkSeal™	Biomateriali	Bm	Film	Wound healing	Transparent, flexible, high oxygen permeability
SpiderNet®	AMSilk	Recombinant spider silk	Mesh	Wound healing, soft tissue repair	High tensile strength, biocompatible, and antimicrobial properties
Spidrex®	Oxford Biomaterials	Spider silk	Fiber	Soft tissue repair, sutures	High tensile strength, biodegradable, biocompatible

Table 2 | List of ongoing/completed clinical trials on various silk-based scaffolds for dental tissue repair/regeneration (retrieved from www.clinicaltrials.gov and http://trialsearch.who.int/)

Clinical trial ID	Material intervention	Application	Trial phase/status	Location
NCT05424380	SF-based Bioink for 3D printed bone graft scaffolds	Alveolar bone defects, Ridge Preservation	Early Phase 1 (Recruiting)	United States
NCT05106366	Resorbable SF barrier membrane (compared to collagen membrane).	GBR in dental implant surgery	Phase 2 (Completed)	Italy, Spain
CTRI/2020/08/027215	SF gel/film is applied as a wound dressing following periodontal surgery.	Periodontitis, Post-surgical healing after periodontal flap surgery	Phase 3 (Not yet recruiting)	India
NCT04839328	SocketGel™ (a silk-derived hydrogel) placed into the extraction socket.	Post-tooth extraction, Prevention of Dry Socket	Phase 4 (Completed)	United States
NCT04153405	Seri® Surgical Scaffold is used for soft tissue reinforcement.	Gingival Recession, Soft Tissue Deficiency	FDA-approved, Post-Market Surveillance (Active)	Multiple Sites
NCT06112366	Silk suture (comparison with tissue adhesive)	Wound closure after the extraction of impacted wisdom teeth	Registered, not applicable	Türkiye
NCT06552065	Composite collagen with SF membrane	Soft tissue augmentation in periodontal/gingival defects, others.	Case study with 10 patients	India
NCT05191082	SF membrane (with or without neurotensin)	Palatal wounds (donor sites) / exodontia & ridge preservation	Completed	Brazil
Not registered	Hydroxyapatite-coated silk scaffold	Silk scaffold with nano-hydroxyapatite, seeded with ligament or pulp cells	Dogs, preclinical	China
NCT06050863	SF as a carrier for chlorhexidine in treating periodontal pockets	Drug delivery in the periodontal pocket	Phase 1 (Not yet recruiting)	United States

studies directly indicated that bare metallic implants composed of titanium (Ti), magnesium, and alloys are not the ultimate answer for better osteogenesis and implant integration. SF from both mulberry and non-mulberry sources is used for surface modification of implants[120]. SF is immobilized on a Ti-surface to facilitate initial cell adhesion, followed by improved cell spreading and enhanced mineralization, thereby achieving better osseointegration. For instance, Quan et al. designed a dual-functional antimicrobial coating strategy using SF-coated Ti implants, which are deposited with iron oxide NPs (FNP/SF-Ti). They have demonstrated that under NIR (808 nm, 1.5 W/cm^2) radiation, the coated implant exhibits a photothermal effect to eradicate the attached bacteria and potentiate the osteogenesis process in vivo[121] (Fig. 6a). Using a biomimetic strategy, apatite-coated porous biomaterial based on SF provides an enhanced osteogenic environment for bone-related outcomes. Sericin and sericin/RGD-functionalized Ti were found to upregulate the expression of bone sialoprotein, osteocalcin, and alkaline phosphatase compared to those on pristine titanium[122]. Autologous bone marrow stromal cells seeded on apatite-SF scaffold managed to repair the bony defects in a mandibular canine model completely. In this line of investigation, a customized 3D scaffold composed of SF composites with gingival tissue-derived stem cells for personalized bone therapy[123] (Fig. 6b). Similarly, an SF/mesoporous silica nanoparticles (SF/MSN) nanocomposite coating modified TiO_2 nanotubes (TNTs) on Ti implants enabled long-term stable drug release and promoted osteogenesis[124](Fig. 6c). Concurrently, antibiotic (gentamicin)-loaded SF (non-mulberry silkworm, *Antheraea mylitta*) nanoparticles are fabricated and deposited over the Ti surface to achieve sustained drug release and to alter the nano-roughness of the implant surface for osteoblast adhesion, proliferation, differentiation and long-term infection preventtion[125].

In parallel, dental resin composites are the most widely employed direct restoration material in dental clinics. Composite resin reinforced with silk nanoparticles exhibits a reduced flexural modulus, which is essential for reducing the chances of failure, as it absorbs more masticatory forces[126]. In this line of investigation, Seo et al. fabricated a Ca-modified ultra-strong adhesive based on SF, which exhibits adhesive characteristics (>800 N m^{-1})[127]. This development opens a new avenue for silk-based dentin adhesives and composite materials.

Silk-based scaffolds as a delivery platform to the dental tissue

Antibiotics have been widely used for the prevention and treatment of bacterial infections in dental tissues. However, conventional delivery methods of antibiotics have several limitations, including low bioavailability and difficulty in achieving sustained drug release. Thereby, silk-based scaffolds have emerged as a promising delivery platform for antibiotics in dental tissue[124,128], owing to its controlled bio-degradation and drug release over an extensive period, and ease of chemical or physical loading with antibiotics[128]. Over the past, various silk scaffolds containing antimicrobial fillers such as antibiotics, growth factors, and nanoparticles have been developed for the prevention and treatment of bacterial infections in dental tissues[48,129]. Recently, an intracanal drug delivery device based on nanofibers has been developed to establish a sterile root-canal therapy[130]. This delivery system presents a promising solution for preventing and treating bacterial infections in dental tissues.

Nonetheless, cell delivery using silk-based scaffolds represents an alternative approach in dental tissue regeneration. These scaffolds can act as a substrate for cell attachment, proliferation, and differentiation, allowing for the formation of new tissue. Specific cell types, such as human dental pulp stromal cells (hDPSCs), have been investigated for their potential in promoting dental tissue regeneration. In this context, silk-based scaffolds utilized as a compatible cell delivery platform, enabling localized presentation and retention of cells, bioactive molecules, or therapeutic agents at the defect site to support spatiotemporally controlled dental tissue regeneration[131]. For instance, non-mulberry SF was grafted onto nanofibrous PCL matrices and co-deposited with hydroxyapatite (HAp) layers for the dual release of growth factors, such as TGF-β and bone morphogenic protein-2 (rhBMP2), for early differentiation of osteoblast-like cells[132,133].

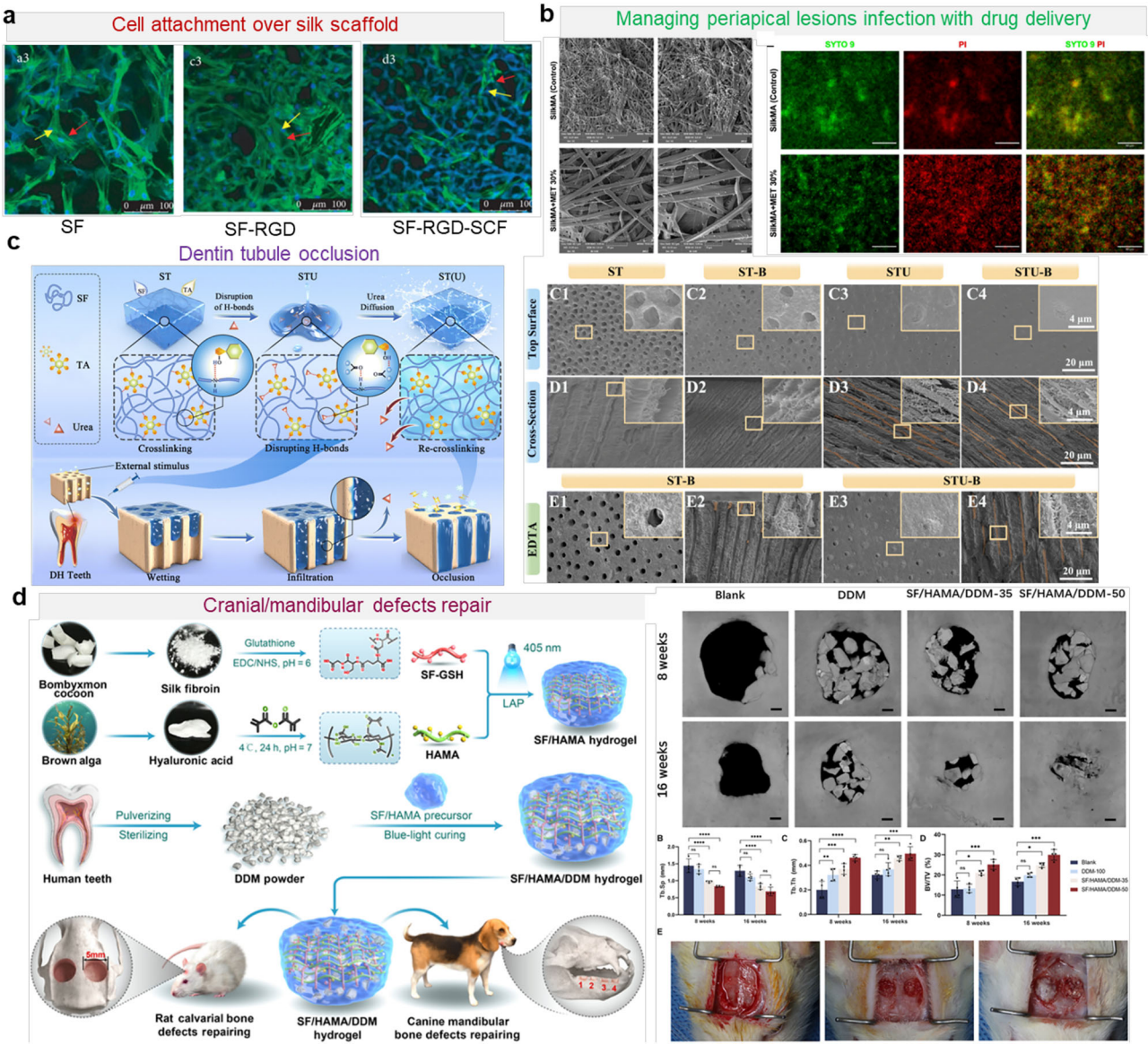

Fig. 5 | Application of silk-based scaffolds in regenerating different aspects of dental tissue. a Confocal microscopy images of the cell cytoskeleton of stem cells of apical papilla (SCAPs) cells, stained with Rhodamine-Phalloidin on a pure SF, SF conjugated with RGD (SF-RGD), and SF-RGD-stem cell factor (SF-RGD-SCF) scaffold after 7d seeding. Reprinted with permission from ref. 95. **b** SEM and confocal live/dead (SYTO9/PI) images of bacterial attachment on a metronidazole-loaded SF methacrylated/silkMA electrospun scaffolds to control infection in root-end resected periapical lesions while supporting bone regeneration. Reprinted with permission from ref. 102. **c** An SF-based hydrogel desensitizer achieves 660 μm dentin tubule occlusion for the treatment of dentin hypersensitivity. Reprinted with permission from ref. 112. **d** A SF/hyaluronic acid/demineralized dentin matrix hybrid hydrogel for alveolar bone graft substitute. The left panel shows the 3D reconstruction and surgical photographs of the rat calvarial defect at 8 and 16 weeks. Reprinted with permission from ref. 115.

Moreover, the ability to target specific cell types and control their growth is a significant advantage of using silk-based scaffolds for cell delivery in dental tissue regeneration[134].

Dental caries prevention

Fluoride ions play a crucial role in preventing the growth of caries-related bacteria and the further acidification of the oral microenvironment[135]. Using fluoride-loaded silk-scaffolds, a sustained and controlled release of fluoride can be achieved for the caries prevention in cavities[101]. This method not only enhances fluoride delivery but also addresses the challenge of interaction with enamel that can hinder the effectiveness of traditional fluoride agents[135]. The scalable nature of this approach aligns with public health interventions aimed at preventing and delaying the development of caries, ultimately enhancing resistance to dental caries lesions.

In addition to caries prevention, fluoride delivery using silk-based scaffolds shows potential for promoting dental tissue regeneration. The incorporation of fluoride into these scaffolds can support the repair and prevention of caries lesions, contributing to the overall health and integrity of dental tissue regeneration[136]. Moreover, this novel strategy not only focuses on repairing existing damage but also on preventing the recurrence of caries, emphasizing the importance of sustained fluoride delivery for long-term dental health. Furthermore, the impact of fluoride delivery via silk-based scaffolds extends beyond dental tissue regeneration to the associated soft tissues in the oral cavity[101]. Commercial sterilizers may not always be sufficient to prevent frequent dental infections, making the introduction of antimicrobial hydrogels crucial for maintaining oral health. By utilizing silk-based scaffolds for fluoride delivery, not only can caries-related bacteria be inhibited, but the risk of dental infections can also be mitigated[136].

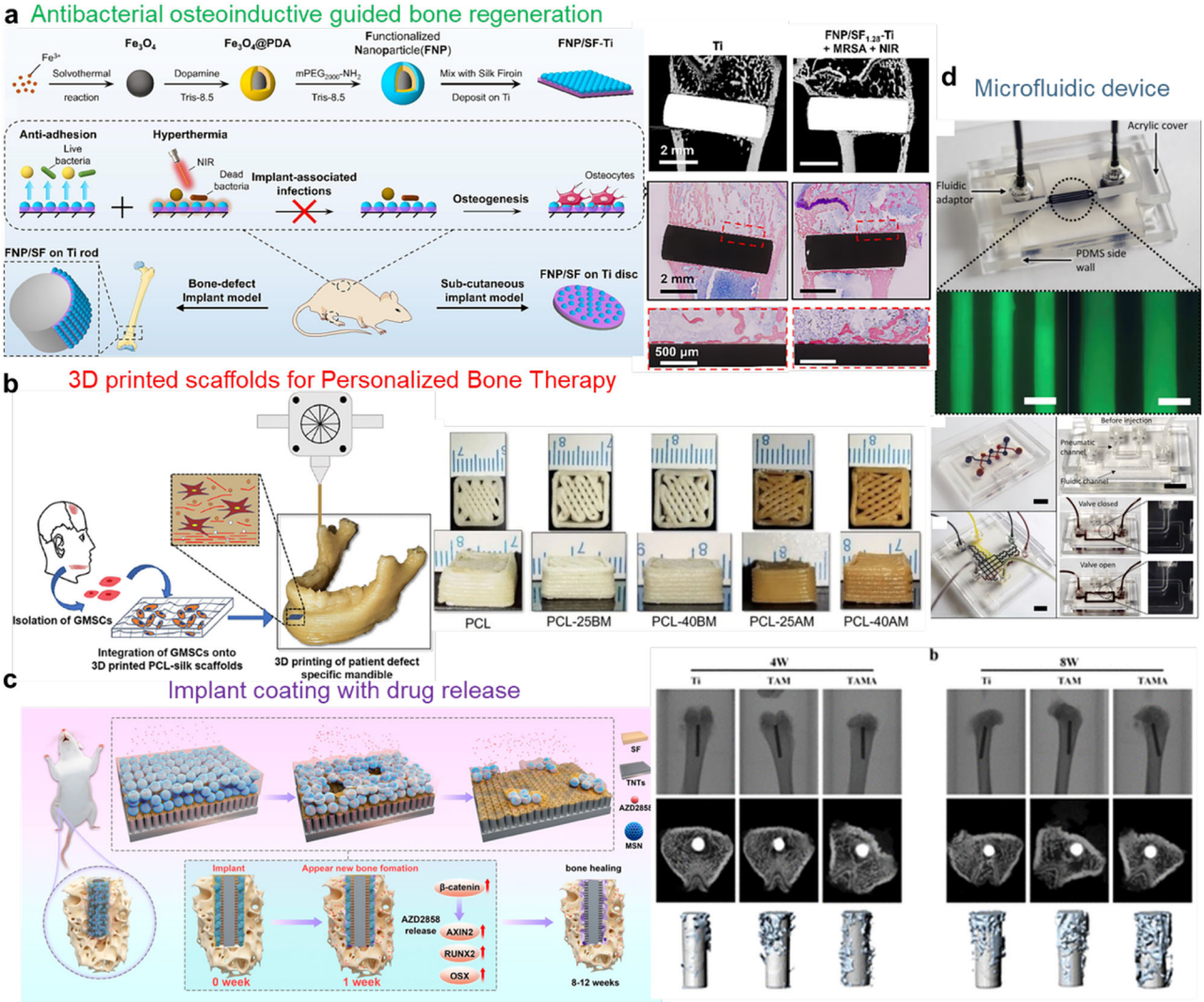

Fig. 6 | Application of silk-based dental implants or coating strategies. a A dual-functional Ti-implant coating composed of iron-oxide nanoparticles with SF (FNP/SF-Ti) for synergistic anti-adhesion and Photothermal effect to mitigate implant-associated infection. The inset micro-CT 3D reconstructions show enhanced bone formation in FNP/SF-Ti groups compared to pure Ti after 4 weeks post-implantation. Reprinted with permission from ref. 121. **b** A 3D customized scaffold composed of SF composites with gingival tissue-derived stem cells for personalized bone therapy. The left panel shows optical images of the scaffolds. Reprinted with permission from ref. 123. **c** An SF/mesoporous silica nanoparticles (SF/MSN) nanocomposite coating modified TNTs with Ti-implant for a long-term stable drug release and promoting osteogenesis. The left panel displays 3D-reconstructed micro-CT images of the bone surrounding each group of implants at 4- and 8-weeks post-implantation. Reprinted with permission from ref. 124. **d** A two-layer silk hydrogel microfluidics device is fabricated using gelatin molding and layer-by-layer stacking methods, as reprinted with permission from ref. 168.

Immunomodulation and vascularization

The immunomodulatory effect of silk can be broadly categorized into the direct modulation of the host's inflammatory response, either through its inhibition or active resolution[137]. SF is recognized for its anti-inflammatory characteristics, which help regulate the local inflammatory environment in dental tissues[138]. In oral and dental tissue engineering, where immune homeostasis is critical due to high vascularity and microbial exposure, silk-based scaffolds demonstrate advantages. While silk cocoons (fibroin + sericin) are generally considered biocompatible, any protein-based biomaterial can potentially elicit an immune reaction[12,139]. Consequently, the ability to control the host immune response to favor healing and integration is a vital aspect of successful dental regeneration using SF-based platforms[71,140]. It is essential to note that the degradation rate of regenerated SF biomaterials is typically higher than that of native silk fibers, as the breakdown process involves enzymatic activity and the involvement of immune cells[141]. Kweon et al.[142] studied that whole silk cocoon membranes, containing both fibroin and sericin without extensive removal of sericin, may be used as biocompatible barrier membranes in GBR because they can support osteogenic activity and new bone growth without provoking strong adverse immune reactions.

Sericin, one of the two primary proteins constituting silk fibers exhibits anti-inflammatory effects through several specific mechanisms[143]. Primarily, it suppresses the infiltration and proliferation of inflammatory cells into the damage area; secondarily it reduced the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and IL-23 from macrophages and enhances the production of anti-inflammatory cytokines like IL-4 and IL-10 [144]. Notably early concerns regarding the immunogenicity and allergenic potential of silk, especially sericin, have been largely disproven by recent in vivo and in vitro studies[143]. Contemporary evidence indicates that silk-based scaffolds do not elicit severe inflammatory or foreign-body reactions; instead, they induce a mild and transient immune response that is conducive to tissue regeneration. For instance, Jiao et al. demonstrated that sericin induces only low levels of inflammatory cell infiltration in vivo, comparable to alginate and fibroin, and substantially lower than chitosan[145]. Their findings further showed that sericin is capable of recruiting

regeneration-promoting cells, including vascular endothelial cells. Moreover, sericin did not trigger allergenic reactions and exhibited low, acceptable immunogenicity[139,145]. Despite these favorable biological properties, sericin is highly soluble and degrades rapidly in aqueous environments, including saliva and tissue fluids, which limits its long-term applicability in dental tissue engineering[30,146]. Sun et al. further elucidated that sericin inhibits inflammation by targeting key signaling pathways, including Toll-like receptor and NOD-like receptor pathways, and by downregulating critical adapter proteins like MyD88 and NOD1[147]. At a cellular level, particularly low-molecular-weight fractions of sericin can promote an anti-inflammatory phenotype in macrophages (M2 polarization) and influence T-cell and dendritic cell activity, leading to a more regulated immune environment. When incorporated into SF-based scaffolds, sericin can confer immunomodulatory functionality at the material–tissue interface, promoting macrophage M2 polarization and regulated immune responses that collectively support a pro-regenerative microenvironment[148].

Beyond its structural role, silk fibroin actively contributes to the regulation of the inflammatory microenvironment during dental tissue regeneration. Regenerated silk fibroin scaffolds have been shown to modulate macrophage polarization, promoting a shift from a pro-inflammatory M1 phenotype toward a pro-healing M2 phenotype[149,150]. At the molecular level, silk-based scaffolds attenuate classical pro-inflammatory signaling pathways associated with M1 macrophages[151,152]. In particular, the TLR4–MyD88–NF-κB axis has been observed, resulting in reduced transcription of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6[153,154]. Concurrent downregulation of inducible nitric oxide synthase further limits oxidative stress and tissue damage, thereby preventing chronic inflammation and foreign-body reactions commonly associated with other synthetic biomaterials[155,156]. This immunomodulatory transition is associated with reduced secretion of inflammatory cytokines such as TNF-α, IL-1β, and IL-6, alongside enhanced expression of anti-inflammatory mediators including IL-10 and TGF-β[157,158]. Such controlled immune responses are particularly critical in dental and periodontal tissues, where unresolved inflammation can impair stem-cell recruitment, angiogenesis, and matrix deposition[159]. Collectively, these anti-inflammatory and immunoregulatory properties position silk-based scaffolds not merely as passive matrices, but as active regulators of the healing cascade that support favorable tissue regeneration outcomes.

The formation of a functional blood supply, or vascularization, is indispensable in dental regeneration, as it supports the viability of engineered tissues such as dental pulp, which is highly vascularized. SF induces angiogenesis by inducing the expression of potent angiogenic growth factors[160,161]. Most notably, SF induces the expression of vascular endothelial growth factor (VEGF), a primary regulator of angiogenesis. VEGF directly drives endothelial cell proliferation, migration, and the assembly into new capillary tubes, establishing the nutrient and waste exchange networks essential for regenerating dental tissues[162,163]. Furthermore, SF upregulates angiopoietin-1 (ANG-1), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF), which aid in recruiting the necessary cell types for vessel formation[164,165]. Furthermore, several studies analyzed the gene expression after SF-scaffold application, which have shown increased endothelial markers (CD31, VE-cadherin) and activation of the PI3K/Akt and ERK/MAPK signaling pathways, which are critical for endothelial cell migration, proliferation, and neovascularization[166,167]. Nonetheless, recent advancements in the 3D micro/nanopatterning strategy open a window for constructing interconnected, 3D microchannel networks in silk hydrogels at 100 μm minimum feature resolution, which could mimic the vascularize dental tissue[168] (Fig. 6d). In parallel, Mu et al. developed a 3D bioprinting strategy of SF based on the aqueous solvent-directed molecular assembly, which could be translated for the bioprinting of a vascularized dental scaffold[169]. Collectively, these angiogenic cues position SF as an effective pro-vascular biomaterial, capable of supporting rapid vascular integration and sustaining the metabolic demands of regenerating dental tissues[159,170]. In summary, current evidence establishes that silk-based scaffolds actively modulate host immune responses through precise regulation of macrophage signaling pathways rather than merely avoiding immune recognition.

Outlook

Silk-based scaffolds have become versatile biomaterials for dental and soft tissue regeneration due to their biocompatibility, mechanical resilience, and ability to support cell growth and tissue repair. Recent advances have focused on enhancing scaffold biodegradability in order to mimic natural healing timeline, thereby ensuring sustained structural support during recovery. Over the past decades various efforts have been made to incorporate bioactive molecules, such as growth factors, peptides and antimicrobial agents to enhance their regenerative capacity by promoting cell activity and reducing the risk of infection. Recent development in advanced biofabrication techniques such as 3D micro/nanopatterning, additive manufacturing offers additional opportunities to customize silk scaffolds for personalized medicine. Nonetheless, combination strategies with the silk-based biomaterials, including integration with stem cell therapy and guided tissue regeneration, show promise for accelerating repair and improving outcomes.

Despite these advances, clinical translation of silk-based scaffolds into the dental clinical practice remains limited. The key challenges include variability in silk sources and processing methods, which complicate the reproducibility and scalability. Therefore, developing standardized protocols and identifying critical quality control parameters will be essential for regulatory approval and clinical translation. Nevertheless, recently developed large language machine learning and multiscale modeling could be employed to predict and design the next-generation precision-engineered silk fiber with desired characteristics before the physical synthesis. Furthermore, well-designed preclinical model with microfluidics and clinical studies are urgently needed to validate safety, efficacy, and long-term performance of the silk-based scaffolds. Looking ahead, silk scaffolds are not only promising for soft tissue repair but also for broader dental applications, including bone regeneration, periodontal reconstruction, and pulp restoration. Moreover, the development of multifunctional next-generation modified silk-scaffold is likely to opens new avenue for its clinical translation into the dental practice.

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Sumanta Ghosh: Conceptualization, Writing – original draft. Simran Gupta: Writing – original draft. Govinda Kapusetti: Writing – review & editing, Supervision, Funding acquisition. Subhas C. Kundu: Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Competing interests

The authors declare no competing interests.

Additional information

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