International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 5, May 2025 **ijppr.humanjournals.com** ISSN: 2349-7203

Advanced Biodegradable Scaffolds for Enhanced Wound Healing: A Review

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Received: 2025-04-28 Revised: 2025-05-15 Accepted: 2025-05-20

ABSTRACT:

Wound healing is a complex, multi-stage process involving tissue regeneration, inflammation, and remodeling, which can be hindered by factors like infection, chronic conditions, or insufficient vascularization. Biodegradable scaffolds, which simulate the extracellular matrix (ECM) and provide structural stability, have emerged as a promising solution to enhance the healing process. This review presents a comprehensive analysis of advanced biodegradable scaffolds, focusing on their materials, fabrication techniques, and functional modifications aimed at improving wound healing outcomes. Natural polymers (e.g., collagen, chitosan, alginate) and synthetic polymers (e.g., polylactic acid, polycaprolactone) are explored for their biocompatibility, degradation rates, and mechanical properties. Emerging strategies such as nanofiber-based scaffolds, bioactive molecule incorporation, and smart scaffolds responsive to stimuli are discussed. Furthermore, recent developments in scaffold design for skin regeneration, diabetic wound healing, and chronic wound treatment are highlighted. The review concludes by addressing the challenges in clinical translation and future directions, emphasizing the need for personalized, multifunctional scaffold systems to optimize wound healing across different patient profiles.

Keywords: Wound healing, Biodegradable scaffolds, Extracellular matrix (ECM), Nanofibers, Bioactive molecules, Diabetic wound healing

INTRODUCTION

Wound healing constitutes a complex physiological process comprising multiple sequential phases. In the case of acute wounds, this process typically progresses through haemostasis, inflammation, proliferation, and remodeling. Conversely, chronic wounds may experience extended durations within these stages, often culminating in non-healing ulcerations [1]. Numerous factors—including nutritional deficiencies, underlying comorbidities, tobacco use, and pharmacological agents—can adversely affect wound healing and ultimately compromise clinical outcomes [2]. The skin, being the body's largest organ, plays a crucial role in protecting against external threats and maintaining homeostasis, emphasizing the importance of prompt wound healing to restore its functions [3]. Hemostasis involves blood clotting to stop bleeding, while inflammation clears debris and prevents infection. Proliferation is characterized by cell growth, tissue formation, and angiogenesis, promoting wound closure. Remodeling focuses on restructuring the extracellular matrix, leading to scar tissue formation [4]. Normal wound healing is influenced by a variety of local and systemic factors. Local factors such as oxygenation and infection play a crucial role in the healing process [5]. Systemic factors including age, gender, diabetes mellitus, obesity, alcohol, and smoking can also significantly impact wound healing. Chronic wound healing involves a disruption in the normal phases of wound repair, leading to prolonged inflammation and impaired tissue regeneration. However, chronic wounds often stall in the inflammatory phase or exhibit deficiencies in the proliferative phase, hindering the healing process. Chronic wounds display a perpetual inflammatory state with increased proteolytic activity, mainly due to excessive matrix metalloproteinase (MMP) production, which degrades the extracellular matrix and inhibits essential growth factors for tissue regeneration. Moreover, chronic wounds are characterized by an imbalance between ECM deposition and degradation, impaired cell recruitment, and insufficient neovascularization, further impeding the healing process [6]. Understanding these disruptions in the wound-healing phases is crucial for treating chronic wounds effectively. Wound dressing materials play a crucial role in wound healing, with advancements focusing on natural polymers like collagen, chitosan, cellulose, and polyvinyl alcohol (PVA) to address the limitations of synthetic polymers [7-8]. These natural polymers offer biocompatibility, biodegradability, and properties similar to the human extracellular matrix, aiding in the healing process. Polymer-based wound dressing materials loaded with bioactive agents show promise for treating diabetic wounds by improving antimicrobial properties, moisture retention, and overall therapeutic outcomes in wound healing.

CONVENTIONAL TREATMENTS FOR WOUND HEALING

A range of both traditional and modern approaches to wound healing have been explored in scientific literature. Traditional techniques involve mechanical cleaning, use of antiseptic solutions for disinfection, removal of dead tissue (debridement), wound closure, application of topical antibiotics, and dressing the wound [9]. Moreover, growth factors such as epidermal growth factor (EGF), transforming growth factor-beta (TGF-β), and platelet-derived growth factor (PDGF) are essential in promoting wound healing by enhancing the formation of new blood vessels (angiogenesis) and encouraging cell growth. Moreover, In-situ formed wound dressings, polymeric biomaterials, and nanotechnology-derived biomaterials have shown promise in accelerating wound healing by providing proper structure, support for cellular migration, and protection against microbial invasion [10].

SCAFFOLDS FOR WOUND HEALING

A novel approach for wound healing is the scaffold-mediated delivery systems which overcomes many challenges like poor moisture retention and biocompatibility associated with traditional wound dressings. These scaffolds enhance wound healing by providing a controlled and localized drug delivery system, creating an optimal environment for tissue repair [11].

SCAFFOLD FABRICATION TECHNIQUE

Scaffold fabrication techniques are crucial in tissue engineering and regenerative medicine, with techniques like solvent casting, Thermally-induced phase separation, freeze drying, gas foaming, and advanced techniques like electrospinning and 3D printing. These techniques aim to achieve desired scaffold properties like porosity, pore size, and mechanical strength.

Solvent casting

Solvent casting involves dissolving a polymer-ceramic mixture in a solvent and casting it into a mold. As the solvent evaporates, a scaffold forms. This technique is simple and requires minimal equipment but is limited to producing simple shapes and may leave harmful residual solvents. A variation of this method uses porogens (like salt or sugar) to create porous scaffolds (Fig. 1). The size and proportion of porogens control the pore structure. After solvent evaporation, porogens are removed, leaving behind a porous scaffold. This method shares the advantages and disadvantages of the basic solvent casting technique [12]. The solvent casting technique has several benefits, such as consistent thickness, cheap processing costs, convenience of use, and enhanced physicochemical qualities. Because of its low solvent removal temperatures, it is also utilised to create films containing heat-sensitive active pharmaceutical ingredients (APIs).

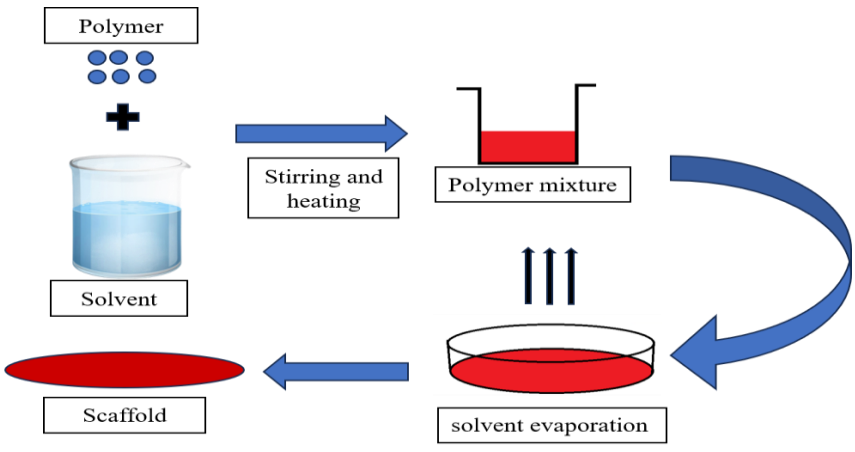

Fig.1: Solvent casting method

The technique produces films with exceptional optical clarity and porosity by enabling the tuning of mechanical and optical characteristics. It offers flexibility, cost-effectiveness, porosity, transparency, and impermeability in wound healing. Its drawbacks include a lengthy drying period, extensive solvent consumption, and an inability to adjust film thickness [13].

Freeze-drying

Freeze-drying, or lyophilization, is a commonly employed technique in material fabrication. It involves freezing a synthetic polymer dissolved in a selective solvent at temperatures ranging from -20°C to -80°C, which solidifies the solvent. The frozen mixture is

then subjected to sublimation in a lyophilizer, leaving behind a porous solid scaffold with interconnected structures. This method is advantageous in biomedical fields because it typically uses water-based solvents instead of harmful organic ones. Nevertheless, it is still difficult to classify scaffold structures resembling vascular systems for biomedical use, primarily due to the high energy demands and the toxicity of solvents used during polymer mixing. Freeze-drying techniques are another common way to fabricate 3D scaffolds. They can be used to make scaffolds from heat-sensitive materials for tissue engineering and other uses. The four essential components of a freeze-dryer device are pretreatment, freezing, primary and secondary drying, and a refrigeration and vacuum system, control system, product chamber, and condenser.

Precursor materials are first treated to enhance their mechanical and biological properties, such as their ability to withstand low pressure. Using specialised equipment or materials, the modified precursors are then placed into the mould and allowed to cool. During the sublimation process, the remaining solvent unfrozen molecules evaporate and the water in frozen ingredients leaches out (Fig. 2) [14].

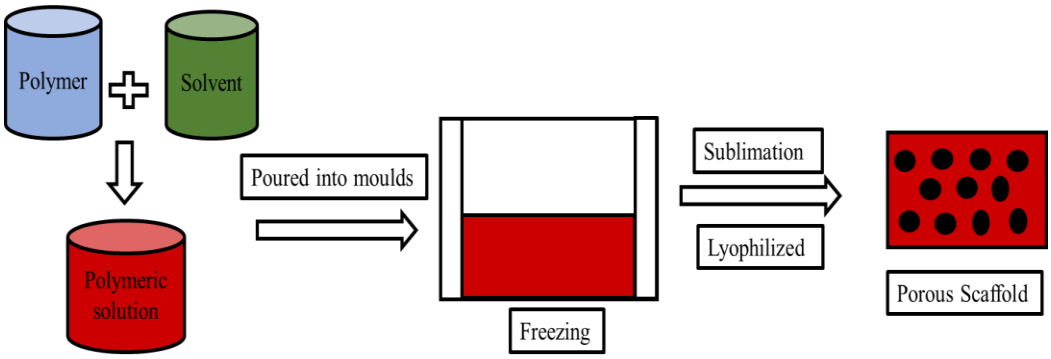

Fig.2 Freeze-drying

Freeze-drying, or lyophilization, is a versatile technique widely used to fabricate porous 3D scaffolds for biomedical applications, enabling precise control over pore architecture by adjusting freezing parameters[15]. This method is compatible with various biomaterials, including collagen, gelatin, chitosan, and PLGA, which allows the creation of scaffolds that mimic native extracellular matrix properties to improve cell adhesion, proliferation, and function [16]. Additionally, the low temperatures used during freeze-drying help retain the bioactivity of sensitive agents like growth factors, drugs and proteins, enhancing the scaffold's therapeutic potential for wound healing and tissue regeneration [17]. Freeze-drying is also scalable and reproducible, making it suitable for commercial biomedical products, though its high energy and cost requirements remain a limitation compared to other fabrication methods [18].

Thermally-induced phase separation (TIPS)

Thermally-induced phase separation (TIPS) is a technique used for fabricating porous scaffolds, enabling precise control over pore size and producing highly organized hierarchical materials. This method is particularly advantageous for creating clinical tissue engineering scaffolds, as it supports the production of membranes made from semi-crystalline polymers. By adjusting the manufacturing process parameters, the pore size and morphology can be tailored, resulting in isotropic microporous structures. The polymer solution separates into two phases either by introducing an immiscible solvent or cooling the solution below its solubility temperature driven by thermal energy. Factors such as polymer type, concentration, cooling rate, and solvent composition influence the final scaffold design. Additionally, polymer chemistry, molecular weight, and hydrophilicity/hydrophobicity define the scaffold's structure. When the polymer concentration falls below a critical level, the polymer-lean phase dominates, causing the porous structure to collapse during solvent removal [19].

Gas foaming

This technique uses inert gas foaming agents like ammonium bicarbonate to create a biodegradable polymer paste. The paste is mixed with salt particles, and then immersed in hot water. This results in the evolution of ammonia and carbon dioxide, which are then leached out to form a solidified polymer matrix with high interconnectivity pores. The porous microstructure may be formed due to bubble growth from escaping carbon dioxide. The structures have pore sizes of 30-700µm and porosity of 85-93% [24]. The porosity and pore size can be finely tuned by altering factors like gas concentration, salt particle size, and the polymer's chemical properties. Gas foaming is also advantageous as it eliminates the need for organic solvents, reducing cytotoxicity risks and supporting the bioactivity of sensitive molecules that may be embedded within the scaffold [20].

Electrospinning

Electrospinning is a versatile technique used to produce nanofibers with diameters ranging from sub-micron to nanoscale, leveraging electrohydrodynamics to create fibrous membranes from polymer solutions or melts (Fig.3). The process begins with forming a Taylor cone at the tip of a charged solution, which, when the electric field surpasses surface tension, ejects a jet that solidifies into fibers as the solvent evaporates during its travel to a collector plate [21]. Recent advancements, such as multiplex electrospinning, enhance control over fiber deposition, creating complex structures without intricate surfaces [22]. The technique's advantages include high surface area, tunable porosity, and the ability to manipulate various parameters, making it suitable for applications in biomedical devices, filtration, and drug delivery [23]. However, challenges remain, such as the stochastic nature of fiber deposition, which can affect the reproducibility of the process [22]. Electrospinning continues to evolve, driven by ongoing research and technological improvements.

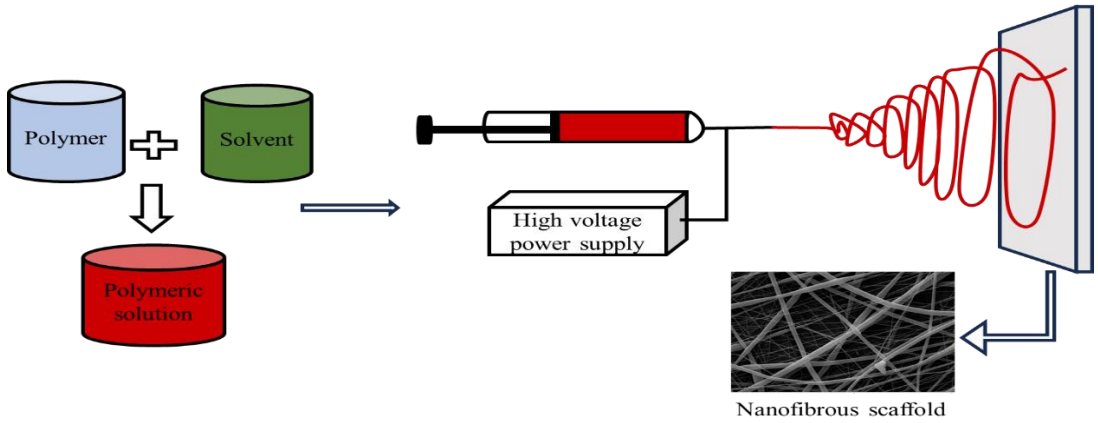

Fig. 3: Nanofibrous scaffold by Electrospinning Method

Rapid prototyping manufacturing

Rapid prototyping manufacturing (RPM) is a mature technology that focuses on manufacturing complex three-dimensional physical entities using CAD models. It includes 3D printing, fused deposition modeling, selective laser sintering, and stereolithography. RPM's biggest advantage for TERM is meeting individual requirements for fabricating patient-specific scaffolds [24].

3D printing

3D printing technologies are gaining interest in 3D scaffold fabrication due to their ability to simulate the intrinsic features of the native extracellular matrix (ECM), which is crucial for efficient tissue formation. 3D printing is a layer-by-layer manufacturing technique that adds a new layer of material to the previous one, allowing for the interpretation and creation of functional prototype features (Fig. 4). 3D printing (3DP) is an emerging fabrication technique in tissue engineering (TE) that offers precise control over scaffold structures at the micron scale. The process involves layering powdered material and selectively fusing it using an "inkjet" method, where adhesive is applied to specific areas. After multiple layers are deposited, the unbound powder is removed, resulting in a complex 3D object. 3DP can be used to produce ceramic, metal, and metal/ceramic composite parts, functioning either to directly print the final part or create a mold. However, 3DP scaffolds still have limitations in replicating the nanoscale extracellular matrix properties of the tissues they are designed to replace [25].

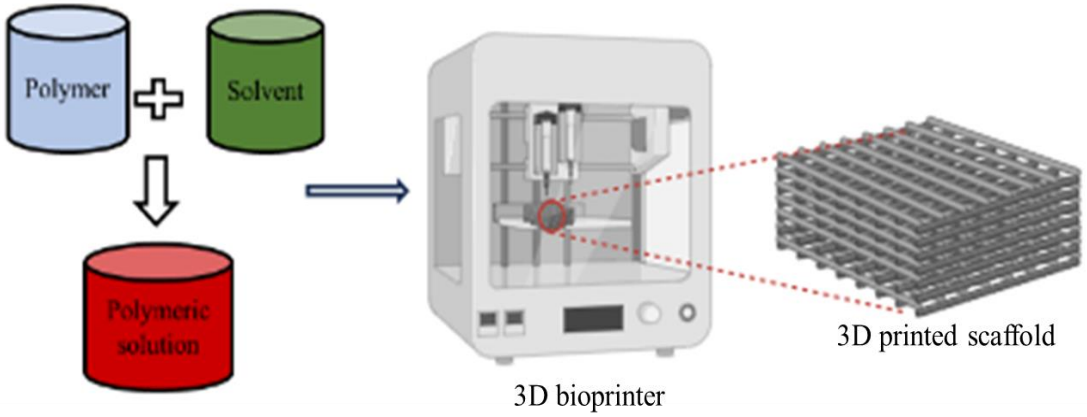

Fig. 4: 3D scaffold fabrication using 3D printing

POLYMERS USED IN THE FABRICATION OF SCAFFOLDS:

Polymers play a crucial role in fabricating scaffolds for wound healing, offering a variety of properties that enhance tissue regeneration. Both natural and synthetic polymers are utilized to create scaffolds (Table 1) that mimic the extracellular matrix (ECM), facilitating cell adhesion and proliferation.

Natural Polymers: Natural polymers commonly include collagen, chitosan, hyaluronic acid, keratin, and gelatin. These materials are biocompatible and biodegradable, promoting cellular activities essential for wound healing [26-28].

Synthetic Polymers: Polylactic acid (PLA), polyglycolic acid (PGA), and Polycaprolactone (PCL) are favored for their mechanical strength and tunable properties. They can be processed into various forms, including electrospun nanofibers, which provide a scaffold-like structure for tissue growth [29-31].

MECHANISM OF ACTION:

Scaffolds play a crucial role in wound healing by facilitating cell recruitment, enabling controlled drug release, and promoting tissue regeneration. Their design and material properties significantly enhance the healing process.

Cell Recruitment

Scaffolds, such as the radially aligned nanofiber scaffold (RAS), create pathways that facilitate cell migration from the wound edges to the center, enhancing healing efficiency.

The incorporation of growth factors like EGF and VEGF in scaffolds promotes cell proliferation and angiogenesis, respectively, which are vital for effective tissue repair [32].

Controlled Drug Release

Scaffold-mediated drug delivery systems allow for localized and sustained release of therapeutic agents, improving the healing environment and addressing challenges associated with traditional dressings [33].

Nanofiber scaffolds, due to their high surface area and porosity, are particularly effective in drug loading and release, ensuring that therapeutic agents remain active and are delivered at the right time.

Tissue Regeneration

Advanced scaffolds not only support cell attachment and growth but also mimic the extracellular matrix, promoting collagen deposition and re-epithelialization, which are essential for tissue regeneration [34]. The use of multifunctional scaffolds has shown significant improvements in granulation tissue formation and overall wound healing outcomes.

Table 1: Commonly used polymers and methods for fabrication of scaffolds.

Polymer	Bioactive agent	Fabrication technique	Summary	Reference
Collagen + Chitosan	Norfloxacin	Freeze drying	Enhance wound healing through effective drug delivery	34
Chitosan+ Gelatin	Ciprofloxacin	Freeze drying	Strong antibacterial properties and excellent biocompatibility.	35
Polycaprolactone (PCL)	Pomegranate Peel Extract	Electrospinning	Exhibited significant antioxidant properties, higher antimicrobial activity,	36
Polycaprolactone, Hyaluronan	Epidermal growth factor (EGF)	Electrospinning	Promoted cell proliferation and infiltration, upregulated wound-healing genes (collagen I, collagen III, and TGF-β), and enhanced tissue regeneration.	37
Polycaprolactone (PCL)	Levofloxacin	3D printing	Excellent mechanical properties and sustained drug release	38
Polyvinyl alcohol	Quercetin	Freeze drying	Improved mechanical strength and water resistance	39
Collagen, Silica	*Cynodon dactylon* extract	Freeze drying	Enhanced stability and accelerated healing with enhanced collagen deposition	40
Silk fibroin, poly(lactic-co-glycolic acid) (PLGA)	Curcumin	Thermally Induced Phase Separation	Sustained drug release	41
Polycaprolactone, Polyvinyl alcohol	Metformin	3D printing	Controlled Drug Release, Improved Biocompatibility	42
Collagen, Chitosan	Pioglitazone	Freeze drying	Sustained drug release, accelerated diabetic wound recovery	43
Polyvinylpyrrolidone	Aloe vera	Electrospinning	Increased thermal stability and provided antibacterial effect	44
Chitosan, Alginate	Silver sulfadiazine	3D printing	Strong antimicrobial activity	45
Fibrin, Chitosan, Keratin	Ferulic acid	Freeze drying	Extended drug release, improved cell adhesion and proliferation, and strong antibacterial activity	46
Collagen, Chitosan	Glibenclamide	Freeze drying	Enhanced wound healing with no scarring	47
Poly(lactic-co-glycolic acid), silk fibroin	Zinc oxide	Electrospinning	Improved wound closure, accelerated re-epithelialization, enhanced granulation tissue formation, and increased collagen deposition.	48

Recent studies highlight the potential of biodegradable polymers and composite materials in wound treatment, which support tissue regeneration, provide controlled drug delivery, and have antibacterial properties. These scaffolds have gained attention for enhancing healing processes across wound types like diabetic ulcers [49].

Diabetic Ulcers

Bioactive ingredients in polymer-based dressings, particularly for diabetics, have shown promising results in wound care and healing, including antibiotics, phytoconstituents, anti-diabetic agents, and growth factors [49].

Antibiotics

Research on antibiotic-loaded nanofibrous scaffolds for wound dressings, particularly for diabetic wounds, focuses on delivering localized therapy. These scaffolds provide targeted treatment, enhancing effectiveness while minimizing the adverse effects associated with systemic antibiotic absorption [58].

Lee *et al*. developed nanofibrous PLGA scaffolds loaded with vancomycin, gentamicin, and platelet-derived growth factors (PDGF) for diabetic wound repair. These scaffolds release PDGF, vancomycin, and gentamicin over three weeks. In the early phases of infected diabetic wound repair, the scaffolds decrease the content of phosphatase and tensin homolog, improve angiogenesis indicators, and speed up wound healing. [50]. Jafari *et al*., fabricated bilayered nanofibrous scaffolds made from polycaprolactone and gelatin, containing amoxicillin and zinc oxide nanoparticles, demonstrated their potential for wound healing. The scaffolds showed smooth microstructures, sustained release of amoxicillin, and antibacterial activity. In vivo tests on full-thickness rat models

showed they accelerate wound contraction, increase collagen deposition, angiogenesis, and prevent scar formation, making them promising candidates for full-thickness wound treatment [51].

Herbs and Phytoconstituents

Phytochemical-loaded scaffolds are gaining prominence as innovative solutions for diabetic wound healing, capitalizing on the therapeutic potential of natural extracts. Recent research underscores several cutting-edge strategies that enhance wound recovery in diabetic patients, offering a promising avenue for more effective and natural treatment options. Curcumin, a key component of turmeric, is a naturally occurring polyphenol known for its wide range of beneficial biological effects [52]. These include anti-cancer, antioxidant, and anti-infective properties, as well as angiogenic, neuroprotective, and anti-inflammatory activities [53]. Additionally, curcumin possesses inherent antimicrobial characteristics, making it a potent compound for various therapeutic applications. Yadav *et al.* developed an electrospun multifunctional nanofiber composed of a chitosan-polyvinyl alcohol (PVA) blend, loaded with curcumin and zinc oxide, aimed at enhancing dediabetic wound healing in STZ-induced diabetic rats. The nanofiber exhibited sustained release of Curcumin and Zinc oxide, demonstrated low cytotoxicity, and showed strong antibacterial and anti-biofilm properties [54]. Karri *et al*. developed a novel nanohybrid scaffold by incorporating curcumin into chitosan nanoparticles (CUR-CSNPs) to enhance curcumin's stability and solubility. This nanohybrid was integrated into a collagen scaffold to promote tissue regeneration. Various evaluations, including particle size, zeta potential, morphology, and biodegradability, were conducted on the CUR-CSNPs. The results indicated that the CUR-CSNPs significantly improved curcumin's stability and solubility. The nanohybrid scaffold exhibited favorable in vitro properties such as enhanced water uptake, biocompatibility, and sustained drug release. *In vivo* studies showed that wounds treated with the nanohybrid scaffold contracted much faster compared to those treated with control or placebo scaffolds [55]. Plant extracts have long been recognized for their wound healing properties, and various botanical sources have been explored for this purpose [56]. Aloe vera is one of the most widely used plant extracts due to its anti-inflammatory, antimicrobial, and moisturizing properties, which promote faster wound healing and reduce scarring [57]. Ghorbani *et al*. developed nanofibers (NFs) made from Zein, polycaprolactone (PCL), and collagen using the electrospinning technique, incorporating zinc oxide nanoparticles (ZnO NPs) and Aloe vera (Alv) into the fibers. Among the formulations, NFs with 1% ZnO and 8% Alv, in a Zein/PCL ratio of 70:30, showed the best thermal stability and mechanical strength. Cell culture studies demonstrated that these NFs were cytocompatible and supported cell adhesion. Additionally, the NFs containing ZnO and Alv exhibited antibacterial properties against Staphylococcus aureus and Escherichia coli. These results suggest that the prepared NFs could be promising scaffolds for wound healing applications [59]. Resveratrol is a natural polyphenolic compound found primarily in the skin of red grapes, berries, and some nuts. It is well-known for its antioxidant, anti-inflammatory, and anti-aging properties. Resveratrol is considered a promising compound in wound healing applications, especially when incorporated into topical formulations or wound dressings. It offers a multifaceted approach to enhancing the body's natural healing processes while also protecting against secondary complications like infection and excessive inflammation [60]. Moghaddam *et al*., developed a polyelectrolyte complex using electrospinning to create nanofibrous mats composed of chitosan (CS) coated with hyaluronic acid (HA), resveratrol (RS), and adipose-derived stem cells (AD-MSC). The CS/HA/RS scaffold combined with AD-MSC was tested as a wound dressing in a male rat skin wound model. The scaffold demonstrated over 80% cell viability when tested with human dermal fibroblasts and showed good cytocompatibility [61].

Anti-Diabetic agents

Metformin is a widely used glucose-lowering agent and first-line medication for type 2 diabetes mellitus. Recent studies have shown that it can accelerate wound healing, making it a valuable treatment option. Tombulturk *et al*., found that topical metformin application promoted cell growth, reduced cell death, and increased collagen production, especially in diabetic wounds. This suggests that topical metformin could counteract diabetes negative effects on wound healing, potentially leading to faster healing and improved repair [62]. M.E. Cam *et al*., created nanofibrous scaffolds containing oral antidiabetic drugs, pioglitazone, metformin, and glibenclamide, to accelerate diabetic wound healing in type-1 diabetic rats. The combination therapies, including chitosan/ gelatin/polycaprolactone and polyvinyl pyrrolidone/PCL composite nanofibrous scaffolds, improved dermis and epidermis regeneration, reduced inflammation, and hair follicle formation. The study concluded that metformin and pioglitazone-loaded nanofibrous scaffolds offer high bioavailability, fewer side effects, and reduced drug dosage and amount [63].

Growth Factors

Growth factors are essential signaling molecules that play a crucial role in various biological processes, including wound healing. In the context of diabetic wounds, certain growth factors are particularly important for promoting tissue regeneration and preventing complications. Choi, J.S *et al*., developed electrospun nanofibers containing recombinant human epidermal growth factor (EGF) for diabetic wound healing. The EGF-conjugated nanofibers were biocompatible and promoted keratinocyte differentiation in vitro. In vivo studies demonstrated superior wound healing activity in diabetic animals compared to controls or EGF solutions. The increased expression of EGFR in the EGF-nanofiber group suggests a potential mechanism for enhanced wound healing [64].

Losi P *et al*., developed a scaffold containing poly(ether)urethane–polydimethylsiloxane, fibrin, and vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) -loaded PLGA nanoparticles for diabetic wound healing. The scaffold significantly accelerated wound closure in diabetic mice compared to controls, with complete re-epithelialization and enhanced tissue formation. These findings suggest its potential as a dressing for diabetic foot ulcers [65].

CONCLUSION

In conclusion, advanced biodegradable scaffolds represent a promising frontier in wound healing, offering innovative solutions to improve tissue regeneration and recovery. Through a combination of biocompatibility, structural support, and bioactive functionalities, these scaffolds play a critical role in creating an optimal healing environment. Advances in fabrication techniques, such as 3D printing and electrospinning, allow for precise control over scaffold architecture, enhancing their ability to mimic natural tissue. The incorporation of bioactive compounds, growth factors, and cells into scaffold designs further augments their capacity to accelerate wound healing and reduce complications like infections or chronic wounds.

While significant progress has been made, challenges remain in terms of translating lab-scale successes to clinical applications. Future research should focus on refining scaffold properties to better tailor them to specific wound types, as well as on scaling up production for widespread clinical use. Additionally, long-term studies are needed to fully understand the interaction between biodegradable scaffolds and the biological environment over time. Nonetheless, the potential of biodegradable scaffolds to revolutionize wound care and promote efficient healing cannot be overstated. Their development is set to play a pivotal role in advancing personalized and regenerative medicine.

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How to cite this article:
Grace Rathnam et al. Ijppr.Human, 2025; Vol. 31 (5): 296-305.
Conflict of Interest Statement: All authors have nothing else to disclose.