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Advancements in Wound Care: A Review of Electrospun Nanofibrous Dressings Enriched with Phytoconstituents

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ABSTRACT

The wound healing process is a revelation of the complexity of the human system, often challenged by pathogens that overpower even the best antibiotics and render treatment regimens ineffective. Further, persistent disorders like diabetes and critical conditions like in-depth wounds are potential hurdles in wound care management because of inadequate antibacterial, antioxidant, and anti-inflammatory properties of the current wound dressings. A few multifunctional wound dressings with tailored antibacterial, antioxidant, and anti-inflammatory properties are presented, emphasising the imperative need to improve them in order to reduce the high morbidity and mortality rates. A critical survey of the recent wound-care products indicated a limited use of phytochemicals like volatile oils, alkaloids, flavonoids, phenols, quinines, saponins, and glycosides. Bioactives, such as curcumin, baicalin, limonene/black pepper oil, *Acacia* extract, *Momordica charantia* pulp, *Agrimonia eupatoria* L. extract, surfactin, hesperidin, and metal nanoparticles, viz. zinc oxide, cerium oxide, titanium dioxide, silver, copper, and gold analogues, used in the fabrication of synthetic or hybrid polymeric dressings, are discussed. The need and rationale of the production of biological and/or chemical polymeric nano-fibrous composite-based "smart dressings" by electrospinning and the inclusion of phyto-constituents that delay the onset of infection and alleviate antibiotic drug resistance are highlighted.

1. INTRODUCTION

"Wound" refers to deformities of the skin or mucosal surface as a consequence of mechanical forces, chemical injuries, surgeries, burns, and sores from certain chronic diseases [1]. Wound healing aims at a fast closure of the wound, and one of the treatment strategies is the implementation of proper wound dressing. Wound care management is a challenge of the 21st century because of the increased incidence of accidents, surgeries, diabetes, burns, and perennial ailments. Throughout the world, approximately $312.9 million people are suffering from surgical wounds every year, and around 76 million people are inflicted with wounds caused by complications of diabetes and cardiovascular diseases [2]. The global wound care market has steadily increased since the late 1990s, and is estimated to reach $8,460 million in 2025 [3]. In India, the advanced wound care management market was of $230 million in 2020 and is predicted to enhance its Compound Annual Growth Rate (CAGR) by 5.5% for the years 2020-2027. Traditional/conventional dressings, viz., gauze, lint, bandages, and cotton, have the advantages of low cost and good absorbance, but act passively by just sequestering the contaminants from the wound. Besides this, they may cause wound dehydration and enhance adhesion, causing pain and delayed wound healing in the patient [4]. A remarkable progression in modern wound dressings is reflected in smart materials being used to protect the wound from dehydration and facilitate healing, not just closure, and they are hydrocolloids, hydrogels, sponges, alginates, transparent films, etc. But these dressings are not superior for wound closure.

Nanofibrous materials have a small pore size, a high ratio of surface area to volume, and are considered best for wound dressing because of their closeness to the extracellular matrix, which plays a significant role in cellular growth, adhesion, and proliferation. Electrospinning is a better way for fabricating orderly-layered nano-membranes by means of high-voltage electrostatic action, including spraying, stretching, and/or melting. The advantages of electrospinning are greater versatility in polymer material selection, greater flexibility in introducing a number of drugs and bioactive compounds, and ease of control over fiber formation.

The present review is aimed at providing insights into the research work done on the synthesis of electrospun nanofibers and their potential as antimicrobial and antioxidant agents since the last five years, as well as the commercially available wound care products in the Indian and global markets. Despite extensive research into the production of nanofibers, there is a lack of scale-up to industrial levels. According to our knowledge, a few nanofibers are available on the market as wound dressings, and to mention one, "Durafiber" and its related products. So, the gap should be filled in future years to

obtain all-purpose/ideal wound dressings, and the regulatory bodies should encourage nanofiber-based wound dressings for better patient care. Further, the review offers a gist of the diabetic and burn wound injuries and the challenges in their wound healing because of their current augmented prevalence. Globally, more than $40 million patients are suffering from chronic skin wounds, with an annual cost exceeding $15 billion by 2022. Worldwide, 10% of adults are affected by diabetes, and approximately 15% of diabetic patients present foot or limb ulcers [5]. A survey conducted worldwide by the World Health Organization (WHO) indicates that every year nearly 11 million people suffer from burn injuries, of which 180,000 are fatal. Heat from hot liquids, solids, or fire and, in addition, friction, radiation, chemical, or electrical sources also cause heat or burn injuries to a certain extent. The desirable characteristics of herbal wound dressings are their skin-friendly nature, anti-microbial activity, natural ability to cure the wound, and a limited need for antibiotic medication, which therefore wards off the complications of developing resistance to antibiotics in wound patients.

As a result of growing demand in health care and biomedical applications, the nanofiber market is expected to reach $3,598.78 million by 2030, with a compound annual growth rate (CAGR) of 21.8% from 2023 to 2030, according to an SNS Insider report. The market was valued at $742.98 million in 2022 (https://www.globenewswire.com/news-release/2024/02/02/2822697). Smith & Nephew, Molnlycke Health Care, 3M Health Care, ConvaTec, Coloplast A/S, BSN Medical, Hartmann Group, B. Braun, and Acelity are some of the leading makers of nanofiber medical wound dressings worldwide (https://www.absolutereports.com/global-nanofiber-medical-wound-dressing-market-27003521).

2. WOUNDS

Wounds are classified into acute (mechanical and chemical injuries, superficial burns, and incisional wounds) and chronic (diabetic foot, pressure, and venous leg ulcers) based on the time-dependent cellular changes in the healing process [6]. Acute wounds follow the normal wound healing process, whereas chronic wounds are open for more than one month, impose a heavy burden on healthcare systems, and are susceptible to inflammatory bacteria [7, 8]. Local factors like pressure, impaired blood perfusion, and nerve damage, as well as systemic factors including age, nutritional status, and genetic vulnerability, affect the cellular functions. Individual habits such as smoking, alcohol consumption, and hormonal drug use delay the healing process [9].

2.1 Wound healing cascade

"Wound healing" is a complex and interconnected network of events that involves a number of cells, cytokines, growth factors, and the maintenance of a local good wound environment conducive to growth. The wound healing process is an integration and overlapping of physiological events such as hemostasis, inflammation, proliferation, and remodeling [10].

Hemostasis is the first phase of wound healing, activated by platelets that adhere to the injured endothelium. Platelets and their derived growth factors, together with coagulation factors like fibronectin, fibrin, vitreous connexin, and thrombin, form the blood clot. Within 24-36 hours after injury, neutrophils are the prime cells mobilized to the lesion site in the inflammation phase. Immune cells like macrophages, neutrophils, and T lymphocytes gather at the wound site to phagocytose the bacteria and necrotic tissue. During cellular proliferation, chemical molecules secreted by M2 macrophages modulate cellular neo-vascularization, granular tissue, and re-epithelialization. Fibroblasts play the key role at the wound site as proliferation progresses. The remodeling phase can last from a few weeks to several years. The new skin is formed and completely covered by fibroblasts. TGF and EGF play a vital role in re-epithelialization, angiogenesis, and granular tissue formation. The synthesis of a high-strength collagen matrix is accompanied by the transformation of granular tissue into mature scar tissue. The new skin is finally formed and completely covered by the fibroblasts.

2.2 Diabetic wounds and challenges

The etiology of diabetic foot and limb ulcers is multifactorial. The general causes are poor glycemic control, calluses, underlying neuropathy, peripheral vascular disease, ill-fitting footwear, foot deformities, and dry skin leading to diabetic foot ulcers in *Diabetes mellitus* patients [3]. Wagner and the PEDIS [perfusion, extent (size), depth (tissue loss), infection, and sensation (neuropathy)] system classify wounds based on the depth of the lesion [11].

Glycosylation of the conjugated blood protein hemoglobin, alterations in the erythrocyte membrane, and hyperglycemia causing occlusion or narrowing of the capillaries that supply the injured area affect the wound's ability to heal due to dysregulated nutrient and oxygen supply. In diabetic patients, oxidative stress and hyperglycemia accompanied by local hypoxia result in the excitation of macrophages and the subsequent release of pro-inflammatory cytokines. Prolonged inflammation causes irregular apoptosis of fibroblasts and keratinocytes and affects the progression from the inflammatory phase to the proliferative phase. Furthermore, reactive oxygen species (ROS), at low concentrations, effect the normal synthesis of collagen in fibroblasts and keratinocytes and thus promote re-epithelialization. At higher levels, however, the inflammatory phase is prolonged and wound healing is slowed by preventing entry into the normal proliferation and remodeling stage. Decreased fibroblast proliferation and differentiation, as well as impaired ECM formation due to decreased expression of IGF-1, TGF, VEGF, and PDGF (which delays angiogenesis), are factors that contribute to delay in wound healing.

2.3 Burn injuries and challenges

Burns are classified as being of the first, second, third, or fourth degree based on their size and depth. First-degree burns are superficial and affect the epidermis alone; in this type, the skin becomes red, dry, and painful, turns white when pressed, and spontaneous wound closure occurs. Second-degree, but superficial and of partial thickness, injuries affect the dermis layer, and the wound appears red, moist, blistered, and painful; it turns white when pressed, with spontaneous epithelialization, and leaves no or a negligible scar. Second-degree, but deep, partial-thickness wounds affect the dermis in a similar way as the previous one, but form scar tissue. Third-degree burns affect the dermis and subcutaneous tissues too, and the wound appears white, leathery, charred, and dry. Fourth-degree burns extend to deeper subcutaneous tissues, muscle, and bone; the

affected area turns dark and often ends up with the loss of the injured segment.

Healing of burn injuries is a complex and an extended process that depends mainly on the functional status of the immune system. After injury, the burn wounds are divided into three zones from inside to out and are identified as the zones of coagulation (the deeply affected central portion), stasis or ischemia (demonstrating decreased perfusion), and hyperemia (the outermost region with inflammatory vasodilation) in the order. Within a few hours, an intensive mis-regulated inflammatory reaction develops in the host which can be recognized from the elevated cyto- & chemokines, proteins characteristic of acute-phase and hyper-metabolism [12]. A hypermetabolic response in association with catabolism increases bacterial infection, organ failure, and death. Another major complication is the formation of biofilm; during the initial phases of infection, Gram-positive cocci are high, while in the progression of healing, Gram-negative bacteria predominate. In addition to this, burn patients may develop pneumonia, urinary tract infections, and blood stream infections [13].

In the wound care market, currently 3000 wound dressings are available for different types of wounds but challenging wounds like pressure/venous ulcers, burn and diabetic wounds are difficult to heal due to the constraints like low anti-inflammatory/antioxidant potential, creation of dryness of the wound area and demanding frequent dressing change. Further, the regenerated skin tissue often shows improperly reorganized scar tissue and lacks vital appendages like hair follicles, sebaceous glands, and nerves. The said problems can be addressed by the electrospun, phytoconstituent-enriched nanofibrous dressings that significantly reduce the healing time period.

Functional assays constitute an important tool to assess the biological functions of any chemical moiety that include one or more of the anti-inflammatory, antioxidant, hypoglycemic, antimicrobial potentials. The anti-inflammatory activity of Chitosan- polyvinyl alcohol loaded with bioactive ursolic acid (CS-PVA-UA) nanofiber mats was assayed using RAW264.7 cells and the two inflammatory cytokines viz. Tumor necrosis factor (TNF - α) and interleukin 6 (IL-6) were measured through ELISA kit. The expression levels of these factors decreased in the cells treated with chitosan- polyvinyl alcohol loaded with bioactive ursolic acid (CS-PVA-UA), indicating that the phytoactive, ursolic acid reduced the secretion of proinflammatory cytokines. Flow cytometry is a technique adopted to quantify the intended measurements of biological activity in terms of strength/intensity or number. Further, the antioxidant capacity of nanofibers was determined with dichlorodihydrofluorescein diacetate (DCFH2-DA)-labeled flow cytometry test and intensity was measured in FACScanTM flow cytometer. The reactive oxygen species (ROS) in the CS-PVA-UA group was significantly lower than that of the CS-PVA group, indicating the effect of the UA component [14]. The antimicrobial activity of electropsun PVA-*Azadirachta indica* (neem)-chitosan blended nanofibrous mat showed the zone of inhibition (ZOI) with a diameter of 14.5mm against *Staphylococcus aureus* while PVA alone did not form the ZOI [15].

3. WOUND DRESSINGS

An ideal wound dressing should satisfy the critical requirements like absorbing excess wound exudates while providing moist healing environment at the wound site, prevent bacterial intrusion, facilitate oxygen permeability. Further it should be biocompatible and degradable, non-adhesive to healing tissue, adequate mechanical strength, promote cell proliferation and tissue regeneration [16, 17]. A dressing should be nontoxic, support a quick wound heal with cost effectiveness and little discomfort to the patient. Collagen products, biological dressings, keratinocytes, silver products, and platelet-derived growth factors are among the advanced wound care products developed with the aforementioned characteristics. The major players in the Indian market are Smith & Nephew Plc, Coloplast A/S, Johnson & Johnson, 3M, Convatec Group Plc, Cologenesis Healthcare Pvt. Ltd., Mil Laboratories Pvt. Ltd., and Essity AB. In February 2019, AxioBiosolutions launched "Maxiocel," made of chitosan, in New Delhi, India.

3.1 Electrospinning

The methods used to prepare nanofibers such as drawing [18], self-assembly [19], phase separation [20] and template synthesis [21] are associated with the demerits of cost and time intensiveness, and low-efficiency. Electrospinning technology evolved to manufacture the nanofibers by a one-step, easy, top-down preparation method that can be scaled up from lab research to industrial production and is highly cost-effective, overcoming the problems associated with previous methods. Nanofiber wound dressings resemble the natural extracellular matrix (ECM) in structure and function; porous/double-layer and triple layer core-shell/hollow fibers provide a wide surface area, high load-ability for various bioactive constituents and a microenvironment needed for cell proliferation, localization and maturation [22, 23]. In an electrospun matrix, the natural polymers are biocompatible and the synthetic polymers provide the mechanical strength. The kinetics of drug release from the matrix can be controlled, showing the potentiality of electrospinning technology in the manufacture of high-end bioactive wound dressing materials. Electrospun nanofibers demonstrate profound impact in innumerable multidisciplinary applications viz. treatment of water and air by filtration (Ex: Affinity membranes); biomedical scaffolds, drug delivery systems and sensors of electrical/ optical/ biological applications; solar cells, LEDs, and supercapacitors employed in energy/chemical/textile industries [24]. Thus, the adoption of electrospun products enhances the efficiency and economy of the industrial devices accompanied with the benefits of environmental sustainability, energy conservation and potential harnessing, and realization of the sustainable development goals.

3.2 Evolution of electrospinning

William Gilbert observed that the water droplet forms into a cone on applying electric field while its behavior was elucidated by Lord Rayleigh in 1882. In addition, in 1887, Charles Vernon built an electrospinning apparatus consisting of a small dish. Rayleigh described the production of ultrafine fibers via electrospinning for the first time in 1897. John Cooley and William Morton patented an electrospinning setup as early as in 1902. In 1964, Geoffrey Taylor demonstrated mathematical modeling of the change from spherical to conical shape of a polymer in solution, under the influence of a strong electric field. The term "electrospinning" was popularized in

1990, when Darrell Reneker and Gregory Rutledge electrospun nanofibers from very many types of organic polymers.

3.3 Electrospinning process

The main set up of electrospinning device comprises of spinneret (Syringe needle) connected to a DC or AC power (5 to 50kV) supplier, a syringe injection pump and a grounded or oppositely charged collector (Figure 1a, b). Electrospinning is a hydrodynamic process in which the liquid droplet changes its morphology, electrified to create a Taylor cone or jet, which is then stretched. When the jet flies in air, the solvent volatilization and loss of charge on the fiber surface takes place [25]. Finally, the cone gets stretched to the desired dimensions of micro or nanometers, solidifies and spreads as layers on different collector types [10]. The four major steps involved in the electrospinning process are formation of droplet, taylor cone, whipping jet, and finally deposition as micro/nanofibers on collector plates/drums (Figure 1c).

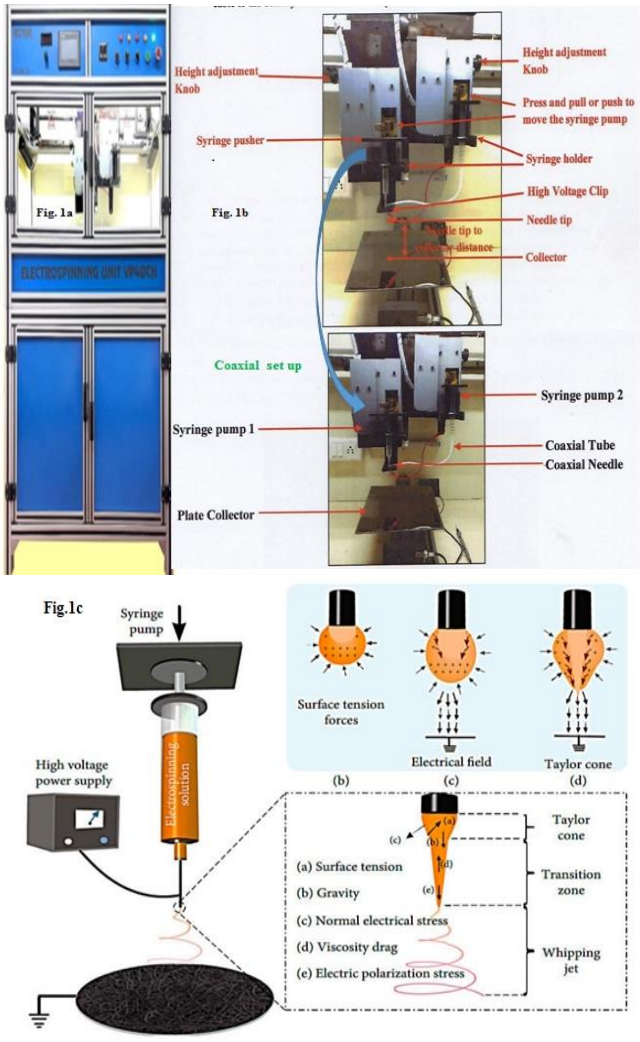

Figure 1. a) Fully automated coaxial Electrospinning Unit; b) Different parts of a coaxial electrospinning; c) Electrospinning process setup [26]

3.4 Factors determining electrospinning

According to Moon et al., the electrospinning process is affected by the nature and type of polymer and its concentration, solvent evaporation rate, flow rate, and viscosity, in addition to the applied voltage, temperature, humidity, and others [27]. Mateti et al. further categorized the main factors as solution, process, and temperature parameters [24]. The morphology, diameter, and porosity of nanofibers are refined by optimizing the parameters. The solution parameters include surface tension, polymer solubility, viscosity, volatility, solution conductivity, molecular weight, and dielectric effects of the solvent. voltage, flow rate, collector plate, needle diameter, and distance from the spinneret to the collector plate were categorized under process parameters. The ambient parameters predominantly include humidity, pressure, and temperature [24]. The parameters are interlinked and their fine inter-play determines the morphology of the nanofibers.

Electrospun nanofibers are divided into inorganic, organic, and inorganic-organic hybrids based on their chemical composition. Electrospinning technology has been evolving steadily over the time from single-fluid (blend and emulsion) to multifluid (triaxial and other multifluid) through double-fluid (coaxial and side-by-side) electrospinning methods (Figure 2).

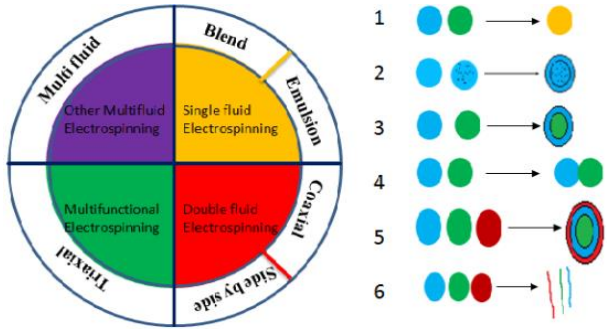

Figure 2. Types of electrospinning techniques: (1) Blend; (2) Emulsion; (3) Coaxial; (4) Side byside; (5) Triaxial; (6) Multifluid electrospinning

3.5 Requirements for electrospun wound dressing

The physico-chemical properties of electro-spun fibers are enhanced by the inclusion of nanostructures and biofunctional molecules which mimic the natural environment [28]. The key factors of wound dressings are biocompatibility, morphology and mechanical strength, hydrophilicity and degradation rate, and drug release behavior.

3.5.1 Biocompatibility

Biocompatibility refers to the fact that the polymer material is suitable for host-scaffold interactions and directing a favorable foreign body response [29]. An ideal wound dressing polymer should be pro-cellular and hostile to foreign and infectious agents. To promote tissue regeneration at the wound site, dressings are engineered with a variety of active agents, including antimicrobial drugs; the interaction between these active agents and the electrospun polymer should be safe for the skin cells and promote regeneration [30-32].

3.5.2 Degradation rate

A gradual breakdown of polymers, by one or more factors like microbes, enzymes of host immune cells, and the mechanical disruptions resulting from skin tissue formation, is called "degradation" [33]. The physical and biochemical agents that are present in the matrix determine the life span, functionality of dressings, and degradation rate. The rate of

polymer degradation is dictated by its own physico-chemical characteristics, like molar mass, crystallinity, morphology, orientation of the atomic chains, etc. [34]. "Crystallinity decreases the degradation rate" is a general rule for polymers. In electrospun dressings, natural polymers are hydrophilic, induce degradation, and are biocompatible and active, [35] while synthetic polymers reduce the degradation rate and lack bioactivity due to insufficient chemical interactions with skin cells.

Polymer degradation products are utilized in the skin regeneration process, which takes place by creating a hypoxic environment and by forming blood vessels by endothelial cells; in the maturation phase, the micro-vessels get replaced by type III collagen followed by type I collagen [36-38] over a short period of time. The natural protein polymers liberate amino acids that are absorbable and toxicity-free [39], trigger inflammation, promote cell migration into the wound area [40], and thus upregulate the metabolic rate. On the contrary, degradation products of synthetic polymers create an extremely acidic environment that can inhibit cell proliferation *in vivo* [41].

3.5.3 Release behavior

The two key parameters that influence scaffolds are the breakdown and permeation rates of functional factors [42]. These active agents in hydrophilic scaffolds cause swelling and reduce 'minimal matrix mass' upon release [43], whereas in hydrophobic ones, the polymers swell only in conjunction with surface-active, copolymers of hydrophilic nature [44, 45].

A number of investigations were done to manipulate dressings' release behavior; one of the approaches is the incorporation of aliphatic polyesters like polylactic acid (PLA), poly-lactic-co-glycolic acid (PLGA), and polycaprolactone (PCL) into the electrospun nanofibers that effect fast release due to their semi-crystalline structure, and a post-annealing process is essential to confer a sustained release property to them [46]. Another approach is adding nanostructures, where the release behavior is controlled by two modes: encapsulation of active agents [47] and incorporation as nucleating agents [48] during electrospinning.

3.5.4 Mechanical strength

Wound dressing must provide adequate mechanical strength. The inclusion of natural polymers in wound dressings causes *in vivo* degradation of matrixes during the healing process, leading to reduced mechanical strength. This can be overridden by the addition of natural non-organic nano-fillers and nanostructures into electrospun scaffolds. Nano-fillers reduce the stress-shielding effect within the polymer matrix and provide tensile strength close to that of natural skin by contributing as reinforcing agents [49, 50].

3.5.5 Morphology

Electrospinning factors mainly optimize the morphology of the electrospun mats. A nonporous, interconnected network provides a suitable platform for wound healing as it is flexible, permits optimal transport of substances across it, and protects the wound [45, 51, 52].

3.5.6 Hydrophilicity

A direct relationship exists between the moisture content of the wound and the healing capacity of electrospun dressings [53]. Dry wound surfaces cause pain in the injured tissue, inhibit epidermal formation, and cause scar formation [54, 55]. Recently developed wound dressings show properties like maintaining hydrophilicity at the wound site, enhancing cell growth and adhesion, further absorbing wound exudates, and decreasing detrimental tissue adhesion [56]. Contact angles in the range of 5-40 increase cell growth rate, which is indicative of an appropriate hydrophilic wound microenvironment [57]. Jiang et al. demonstrated that surface coating with inorganic nanomaterials improves scaffold hydrophilicity [58].

3.6 Biomaterials for developing electrospun nanofibrous wound dressings

Hundreds of polymers are being successfully used to develop electrospun nanofibers. The classification of polymer types that are intensively used in electrospun wound dressings are depicted in Figure 3. Natural polymers like gelatin, collagen, cellulose, chitosan, and silk fibroin, with the properties of biocompatibility, biodegradability, and antimicrobial nature, are specifically recognized by cell integrins, which can promote cell adhesion, migration, and proliferation. Synthetic polymers, like polyvinyl alcohol, polyacrylonitrile, polycaprolactone, polylactic acid, and polyethylene glycol, have conducive mechanical properties, thermal stability, and spinnability, and are widely used as carrier materials. Hence, a combination of natural and synthetic polymers is preferred to improve the quality of wound dressings (Table 1).

To improve the dressing's properties, a number of bioactive agents are added to the dressing. Generally used bioactive ingredients are antibiotics (Ex: ciprofloxacin (CIP), metronidazole, tetracycline, gentamycin, and diclofenac (analgesic)), nanoparticles (of copper, zinc, silver, and cerium oxide), and natural substances (curcumin, honey, essential oils, and growth factors).

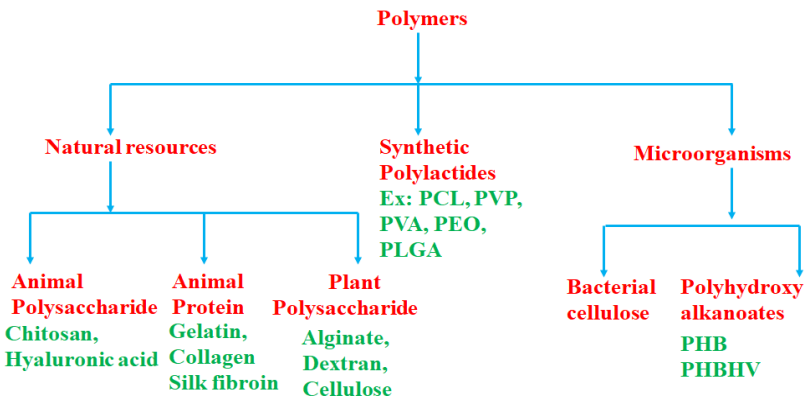

Figure 3. Various types of polymers – Synthetic and Natural

Table 1. Some synthetic polymers used in electrospinning because of their special characteristics that facilitate chemical interactions and formation of nanofibers

Synthetic polymer & Monomer	Mol. Wt. (M) and application
Polyethylene glycol (PEG) $[\text{-O-CH}_2\text{-CH}_2]_n$	<100 kDa, Cross-linker; Improves water solubility and biocompatibility
Poly ethylene imide (PEI) $[CH_2CH_2NH]_n$	43.04 (molar mass per unit(g/mol)); M varies with the number of units; a branched dendrimer with primary, secondary and tertiary amino groups; widely used as a wood adhesive component
Polyacrylonitrile (PAN) $[CH_2CH(CN)]_n$	'M' varies with the composition; consists of acrylonitrile (89-90%), vinyl acetate (non-ionic co-monomer, 4-10%) and ionic co-polymer (1%) with sulfo (SO_3H) and sulfonate (OSO_3H) groups.
Polyvinyl chloride (PVC) $[CH_2CHCl]_n$	Toxic; causes health hazards
Polyvinyl alcohol (PVA) $[CH_2CHOH]_n$	FDA approved for medical applications; water soluble, biocompatible and biodegradable.
Polyamide-6 (PA6) (Nylon 6) $[C_6H_{11}NO]_n$	Aliphatic polyamide used in polymers; made by ring-opening polymerization of ε-caprolactam or self-condensation of ε-aminocaproic acid.
ε-Polycaprolactone (PCL) $[C_6H_{10}O_2]_n$	It is also an FDA approved and EC registered mark polymer that can be used in medical devices and drug-delivery; widely used polymer because of its easy processing, mechanical properties, biodegradability and high miscibility with other polymers.
Polylactic acid (PLA) $[C_3H_4O_2]_n$	Immunologically inert and therefore, used in wound healing and medical implants. It is the second most highly consumed bioplastic in the world and widely used in 3D printing.

4. PHYTOCONSTITUENTS AND THEIR FUNCTIONS IN WOUND HEALING

Plants synthesize a variety of phytochemicals, which are classified as primary or secondary metabolites. Alkaloids, terpenoids, and phenols are some of the secondary metabolites with excellent medical properties along with their antioxidant activity. Effective alternatives to traditional antibiotics are phytoconstituents, namely polyphenols, due to their antimicrobial, regenerative, and antioxidant properties (Table 2) [59-66]. There are more than 8,000 different polyphenols. Depending on the number and binding structure of phenol units, polyphenols are divided into flavonoids, viz., flavonols, anthocyanidins, and non-flavonoids, viz., phenolic acids, tannins, and lignins. Phenolic compounds have some drawbacks, such as low stability and consequently decreased biological performance at the wound site. To overcome these limitations, polymers are used as carriers of polyphenols.

Portulaca oleracea, *Capparis spinosa*, *Plantago major* extracts have been effectively encapsulated in electrospun nanofibers. The incorporation of plant extracts and their bioactives into nanofibrous structures improved the biological activity of the wound dressing materials by enhancing the antibacterial, and antioxidant properties [67-69].

Table 2. Bioactives with their special attributes to promote wound healing

Bioactives	Type of Wound Dressing	Polymers/Materials	Significant Attributes	Reference
Curcumin	Hydrogel	Silane composite nanoparticles	Antimicrobial, burn wounds	[59-61]
	Film	Chitosan and PEG fumarate	Antimicrobial, chronic wounds	[62]
Thymol	Hydrogel	Cellulose	Antimicrobial, third degree burn wounds	[59]
	Film	Gealtin, glycerol, glutaraldehyde	Antimicrobial, antioxidant, burn wounds	[60]
Kaempferol	Ointment	-	Antioxidant, diabetic wounds	[61]
Carcavol	Film	-	Antimicrobial,antioxidant, chronic wounds	[63]
Resveratrol		Hyaluronic acid, dipalmitoylphosphatidyl choline	Antioxidant, diabetic wounds	[64]
Ferulic acid	Ointment	-	Antioxidant, diabetic wounds	[65]
Tannic acid	Hydrogel	Agarose cross-linked with zinc ions chitosan and pullulan trimethylolpropanetriglycidyl ether	Antimicrobial, burn wounds	[66]
Tea tree oil	Nanofibrous scaffold	Polyamide-6, Polyvinyl pyrrolidone	Antibacterial, Antioxidant, Biocompatible and Supports Cell Adhesion	[72]
Ginsenoside of *Panax notoginseng*	Nanofiber membrane	Polycaprolactone, Polyvinylpyrrolidone, AgNPs	Anti-Inflammatory, Antibacterial (inhibit the growth of the *Escherichia coli* and *Staphylococcus aureus*)	[73]
Tea carbon dots	Film	Calcium peroxide, Ethyl Cellulose modified Zein	Antibacterial, Biocompatible	[74]
Quercetin	Electrospun membrane	Ethyl Cellulose, Gelatin, Eudragit L, Polyethylene glycol	Biocompatible	[75]
Capparis spinosa L. ethyl acetate extract	Nanofiber membrane scaffold	Polycaprolactone, Zinc oxide, Polylactic acid	Accelerated cell proliferation	[68]
Neem gum polysaccharide	Nanofibrous mat	Polyvinyl alcohol	Hemocompatible, Biodegradable, Antimicrobial	[76]

Traditional/Conventional wound dressings (Ex: bandages, cotton gauzes and wool) are non-occlusive and absorb exudates and at times, cause secondary injuries due to the adherence of dressing to the wound. The interactive dressings include films, foams and hydrogels and are semi-occlusive or occlusive with poor permeability to air and greater possibility of developing infections. Nanotechnology and electrospun fibrous dressings enriched with bioactives are reported to address these limitations effectively and confer desired characteristics like biocompatibility and biodegradability. Chitosan- polyvinyl alcohol loaded with bioactive ursolic acid dressing showed 99.8% of wound contraction rate, while the control and CS-PVA groups demonstrated 83.6% and 92.1%, respectively. *In vivo* studies of diabetic wounds with CS-PVA-UA nanofiber dressing revealed an increased wound closure rate, added with higher revascularization and re-epithelialization, collagen matrix remodelling and deposition, and hair follicle regeneration. For the treatment of diabetic wounds that are difficult to heal, a nanofibrous dressing candidate with several biological properties, such as anti-inflammation, antioxidation, pro-angiogenesis, and hemostasis activities, is being investigated [14].Curcumin (antioxidant and anti-inflammatory compound from turmeric) loaded silk fibroin/Polycaprolactone, and silk fibroin/Polyvinyl alcohol electrospun nanofibers were tested for their efficacy *in vivo* in streptozotocin-induced diabetic mice and the wound healing rates were shown to be 99% and 96.54% respectively on 14th day, significantly much higher as compared to the control groups [70]. Fabricated marine chitosan and PVA films exhibited wound healing efficacy of approximately 78% in just 8 days, when compared with control and standard. Three groups, each comprising five wistar albino rats, in the weight range of 150-180 g were used in the study and a circular area of 3 x 3 cm wound was made using surgical equipment. The electrospun Chitosan/PVA/AgNPs composite nanofibers with a mean fibre diameter of 240nm, encapsulated AgNPs' mean particle size of 1.31 µm demonstrated a wound efficacy of 96% in wistar albino rats in contrast to a remarkably low wound heal area of 48% with the standard povidone-iodine dressing and 30% in the case of untreated wounds [71].

5. RECENT ADVANCES IN ELECTROSPINNING

Hasan et al. developed chitosan and hyaluronan, a film based wound dressing which has antimicrobial, antioxidant properties by incorporating the phosphatidyl choline-dihydroquercetin [77]. Nanofibers, with PVA-chitosan in the core and PVP-maltodextrin in the shell, were fabricated including essential oil from *Satureja mutica* /*Oliveria decumbens* for controlling bacterial infections [78]. Wound dressing, made of natural and low cost biomaterials, comprising a multi-layer electro spun core-shell nanofibers and films were fabricated and tested on Wistar albino rats (Indian Patent No. 202041052202; Published on 11.12.2020) (Figure 4) [79]. Analytical characterization of electrospun nanofibers are tablulated in Table 3.

Table 3. Analytical characterization of electropsun nanofiber

Analytical Methods	Application
FESEM (Field emission scanning electron microscopy)	Determination of fiber diameters over a wide magnification range of 10× to 300,000x and identification of heterogeneous orientation (random/divergent/aligned patterns).
EDS(Energy dispersive spectroscopy)	Topographical and elemental (C, H, O, N, Mg, Na, K, S etc.) mapping.
XRD (X-ray diffraction)	Non-destructive, used to analyze physical properties such as crystal structure, phase composition, and orientation of entities.
PFM (Piezoresponse force microscopy)	Detection and measurement of local piezoelectric deformation caused by an applied electric field
Micro CT (Microcomputed tomography)	Non-destructive imaging tool for the production of high-resolution three-dimensional (3D) images composed of two-dimensional (2D) trans-axial projections of a target specimen.
FTIR (Fourier transform infrared spectroscopy)	Evaluates the bond configurations and chemical structure

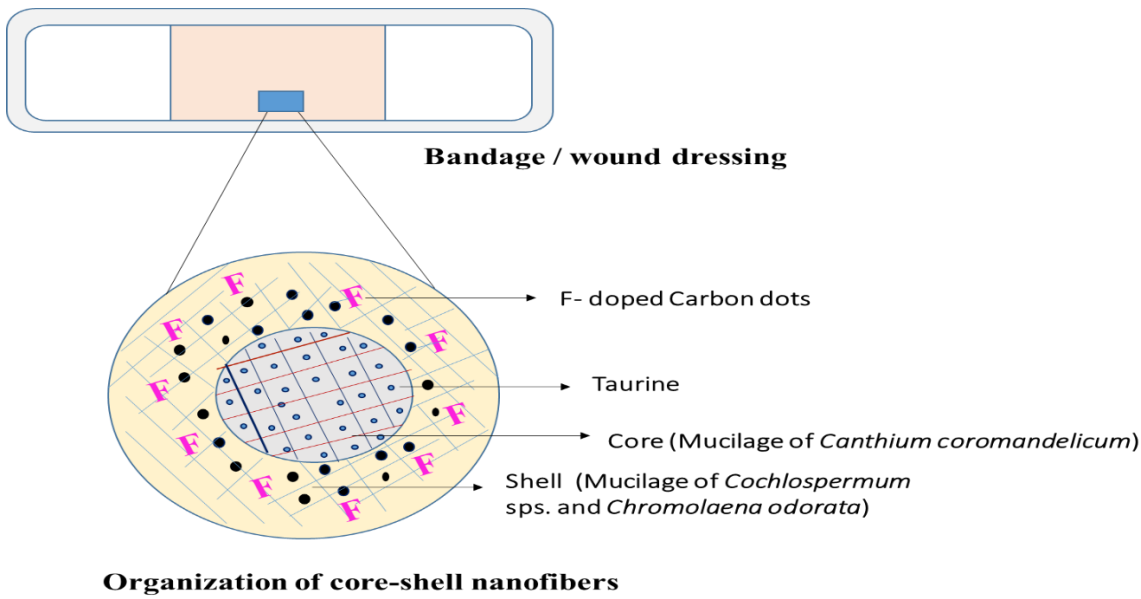

Figure 4. Multilayer electrospun core-shell nanofiber (Smart-Dre-M)

A self-healing injectable hydrogel with antibacterial activity based on N, O-carboxymethyl chitosan, and oxidized chondroitin sulphate was developed. Avossa et al. incorporated melanin-TiO_2 hybrid nanostructures into the PHB and PCL-based wound dressing for bactericidal action [80].

Pillai et al. used two techniques viz. solvent casting and electrospinning to synthesize multifunctional (antimicrobial, antioxidant, and anti-inflammatory) bilayer dermal patches. In these patches, the top layer consisted of polycaprolactone and chitosan, while the bottom layer consisted of polyvinyl alcohol, curcumin, and eggshell membrane protein. These dermal patches with bioactive agents were hemo-compatible, bacteriostatic/bactericidal, and facilitated loading with wound exudates, and support for the recruitment of cells, and deposition of extracellular matrix when compared to their commercial counterparts in a full-thickness excision wound model in rats [81].

6. CONCLUSIONS

The goal of wound care management is to provide a wound dressing material that can heal the wound quickly with little discomfort to the patient and a minimum number of dressings that are affordable to a larger section of society. For chronic wounds of the surgical and the traumatic types, diabetic foot / pressure / venous leg ulcers, burns, and persistent infections, developing customized wound dressings is a big challenge. Yet another daunting task is the minimization of drug resistance in patients to the available antibiotics and thereby reducing failure cases in wound management, which otherwise, culminate in high morbidity and mortality rates. The basic criteria required for successful wound healing are that the wound should be kept sterile and the patient should not develop resistance to antibiotics. Commercially, a variety of wound dressings are available, but in the case of chronic wounds, the patients may develop antibiotic resistance; further consequences are organ failure, coma, and death. The solution to overcome the problems is to develop an herbal bioactive wound dressing. Use of herbs and medicinal plants, which have natural antimicrobial, antioxidant, and anti-inflammatory properties, either as a crude extract or in nanoform instead of synthetic drugs while fabricating a wound dressing can eliminate the development of multi-drug resistance in chronic disease patients. The challenge for diabetic patients is to maintain a normal blood sugar level. An ideal antidiabetic wound dressing may be manufactured by using anti-diabetic herbs, plants, or biomaterials that can quickly and effectively heal the wound by controlling the blood sugar levels locally and preventing infections, which otherwise would be alarming. The mechanism of action of bioactives in wound healing is not clear, hence the molecular level exploration of compounds is necessary. The continuous screening of plants and their derivatives is required. For large scale production and commercialization of electrospun nanofibers, the technology and process parameters to be optimized and appropriate scaling up of equipment is warranted. In a nutshell, wound dressings must be developed through the right blend of advanced techniques like electrospinning and traditional knowledge of bio-based active constituents.

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