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Bioinspired nanofibers: advancing drug delivery for enhanced therapeutic applications

Amisha S. Raikar[1], Bhavana B. Bhat[2*], Sandesh N. Somnache[3]

[1]Department of Pharmaceutics-SSPM's VP College of Pharmacy, Madkhol, Sawantwadi, Maharashtra, India.
[2]Department of Pharmaceutical Regulatory Affairs and Management, MCOPS, MAHE, Manipal, India.
[3]Department of Pharmaceutics PES Rajaram and Tarabai Bandekar College of Pharmacy, Ponda, Goa.

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ABSTRACT

Nanomedicine is advancing with bioinspired nanofiber-based drug delivery systems (DDSs). This field explores the use of collagen and spider silk-like nanofibers to transport therapeutic agents to anatomical locations in the system. Nanofibers have a larger surface-area-to-volume ratio, mechanical strength, and ECM-mimicking properties. They are made with organic and artificial polymers, but natural polymers are better for biocompatibility and ECM resemblance. Synthetic polymers are versatile and can be customized to meet specific needs. Various techniques such as electrospinning, self-assembly, and templating are used to make bioinspired nanofibers. Electrospinning creates versatile and robust nanofibers that can be functionalized to boost therapeutic benefits. Control/extended DDSs using nanofibers are attainable by adjusting their physical and chemical properties (e.g., diameter, surface chemistry, and porosity). The nanofiber DDSs inspired by biology have shown promising use in wound healing, cancer therapy, and regenerative medicine. Creating these systems requires achieving biocompatibility, reducing toxicity, maintaining stability, long drug release, scalability, and cost-effectiveness.

INTRODUCTION

In recent decades, therapeutic delivery systems have been extensively researched and analyzed with the aim of enhancing the effectiveness and safety of therapeutic substances for diverse biomedical use. The implementation of nanostructured systems has been proposed as an effective strategy to address the limitations associated with drug delivery, namely inadequate drug dispersion, insufficient penetration across biological barriers, and unintended off-target effects [1–3]. The incorporation of bioinspired nanomaterials into the surfaces of drug carriers presents a promising approach for modulating the drug carrier-biological systems interaction [4].

At the nanoscale level, diverse biological events take place, consequently rendering engineered nanomaterials as valuable tools capable of regulating bio-interfaces and bioprocesses to enhance therapeutic efficacy. The utilization of nanoparticle drug carriers has been shown to enhance the stability and prolong the serum half-lives of drugs, thereby ensuring sustained therapeutic drug concentrations. Nanostructured thin films, patches, and devices have emerged as wearable and implantable materials, wherein the bio interfaces are engineered to cater to the reduction of the foreign body response and inflammation, while simultaneously facilitating sustained drug release.

The extracellular membrane surrounds cells and holds significant importance in regenerative medicine and drug delivery, providing a scaffold for cell growth and regulating drug activity. Integrins bind to ligands and are crucial for cell-extracellular matrix (ECM) interactions, affecting both embryonic development and mature tissue function. ECM molecules bind to cell surface receptors, including integrins. Drug delivery system (DDS) can use ECM molecules as ligands for drug targeting.

*Corresponding Author
Bhavana B. Bhat, Department of Pharmaceutical Regulatory Affairs and Management, MCOPS, MAHE, Manipal, India.
E-mail: bhavana.bhat@manipal.edu

Types of ECM molecules

The ECM consists of collagen, elastin, and glycoproteins such as laminin and fibronectin as shown in Figure 1. Collagen and fibronectin play key roles in tissue strength and cellular processes. Fibronectin governs a myriad of cellular processes, encompassing adhesion, movement, proliferation, and recuperation. This structure is made of connected homogenous parts with disulfide bridges. Subunit III in Figure 1 has 100 amino acids organized in β sheets, with domains for binding integrin and heparin [5]. Laminin improves attachment, movement, neurology, and blood vessel formation. It is in the basement membrane with type IV collagen, 19 forms are created by three subunits (α, β, and γ) of glycoproteins. Each isoform has unique roles related to cell differentiation, morphology, motion, and tissue viability. Isoforms attach to integrin receptors to influence cells and interact with other ECM proteins [6]. The ECM forms the structural framework with polysaccharides such as chondroitin sulfate, heparin sulfate, dermatan sulfate, keratin sulfate, and hyaluronic acid. Cell interaction is indirect through intermediary proteins. Heparin consists of GlcNAc and GlcA segments in a polysaccharide configuration, produced by connecting to cell proteins sodium deoxycholate and gel permeation chromatography. Syndecans and glypicans absorb ligands, while heparin interacts with proteins to enhance biological activities and receptor binding. Heparin and proteins interact to create useful DDSs. Heparin hydrogels often deliver growth factors for tissue regeneration. Incomplete cellular receptors such as CD44 cling to chondroitin sulfate and hyaluronic acid, which is formed by repetitive segments of glucoronate combined with β-1.3 (GalNAc) and D-glucuronic acid bonded to β-1,3. Chondroitin sulfate's role differs based on sulfation and affects signal regulation, cell development, and central nervous system function. Hyaluronic acid has no sulfation and has a unique pattern of repeat units. Hyaluronic acid boosts precise and prolonged drug delivery by contributing to tissue structure, cellular function, and regeneration [7]. It is widely used as a pharmaceutical transporter due to its strong attraction to cellular receptors. Gene therapy in the liver, kidneys, lymphatic vessels, and tumors. Various types of ECM molecules along with their functions are listed in Table 1.

BIOINSPIRED NANOFIBER-BASED DDSS

The uses of bioinspired nanofiber-based therapeutic delivery systems have appeared as a highly promising approach in the field of nanomedicine. The aforementioned systems employ nanofibers, which are modeled after fibers present in organisms that are alive, such as collagen or spider silk, to

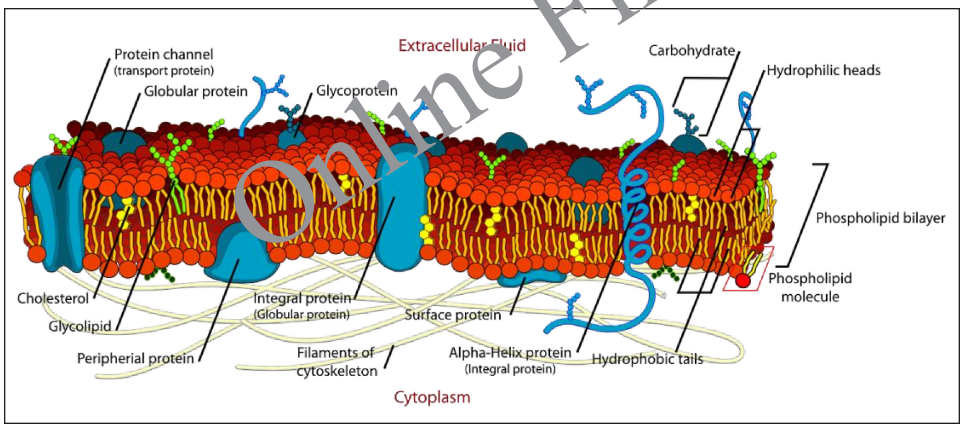

Figure 1. Systematic representation of extracellular membrane.

Table 1. Different types of ECM molecules.

ECM molecule	Role in drug delivery	Additional information	Ref.
Hyaluronic acid (HA)	Enhances drug bioavailability and retention within tissues by promoting slow drug release.	Hyaluronic acid (HA) is a significant constituent of the ECM in numerous tissues and has been greatly employed as a biomolecule for drug administration due to its biocompatibility and capacity to generate hydrogels.	[7]
Collagen	Provides a structural scaffold for drug delivery vehicles, enhances tissue targeting.	Collagen represents the predominant protein in the ECM and is used in regenerative medicine and therapeutic applications due to its biodegradability and biocompatibility.	[8]
Fibronectin	Enhances cell adhesion and promotes drug delivery to specific cell types.	Fibronectin is a glycopolypeptide present in the ECM and assumes a vital function in cellular adhesion, migration, and differentiation.	[9]
Laminin	Enhances cell adhesion and promotes tissue regeneration.	Laminin is a glycoprotein that forms one of the major components of the basal lamella membrane in many tissues and is involved in cell adherence, proliferation, and regenerative medicine.	[9]
Elastin	Provides elasticity to tissues and enhances drug delivery to elastic tissues.	Elastin renders elasticity to many tissues and is used as a transport system for pharmaceutical delivery to elastic tissues such as blood vessels.	[10]

convey medicinal substances to designated sites within the body [11]. Nanofibers exhibit distinct characteristics, rendering them potentially advantageous for drug delivery purposes, such as their expanded surface area and proportionality factor, as well as their capacity to imitate the ECM of tissues. Diverse methodologies including electrospinning, self-assembly, and templating can effectively facilitate the manufacturing of bioinspired nanofibers. The controlled drug administration through nanofibers may be achieved through the modulation of their physical and chemical characteristics, including but not limited to, fiber diameter, surface chemistry, and porosity [12]. Nanofibers possess the capability of being subjected to functionalization with targeting moieties, including antibodies or proteins, to selectively bind to selected cells or tissues of interest [13]. The utilization of bioinspired nanofiber-based DDSs has exhibited remarkable potential in sundry domains, including but not limited to tissue regeneration, cancer therapy, and regenerative medicine. Notably, the production of biocompatible nanofibers can be achieved through deliberate material selection and meticulous optimization of the production process. The careful deliberation of the physiochemical properties of the nanofibers and the selection of the drug and its accompanying release mechanism are imperative for the successful implementation of the drug-delivery strategy. Scalability and commercial viability are crucial factors to contemplate in the advancement of bioinspired nanofiber-mediated drug delivery mechanisms. For the purpose of facilitating sizable manufacturing of these systems, it is imperative that the production process exhibit scalability and cost-effectiveness. The utilization of these

Table 2. Naturally obtained bioinspired nanofibers.

Natural bioinspired nanofiber	Properties	Applications	Source	Fabrication methods	Ref.
Collagen nanofibers	Biocompatible, high surface area, high porosity, excellent mechanical strength	Wound healing, tissue regeneration, drug delivery	Animal tissues (skin, bone, cartilage)	Electrospinning, self-assembly	[14]
Elastin nanofibers	Biocompatible, high tensile strength, flexibility	Cardiovascular, skin-related drug delivery	Tissues that require elasticity (skin, lungs, blood vessels)	Electrospinning, self-assembly	[15]
Fibrin nanofibers	Biodegradable, biocompatible, helps in cell proliferation and tissue repair support	Regenerative medicines, pharmaceutical delivery	Blood plasma	Electrospinning, co-electrospinning	[16]
Chitosan nanofibers	Biocompatible, biodegradable, antimicrobial, anti-inflammatory	Medication delivery, cellular therapy	Chitin from crustacean shells	Electrospinning, self-assembly, electrostatic spinning	[17]
Hyaluronic acid nanofibers	Biocompatible, ability to promote cell proliferation and migration, ability to retain water	Wound healing, tissue engineering, drug delivery	ECM of connective tissues	Electrospinning, self-assembly	[18]
Silk fibroin nanofibers	Biocompatible, biodegradable, excellent mechanical properties	Tissue engineering, drug delivery	Silk cocoons	Electrospinning, self-assembly	[19]
Keratin nanofibers	Biocompatible, biodegradable, ability to promote cell growth and differentiation	Tissue engineering, drug delivery	Hair, feathers, nails, horns, hooves	Electrospinning, self-assembly	[20]
Gelatin nanofibers	Biocompatible, biodegradable, ability to foster cell adherence and growth	Tissue engineering, drug delivery	Collagen from animal tissues	Electrospinning, self-assembly	[21]
Cellulose nanofibers	Biocompatible, biodegradable, excellent mechanical properties	Tissue engineering, drug delivery	Plant cell walls	Electrospinning, self-assembly	[22]
Alginate nanofibers	Biocompatible, biodegradable, ability to form hydrogels, ability to interact with divalent cations	Wound healing, tissue engineering, drug delivery	Seaweed	Electrospinning, self-assembly	[23]
Spider silk nanofibers	Biocompatible, high tensile strength, flexibility, high surface area, porous structure	Drug delivery	Silk produced by spiders	Electrospinning, self-assembly	[24]
Marine-derived nanofibers	Biocompatible	Drug delivery	Marine organisms such as diatoms	Electrospinning, self-assembly	[25]

systems in human subjects necessitates regulatory sanction, thereby introducing an augmented degree of intricacy to their development.

Natural polymers used in nanofiber fabrication

Bioinspired nanofiber can be fabricated using both organic and artificial polymers. Organic polymers are often preferred due to their non-toxicity to biological systems and ability to reproduce ECM characteristics. Table 2 represents different types of natural nanofibers that mimic ECM.

Synthetic polymers used in nanofiber fabrication

The versatility and capacity for the customization of synthetic polymers render them a highly prevalent option for the manufacturing of bioinspired nanofibers. A range of synthetic polymers appears to be commonly utilized as constituents in the fabrication of nanofibers. Table 3 represents different types of synthetic nanofibers that mimic ECM.

LITERATURE SURVEY

The utilization of nanofibers that are bioinspired has achieved greater attention recently as a result of their exceptional properties and prospective applications across diverse fields. Over time, many investigations have been conducted on bioinspired nanofibers, intricately examining their attributes, fabrication techniques, and usage. This literature review endeavors to furnish a comprehensive inventory of current studies pertaining to bioinspired nanofibers. Specifically, it seeks to elucidate their synthesis methodologies, properties, and applications, as well as to accentuate their potential within various fields.

In research conducted in 2022, a nanofibrous magnet was created to load and deliver bovine serum albumin (BSA) using Iron (III) oxide magnetic nanoparticles coated with polyvinyl alcohol (PVA) and collagen which led to faster BSA release within a period of 3 hours [42]. Collagen from Rana chensinensis skin in China was used as a drug carrier in another study in two volatile compound mixtures systems–blended nanofibers and core-shell nanofibers by blending random copolymer star copolymers (RCSC) and poly-L-Lactic acid (PLLA) in HFIP [43]. Both scaffolds sustained control release for 80 hours, but coaxial RCSC/PLLA were better due to superior mechanical properties and sustained effect. Poly(ε-caprolactone) (PCL)/Col nanofibers loaded with artesunate were prepared to study ART's anti-crystallization and release behaviors [44]. The sustained drug administration up to 48 hours follows the Fickian mechanism analyzed by the Korsmeyer-Peppas equation. The study conducted in 2019 hemostatic patches with a tranexamic acid (TXA) and PVA: chitosan nanofiber (1:1) showed CT of 167 ± 6 s, while 3:2 showed CT of 210 ± 10 s) [45]. Drug release via Fickian diffusion in TXA-chitosan nanofibers can produce hemostatic membranes for clinical and battlefield settings. In another study by Gouda M in 2022 ST-CH nanofibers were made by electrospinning with CH/PVP and characterized by scanning electron microscopy (SEM) containing chlorinated N-amido-cholestano-aziridine and acetylated N-amido-cholestano-aziridine showed strong efficacy against Staphylococcus aureus and E. Transport exponent estimated that solvent migration and polymer chain relaxation were involved in ST-CH nanofibers, which are promising DDSs [46].

Evaluative research where hybridizing hyaluronic acid blends with cumulative drug release (CDF) nanofiber mats were tested against bacteria and CDF/Cur against S. aureus DHFR enzyme receptor. Cur and CDF had similar anti-bacterial properties; their nanofiber mats released 25% and 37% of Cur and CDF *in vitro*, respectively [47]. CDF remains both antibacterial and effective against cancer, making it a promising choice for treatment. Dadras Chomachayi in his investigation prepared nanofiber comprising of silk fibroin (SF) and gelatin (GT) was further analyzed and loaded with triethyl orthoacetate (TEO) and dichloromethane (DCMH) as antibacterials [48]. TEO was released in 3 hours, while DCMH had a 48-hours sustained release. In 2021, keratin/poly (butylene succinate) blend. Rhodamine B-doped with keratin/poly (butylene succinate) electrospun mats were examined [49]. Keratin electrophoresis proved the solvent's inability to degrade protein whereas else Keratin/phosphate-buffered saline blends depict higher polymer orientation with shear stress. RhB release increased with higher keratin content and drug diffusion combined. Nano scaffolds with drug-loaded Poly (lactic-co-glycolic acid) (PLGA) and PLGA/GT were tested for fasting blood glucose (FBF) release. More GT led to increased FBF release and aligned scaffolds released FBF slower than randomly oriented ones. Crosslinking reduces burst release of FBF in PLGA/GT nanofibrous scaffold. pH of the buffer solution can alter the polymer state and affect the FBF release rate [50]. Zeynep Aytac and his co-researchers combined Sprague-Dawley female rats (SFS) with HPβCD in hydroxypropyl cellulose (HPC) nanofibers by electrospinning, and the resulting SFS/HPβCD-IC complex was analyzed using differential scanning calorimetry (DSC) and Job's plot for formation and stoichiometry [51]. More SFS released from HPC/SFS/HPβCD-IC-NF than HPC/SFS-NF due to increased solubility. PCL-HPC/SFS/HPβCD-IC-NF had slower SFS release compared to sandwiches of HPC/SFS/HPβCD-IC-NF. Another examination was carried out where Alginates were added to wound dressing PVA with Glutaraldehyde which reinforce nanofibers during electrospinning [52]. Dexpanthenol was added to polyvinyl alcohol and sodium alginate to speed up healing. Chitosan at 1% in the shell improved drug release. Dexpanthenol-added PVA/SA/Triton-Chitosan nanofibers improved fibroblast morphology and attachment, making them ideal for tissue engineering. BAP2 fiber reduces inflammation and promotes angiogenesis, proven effective in pharmacokinetic tests. To test the healing properties Huang X and his co-fellows proved that this biomaterial can improve diabetic wound healing by mimicking ECM and healing full-thickness epidermis and dermis wounds in murine models of diabetes [53].

In 2013, researchers showed the mouse cells on TCH/HNTs/PLGA nanofibers were cytocompatible and released antimicrobial TCH for 42 days. PCL/f-CNOs nanofibers were created via Forcespinning® by Narsimha Mamidi and fellow researchers in 2020 [54]. PCL/f-CNOs released doxorubicin in response to pH, reaching 87% at pH 6.5 and 99% at pH 5.0 in 15 days [55]. SA/Polyethylene oxide (PEO) nanofibers with VC were made in 2019 using co-electrospinning and coaxial electrospinning and the drug release was evaluated which showed

Table 3. Synthetically obtained bioinspired nanofibers.

Synthetic fibres	Properties	Application	Fabrication method	Ref.
PLGA	Degradable, Safe for biological use, tunable mechanical properties, control over drug release kinetics	Cancer therapy, wound healing, tissue engineering	Electrospinning	[26]
PCL	Biodegradable, biocompatible, tunable mechanical properties, slow degradation rate	Wound healing, tissue engineering, drug delivery	Electrospinning, melt blowing	[27]
PVA	Biodegradable, water-soluble, tunable mechanical properties, biocompatible	Wound healing, tissue engineering, drug delivery	Electrospinning	[28]
PEO	Biodegradable, water-soluble, high flexibility, low toxicity	Drug delivery	Electrospinning	[29]
Polyethylene terephthalate (PET)	Biocompatible, high mechanical strength, low toxicity	Tissue engineering, drug delivery	Electrospinning, melt blowing	[30]
Polyaniline (PANI)	Conductive, biocompatible, tunable mechanical properties	Drug delivery, tissue engineering	Electrospinning	[31]
Polycaprolactam (Nylon 6)	Biodegradable, biocompatible, high mechanical strength	Tissue engineering, drug delivery	Electrospinning	[32]
Polyurethane (PU)	Biodegradable, biocompatible, tunable mechanical properties	Tissue engineering, drug delivery	Electrospinning	[33]
Polyacrylonitrile (PAN)	Biocompatible, high mechanical strength, tunable porosity	Tissue engineering, drug delivery	Electrospinning	[34]
Poly(ethylene glycol) (PEG)	Biocompatible, water-soluble, low toxicity	Drug delivery	Electrospinning	[35]
PTMC	Biodegradable, biocompatible, tunable mechanical properties, slow degradation rate, good thermal stability	Tissue engineering, drug delivery	Electrospinning	[36]
PGS	Biodegradable, biocompatible, elastomeric, tunable mechanical properties	Tissue engineering, drug delivery	Electrospinning	[37]
Poly(aspartic acid) (PAA)	Biodegradable, biocompatible, hydrophilic, tunable mechanical properties	Drug delivery, tissue engineering	Electrospinning	[38]
Poly(N-vinylcaprolactam) (PNVCL)	Temperature-responsive, biocompatible, tunable mechanical properties	Drug delivery	Electrospinning	[39]
Poly(2-oxazoline) (POx)	Biocompatible, hydrophilic, tunable mechanical properties, ability to self-assemble into micelles	Drug delivery	Electrospinning	[40]
Poly(lactide)-poly(ethylene oxide) (PLA-PEO)	Biodegradable, biocompatible, tunable mechanical properties, controlled drug release	Cancer therapy, wound healing, tissue engineering	Electrospinning	[41]

a controlled release of the drug [54], [56]. In another research analysis, PET nanostructured membranes were electrospuned and silver nanoparticles were added for antimicrobial purposes. Silver fibers have potential as an antimicrobial with lower toxicity, reduced inflammation, and better antibiofilm activity [57]. In 2021, CH/PANI nanofibers are made by polymerizing aniline with CH, producing a suitable drug encapsulation network. Ketoprofen was added to the hybrid and subsequently tested for release in three different pH buffers resembling oral administration (2, 6.7, and 7.4) [58]. pH affected drug release rate; various models studied kinetics. Veronika Pavliňáková and associate researchers in 2018 made a nanofibrous elastic material from PCL, Gel, and HNTs using green chemistry principles which showed improved mechanical properties w/0.5 wt% and Safer halloysite nanotubes nanofibers for drugs [59]. PU/HPC nanofibers with donepezil hydrochloride were made in 2017 for transdermal drug delivery and characterized using SEM, DSC, and Pascal mercury porosimetry [60]. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay revealed skin tolerance to the PU/HPC nanofiber mat with no irritation. The work of Zhang X demonstrated Dexamethasone loaded into poly (lactic acid) fibers and integrated into Poly(trimethylene carbonate) (PTMC) resin to produce hybrid films [61]. These hybrids have superior mechanical and UV protection properties compared to PTMC-only films. A scaffold of PCL, Poly(glycerol sebacate) (PGS), Hydroxyapatite nanoparticles, and simvastatin was created in 2020 to mimic bone ECM and enhance bone cell regeneration [62]. SIM had sustained release via diffusion. *In vitro* tests showed enhanced cell proliferation and adhesion with PCL-PGS-HA for improved regeneration.

It can be seen that Nanofiber-based DDSs have been explored in recent years for their unconventional properties, including elevated surface/volume proportion, tunable pore size, and ability to control drug release. Various types of both organic and synthetic polymers are utilized to produce nanofibers for therapeutics, and fibers are then loaded with different types of drugs, including antimicrobial agents, chemotherapeutic drugs, and tissue regenerating agents. The drug release mechanism has been analyzed using mathematical models, and the diffusion rate has been shown to be affected by a variety of factors, such as polymer type, drug loading, and nanofiber morphology. These studies present revelations into the development of nanofiber used for pharmaceutical delivery and their probable use in medicine.

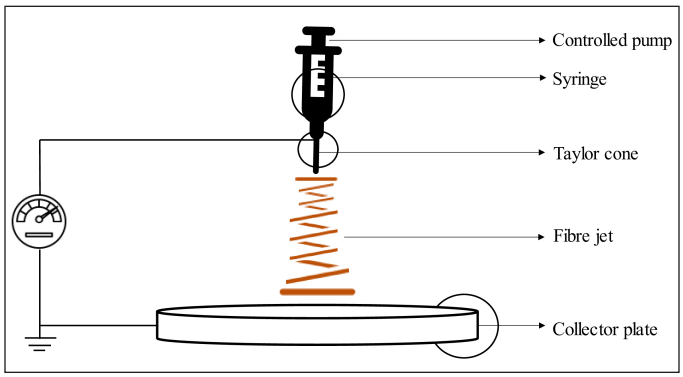

Figure 2. Nanofiber production through electrospinning.

FABRICATION METHODS FOR BIOINSPIRED NANOFIBER

To accurately replicate the structural and functional properties of the ECM, the process of producing nanofibers must be appropriately adapted. The utilization of fabrication techniques that draw inspiration from biological processes has gained noteworthy popularity for the purpose of enhancing therapeutic delivery based on nanofibers. The employment of these techniques has enabled the production of nanofibers possessing regulated morphology, mechanical characteristics, and surface composition, all of which are pivotal in facilitating the effective administration of therapeutic agents.

Electrospinning

This is a widely used technique that involves the application of an electrostatic field to a polymer dispersion or melt to produce a charged jet that is collected on a fixed target depicted in Figure 2.

The resulting fibers exhibit diameters that span from tens of nanoscale to micrometer scale, and their characteristics can be customized for precise drug delivery purposes through meticulous regulation of process factors [63]. Electrospinning is a highly versatile method that offers precise control over fiber diameter, orientation, and surface morphology. It is compatible with an extensive variety of polymers, enabling the creation of fibers with diverse compositions and drug-loading capacities. This technique involves the stretching and formation of fibers using an electrified droplet [64]. The essential equipment comprises a high-voltage electrical source, a capillary tube fitted with a compact pipette or needle, and a metallic collecting screen. One electrode is positioned inside the polymer solution, while a second electrode is connected to the collector. At the tip of the capillary tube, an electric field is employed, which retains the polymer solution in position as a result of surface tension forces. This electric potential elicits a charge on the liquid. As the electric field strength increases, the previously curved fluid surface at the tip of the capillary stretches, eventually forming a cone-like structure called the Taylor cone. Once the field reaches a certain threshold, a threshold is reached where the repelling electrostatic force becomes more influential than the surface tension force in the system. Consequently, a charged fluid jet is forcefully ejected from the tip of the Taylor cone as a direct result of this phenomenon. This phenomenon has noteworthy implications for a wide range of practical applications and warrants further investigation from a scientific standpoint. The polymer solution jet, subsequent to being discharged, exhibits instability which leads to extention and consequent decrease in jet thickness [65]. This phenomenon allows the jet to attain considerable length and diminutive diameter. The polymeric fibers become charged due to the effects of high electric potential and subsequently solidify through the process of solvent evaporation. Upon completion of this process, a collection of randomly oriented nanofibers is obtained on the surface of a designated collector [66]. The generation of highly aligned nanofibers can be facilitated by

Table 4. Different types of self-assembly techniques used in nanofabrication.

Technique	Description	Potential applications
Self-assembly of peptides	Peptides can self-assembled into nanofibers with a variety of morphologies, such as helical, sheet-like, and nanotube structures. Such structures have the potential to serve as scaffolds for regenerative medicine or as carriers for pharmaceutical agents [68].	Regenerative medicine, pharmaceutical delivery, biosensors, nanoelectronics.
Self-assembly of proteins	Proteins can also self-assemble into nanofibers, such as amyloid fibrils, which have been implicated in several neurodegenerative diseases [69].	Disease diagnosis, drug delivery, tissue engineering.
Template-assisted self-assembly	Uses a template to guide the self-assembly of nanofibers. For instance, scientists have employed DNA templates to direct the self-assembly process of gold nanowires [70].	Nanoelectronics, nanophononics, sensors.
Co-assembly of polymers and peptides/proteins	Polymers can be co-assembled with peptides or proteins to create hybrid nanofibers with unique properties [71].	Tissue engineering, drug delivery, biosensors.
Layer-by-layer assembly	Alternates layers of opposite charged polymers to create multi-layered nanofibers [72].	Drug delivery, tissue engineering, biosensors.

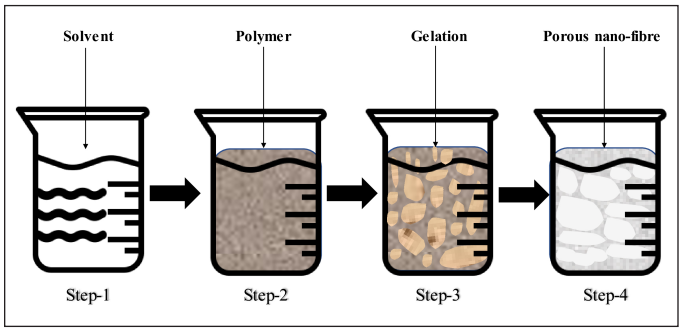

Figure 3. Steps involved in thermal induced phase separation.

employing specific collection methods, including the use of a rotating drum, metal frame, or a system with two parallel plates. To maintain consistency in nanofiber diameter and morphology, it is essential to control several parameters, such as the jet stream flow and the concentration of the polymer solution. The resulting electrospun nanofiber network exhibits a remarkable similarity to the ECM with a high level of accuracy.

Self-assembly

This approach involves the self-assembly of molecules or polymers into organized structures through non-covalent interactions. Self-assembling polypeptides, for example, can form nanofibers via intermolecular hydrogen bonding and van der Waals interactions. These fibers can be functionalized with active pharmaceutical ingredient or other excipients for drug delivery applications. Self-assembly can produce fibers with high order and regulated surface properties [67]. It is also a straightforward and adaptable technique that finds application with a diverse array of materials, encompassing natural peptides and proteins. The fiber morphology and drug release properties can be affected by the specific self-assembling system used as shown in Table 4, and the process can be challenging to scale up for industrial production.

Thermal induced phase separation

Thermal-induced phase separation is a process that triggers the segregation of a homogeneous polymeric dispersion into multiple phases by making thermodynamic changes, thereby generating a multi-phase system. This method involves several sequential steps, as can be seen in Figure 3, including polymer dissolution, phase separation between liquid-liquid or liquid-solid phases, polymer gelation, solvent extraction utilizing water, and ultimately freeze-drying under vacuum conditions [73].

The initial step involving the homogenous polymer solution is characterized by thermodynamic instability, resulting in a tendency for segregation into separate phases comprised of polymer-rich and polymer-lean components, provided the appropriate temperature conditions are met. Upon solvent evaporation, the polymeric phase ultimately hardens to yield the matrix, while the polymeric phase depleted in content progresses into the formation of pores [73]. Thereon, two forms of phase separation, contingent on the intended configuration, may be conducted on the polymeric solution. The process of liquid-liquid separation is commonly employed to generate dual-phase architectures, whereas the technique of precipitation is typically employed to create crystalline structures. Recent research has demonstrated that the process of gelation is dependent on various factors, including temperature, polymer concentration, and solvent characteristics. The temperature plays a critical role in shaping the architecture of the fiber network. Lower gelation temperatures promote the growth of nanofiber network architectures, whereas higher gelation temperatures promote the development of platelet-like structures. The properties of the fibers are interconnected with the concentration of the polymer, as higher polymer concentrations are linked to reduced porosity and enhanced mechanical characteristics, such as increased tensile strength [74]. After the gelation process, the resulting gel is soaked in distilled water to enable solvent exchange. The subsequent step entails the separation of the gel from the aqueous solution, followed by subjecting it to the process of freezing and subsequent lyophilization. Subsequent to its preparation, the substance is conserved within a desiccator until subjected to characterization.

Template synthesis

The template synthesis approach employs a nano sieve membrane scaffold, characterized by the presence of uniform cylindrical pores, to generate fibrils (i.e., solid nanofibers) and tubules (i.e., hollow nanofibers) as depicted in Figure 4. The proposed technique has the potential to generate fibrous

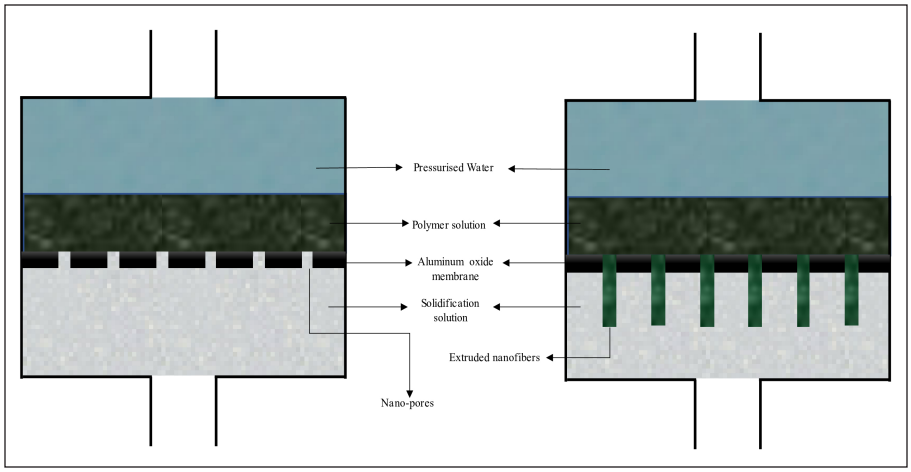

Figure 4. Template synthesis approach for synthesis of nanofibers.

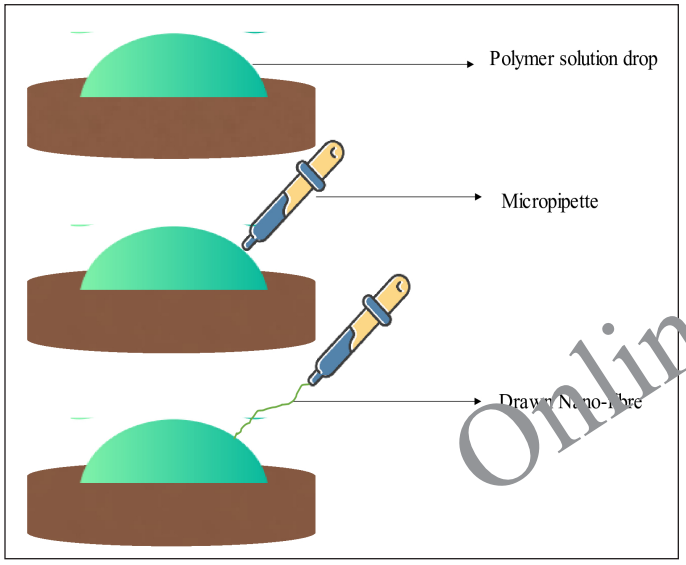

Figure 5. Drawing process for nano-fibre synthesis.

and tubular structures of various materials, such as metals, semiconductors, and electrically conductive polymers.

The homogeneous pores in the structure facilitate the regulation of fiber size, thereby enabling the manufacturing of nanofibers with exceptionally minute dimensions using this method. One limitation of this approach is its incapacity to produce singular nanofibers consecutively [75].

Drawing

The drawing technique enables the production of elongated nanofibers individually, one strand at a time as shown in Figure 5. During the pulling process, the solubilized fibrous material undergoes solidification, transforming into a solidified fiber. For melt spinning, a cooling step is required, while for dry spinning, solvent evaporation is necessary. Besides this, a limitation of this method is that only viscoelastic materials capable of enduring significant deformity while maintaining adequate binding to withstand the strains generated during elongation can be transformed into nanofibers using this technique [76].

The initial step in the process of polymer preparation involves the generation of a solution or a melt of the polymer, which is capable of being drawn into nano-sized fibers. The polymer ought to possess commendable mechanical characteristics while having the ability to undergo dissolution or melting, allowing it to form a solution. The precise method of solution preparation for a given polymer is contingent upon the specific variety employed and may entail either complete dissolution of the polymer in a solvent or controlled melting of the polymer.

The drawing setup involves the loading of a polymer mix or melt into a syringe or spinneret, which is subsequently attached to a motorized stage. The stage serves the purpose of imposing a regulated mechanical stimulus onto the polymer solution or melt while it is being extruded from either a syringe or spinneret. The spinneret may take the form of a needle or capillary tube with a fine tip, serving to regulate the diameter of nanofibers being manufactured. The act of drawing in the production of polymers involves the controlled mechanical force applied to extract the polymer dispersion or melt from either the syringe or spinneret. Various determinants, such as the drawing rate, ambient temperature, and humidity levels, can exert influence over the nanofibers and properties of the resulting nanofibers [77]. The application of either uniaxial or biaxial stretching is determined by the desired orientation of the fibers. Subsequent to the fabrication process, the resultant nanofibers are gathered onto a substrate or collector, thereby rendering them liable for further processing that serves to enhance their mechanical and electrical characteristics. The application of annealing has the potential to induce fiber alignment and augment their level of crystallinity, while electrospinning may prove viable in generating fiber mats with a distinctive sense of orientation [78].

Upon examination of the aforementioned techniques, it becomes apparent that each possesses distinctive characteristics that may be leveraged to purposely generate nanofibers

Table 5. Summary of different techniques with distinct advantages.

Technique	Advantages	Types of nanofibers
Electrospinning	High production rate, versatile, easy to scale up	Polymeric, ceramic, metallic
Self-assembly	Simple and low-cost, high control over fiber alignment and morphology	Peptide, protein, DNA, block copolymers
Thermal induced phase separation	Good mechanical properties, high porosity	Polymeric, ceramic
Template synthesis	High control over fiber diameter and morphology, customizable	Metal oxide, carbon nanotubes
Drawing	High aspect ratio, uniform diameter, good mechanical properties	Polymeric, metallic, ceramic

exhibiting desirable properties. Table 5 presented below offers a summary of the techniques, distinguished by their distinct advantages.

Applications of bioinspired nanofiber in DDSs

With their distinctive properties and adaptable applications, bioinspired nanofibers in pharmaceutical deliveries have the capacity to bring about a paradigm shift in the field of drug delivery and regenerative medicine. The particular role of these systems in specific applications is contingent upon the specific characteristics of the nanofibers themselves and the drugs being transported. For example, in cancer therapy, nanofiber can be designed to selectively deliver therapeutic agents to cancer cells by incorporating targeting moieties such as antibodies or peptides into the nanofibers [79]. Nanofiber-based dressings designed for regenerative medicine purposes can be designed to facilitate the creation of a moist environment at the site of injury and mitigate exposure to infections. This can be achieved by incorporating antimicrobial agents directly into the nanofibers of the dressings [80]. In tissue regeneration, nanofiber-based scaffolds can be designed to imitate the ECM and promote the proliferation of stem cells by incorporating growth factors or other bioactive molecules into the nanofibers [81].

The following section provides an overview of the different applications of nanofibers in therapeutic delivery and tissue engineering and a discussion of the role of nanofiber-based therapeutic systems in specific applications.

Cancer therapy

Nanofiber-based pharmaceutical delivery systems have exhibited significant potential in cancer treatment by means of their capacity to selectively administer drugs to cancer cells, while reducing the harm to healthy cells. The administration of nanofibers embedded with an anticancer agent offers the advantage of prolonged and localized drug release within specific targeted areas. This is due to their unique ability to be directly implanted within solid tumor cells, enabling them to serve therapeutic purposes. Within the context of this application, the utilization of nanoparticles may induce the accumulation of colloidal polymer carriers in the liver and spleen during systemic circulation, culminating in a reduction of the overall therapeutic efficacy. Mehnath et al. introduced a responsive polymeric nanofibrous patch for localized drug release to address the limitations associated with injection methods and reduce toxicity to healthy tissues in breast cancer treatment. The initial strategy involved encapsulating paclitaxel within micelles formed by linking chitosan acid (CA) with poly (bis (carboxyphenoxy) phosphazene). These micelles were additionally coated with a shell comprised of psyllium husk mucilage. The CA ligand, recognized for its strong attraction to the farnesoid X receptor, played a critical role in enhancing the uptake of the micelles by cancer cells. In an ex vivo study on skin permeation, it was observed that the formulation displayed increased penetration and retention in the skin. By positioning the drug delivery system adjacent to the tumor site, the medications could be concentrated on cancer cells, resulting in improved therapeutic effectiveness and reduced harm to other organs. In an alternative investigation, Li et al. fabricated a device composed of nanogel-in-microfiber architecture, featuring a temperature-responsive mechanism for drug release. The device comprises polymer fibers with a core/shell structure, wherein the drug is enclosed within a PEO core, while the shell contains temperature-responsive nanogels. The nanogels exhibit varying permeability in response to temperature changes, enabling precise control over drug release. *In vitro* experiments demonstrated efficient suppression of breast cancer cells at elevated temperatures, while preserving cell viability at lower temperatures. This approach shows potential for targeted treatment of tumors with minimized adverse effects on healthy tissues [82]. The nanofibers possess a notable feature of exhibiting a significantly elevated surface area to volume ratio, enabling them to hold substantial amounts of drug molecules. The diminutive dimensions of nanofibers potentially enable their infiltration into neoplastic tissues. Nanofiber-mediated drug release platforms have demonstrated efficacy in treating a diverse range of malignancies, such as breast carcinoma, lung carcinoma, and pancreatic carcinoma.

Wound healing

The utilization of nanofibers for the purpose of wound healing is due to their unique characteristics such as surface area, significant porosity, and an amplified surface-area-to-mass ratio. The utilization of wound dressings comprising nanofibers has demonstrated superior capacity in facilitating a conducive environment for tissue healing compared to conventional dressings. The augmented surface area of nanofibers enables a heightened rate of wound exudate absorption, thus mitigating the likelihood of infection and advancing the rate of wound healing. Nanofiber dressings exhibit superior permeability and breathability, fostering a conducive, moist milieu for regenerative medicine [83]. In the study carried out by Prarthana Mistry *et al*, nanofibrous bandages composed of starch-thermoplastic polyurethane (TPU) were manufactured using electrospinning. The bandages exhibited improved water stability, mechanical properties, water retention, and wound healing capabilities compared to traditional cotton gauze dressings, making them promising materials for rapid and effective wound healing [84]. The presence of moisture within the environment serves as a facilitator for cellular transport, regeneration, and differentiation, all of which are considered indispensable in the process of tissue generation.

Antibiotic delivery

The application of bioinspired nanofiber technology has demonstrated potential efficacy in the targeted delivery of antibiotics for antibacterial therapy. The enhanced surface area of nanofibers enables augmented drug encapsulation with continuous discharge, thereby increasing the effectiveness of the treatment and diminishing the possibility of antibiotic resistance evolution. These nanofibers enable the simultaneous administration of multiple drugs, are straightforward to produce, and are cost-effective [85]. Accordingly, considerable focus has been directed toward the development of electrospun nanofiber structures as a potentially efficacious vehicle for the delivery of antibacterial agents. Various drugs and substances beyond the previously mentioned examples have been successfully integrated into nanofiber frameworks using diverse techniques and approaches. These include antifungal agents such as fluconazole and ketoconazole, anti-inflammatory drugs such as dexamethasone and indomethacin, antioxidants such as vitamin C and resveratrol, antiviral agents such as remdesivir and ribavirin, growth factors including EGF and FGF, and pain-relieving drugs such as lidocaine and ibuprofen. By incorporating these diverse drugs into nanofibers, researchers are expanding the possibilities for targeted drug delivery, wound healing, infection control, and tissue engineering applications, leading to advancements in the field of nanofiber-based therapeutics.

Cardiovascular disease

Nanofibers possess the potential to serve as an effective carrier for delivering drugs intended for the treatment of cardiovascular ailments, including those that inhibit blood coagulation as well as those that mitigate inflammation [86]. The elevated surface area of nanofibers facilitates enhanced drug loading and sustained release, thereby potentially augmenting their efficacy while minimizing detrimental side effects. Fleischer, S *et al* research yielded findings that demonstrated the existence of three distinct fiber groups within the myocardium, distinguished by size and functionality [87]. The utilization of electrospinning fiber stent presents a potential tool to facilitate advancements in cardiac-vascular tissue remodeling [88]. Kumar *et al* employed the electrospinning technique in the creation of a patch composed of PCL and GT nanofibers [89], [90]. Cardiac patches have been observed to elicit synchronized contractions and prompt drug responsiveness in their constituent cells, thereby bestowing them with the potential to serve as a drug screening platform in cardiotoxicity investigations. Despite achieving certain levels of success, numerous scaffolds still exhibit restricted cell infiltration along with low survival rates. The author Seif-Naraghi and colleagues: A GAG mimetic peptide nanofiber gel was synthesized and subsequently administered as an injectable agent at the site of myocardial infarction. This intervention was performed with the aim of promoting neovascularization and facilitating myocardial tissue repair and was achieved without the involvement of biological factors or stem cells. The implementation of electrospinning technology utilizing nanofibrous hydrogels as a means of fabricating tissue engineering constructs appears to offer potential benefits in mitigating suturing-related damage to heart patches. The researchers also developed conductive nanofibrous membranes, taking inspiration from the adhesive properties of mussels, as a potential therapeutic strategy for mending myocardial infarction [91]. The findings of this study demonstrate a notable decrease of 50% in infarct size, a consequential increase of 20% in left ventricular fraction, and a substantial 9-fold escalation in neovascularization subsequent to 4 weeks of patch transplantation. In an effort to replicate the characteristics and attributes exhibited by the heart, Walker and colleagues (Walker et al.) endeavored to develop a model that could effectively mimic these features. Cardiac patches have been generated through the implementation of GelMA and bio-IL fibrous scaffolds, resulting in robust adhesion to rat myocardium, sans the need for sutures, courtesy of ionic bonding [92]. For the assessment of the functional efficacy of engineered cardiac tissue (ECT), a scaffold for 3D printing and electrospinning was fabricated using polylactic acid and polycaprolactone (PCL). Subsequent to the isolation of cardiomyocytes from SFS, they were cultivated atop to manufacture ECT. The robustness and compatibility of the scaffold were evaluated by scrutinizing the viability of the cells and their mechanical propensity to contract. A novel methodology for the assessment of electroconvulsive therapy that is applicable to pharmaceutical investigations has been developed.

Skin care

Bioinspired nanofibrous materials possess the potential to efficiently deliver active ingredients, such as vitamins, antioxidants, and moisturizers, in various skincare formulations. The magnified surface area of nanofibers facilitates augmented absorption of active constituents within the skin, thereby enhancing effectiveness and minimizing wastage. Transdermal DDSs (TDDSs) have emerged as a well-received and widely accepted technique for providing drug administration via the skin. "Nanofiber-based TDDSs have gained popularity in the pharmaceutical industry owing to their low toxicity, high efficiency, and ability to prevent metabolization." The utilization of natural nanofibers for transdermal delivery presents a plethora of advantageous features such as targeted delivery, sustained release, and responsive mechanisms. Recent research efforts have placed emphasis on developing nanofibers and nano-emulsions with significantly enhanced skin penetration properties [93]. The utilization of natural polymeric scaffolds in TDDSs has potential therapeutic implications in the management of diverse pathological conditions. The implementation of tailored scaffolds has the potential to enhance vaccination efficacy and streamline the process of self-administering medication.

Challenges and future prospects

Nanofiber in DDSs has shown immense potential in improving therapeutic delivery efficiency, bioavailability, and targeted delivery to specific cells or tissues. However, there are several impediments associated with these systems that need to be overcome for their successful translation into clinical practice. Scalability is one of the major challenges associated with nanofibers in DDSs. Currently, the production

of nanofibers is limited to small-scale laboratory processes, which may not be cost-effective for large-scale production. The reproducibility of these systems can be influenced by a variety of factors such as ecological circumstances, polymer properties, and processing parameters, making it difficult to achieve consistent results. Another major challenge is the cost-effectiveness of nanofibers. The high cost of raw materials, manufacturing processes, and equipment can make these systems prohibitively expensive, especially for developing countries where affordable healthcare is a major concern.

Despite these challenges, there are several future prospects for bioinspired nanofiber. One potential approach is to combine nanofiber-based DDSs with other technologies such as microfluidics and 3D printing to enhance their scalability and reproducibility. These technologies can enable the production of large quantities of nanofibers with consistent properties and high precision. Many preclinical studies have shown promising results, and several nanofibers in DDSs are currently undergoing clinical trials. These systems have the potential to revolutionize drug delivery by enabling targeted and sustained drug release, reducing side effects, and improving patient compliance.

CONCLUSION

In this review article, we discussed the challenges and future prospects of bioinspired nanofiber in drug delivery. In terms of the potential impact of bioinspired nanofiber on drug delivery and tissue engineering, these systems have the potential to revolutionize healthcare by enabling targeted and sustained drug release, reducing side effects, and improving patient compliance. These systems can be used for regenerative medicine applications, including regeneration of impaired tissues and organs. Nanofiber-based scaffolds can mimic the natural ECM and provide an environment for cellular proliferation and differentiation.

In conclusion, bioinspired nanofiber in pharmaceutical delivery has immense potential to improve drug delivery efficiency, bioavailability, and targeted delivery to specific cells or tissues. These systems also have the potential to advance tissue engineering applications. Continued research and development of these systems can lead to significant improvements in healthcare outcomes and patient quality of life.

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Conceptualization, A.S.R, B.B and S.N.S; methodology, A.S.R, B.B and S.N.S, validation, A.S.R, B.B and S.N.S, formal analysis,B.B and S.N.S, data curation, A.S.R, writing—original draft preparation, A.S.R, writing—review and editing, A.S.R, B.B and S.N.S visualization, A.S.R, B.B and S.N.S.; supervision, B.B and S.N.S.

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This study does not involve experiments on animals or human subjects.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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