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Fabrication of Zein-Based Fibrous Scaffolds for Biomedical Applications—A Review

Mustafijur Rahman, Tanvir Mahady Dip, Tina Haase, Yen Bach Truong, Tu C. Le, and Shadi Houshyar**

Zein, which accounts for around 80% of the total protein composition in corn, is a biocompatible and biodegradable substance derived from renewable sources. Although insoluble in water, its amphiphilic characteristics are utilized to generate nanoparticles, nanofibers, microparticles, and even films. Numerous recent studies have demonstrated the potential of zein as a prospective biomaterial to develop fibrous scaffolds for biomedical functions owing to its biocompatibility, fibrous formation, and encapsulating qualities. Fabrication of zein-based fibrous scaffolds for biomedical applications is achieved by a wide variety of techniques, including electrospinning, wet spinning, freeze drying, and additive manufacturing. This article overviews current advancements in manufacturing techniques for zein-based fibrous scaffolds. In addition, it summarizes the most recent biomedical applications and research activities utilizing zein-based fibrous scaffolds. Overall, zein is proposed as a potential biomaterial for the production of fibrous scaffolds that stimulate cell adhesion and proliferation in a number of exciting biomedical applications due to its biodegradability, biocompatibility, and other unique features related to its structure.

1. Introduction

The emergence of biopolymers has sparked a wave of exploration and utilization of various techniques and monomer materials to create materials possessing a multitude of properties that find value across a broad spectrum of applications. Notably, the biomaterials sector has witnessed significant progress as these developed materials, with their diverse attributes, have contributed to advancements in medical and healthcare fields.[1] Applications of biopolymers range from gels used to retain moisture in eyedrops or as laxatives to flexible scaffolds used for various tissue replacements or rigid materials necessary for support structures.[2] Particularly, polymers derived from spun fibers can be utilized to create filaments, sheets, and coaxial scaffolds with characteristics that are advantageous for biomedical applications, including being porous, flexible, and having a large surface area.[3] Often, medications are also included in the polymer chain, and certain polymers are engineered to preserve their structure upon the release of a drug that is covalently attached in a pendant-like form to the surface of the polymer.[4,5] In addition, different natural and artificial polymers have been employed in biomedical applications such as heart valves, hard contact lenses, enteric pharmaceutical coatings, drug encapsulation, wound dressings, surgical meshes, nerve regeneration, and bone tissue regeneration.[6,7]

M. Rahman
Center for Materials Innovation and Future Fashion (CMIFF), School of Fashion and Textiles
RMIT University
Brunswick 3056, Australia
M. Rahman
Department of Dyes and Chemical Engineering
Bangladesh University of Textiles
Dhaka 1208, Bangladesh

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/mame.202300175

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T. M. Dip
Department of Materials
University of Manchester
Oxford Road, Manchester M13 9PL, UK
T. M. Dip
Department of Yarn Engineering
Bangladesh University of Textiles
Dhaka 1208, Bangladesh
T. Haase
School of Science
RMIT University
Melbourne, Victoria 3001, Australia
T. Haase, T. C. Le, S. Houshyar
School of Engineering
RMIT University
Melbourne, Victoria 3000, Australia
E-mail: shadi.houshyar@rmit.edu.au
Y. B. Truong
CSIRO Manufacturing
Research Way, Clayton, Victoria 3169, Australia
E-mail: Yen.Truong@csiro.au

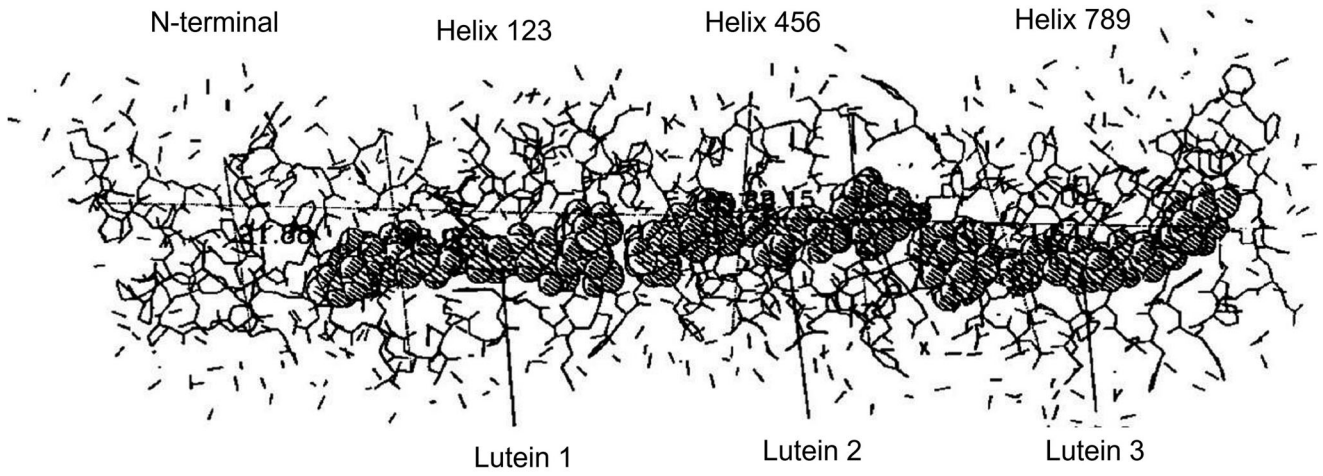

Figure 1. The structure of α-zein with three triple superhelix sections and an N-terminal segment. Reproduced with permission.[25] Copyright 2006, American Chemical Society.

Naturally derived polymers can be acquired from both plant and animal resources and are environmentally friendly and sustainable substitutes compared to their synthetic counterparts.[8] Examples of naturally derived protein compounds that can be employed to manufacture polymers include fibroin, the primary component of silk, collagen, keratin, gelatin, and zein.[9,10] Fibroin is a natural protein utilized as a biomaterial in ligament replacement structures, including the commonly injured anterior cruciate ligament, and possesses high tensile strength and enough elasticity.[11,12] Recent research on promising protein-based natural biopolymers has led to the consideration of zein as a potential candidate for usage in biomedical applications due to its unique characteristics like biocompatibility, biodegradability, and mechanical strength.[13] Zein is the structure of protein stored in the endosperm tissue of corn and accounts for over 80% of the total protein substance of maize.[14,15] Zein-based compounds emphasize the features provided by intriguing natural substances such as excellent resistance to water, heat, abrasion, and humidity. Furthermore, maize zein protein can increase the prospect of prolonged lifespan for biomolecules.[13,16] In addition to its structural integrity, zein has excellent mechanical properties and can be used to produce films.[17] Hence, current scientific activities focus on investigating its innovative biomedical applications, such as the controlled delivery of biologically active compounds or for tissue regeneration.[18,19] A variety of techniques have been applied to manufacture scaffolds and biomaterials from zein with varying structures and wide-scale characteristics. Therefore, this review aims to summarize recent fabrication techniques used to develop zein-based fibrous scaffolds, as well as recently developed biological applications and any research activity involving zein-based fibrous scaffolds. Furthermore, the fundamental characteristics and properties of zein as a prospective biomaterial are addressed.

2. Properties of Zein

Zein is the primary protein originating in the endosperm of maize.[20] Generally, zein is extracted using a solvent from corn gluten meal, a protein-oriented derivative of wet milling corn.[16] It is most commonly accessible as a fine yellow powder.[21] Zein contains a large number of nonpolar and low-polar amino acid remnants, enhancing its solubility.[22,23] In terms of solubility, there are four separate classes of zein proteins: α, β, γ, and δ, with α-zein being the most prevalent.[24]

α-zein comprises roughly 80% of the overall prolamins found in maize with a molecular weight between 21 and 25 kDa.[16,17] While β and γ-zein are often detected between 10% and 15%, and the remainder is δ-zein.[22] The molecular weight of β-zein is estimated at 17 kDa, δ-zein at 10 kDa, and molecular weight of γ-zein fluctuates between 18 and 27 kDa.[26] The α-form is generally found in commercial grades of zein (structure of α-zein is shown in **Figure 1**), while the other forms are discarded due to their correlation with gelling, a characteristic which is avoided in polymer production.[27] Some significant physio-chemical properties of zein are summarized in **Table 1**.

Zein is not soluble in water which can be attributed to its amino acid composition. It includes a significant portion of nonpolar amino acids and a small proportion of polar amino acids.[48] Consequently, the α-structure of zein can be dissolved in high-concentration aqueous alcohols without the necessity for reducing agents, as is the case for the dissolution of other zein structures.[49] The optimum solubility for the entire zein was attained in a 70% ethanol-aqueous solution, which was the solvent employed to extract zein from dry-milled maize.[49,50] However, zein can also be solubilized in the presence of anionic detergents, alkaline solutions (pH $\geq$ 11), and extremely concentrated urea.[42] The amino acid sequence in zein is accountable for its peculiar solubility characteristic as over 50% of the amino acids in zein are proline, leucine, valine, isoleucine, phenylalanine, and alanine.[49]

Nonetheless, zein is not solely composed of hydrophobic domains; it also comprises hydrophilic areas, rendering it an amphiphilic protein.[51] Due to its amphiphilic nature, zein has a significantly higher propensity to engross water and swell than other structural proteins like keratin or silk.[20] In addition, as an amphiphilic polymer, zein tends to self-assemble.[52] As a result,

Table 1. Physio-chemical properties of zein.

Properties	Characteristics	References
Physical, structural condition	Amorphous	[28]
Denaturation (°C)	80.32–87.31	[29]
Glass transition (°C)	165	[30, 31]
Melting point (°C)	266–283	[32]
Thermal degradation (°C)	320	[30, 33]
Degree of polymerization	210–245	[17]
Isoelectric point	pH 6.2	[34]
Density (g cm^{-3})	1.23 g cm^{-3}	[35, 36]
Partial specific volume	0.771	[37]
Particle size (nm)	150–550	[38–40]
Water content (g/100 g)	10.5, at a water activity of 0.753 in 25 °C	[41]
Solubility	Almost impossible to dissolve in 100% ethanol, acetone, or water; Soluble in acetone solutions (60–80% v/v), extremely concentrated urea, and glycols; Soluble in alkaline solutions of pH ≥ 11.5	[20, 35, 42]
Viscosity coefficient	25	[43]
Diffusion coefficient (m^2 s^{-1})	3.7×10^{-14}	[43]
Flavor	Tasteless	[44]
Odor	Odorless	[45]
Color	Yellowish	[46]
Composition (%)	Glutamine 21–26 Proline 10 Leucine 20 Alanine 10	[47]

zein is easily transformed into nanofibers, nanoribbons,[53] nanoparticles,[54] microspheres,[55] thin coatings,[56] and Janus fibers.[57]

Zein possesses exceptional characteristics like flexibility, high surface area, low cytotoxicity, biocompatibility, and biodegradability.[37,58] It has also excellent compatibility with extracellular matrix (ECM) constituents.[59] Zein inhabits superior thermal and pH stability in comparison with other proteins,[60] and even when wet, zein retains a high degree of mechanical strength regarding compressive structural strength, kink resistance, and bending rigidity.[61–63] Scaffolds based on zein have been shown to have exceptional mechanical strength.[64,65]

Furthermore, zein protein and peptides have shown antioxidant efficacy and confrontation with microbiological contaminants.[66,67] It has been demonstrated that zein can inhibit microbial deterioration.[68] As a result of its hydrophobic nature, the existence of zein in a specific substrate could have an antibacterial impact against *Escherichia coli*, as decreased surface energy in hydrophobic areas reduces bacterial adhesion and proliferation in the substance.[69] Zein and its breakdown products have demonstrated excellent cell compatibility.[70,71] The U.S. Food and Drug Administration has designated zein as "generally recognized as safe" since it is biocompatible with human cells and degrades rapidly.[53] In addition, it possesses biological activity and encourages cell adhesion and proliferation.[72,73] The amino acids contained in zein, notably leucine and proline, assist in controlling protein metabolism and enhancing the bioactivity of osteoclasts, rendering it suited for stimulating cell adhesion, expansion, and proliferation.[74,75] Zein is also readily available and cheap because as a potential food it lacks essential amino acids, which lowers its nutritional value.[76] These unique properties signify the immense potentiality of zein protein as an essential biopolymer to fabricate fibrous scaffolds in various biomedical applications.

3. Fabrication Techniques

The goal of fabricating fibrous scaffold is to emulate the functionalities of an ECM.[77] The additional advantage of enhancing performance and functionalities by engineering scaffold structure is prospective for effective applications in various fields. Furthermore, the resulting microenvironment comparable to natural ECM is the reason for good biocompatibility and hence exhibits rapport with biological cells.[78] Zein in nanostructures has endless potential in biomedical applications at the molecular level, like health monitoring, reconstruction, healing, medicine carrying, etc. This is because of the structural resemblance to the cells and tissues.[77] In recent times, various types of techniques have been applied for the fabrication of zein-based fibrous scaffolds such as electrospinning, centrifugal spinning, 3D printing, particle leaching, and so on.

3.1. Electrospinning

Electrospinning (as shown in **Figure 2**) is a highly recognized technology which is particularly interesting for biomedical applications as the fibrous structure offers enlarged surface area, a more significant number of interconnected porosities for nutrient transportation and cell migration, controlled drug release (immediate, pulsatile, delayed, sustained, and biphasic),[79] controllable ECM structural similarities for cellular signals and arrangements, in situ drug encapsulation ability, etc.[80]

Studies concerning zein electrospun structures targeted for biomedical applications are being explored worldwide. Horuz and Belibağlı in 2019 developed a composite zein nanofibrous structure combining carotenoid extract with zein–acetic acid solution. Carotenoid is a plant-derived precursor of vitamin A, known for its antioxidant activity, which is useful in a variety of oral, and topical biomedical applications. The aim of the study was to explore the encapsulation capacity of the electrospun composite structure for achieving potential stability to be applied as food colorant, supplement, etc. The electrospinning technique was employed to achieve a high encapsulation efficacy with smooth, bead free, and homogenous fiber distribution. Scanning electron microscope (SEM) observation revealed, similar fiber diameter distribution was achieved all over the zein nanofibrous structure with and without carotenoid extract. The maximum extract loading capacity and encapsulation efficacy were recorded at 19.39 ± 0.20% and 96.95 ± 0.99%, respectively. Concurrently, carotenoid improved viscosity and thermal stability substantially compared with carotenoid-free zein nanofibers.

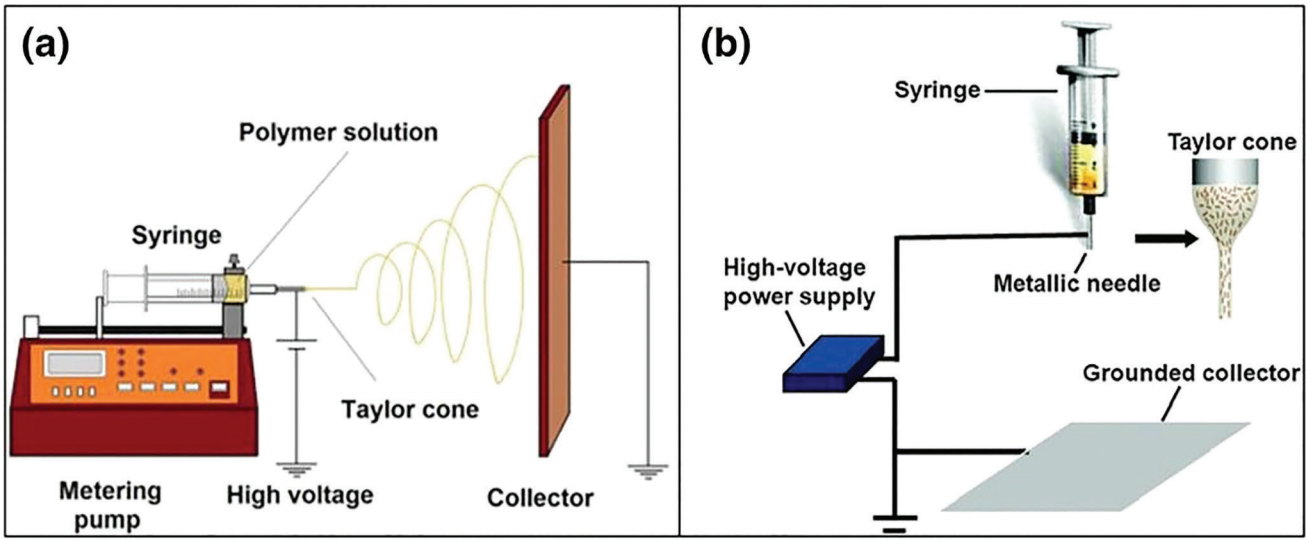

Figure 2. Schematics of electrospinning. a) horizontal setup, b) vertical setup. Reproduced with permission.[81] Copyright 2019, Springer Nature Switzerland AG.

Thermal stability is important to ensure storage stability, especially due to the effect that thermal conditions can have on the existing oxidative degradation rate. Differential scanning calorimetry (DSC) study ensured the carotenoid's amorphous nature after electrospinning. However, a decreasing trend of glass transition temperature (T_g) due to a plasticizing effect was recorded with enhancing carotenoid extract concentration in the zein-AA solution.[82] Huang et al. in 2013 synthesized drug-loaded zein nanofibrous structure employing the modified coaxial electrospinning technique. Zein/ibuprofen (IBU) solution and *N,N*-dimethylformamide (DMF) were applied as sheath and core elements. 0.11 and 0.25 sheath-to-core flowrate ratios resulted in average fiber diameters of 0.94 ± 0.34 and 0.67 ± 0.21 µm, respectively. Analysis via X-ray diffraction and DSC ensured the amorphous nature of IBU after electrospinning to facilitate effective functionality. A sustained drug release behavior was recorded between 88.3% and 97.1% release within the first 6 h.[83] Miyoshi et al. in 2005 reported electrospinning of ultrafine zein fibrous membrane using 80 wt% ethanol aqueous solution as solvent. SEM results revealed the dimensions of the produced fibrous structure heavily depended upon the concentration of zein in the solution. Under the same voltage, as zein concentration increased from 18 to 25 wt%, the fibrous structure changed from nanofiber bridging beads to fibers much thicker in dimension. Another determinant factor was the electric field. It was observed that zein fibrous structures started forming when the concentration was at least 21% at 15 kV. As the electric field was expanded to 30 kV, the same fibrous structure started to form as low as 18% zein concentration.[84]

Some of zein's weaker characteristics, like poor mechanical behavior, can be avoided by combining them with other materials.[85] Materials like single-walled carbon nanotube (SWCNT) and ethyl cellulose (EC) can be added to zein solution for producing electrospun nanocomposite fibrous scaffolds with enhanced performance. A study reported zein–EC nanocomposite electrospun scaffolds capable of carrying both single and multiple drugs. Polyethylene oxide (PEO) was further included in the mix to improve drug release behavior. The average fiber diameter for single and double drug-loaded scaffolds was found to be 312 and 437 nm, respectively. Good water stability (contact angle 133°), mechanical strength (4.39 ± 0.79 MPa), Young's modulus (207.52 ± 21.7 MPa), and in vitro drug release behavior (>70% in initial 7.5 h) were also reported.[80] Dhandayuthapani et al. in 2012 designed a blood-compatible electrospun scaffold with zein–SWCNT nanocomposite fibers. The scaffold exhibited remarkable improvements in terms of uniformity, mechanical characteristics, thermal stability, and antiadhesion to blood platelets. The average diameter for electrospun fibers produced with 0, 0.2, 0.5, 0.8, and 1 wt% SWCNT in the zein solution was less than 300 nm. The extremely high strain rate during the electrospinning process also enabled SWCNT to be highly aligned with the resultant zein fiber axis, which results in improvement in maximum mechanical strength of 7.7 MPa. Furthermore, the thermal stability of the composite improved from onset degradation temperature of $T_d = 455$ °C to $T_d = 370$ °C compared with pure zein. In terms of the hemolysis study, all samples exhibited values <4%, which is well within the permeable limit for biocompatibility.[86] More recent studies on zein-based composites made with electrospinning are summarized in **Table 2**.

3.2. Centrifugal Spinning

Another type of emerging spinning technique to fabricate zein fibrous scaffold is centrifugal spinning. The principle of this spinning technique involves the implementation of centrifugal force to fabricate the fibrous scaffold. Back in 1990, Wagner et al. first introduced and patented this technique, where a thermoplastic material was extruded through a fast-rotating perforated disk.[95] This rotating perforated reservoir was the principal element that held the polymer solution. As the centrifugal force overcame the liquid surface tension, the liquid jet was shot

Table 2. Recent studies concerning zein-based electrospinning scaffold targeted for biomedical areas.

Technique[a)]	Dope composition [w/v%]	Solvent purity [%]	Additives [%]	Input parameters (flow rate, input voltage, collection distance)	Result	Special properties	Ref.
Electrospinning	22% Zein + 0.8% SWCNT	TFE (100%)	-	0.5 mL h^{-1}, 2.0 kV cm^{-1}, 10 cm	230–300 nm diameter (20–40 nm for fiber web), 3.2 MPa tensile complete strength, full thermal degradation at 470 °C, 109 ± 0.45% water uptake	The hemolysis evaluation showed a good compatibility value (<4%). Platelet adhesion and activation trend was observed with intracomponent CNT component.	[86]
Electrospinning	25% Zein + 1% MMT (1%)	Ethanol (>99.5%)	*Hypericum perforatum* oil	5 mL h^{-1}, 20 kV, 10 cm	311–360 µm bilayer thickness, 4.8 ± 1.2 MPa tensile strength, 40°–37° water contact angle	Demonstrated antibacterial activities against *E. coli*, *S. aureus*, and *C. albicans* with no toxic effect	[87]
Electrospinning	Zein (35%, 40%, and 45% wt/v)	Glacial acetic acid	-	0.5 mL h^{-1}, 20 kV cm^{-1}, 15 cm (for 35% and 40% w/v) and 0.5 mL h^{-1}, 25 kV cm^{-1}, 15 cm (for 45% w/v)	153 ± 18 nm (at 35%) to 344 ± 27 nm (at 45%) diameter, ultimate tensile strength 0.06–0.14 MPa (hydrated scaffold), fiber remained intact after hydration	Zein swell-compatible compatible for human dermal fibroblasts and other cell cultures	[88]
Electrospinning	Zein + Silk fibroin (SF)	Formic acid (98%)	-	6 mL h^{-1}, 14–16 kV cm^{-1}, 12 cm	230 to 265 nm average diameter, tensile strength ranged from 13.2 to 14.3 MPa, a maximum 30% in vitro degradation was recorded after 16 weeks	Excellent biocompatibility and no trace of toxicity was identified when experimented on L929 mouse fibroblast cells	[89]
Suspension electrospinning	Zein (15% w/v) + PCL (20% wt/v) + Gum Arabic (6% wt/v)	Formic acid (99.8%) + Acetic acid (95%)	Calendula officinalis extract (2% v/v)	0.2 mL h^{-1}, 18 kV cm^{-1}, 15 cm	405.3 ± 384.2 nm diameter, tensile strength >2 MPa, elongation at break <50%, apparent density 0.192 ± 0.008 g cm^{-3}, porosity 83.74 ± 0.70%, and pore size 3.69 ± 3.62 µm	The scaffolds demonstrated good hydrophilicity due to high porosity (80%). The scaffolds showed favorable adhesion and proliferation performance against fibroblast cells along with biodegradability and antibacterial properties	[90]
Two nozzle electrospinning					579.7 ± 219 nm diameter, tensile strength >2 MPa, elongation at break ≈50%, apparent density 0.262 ± 0.023 g cm^{-3}, porosity 77.28 ± 2.03%, and pore size 4.04 ± 3.51 µm		
Multilayer electrospinning					370.5 ± 252.7 nm diameter, tensile strength about 3 MPa, elongation at break <50%, apparent density 0.249 ± 0.026 g cm^{-3}, porosity 78.62 ± 2.21%, and pore size 3.93 ± 3.88 µm		

(*Continued*)

Table 2. (Continued).

Technique[a)]	Dope composition [w/v%]	Solvent purity [%]	Additives [%]	Input parameters (flow rate, input voltage, collection distance)	Result	Special properties	Ref.
Electrospinning	Zein + Gelatin (30% wt/v)	Acetic acid (80% v/v)	-	1.0 mL h^{-1}, 1 cm	Diameter increased from 380.3 nm to the 695.5 nm as gelatin weight ratio increased from 33.3% to 100%, porosity 65.5%, water contact angle of 118°, and maximum elastic modulus 72.1 MPa	Stable 3D porous structure was observed even after wetting for 24 h	[91]
Electrospinning	Zein	Ethanol/water (80/20, v/v), glacial acetic acid, and HFIP	-	0.2 mL h^{-1}, 27 ± 1 kV, 10 cm	180 nm (produced in acetic acid solution), 1300 nm (produced in ethanol–water solution), and 900 nm (produced in HFIP-loaded; HFIP-loaded zein scaffolds demonstrated better efficacy toward gram positive bacteria than gram negative)	The electrospun structure stabilized the initial released of drugs releasing just 15% in the first hour; The inner and outer rate of feeding can influence both drug encapsulation and release	[92]
Electrospinning	Zein (28 wt%) + ATPPB (6.9 wt%)	Acetic acid	-	0.2 mL h^{-1}, 27 ± 1 kV, 10 cm			
Coaxial electrospinning	Zein	Acetic acid or ethanol–water	HAP (1 wt%)	0.1 mL h^{-1} (inner syringe) and 1.0 mL h^{-1} (outer syringe), 27 ± 1 kV, 10 cm			
Coaxial electrospinning	Zein (28 wt%)	Acetic acid	ATPPB (20 wt%)	0.1 mL h^{-1} (inner syringe), 0.1, 0.2, 0.4, and 0.6 mL h^{-1} (outer syringe), 27 ± 1 kV, 10 cm			
Coaxial electrospinning	Gelatin + Zein (25% wt/v)	Acetic acid (90%)	-	6 mL h^{-1}, 10–18 kV cm^{-1}, 10 cm	1.48 to 890 nm diameter range, water contact angle 121.7° ± 0.6° to 105.5° ± 0.4°, minimum blood loss (50.7 ± 3.8 mg)	The fibrous matrix provided adequate hemostatic efficacy to conduct blood clotting when experimented on rabbit auricular vein, middle auricular artery, and liver	[93]
Coaxial electrospinning	PVA-SbQ + Zein	Acetic acid (70%)	-	1 mL h^{-1}, 25 kV cm^{-1}, 15 cm	455 nm diameter, maximum stress > 14 MPa at 9% strain, in vitro degradation was ≈28% after 14 days	Addition of Vaccarin drug to scaffold improved cell viability and proliferation remarkably	[94]
Modified coaxial electrospinning	Zein/ibuprofen (IBU) co-dissolving (core) solution and DMF (sheath) solution	Ethanol (80%) and DMF	-	0.3 and 0.7 mL h^{-1} (for sheath and core fluids, respectively), 14 kV, 15 cm	0.94 ± 0.34 and 0.67 ± 0.21 µm diameter for sheath–core ratio 0.11 and 0.25, respectively. Good in vitro drug release rate up to 10 h with maximum 97.1% in the initial hour	Due to H bonding, zein showed good compatibility with IBU	[83]

[a)] Abbreviation: SWCNT = single-wall carbon nanotube; TFE = trifluoro ethanol; MMT = nanoclay (montmorillonite); HFIP = hexafluoroisopropanol, ATPPB = allyltriphenylphosphonium bromide, HAP = hydroxyapatite, DMF = dimethylformamide; PVA-SbQ = poly(vinyl alcohol)-stilbazol quaternized.

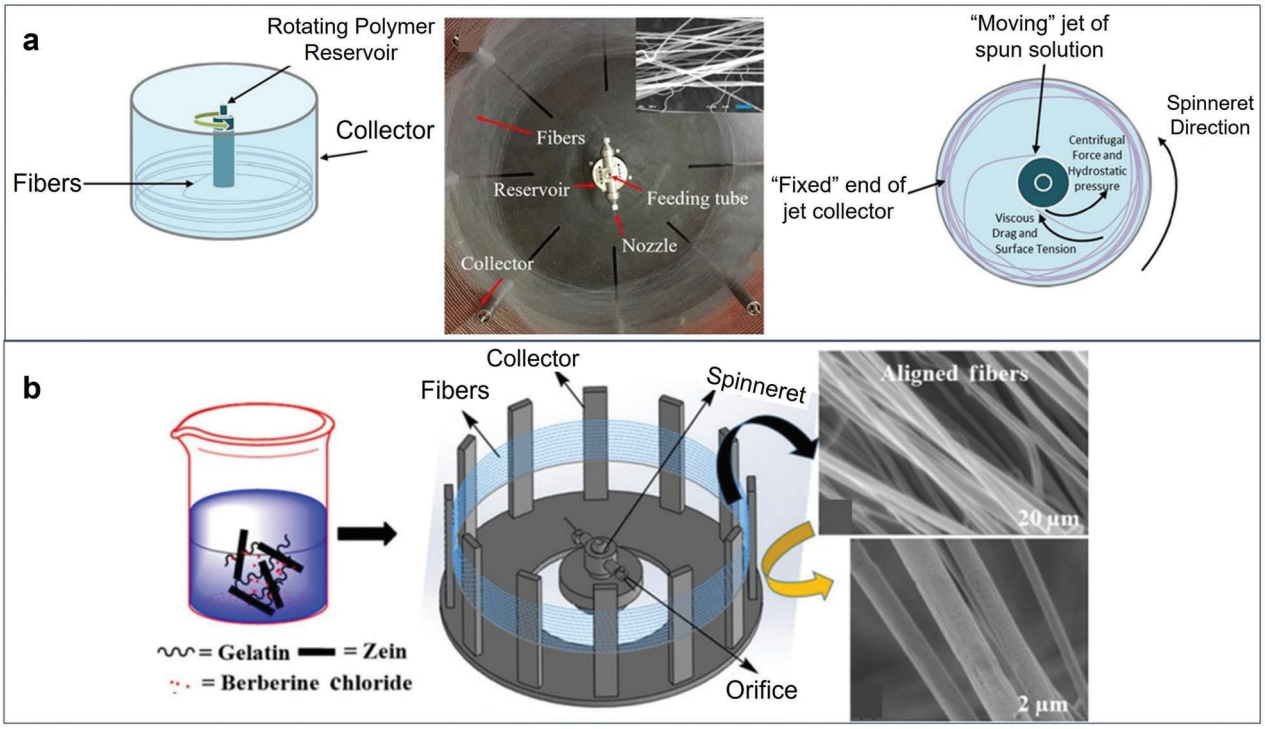

Figure 3. a) Key components and working principle of a centrifugal spinning setup. Reproduced with permission.[78] Copyright 2021, Elsevier Ltd. b) Schematics of centrifugal spinning to prepare zein-gelatin-berberine chloride fibrous scaffold. Reproduced with permission.[23] Copyright 2018, Materials Research Society.

through the perforations. The solvents evaporated to solidify the remaining polymer in the form of fine fibers (as shown in **Figure 3**a).[96,97] In a recent study, Mamidi et al. employed the centrifugal principle-based Forcespinning technique (as shown in Figure 3b) to produce the fibrous scaffold from zein and gelatin proteins with targeted drug delivery and tissue engineering application.

Zein along with gelatin and berberine chloride was dissolved in the acetic acid solvent. The device contained a spinneret at the center having small openings on two opposite sides. This spinneret was surrounded by collector plates which accumulated fibers coming out of the spinneret orifices upon rotation. Improved hydrophobicity (maximum contact angle 133.5°) along with cell viability, adhesion, proliferation, and drug release performance (53–89% by 15 days) was reported. Mechanical behavior showed a positive correlation with increasing zein concentration. Pore size and pore distribution were reported 6.22 μm and 2.2–10.8 μm, respectively.[23]

3.3. Printing

The cell–matrix interactivity largely depends upon controlling the microstructure during scaffold development, making it an important aspect to consider in manufacturing technique.[98] 3D printing (3DP) is an additive manufacturing technique that has gained popularity as it facilitates many advantages like architectural flexibility, reproducibility, and minimum amount of waste generation.[99] Tunability of different printing parameters during fabrication enables the user to have better and more precise control over the structure and dimension of the final product. Zein has been explored as a promising 3DP ink. Commercial zein in powder form dissolved in ethanol and a plasticizer demonstrated shear thinning properties and hence can be used as a medium suitable for printing.[100,101] A recent study by Ruther et al. in 2022 reported 3DP of poly(glycerol sebacate) (PGS)/zein/NaCl inks to produce the scaffold intended for cardiac tissue engineering (as shown in **Figure 4**a). Improved printability, shape fidelity, and thermal cross-linking could be achieved by adding the protein corn zein and ground NaCl particles with the PGS pre-polymer. Mechanical and hydrolytic stability was found to be sufficient to withstand the harsh thermal cross-linking process. Cell culture and viability studies conducted with C2C12 cells revealed the noncytotoxicity of the scaffold.[102] 3DP in combination with other popular techniques like electrospinning has also been explored to develop effective structures. Dos Santos et al. in 2021 employed 3DP in tandem with coaxial electrospinning to fabricate a double-layered platform capable of delivering drugs for tissue regeneration. A 3D-printed honeycomb base layer was prepared with polylactic acid/zein/curcumin composite and a second layer composed of zein/poly(ϵ-caprolactone) (PCL)-coated core–sheath electrospun nanofiber was deposited upon it. The fabrication technique is illustrated in Figure 4b. The researchers studied various zein percentages (10%, 20%, 30% w/w relative to PCL) to control the drug release behavior. Moreover, experiments conducted with human oral keratinocytes (Nok-si) cells revealed

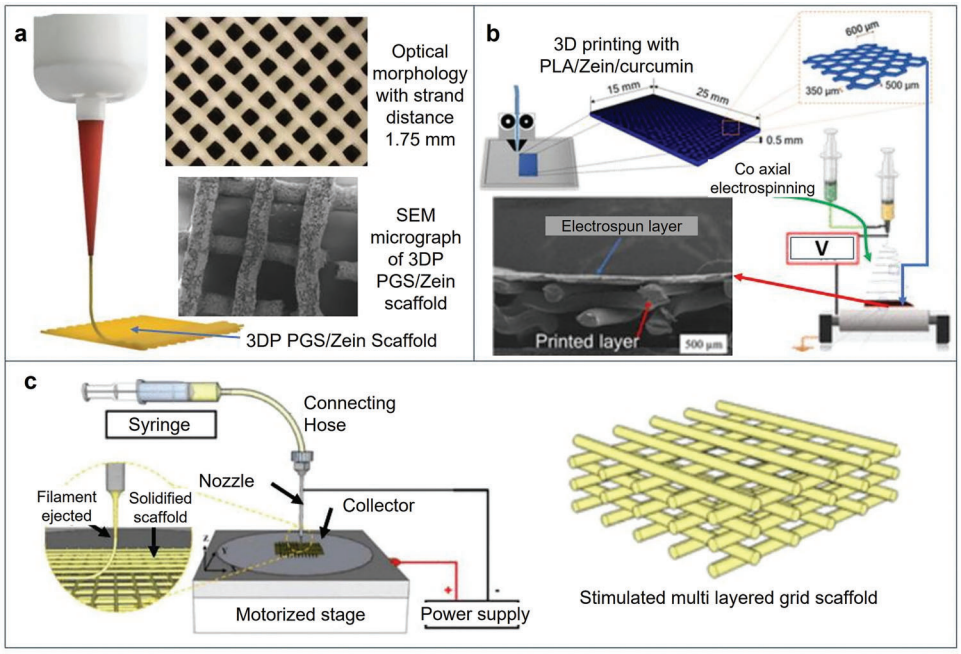

Figure 4. a) 3D-printed PGS/zein scaffold for cardiac tissue engineering with optical and SEM micrographic view. Reproduced with permission.[102] Copyright 2022, Wiley-VCH. b) Illustration of combining 3DP and coaxial electrospinning to produce drug delivery platform for tissue reengineering. Reproduced with permission.[103] Copyright 2022, American Chemical Society. c) Schematics of an EHDP printing for developing a scaffold. Reproduced with permission.[104] Copyright 2018, American Chemical Society.

good cell viability (>80%) and inhibition against *Porphyromonas gingivalis* and *Treponema denticola* bacteria strains.[103]

Electrohydrodynamic printing (EHDP) is another printing technology for fabricating customizable fibrous scaffolds intended for biomedical applications. Raw materials are fed in the form of inks. In a recent study, Jing et al. reported a self-made EHDP technique to evaluate the performance of PCL–zein composite ink for developing a biomedical scaffold. Zein was incorporated to improve PCL's lack of degradability while providing suitable biocompatibility to the finished product. The schematics of the device are depicted in Figure 4c. It comprised of a computer-controlled *XYZ* movable stage, syringe pump, and voltage source. A continuous flow of ink was subjected to the electric field generated between the needle tip and the conductive collector. The continuous deposition of layer-by-layer stacking formed the scaffold. Significant improvement of PCL/zein scaffold in terms of Young's modulus (102.1–241.4 MPa) and yield stress (3.8–6.3 MPa) was reported compared with those of 100% PCL scaffold. Further, the biodegradability test conducted in phosphate-buffered saline (PBS) buffer (10×10^{-3} M, pH 7.4) at 37 °C revealed significantly quicker degradation of PCL/zein (50%) compared to 100% PCL (1.7%). The biocompatibility study conducted with H1299 cell culture demonstrated a much better performance of PCL/zein.[104]

At day 1, almost double cell attachment was seen for PCL/zein compared to 100% PCL.[104] In a more recent study, Jing et al. utilized EHDP technology where PCL/gliadin and PCL/zein were applied as printing inks. The study found that even relatively tiny portions of the plant protein like zein could significantly improve mechanical properties. Maximum Young's modulus, yield stress, and strain were found to be 338.7 ± 38.9 MPa, 14.2 ± 0.6 MPa, and 6.0 ± 1.0%, respectively, with 20% w/v zein in PCL (PCL/zein-20) composite. Further, improved cell proliferation, migration, and adhesion were reported from experiments conducted on NIH/3T3 mouse fibroblast cells. On the fifth day of the experiment, the number of cells was calculated to almost double for the PCL/zein-20 compared to the pure PCL scaffold.[105]

3.4. Particle Leaching Method

Among other techniques, a particle leaching method to prepare pure zein and zein-based composite scaffold was reported by El-Rashidy et al. in 2018.[106] Sodium chloride (NaCl) was incorporated as a porogen into zein powder (zein:NaCl 1:2). Further, sol–gel-derived bioactive glass (BG) particles were added to the mix to introduce bioactivity. An electrohydraulic pressing device (pressing load 2×10^4 Pa) was used to compress the mixture to shape the 3D scaffold. Later, the scaffold was subjected to salt leaching in a hot bath under stirring, then washed using distilled water before freezing (−20 °C) and freeze-drying. The experiment conducted in simulated bodily fluid (SBF) revealed the formation of a highly reactive carbonated (HA) layer and antibacterial activity against *E. coli* and *S. aureus*. The pure zein scaffold further showed a compressive strength of 5 ± 2 MPa and interconnected porosity of 67 ± 2%.

4. Manufacturing Parameters

High surface area to volume ratio, superior mechanical performance, flexible surface components, and a high degree of

Table 3. Parameters for different fiber manufacturing technique which affect the fiber properties.

Process	Parameters	Affecting properties	Reference
Wet spinning	- Polymer, solvent, coagulating aent thermodynamic condition - Polymer viscosity, extrusion rate, spinneret hole size - Coagulation kinetics	Fiber morphology, diameter, pore size	[110–112]
Melt extrusion	- Spinneret hole size - Temperature - Polymer viscosity - Extrusion rate - Solidification rate	Fiber diameter and morphology	[78, 113]
Phase separation	- Constituent material properties - Polymer type - Solution concentration - Processing temperature	Fibrous structure and morphology	[114, 115]
Electrospinning	- Voltage - Flowrate - Solution viscosity - Nozzle to collector distance - Solution concentration and composition - Solution surface tension	Nanofiber morphology	[80, 91, 101]
Centrifugal spinning	- Centrifugal force - Solution surface tension - Viscoelasticity - Spinneret rotating speed - Perforation size	Fiber morphology and resulting fiber size	[107, 115–117]
Additive manufacturing	- Printing parameters (speed, temperature, pressure, *X*, *Y*, *Z* axis offsets, etc.)	Dimension and geometries	[102]

porosity make a high-quality fibrous scaffold. It is possible to optimize electrospinning parameters to get the required fibrous characteristics suitable for intended applications. For instance, the nanofibrous morphologies can be adjusted by regulating electrospinning parameters like flow rate, voltage, distance from the nozzle to the collector, and solution viscosity.[80,91] In the case of modified techniques like coaxial electrospinning, some additional parameters like dimensions of the outer and inner needle, outer and inner feeding rates, are also important.[92] Compatibility, growth, and attachment of various cells and body organ parts largely depend on these characteristics,[77] and in the case of centrifugal spinning, centrifugal force is the main driving force. Along with force, solution properties and operation parameters, such as speed of rotation and spinneret orifice size, largely control the generated fibers' properties including the surface characteristics, uniformity, and scaffold thickness. The rotational speed must reach a critical minimum level at which the centrifugal force can overcome the solution surface tension.[23,107–109] The parameters that have direct impacts on manufactured nanofiber characteristics are listed in **Table 3**.

5. Biomedical Applications

Zein is a protein derived from corn, and its biomedical implications have been extensively studied.[118] In recent times, numerous research has reported biomedical applications of zein-oriented fibrous scaffolds in different fields, for instance nerve guide conduits (NGCs) for nerve regeneration, controlled drug release, wound dressings, and bone tissue regeneration, as illustrated in **Figure 5**.

5.1. Nerve Guide Conduits

Zein-based NGCs exhibited excellent mechanical stability and nerve regeneration effectiveness in vivo studies.[61,65] Wang et al. in 2017 established a 3D porous zein NGC utilizing a dipping-leaching method to treat rats with a 10 mm nerve injury. The intraluminal microtubes of the zein NGC facilitated nerve regeneration and functional recovery comparable to autografts.[61] Another study fabricated ciprofloxacin-loaded zein NGC applying a simple rolling technique that showed decent mechanical characteristics. In vivo antibacterial tests revealed that inclusion of ciprofloxacin in zein NGC significantly reduced the risk of tissue infection following subcutaneous implant, in comparison to NGC without ciprofloxacin.[65] However, the uncontrolled degradation rate of the NGC is a concerning issue. In a recent study, Hayat et al. integrated polyvinylpyrrolidone (PVP) into the zein-based NGC at a concentration of 0.2–32 wt% to control the rate of degradation. They effectively controlled the in vivo degradation rate by adjusting the proportion of PVP in conduits. The developed conduit also demonstrated superb antibacterial efficacy against *E. coli* and *S. aureus*.[119]

A few researches have indicated that combining zein with polymers can enhance the resilience of zein conduits in a moist atmosphere. Monfared et al. in 2019 blended zein and tannic acid (TA) nanofibers by electrospinning technique to fabricate NGC that exhibited excellent cytocompatibility with Schwann cells (SCs). The results demonstrated that TA substantially influenced nanofibers' endurance to film formation and enhanced the conduit's degradation rate and tensile strength.[120] On the other hand, as a plant protein, the potential immunological reaction of zein in vivo is the most significant factor of concern.

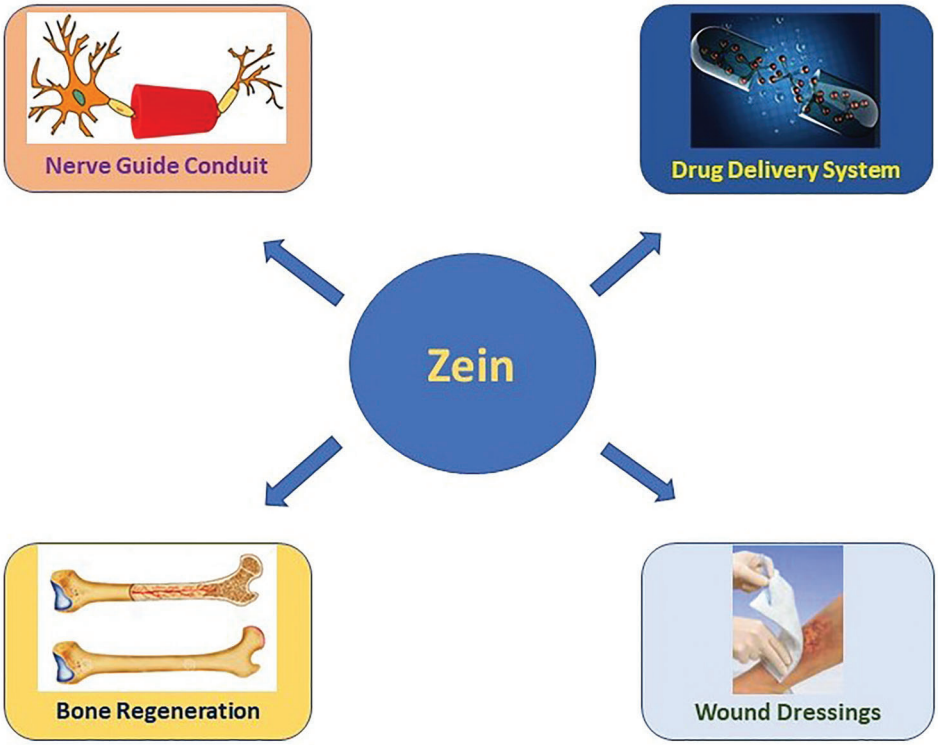

Figure 5. Schematic illustration on the biomedical applications of Zein.

In a recent study, Yu et al. reported that the porous structure of zein NGCs could reduce the inflammatory response generated from zein and boost M2 macrophage polarization, speeding up the nerve restoration process. The study illustrated in **Figure 6** exhibited that zein NGCs with high porosity accelerated nerve regeneration by stimulating other M2 macrophages, leading to a reduced degradation time and enhanced nerve repair efficiency.[63]

Overall, the simple manufacturing procedure, superior mechanical performance, biocompatibility, and antibacterial activity of zein-based NGCs demonstrated their potential for use in nerve regeneration.

5.2. Wound Dressings

In recent years, researchers have attempted to fabricate wound dressings from zein-based biomaterials owing to their distinctive characteristics, including biodegradability, biocompatibility, and antioxidant capacity.[87,121,122] However, zein lacks the antibacterial characteristics that are essential for wound dressings to inhibit microbial development and inhibit undesirable infection.[123] To improve antibacterial characteristics, Dashdorj et al. in 2015 incorporated silver nanoparticles (AgNPs) into electrospun zein fibers. The results indicated a high level of cytocompatibility and cell adhesion to electrospun nanocomposite mat. The antibacterial effectiveness of the manufactured mats against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) was excellent.[124] Moreover, the utilization of natural medicinal extracts, for instance essential oils can enhance the antibacterial properties of the zein-induced wound dressings significantly. Recently, Qin et al. integrated clove essential oil (CEO) with zein to construct an electrospun antimicrobial wound dressing. The fabricated wound dressing exhibited sufficient porosity, superior gas permeability, hydrophilicity, biocompatibility, and antibacterial properties to prevent infection and stimulate wound recovery in mice wound model analysis.[123] In another study, Liu et al. incorporated thyme essential oil (TEO) with zein to construct wound dressings by electrospinning process that demonstrates potent antibacterial activities for the inhibition and treatment of wound injuries. Mice study indicated that the fabricated membrane accelerates healing of wounds by 11 days.[59] Recently, Gunes et al. created a unique bilayer wound dressing consisting of zein-based montmorillonite (MMT) nanocomposite incorporated with *H. perforatum* oil that demonstrated the ability to accelerate skin regeneration, **Figure 7**. The results from wound dressing showed sufficient mechanical and surface wettability to encourage wound healing. Furthermore, it revealed antimicrobial efficacy, no cytotoxicity and encouraged the adhesion, growth, and proliferation of NIH 3T3 fibroblasts cells across the wound surface.[87]

However, the lack of adequate mechanical characteristics is the most significant drawback of the electrospun zein matrices. This fundamental constraint of native zein can be circumvented through blending with additional compatible polymers and cross-linking. Asadi et al. in 2022 demonstrated that the incorporation of graphene oxide (GO) with zein enhanced the

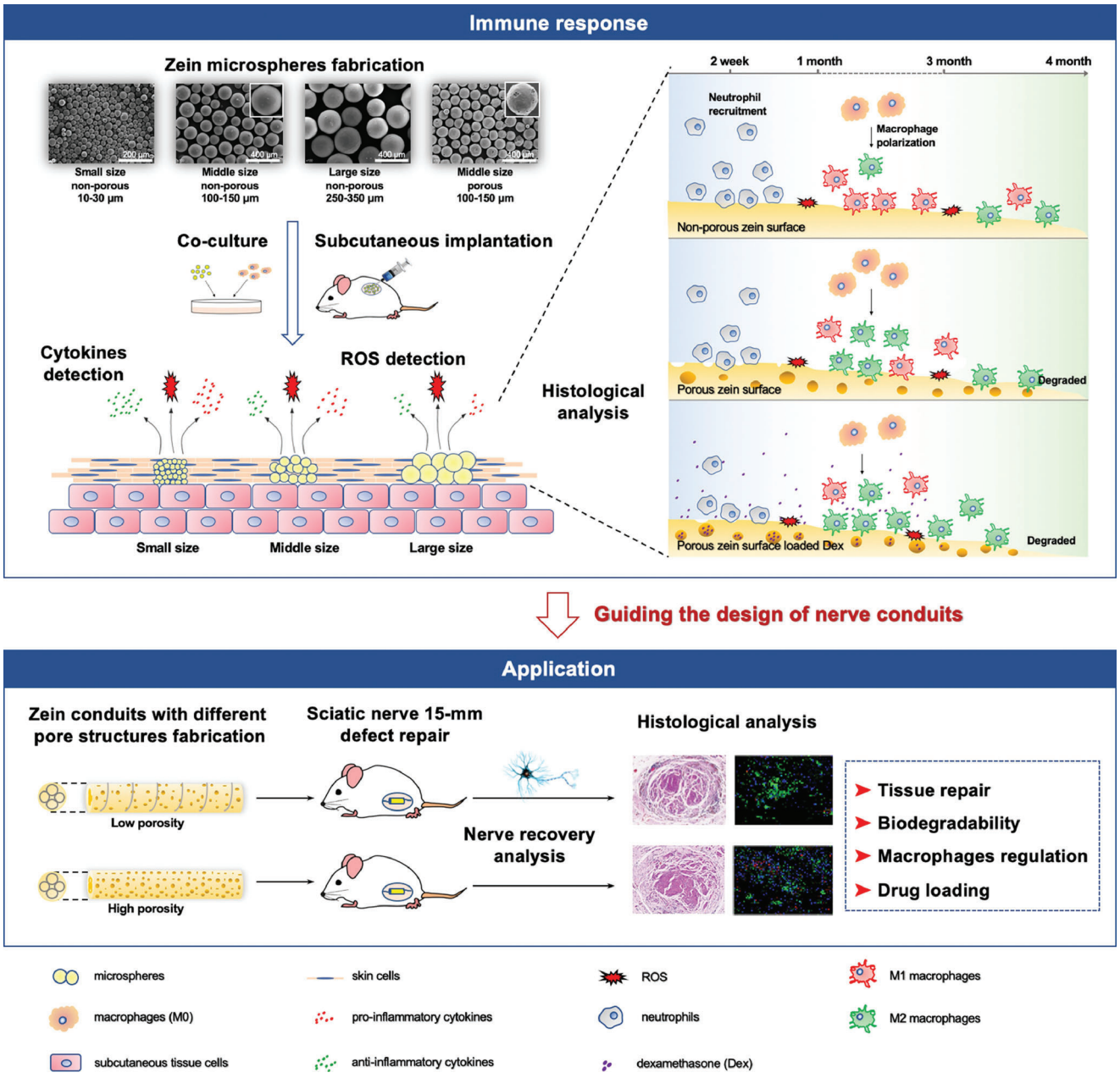

Figure 6. Schematic representation of the fabrication and significance of zein nerve conduits with different porous structure. Reproduced with permission.[63] Copyright 2022, Elsevier Ltd.

wound dressings' mechanical characteristics, hydrophilicity, and antibacterial activities. Moreover, the zein–GO composite wound dressing showed no toxicity, while facilitating the attachment and proliferation of fibroblast cells.[125] In a recent study, Surendranath et al. exhibited the enhancement of mechanical properties of the electrospun wound dressing membrane by combining native zein with PEO and then cross-linking it underneath UV irradiation. In addition, the fabricated membrane augments the production of collagen and wound healing in human dermal fibroblast cells with no toxicity in the in vitro investigation.[126]

5.3. Controlled Drug Delivery

The controlled delivery rate from loaded carriers is a crucial metric for measuring the therapeutic efficacy of a medication.[127] In terms of excipients for controlled drug delivery systems, zein is an attractive system due to its swelling but nondissolving properties.[128] Zein has been employed as a transporter for oral drug distribution techniques owing to its benefits in increased bioavailability, the capacity to create prolonged-release dosage structures, and the ability to target or protect medicines.[26] In addition, zein does not trigger an immunological reaction or

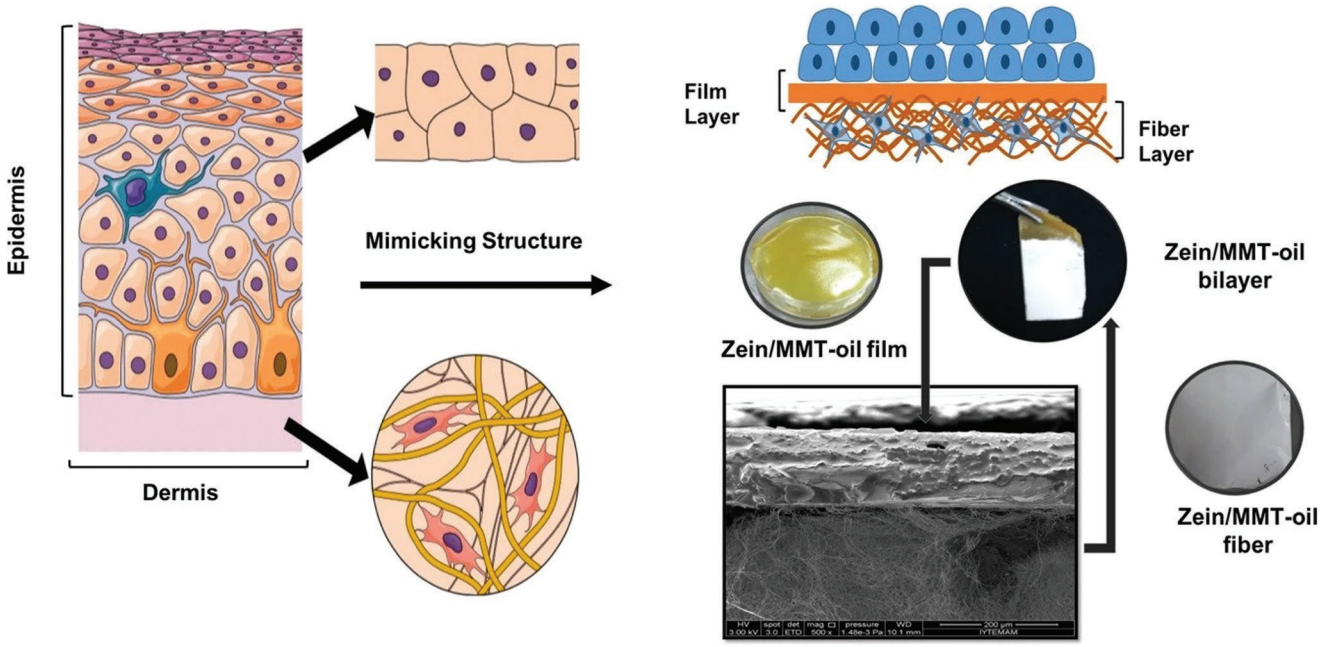

Figure 7. Schematic illustration on the fabrication of zein-based bilayer wound dressing that simulates the structure of skin. Reproduced with permission.[87] Copyright 2020, Springer Nature.

Celiac disorder.[129] In comparison to other proteins, zein has an enormous amount of hydrophobic amino acids, resulting in a greater capability for hydrophobic drug loading and self-assembly into durable nanomaterials without the use of hazardous chemical cross-linking agents.[76,130] The structural characteristics of zein allow it to preserve loaded compounds even in the gastrointestinal environment, and provide a technique for regulated delivery.[131]

Bouman et al. in 2015 developed controlled oral drug delivery with tunable dosage levels utilizing zein as the main component. A straightforward two-step technique was used, hot melt extrusion (HME), in conjunction with injection molding (IM). The mixture of zein, water, and crystalline paracetamol were subjected to HME at 80 °C and then molded into caplet shapes using IM. The combination of HME and IM is an innovative and effective method for producing personalized matrix dosage formulations with precise shape and size. This is especially significant for drug release mechanisms where the dimensions and shape of the device have a considerable impact on the drug's release rate. The study indicates that zein, a sustainable natural polymer, has the potential to be utilized as the only excipient to manufacture a device that controls Fickian diffusion. The controlled release device can be adjusted to have a tunable release rate and can be produced using a straightforward solvent-free technique that combines HME and IM.[128] In another study, Lee et al. created an oral medication delivery approach based on zein-alginate nanomaterials for superoxide dismutase (SOD), **Figure 8**A. This study showed that zein shields SOD from the severe conditions present in the gastrointestinal tract, whereas alginate improves their enzymatic activity by delivering SOD into the small intestine. This tactic inhibits exogenous superoxide, decreasing internal reactive oxygen species and protecting Caco-2 cells from the toxicity of superoxide.[132]

Zein's amphiphilic characteristics allow its hydrophobic portions to generate colloidal particles that can bind and store lipophilic medicines, while protein's polar regions can interface with water soluble substances.[53,133] Because of this, zein has been utilized to entrap medicines. Gagliardi et al. in 2018 reported that sodium deoxycholate-treated zein nanomaterials are durable biocompatible colloidal nanocarriers that can be utilized as effective drug release platforms.[134] The zein nanoparticles are capable of retaining different quantities of hydrophilic and lipophilic medicines; hence, more research on the delivery rate of encapsulated compounds as a consequence of the modification of different parameters is required.

The use of zein nanoparticles (ZNPs) as a drug transporter shows promise in the prevention and medication of cancer. Shinde et al. in 2019 demonstrated that ZNPs stabilized with sodium caseinate have the potential to transport small-scale molecules such as luteolin with high nutraceutical relevance, increasing bioavailability and strengthening effectiveness in anticancer capability. The ZNPs with luteolin exhibited increased cytotoxicity toward SW480 colon cancer cells and induced apoptosis.[135] In recent research, Yu et al. showed that Maytansine (DM1)-loaded ZNPs have substantial anti-A549 tumor cell activity compared to DM1 in vitro and in vivo. The biodistribution analyses indicated that ZNPs can target tumors. They also improve cellular absorption and accrue in tumors through the enhanced permeability and retention effect. Thus, DM1-integrated ZNPs can be employed as a potentially effective medication for nonsmall cell lung cancer.[136] However, ZNPs lack the specific tumor targeting characteristic that is essential in cancer treatment.[137] To resolve this issue, Zhang et al. in 2022 showed that the integration of polysialic acid (PSA) into ZNPs has the potential to increase specificity via ligand-receptor detection and improve physiological durability. PSA-modified ZNPs were created

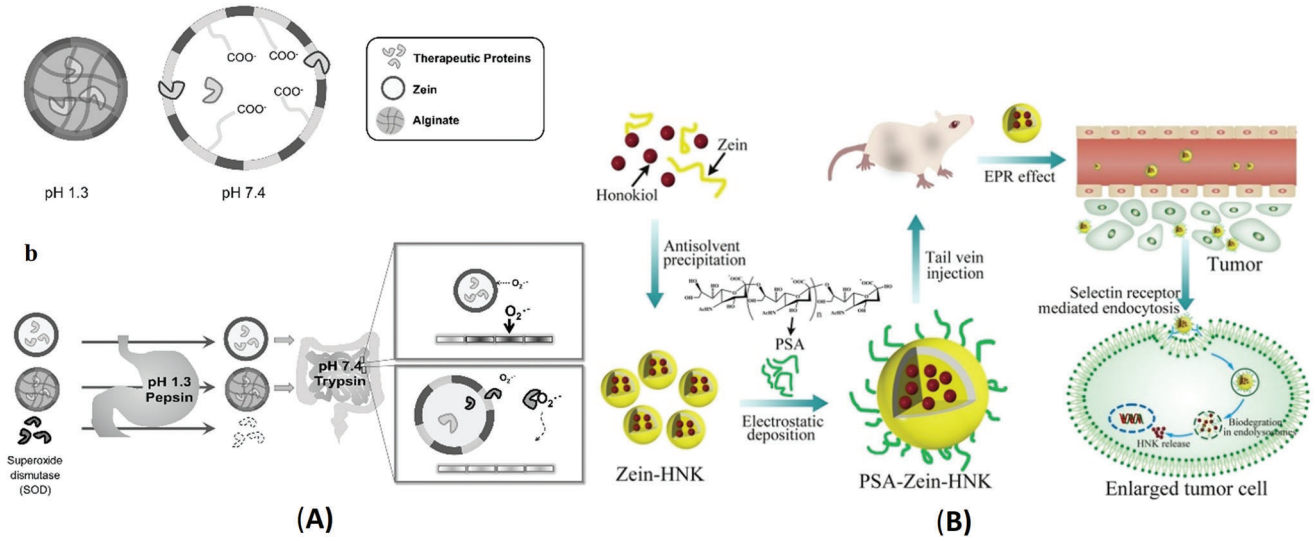

Figure 8. A) Zein-alginate oral drug release system; a) Deprotonation of carboxyl groups in the gastrointestinal pH leads zein-alginate nanomaterials to swell; b) exogenous superoxide is effectively scavenged by SOD that is protected by zein-alginate nanoparticles at pH 1.3 and liberated from the nanomaterials at pH 7.4. Reproduced with permission.[132] Copyright 2016, Elsevier Ltd. B) Schematic representation of HNK delivery through PSA-modified zein core/shell nanomaterials for breast cancer treatment. Reproduced with permission.[137] Copyright 2022, Elsevier Ltd.

for selective administration of honokiol (HNK) in order to enhance medication delivery efficacy and precise biodistribution at the cancerous site. After intravenous administration, PSA-Zein-HNK nanoparticles displayed satisfactory tumor suppression efficiency and did not produce systemic toxicity throughout the entire treatment phase. Their findings demonstrated that PSA-Zein-HNK nanoparticles inhibit lung metastasis in breast cancer effectively in comparison with nontargeting ZNPs (illustrated in Figure 8B).[137]

5.4. Bone Tissue Regeneration

Zein is a great option to fabricate biomaterial scaffold for bone regeneration due to its biocompatibility, biodegradability, outstanding mechanical characteristics, including strength, flexibility, and compressibility, as well as antioxidant capacity and microbiological resistance.[47,138,139] It has been demonstrated that scaffolds fabricated from zein-based composites stimulate osteogenesis differentiation, rendering them appropriate for bone tissue regeneration.[140,141] Zhang et al. in 2014 have shown the viability of synthesizing zein/calcium phosphate hybrid nanofibers by a simple mineralization method, which has been expanded to synthesizing other nanomaterials, including protein and inorganic components. The results demonstrated that electrospun nanofiber composite consisting of zein and minerals, with morphological and structural characteristics identical to natural bone, may serve as a suitable scaffold for cellular proliferation and osteogenic transmission in bone tissue regeneration (**Figure 9**).[139] In another study, Wu et al. developed zein/PCL nanocomposite scaffolds for bone tissue regeneration with a well-connected porous structure utilizing the solvent casting–particulate leaching technique. The fabricated scaffold was more hydrophilic and degraded rapidly compared to the PCL scaffold. Moreover, the rate of degradation of the scaffold could be altered by adjusting the concentration of zein in the compound.[71]

Recent research indicates that the BG-based scaffold coated with zein has superior qualities in bone regeneration over the bare scaffold. Arango-Ospina et al. in 2021 demonstrated that 45S5 BG-based scaffolds constructed using the foam replica approach and coated with zein and Manuka honey enhanced the mechanical capabilities of fragile scaffolds and conferred antibacterial characteristics.[142] In another recent research, Ranjbar et al. coated a permeable scaffold constructed from 58S BG with zein, which enhanced its mechanical capabilities and served as a medium for kaempferol-controlled release. The scaffolds coated with a zein solution (7% wt/v) displayed the maximum mechanical strength and reasonable porous structure. In addition, the findings indicate that the developed scaffolds could facilitate an optimal kaempferol discharge and a favorable atmosphere for cell adhesion (**Figure 10**A).[143] Therefore, scaffold coated with zein could be considered a feasible alternative for bone regeneration.

On the other hand, the ECM of bone is comprised of mineral substances, including hydroxyapatite (HAp).[144,145] In a recent study, Lian et al. developed a unique membrane composed of HAp nanowires and zein that showed potential to replace rigid tissue in bone repair and regeneration purposes. Results indicated that the incorporation of HAp with zein improved fibrous microstructure, enhanced mechanical characteristics, and stimulated the osteogenic proliferation and differentiation of mesenchymal stem cells (MSCs). Overall, the HAp/zein 9/1 nanocomposite membrane has demonstrated remarkable morphological, structural, and mechanical characteristics.[146] Ou et al. in 2019 constructed zein/gelatin/nano-HAp nanofiber membrane by electrospinning technique. The developed membrane was shown to be osteoinductive and biocompatible with human periodontal ligament stem cells in both in vitro and in vivo studies.[147] Shahbazarab et al. in 2018 investigated bone

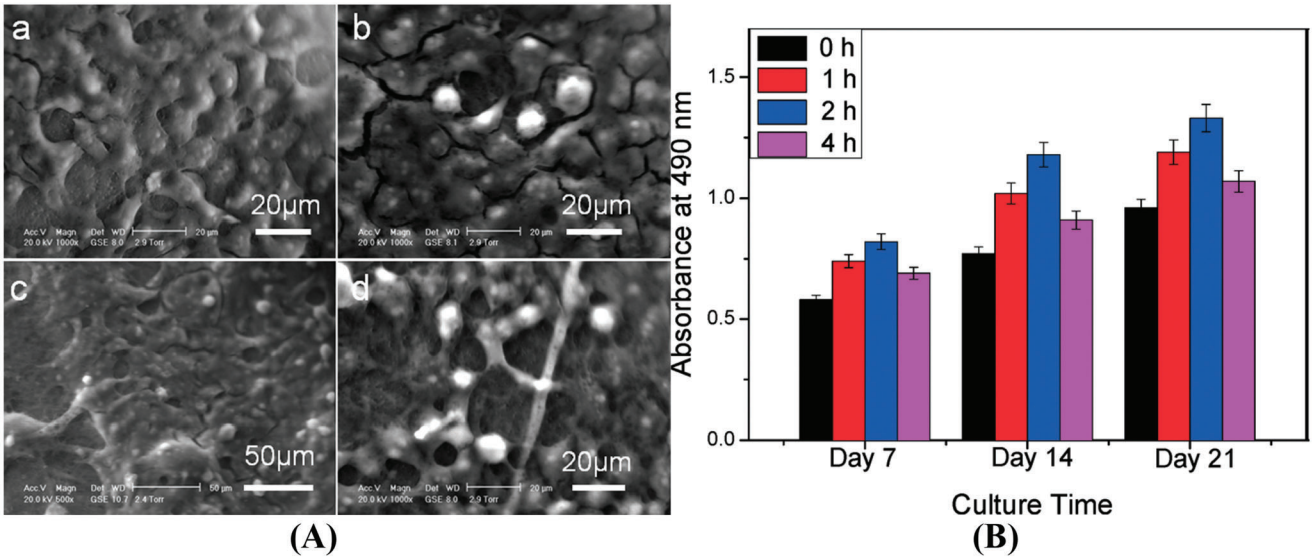

Figure 9. A) a) Adipose derived stem cells (ADSCs) cultivated for 14 days on electrospun zein scaffolds as visualized by ESEM, electrospun zein scaffolds after mineralization for b) 1, c) 2, and d) 4 h; and B) Proliferation of ADSCs sown on electrospun zein scaffolds on days 7, 14, and 21 (black) and its mineralized scaffolds for 1 h (red), 2 h (blue), and 4 h (magenta), individually. Reproduced with permission.[139] Copyright 2014, Royal Society of Chemistry.

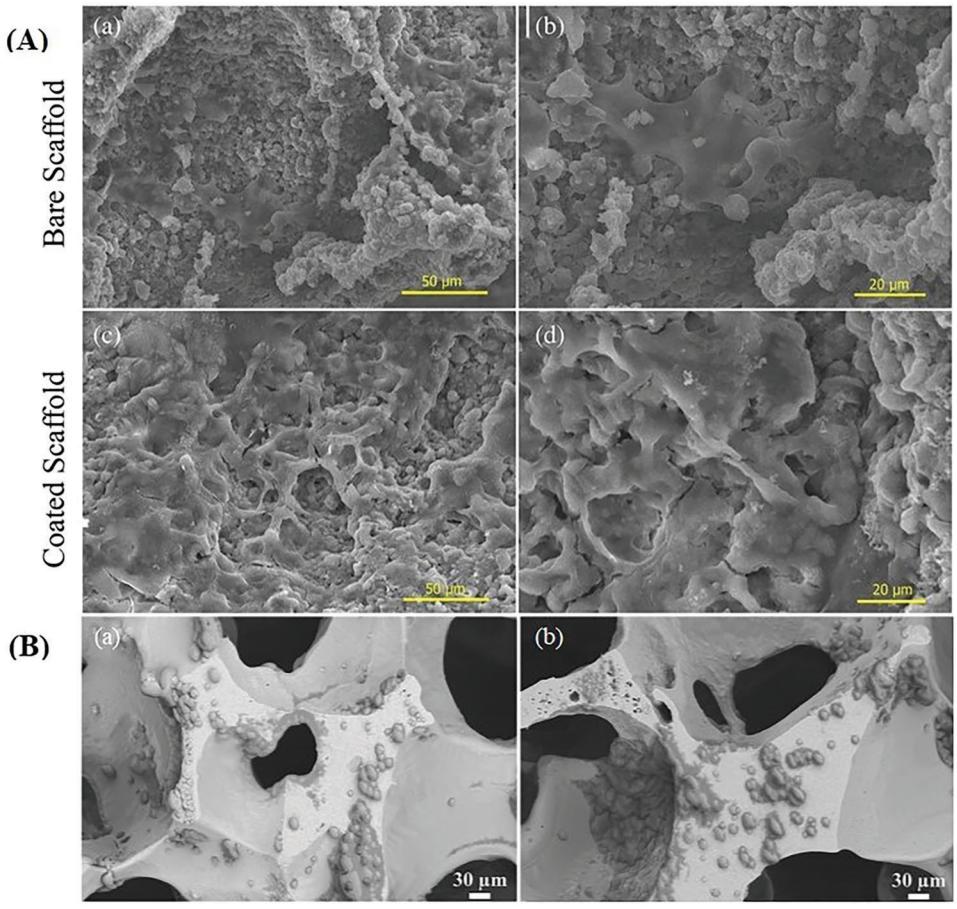

Figure 10. A) SEM images of MG-63 cells cultured on a,b) the bare and c,d) zein-coated scaffolds at various magnifications. Reproduced with permission.[143] Copyright 2021, John Wiley and Sons. B) SEM illustrations of C2C12 cells following 1 week of culture on a) zein and b) zein/nHA scaffolds, respectively. Reproduced with permission.[149] Copyright 2022, SAGE Publications Inc.

Table 4. Patent details of zein-based fibrous scaffolds.

Patent Number	Zein scaffold	Date of patent	Reference
US20170319743A1	Application in wound healing, regenerative medicine, and drug delivery	9 November, 2017	[150]
US10245152B2	Application in surgical implant	2 April, 2019	[151]
US20140011416A1	Three dimensionally and randomly oriented fibrous structures	9 January, 2014	[152]
US9902818B2	Isolated and fixed micro and nanostructures	27 February, 2018	[153]

regeneration performance on a zein/chitosan/nano-HAp scaffold fabricated by freeze-drying technique, indicating that the inclusion of chitosan and zein enhanced the proliferation and adhesion of MG-63 cells.[148] Recently, Zaersabet et al. integrated 12.5 wt% nHAp with zein to fabricate 3D scaffold for bone tissue restoration employing the salt leaching approach. The fabricated scaffold has shown the capacity to promote proliferation and adhesion of cells (Figure 10B). The results indicated that the inclusion of nHAp nanoparticles enhanced mechanical integrity and transcriptional rates of osteogenic indicators.[149] In summary, zein composite scaffolds can be utilized as suitable and nontoxic alternatives in bone tissue regeneration.

The patent information regarding the utilization of fibrous scaffolds made from zein in various biomedical fields is summarized in **Table 4**.

The most recent studies on zein-based fibrous scaffolds for use in various biomedical fields are compiled in **Table 5**.

6. Commercial Aspects and Commercialization of Zein Scaffolds

Commercial aspects and the commercialization of zein scaffolds in the biomedical field have gained significant attention in recent years. The porous structure of Zein scaffolds allows for the encapsulation and controlled release of therapeutic agents.[76] Several commercialized zein-based drug delivery products have emerged, such as zein microspheres and nanoparticles.[26] Microspheres made from zein are used as carriers for controlled drug delivery. They can encapsulate a wide range of drugs and provide sustained release profiles, ensuring a controlled and targeted drug delivery system.[165] In addition, zein nanoparticles have gained attention for their ability to encapsulate and protect sensitive drugs. These nanoparticles can improve drug stability and enhance drug delivery efficiency.[49,166]

On the other hand, the biocompatibility and film-forming properties of zein make it suitable for developing advanced wound dressings.[167] Zein can be formulated into films or dressings that adhere to the wound site, provide a protective barrier, and facilitate wound healing. These dressings can help maintain a moist wound environment and enhance the natural healing process.[168] Commercialized zein-based wound dressings aim to improve wound management by offering features such as moisture control, antimicrobial properties, and the ability to facilitate tissue regeneration. These dressings may be tailored for different types of wounds, including acute and chronic wounds.

Furthermore, the porous structure of zein scaffolds promotes cell adhesion, proliferation, and tissue formation.[73] Commercially zein scaffolds can be used as substitutes for damaged or diseased skin. These scaffolds provide a biomimetic environment for cell attachment and promote tissue regeneration.[169] Besides, commercialized zein scaffolds have been developed as bone substitutes or scaffolds for bone tissue engineering. They can support the growth of bone cells and facilitate the regeneration of bone tissue.[170]

Zein scaffolds have also been investigated for their potential as nerve guide conduits in nerve regeneration applications. Commercialized zein-based nerve guide conduits provide a biocompatible and biodegradable structure that can guide nerve regrowth and facilitate neural tissue regeneration. These conduits can help bridge nerve gaps and promote functional recovery in nerve injuries.[171]

In terms of commercial aspects, the successful commercialization of zein scaffolds in the biomedical field involves considerations such as market demand, manufacturing scalability, cost-effectiveness, safety, and regulatory compliance. Intellectual property protection and collaborations between academic institutions, research organizations, and industry partners play a crucial role in advancing the commercialization of zein scaffolds.

It is important to note that the commercial landscape for zein scaffolds in the biomedical field is continuously evolving. Ongoing research and development efforts are focused on improving the properties and performance of zein scaffolds, exploring new applications and developing novel commercial products. Industry partnerships, investment, and market acceptance are key factors that will drive the widespread adoption and commercial success of zein scaffolds in the biomedical field.

7. Conclusions and Future Directions

This article outlines the technological approaches underlying the fabrication techniques of zein-based fibrous scaffolds and their implementations in biomedical areas. The distinctive physicochemical properties and specialized nanostructures of zein molecules enable them to be inherently superior to a variety of natural and synthetic biopolymers. The biomedical community gains an extraordinary resource from zein because of its capability of being shaped and chemical amenability. Zein has been found as a biopolymer having predominantly two major tasks: it provides assistance to cells by acting as a scaffold, and it is effective as a structural component for encapsulating substances that are susceptible to specific environmental conditions. When it comes to biomedical applications, zein scaffolds are efficient stimulators of cellular expansion and proliferation; nevertheless, there are components that can be incorporated to refine suitability for further purposes. The mechanical qualities of the zein scaffolds have been enhanced by integrating them with other substances such as natural polymers, synthetic polymers, and inorganic molecules, however, combining zein with other polymers

Table 5. Zein-based fibrous scaffolds for application in different biomedical fields.

Application area	Materials[a)]	Structure	Manufacturing technique	Output	Bioactivity	Ref.
Nerve guide conduit	Zein + polyaniline (PANi)	PANi-coated zein microtube	Immersion coating of zein microtubes	Microtube porosity 81.44 ± 1.80%; Maximum conductivity 0.030 S cm^{-1}	Quicker recovery in functionality (2 months); Evaluation with PC 12 cells proved cytocompatibility; Faster microtube degradation time (93% weight loss within 13 days); Within 4 months nerve diameter was 623 ± 122 µm comparable with autograft	[154]
Nerve guide conduit	Zein + PVP and ciprofloxacin	PVP added ciprofloxacin-loaded zein conduit	Rolling method	Superior bending stiffness 8.6–31.6 N mm^2; Porosity 66.3–88.7%	Antibacterial effect (increased with increased PVP%); Faster drug release for higher PVP% (>90% in 12 h); Lower PVP% showed good cell viability (95.8 ± 3.0% for 0% and 85.2 ± 2.7% for 2%)	[119]
Nerve guide conduit	Zein + Ciprofloxacin	Ciprofloxacin-loaded zein conduit	Rolling method	Inner diameter 1.57 mm and wall thickness 300 µm; Superior bending stiffness 28.54 N mm^2; Porosity >60%; Slow enzyme degradation (≈87% in 30 days)	Sustainable drug release (up to 42 days); Superior cell compatibility (>90% cell viability and proliferation 3 days); Antibacterial effect (>28 mm inhibition for *E. coli* and >26 mm inhibition for *S. aureus*)	[65]
Nerve guide conduit	Zein + sodium chloride	3D porous conduit with intraluminal microtube	Dipping-leaching technique	Inner diameter 1.5 mm; Wall thickness 500 µm; Porosity 80%; Young's modulus 91.81 ± 5.84 kPa; Permeability for glucose 100 ± 18%; Lysozyme 89 ± 11% and BSA 44 ± 10%; Maximum wall resistance 0.94 ± 0.16 N mm^{-1} for treatment at 120 °C	A faster in vivo biodegradation within only 4 months since implantation; Within 4 months, the sciatic nerve diameter was 545 ± 212 µm comparable with autograft result	[61]
Nerve guide conduit	Zein + polyphenol (tannic acid)	Nanofibrous mat	Electrospinning	Average nanofiber diameter ≈250 nm; Better mechanical properties at lower TA concentration; SCs showed good biocompatibility with 90/10 to 80/20 zein/TA blend	Antioxidant and antibacterial properties; Biodegradation rate could be increased significantly by regulating TA proportion	[120]
Wound dressing	Zein + TiO_2-SPODA	Cross-linked nanofibrous mat	Electrospinning	Average diameter 565 ± 70 nm; Tensile strength 2.71 ± 0.1 MPa; Elongation 17.50 ± 2.20%; Absorbency: Hydrophobic (144 ± 2° CA); Blood repellent (141 ± 1° CA); WVTR (2194 ± 143 mL m^{-2} day^{-1})	Antibacterial (44.5% and 44.89% growth impedance for *E. coli* and *S. aureus*, respectively) and adhesion free around wound; Good degradation resistance (96.51 ± 0.28% remaining after 10 days incubation in PBS at 35 °C)	[155]
Wound dressing	Zein + TEO	In situ electrospun fibrous membrane	Electrospinning	Good gas permeability (154 ± 20.9 m^2 s^{-1}); Absorbency: Super hydrophilic (0° CA); Direct deposit on wound site allows decent shape conformity and comfort	Antibacterial effect (showed growth inhibition areas around both *E. coli* and *S. aureus*); facilitates quick wound healing (within 11 days)	[59]

(*Continued*)

Table 5. (Continued).

Application area	Materials[a)]	Structure	Manufacturing technique	Output	Bioactivity	Ref.
Wound dressing	Zein	UV cross-linked electrospun nanofibrous membrane	Electrospinning	Mean fiber diameter 15.76 ± 4.80 µm; Tensile strength 3.520 ± 0.381 MPa; Elongation at break 486.90 ± 4.3%, WVTR 1500–2000 g m^{-2} day^{-1}; Porosity 67.9 ± 0.07%; Absorbency: Hydrophilic (64.3° CA)	The presence of thiol, amino, and hydroxyl amplified blood clotting response, 99% clotting within 4 min; 84% wound closer within 2 days; Nontoxicity (91% cell viability with human dermal fibroblast cells)	[126]
Wound dressing	Zein + CEO	In situ electrospun fibrous membrane	Electrospinning	Good gas permeability (168.2 ± 43.3 mm s^{-1}); Absorbency: Super hydrophilic (0° CA); Direct deposit on wound site allows decent shape conformity and comfort	Biocompatibility; Antibacterial effect (growth inhibition areas around both *E. coli* and *S. aureus*); Good wound healing performance (complete wound closure within 11 days); Minimum cytotoxicity (fibroblast cell activities > 90% after 24 h)	[123]
Wound dressing	Zein + graphene oxide (GO) and tetracycline hydrochloride	Composite nanofibers	Electrospinning	Diameter 191–137 nm for various GO wt%; tensile strength 10.32 ± 1.07 MPa for 1% GO; Young's modulus 4.56 ± 0.27 GPa for 1.5% GO; Absorbency: Hydrophilic (84.76 ± 1.58 to 64.26 ± 1.27° CA); WVTR 1713.84 ± 19.20 to 1394.97 ± 18.88 g m^{-2} day^{-1}	Drug loading efficiency and loading content 41.9 ± 1.1% and 65.3 ± 0.6%, respectively. Antibacterial effect (inhibition 26.66 ± 1.13 mm against *E. coli* and 29.31 ± 1.23 mm against *S. aureus*); Over 5 days cell culture maximum cell proliferation observed for Zein/GO (1 wt% content)	[156]
Controlled drug delivery	Zein + polyvinyl pyrrolidone (PVP)	Electrospun membrane for propranolol hydrochloride (PL) delivery	Electrospinning	Fiber diameter 3.0 ± 0.7 µm; Tensile strength 3.92 ± 0.13 MPa; Porosity 73.5 ± 0.6%; Adhesion assessment with mucosa tissue 22.1 ± 0.1 g mm	Maximum 96 ± 0.15% drug loading was achieved with 0.01 × 10^{-3} M PL. Maximum loading capacity was recorded 0.018 ± 0.001%. Assessment with mucosa tissue accounted for 22.1 ± 0.1 g mm adhesion and 2.88 ± 0.08 µg mL^{-1} PL permeability within 24 h; Cell viability 99.3 ± 9%	[157]
Controlled drug delivery	Zein + poly(caprolactone) (PCL) and titanium dioxide (TiO_2)	Erythromycin-PCL core-zein-TiO_2 shell nanofiber	Electrospinning	Average nanofiber diameter 625 nm; Drug encapsulation efficiency 94%	Slow drug release (72 h); Antibacterial effect (Inhibition zones for *S. aureus* (40 mm), *B. cereus* (45 mm), *E. coli* (34 mm), and *S. bacteria* (40 mm)); Sustained release up to 72 h (98.1%)	[158]
Controlled drug delivery	Zein + sodium hyaluronate	Dual drug (pitavastatin and tedizolid) loaded porous implant	Solvent-induced phase inversion method	Solidification time between 104.9 ± 4.9 and 104.9 ± 4.9 s based on zein concentration	Sustained drug release 28 days; Release profile with Q_{24h} 38.47 ± 0.74% and rate 14.29 ± 0.52 h^{-1}; Bone healing within 8 weeks	[159]
Controlled drug delivery	Zein + 58S BG	Kaempferol-loaded BG-based porous scaffold	Foam casting and surface coating	Compressive strength 3.06 ± 0.4 MPa; Pore size 200–500 µm	Faster biodegradation at SBF (17.3% after 56 days); Drug-loading capacity 0.06% and drug amount 0.108 mg; Sustainable drug release (48.2% after 3 days and 80% after 9 days); Good cell attachment with MG-63 cells.	[143]

(*Continued*)

Table 5. (Continued).

Application area	Materials[a)]	Structure	Manufacturing technique	Output	Bioactivity	Ref.
Controlled drug delivery	Zein + HAp	Doxorubicin hydrochloride (DOX)-loaded drug delivery NPs	Phase separation and biomimetic mineralization	Particle size 207.2 ± 7.23 nm; Mechanically stable; pH-controlled delivery; zeta potential −27.7 ± 2.45 mV	DOX release behavior, 91.8% at pH 6.86 (tumor environment) and 27.2% at pH 7.4 (normal blood); Reduced heart toxicity and targeting (18.58%) than sole DOX solution; improved cytotoxicity and cell viability by seven times	[160]
Bone tissue regeneration	Zein + HAp and sodium chloride	3D composite porous scaffolds	Salt-leaching	Porosity 61.1–70.6%; Ultimate strength 2.7 MPa; Compressive modulus 79.1 MPa; Average pore size 307 ± 76.1 µm	Relatively slower degradation than pure zein (40% after 30 days); Cell culture study up to 7 days showed constant growth ensuring biocompatibility, cell attachment and proliferation	[149]
Bone tissue regeneration	Zein + trimethylol-propane triglycidyl ether (TMPGE)	Cross-linked fibrous scaffold	Electrospinning	Fiber diameter 1.82 ± 0.42 to 2.73 ± 0.86 µm; Scaffold weight 2.775 ± 1.087 mg (after 1 day hydration)	Cell growth 50 000 (day 7); Cell viability and structural durability up to 30 days; Adequate cell attachment	[161]
Bone tissue regeneration	Zein + albumin, polycaprolactone, MoS_2 nanosheet	2D nanomaterials-incorporated nanofibrous scaffold	Electrospinning	Fiber diameter 0.37 ± 0.18 to 0.14 ± 0.08 µm; Conductivity 4.32 ± 0.03 to 6.25 ± 0.03 µS cm^{-1}; Maximum Young's modulus 17.24 MPa and tensile strength 3.14 MPa; Hydrophilicity (42.2° CA)	Highest degradation 8.01% (incubation for 3 weeks in PBS); Ca/P weight ratio deposition 1.42, suitable for bone tissue regeneration; Cell culture with MC3T3-E1 cell lines revealed enhanced cell viability, improved biocompatibility, cell proliferation, adhesion, etc.	[162]
Bone tissue regeneration	Zein + mannitol particles	Zein fiber reinforced or quenched porous scaffold	Electrospinning	For fiber reinforcement, fiber diameter 1.01 ± 0.25 µm; Porosity 50–80%; Pore size 200–400 µm; Tensile modulus 388.05 ± 35.32 MPa; Compressive modulus 84.36 ± 10.54 MPa; Bending modulus 118.30 ± 13.67 MPa; For quenching, porosity 57.78% ± 0.88%; Compressive strength 20.21 MPa; Tensile strength 8.65 MPa; Flexural strength 17.50 MPa.	For fiber reinforcement, cell viability and increased up to 9 days of incubation: For quenching, zein degradation and new bone formation 28 weeks	[163]
Bone tissue regeneration	Zein + chitosan, polyurethane, and multi-walled carbon nanotubes	Composite polysaccharide-protein-based fibrous scaffold	Electrospinning	Fiber diameter 193 to 356 nm; conductivity 179.83 ± 0.4 µs cm^{-1}; Tensile strength ≈7.05 MPa; Young's modulus ≈ 52.55 ± 2.9 MPa; Hydrophilic (37.85 ± 2.4° CA)	Good biodegradability (≈ 38.3 wt% loss in 16 weeks); Superior cell adhesion, proliferation and osteoinductive properties; Antibacterial inhibition 48.20, 66.81, 89.07, and 59.10% for *E. coli*, *S. aureus*, *M. luteus*, and *S. epidermidis*, respectively.	[164]

[a)] Abbreviation: SPODA = silicone quaternary ammonium salts; WVTR = water vapor transmission rate; CA = contact angle; PEO = polyethylene oxide; BSA = bovine serum albumin; SBF = simulated body fluid; PBS = phosphate-buffered saline.

can reduce the material's already impressive biocompatibility. As a result, more research should be done on the potential cytotoxicity of these hybrid scaffolds. Furthermore, the mechanisms behind how zein and zein-oriented materials' biodegradability is affected by their size, shape, and geometries, should be conclusively established. Nanofibers and nanoparticles, e.g., may have a higher rate of zein degradation in an enzymatic milieu because of the enormous open surface area.

Although zein scaffolds were initially intended to provide support for cells; they can now be filled with biological growth factors to facilitate cellular attachment and proliferation. In addition, trends indicate substantial growth in scaffold fabrication through the electrospinning process as opposed to the 3D-printing method. The remarkable electrospinnability of zein enables the generation of zein nanofibers and zein-based nanomaterials for tissue regeneration and other biomedical applications. One crucial aspect of the biological usage of zein compounds is the potential of hydrolysate peptides to lower blood pressure.

The future standpoint is focused on zein-based scaffolds for application in the biomedical field and a massive enhancement in their design with the assistance of 3D printing. In the foreseeable future, it is feasible that zein-based scaffolds will be utilized in the majority of therapeutic procedures. However, computational advancements will be required to create more exact and precise scaffolds that can effectively imitate the biological environment, allowing for optimum cellular proliferation and development. In addition to expanding the present handful of structural designs, future tendencies also intend to enhance the currently available fabrication techniques. Consequently, researchers need to utilize computational approaches to combine 3D-printing technologies for the design of novel scaffolds. Recently, the concept of using computational methods such as "computer-aided tissue engineering" has emerged to construct scaffolds while contemplating the scaffold's shape, morphology, structure, porosity, and load capacity to optimize the stress dissemination of the scaffold.

Optimizing the nanofibrous scaffold for medical applications and enhancing the seeding procedure of different biological cells to maintain the lifespan impacted by the scaffold's composition, are also additional obstacles to be addressed. In addition, it is crucial to ensure the continued existence of the biological cells following implantation into the patient's body. Improvements in the hydrophilicity of the notoriously hydrophobic zein are an area where more study is needed. Scientists will likely concentrate on developing chemical modification approaches to improve this characteristic. There is still a need for more investigation into the cytotoxicity and biodegradability of zein-based scaffolds, as well as chemical modifications to zein. In reality, the biodegradability and biocompatibility of zein, along with other intrinsic features such as porosity, pore diameter, flexibility, higher surface area, etc., connected with the structure of zein, enable a multitude of promising future uses for zein-based biomaterials.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

M.R.: Conceptualization, writing—original draft, review and editing, visualization. T.M.D.: Writing, editing, visualization. T.H.: Writing and editing. Y.B.T.: Conceptualization, writing—review and editing. T.L.: Writing—review and editing. S.H.: Conceptualization, supervision, writing—review and editing.

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Mustafijur Rahman is currently pursuing his Ph.D. research at the esteemed Center for Materials Innovation and Future Fashion (CMIFF), RMIT University in Australia. With an M.Sc. degree from the renowned University of Manchester in the United Kingdom, Mr. Rahman's academic journey has equipped him with a profound wealth of knowledge and expertise. Through his experience in academia and research, he has honed his research interest in diverse areas such as biomedical textiles, biomaterials, polymer composites, recycling, and novel dyes for biomedical applications.

Tanvir Mahady Dip is a postgraduate (M.Sc.) student in the Department of Materials at The University of Manchester (UoM), United Kingdom. He has also been working as Lecturer at Bangladesh University of Textiles (BUTEX). He completed his Bachelors in Textile Engineering at BUTEX. His research interests are focused on biomedical textiles, functional biomaterials and biopolymers, smart wearables, and nanogenerators.

Yen Bach Truong is a research team leader and principal research scientist at the Commonwealth Scientific and Industrial Research Organisation (CSIRO)'s Manufacturing business unit in Australia. She holds a Ph.D. in Chemical Engineering in fiber science from Monash University, Australia. She has been working in the development and fabrication of electrospun nanofibrous materials for a range of applications and has published over 65 peer-reviewed papers in this area. She chaired the Inaugural International Conference on Electrospinning (Electrospin 2010) in Melbourne, Australia, in 2010. She has been invited to give more than 20 oral presentations at international conferences, seminars, and workshops.

Shadi Houshyar is a senior lecturer at RMIT University in Australia. She obtained her Ph.D. from RMIT University before joining PolyNovo Biomaterials, where she specialized in researching biomaterials for human applications. Following this, she pursued a post-doctoral position at the Commonwealth Scientific and Industrial Research Organisation (CSIRO), focusing on the development of bio-conjugated polymers for drug delivery. In recognition of her achievements, she was awarded a Vice Chancellor's Research Fellowship in 2018. Her diverse research interests encompass biomaterials, flexible implants, medical textiles, and advanced manufacturing.