Wound Dressing Applications of Herbal Based Biological Active Compounds

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Abstract

Wounds are inevitable in life; the rapid healing process can reduce the costs of therapy and hospitalization, but the ideal availability of the drugs for wound healing therapy is limited due to the complex nature of the skin tissue. The novel medicines for wound healing and skin regeneration, herbal-based therapeutic agents, can be alternative medications. Recently, biologically active scaffolds have been widely used for wound healing therapy. These scaffolds are extracellular matrices and can induce tissue regeneration. Here, we present a review of several scaffolds by combining biological polymers with the extracts obtained from various plants. It should be noted that chemical and synthetic agents, which are known to be harmful to the environment and human health, were prepared with completely environment-friendly herbal extracts with biological polymers, which are frequently used in the biomedical field. Plant-based scaffolds augment wound healing and provide better tissue regeneration with minimal negative effects on the skin. Scaffolds can be prepared by choosing proper polymer and extract types, which are combined to get unique properties of scaffolds that lead to an innovative and eco-friendly approach in wound treatment applications.

Keywords: Scaffolds, wound healing, skin, Herbal extracts, biological polymers.

Introduction

Wound healing is a complicated and regulated sequence of several well-coordinated biochemical and cellular phenomena to restore the integrity of the skin. Wound healing involves three main overlapping phases: inflammation, proliferation, and maturation. For patients who have a large area of skin affected and those suffering from chronic wounds, the healing process does not progress in a timely and orderly manner. In such cases, healing stalls in the inflammation phase. And it is characterized by excessive levels of pro-inflammatory cytokines, proteases, and senescent cells, as well as the existence of persistent infection. Hence, the therapeutic intervention is to reduce inflammation and initiate tissue regeneration in a faster and more effective manner. Currently, most therapies for treating wounds are symptomatic, using analgesics and anti-inflammatory agents along with antibiotics to prevent infection and not promote tissue regeneration. It has become a major challenge to health care systems worldwide [1-3].

Tissue engineering is an emerging interdisciplinary field that applies the principles of both biology and engineering. The basic concept of tissue engineering lies in its ability to utilize and extensively exploit living cells. It can be used to facilitate the growth of damaged or diseased tissues by applying a combination of biomaterials and bioactive molecules. Among them, biodegradable polymeric scaffolds have received much attention as they offer a temporal and spatial environment for tissue growth [4-10].

Scaffolds

Scaffolds are 3D artificial porous structures in which extracellular matrix, drugs, and growth factors combine to regenerate tissue. Scaffolds serve as a platform for cellular localization, adhesion, and differentiation, as well as a guide for the development of new functional issues. Scaffold material assists in mimicking natural extracellular lar material and accommodates the cells in their natural milieu. The extracellular matrix (ECM) consists of various growth factors, characteristic proteins, and glycoproteins. It plays a pivotal role in controlling cell adhesion, migration, proliferation, and differentiation. Typically, scaffolds consist of polymers, bio-ceramics, and hybrid materials. The success of scaffolds depends on finding appropriate polymer materials. Scaffolds prepared with singe polymer shows poor physicochemical propertieshich cause difficulty in handling, storage, and application.

Table I: Currently commercially) available scaffolds and its polymers.

Brand name	**Scaffold material**
Apligraf	**Bovine collagen**
Orcel	**Bovine collagen sponge**
Tissue tech autograft system	**Hyaluronic acid membrane**
Laser skin or Vivoderm	**Hyaluronic acid membrane**
Bioseed S	**Fibrin sealant**
Hyalograft	**Hyaluronic acid membrane**

Scaffolds can be manufactured using a number of approaches, including lyophilization, phase separation, electrospinning, stereolithography, and the efficacy of the medicinal plants incorporated into scaffolds. This stimulated the authors to provide a comprehensive review of the plant-based scaffolds obtained by different methods and their effective role in wound healing.

Advantages

1. Promote cell adhesion and ECM deposition
2. Promote cell - biomaterial interactions
3. Permit sufficient transport of gases, nutrients and attachment and proliferation of fibroblasts
4. Biodegradable, al low cell survival, proliferation and differentiation.

Table 2: Natural biomaterials intended for skin substitution which are currently under investigation.

Brand name	Scaffold material
Permaderm/Cincinnati shrines skin substitute	Bovine collagen

Acudress	Fibrin substrate
Allox	Fibrin substrate
Cyzact (ICX -PRO) [chronic wound repair	Fibrin gel
Biodegradable polyurethane Microfibers	Biodegradable polyurethane Microfibers
Silk fibroin and alginate	Silk fibroin /alginate blended sponge
Bovine collagen cross l inked with microbial transglutaminase	Bovine collagen cross l inked with microbial transglutaminase
Collatamp	Multilayer bovine collagen matrix

Novel biodegradable scaffolds can be manufactured using natural extracts and polymers for enhanced wound healing and better tissue regeneration. Plant extracts and their phytoconstituents have been promising wound-healing agents since ancient times. These natural extracts can be preferred over synthetic products due to their high efficacy, low cost, and limited adverse effects. But its use has fallen owing to its poor bioavailability and stability issues. Natural extracts are incorporated into biological-based polymers that aid in wound healing and tissue regenerative processes. Scaffolds with a combination of natural extracts and polymers can enhance skin regeneration, while the limitations of individual components can be overcome simultaneously 1 0 The advantageous efficacy of the medicinal plant-incorporated scaffolds stimulated the authors to provide a comprehensive review of the plant-based scaffolds obtained by different methods and their effective role in wound healing [11-16].

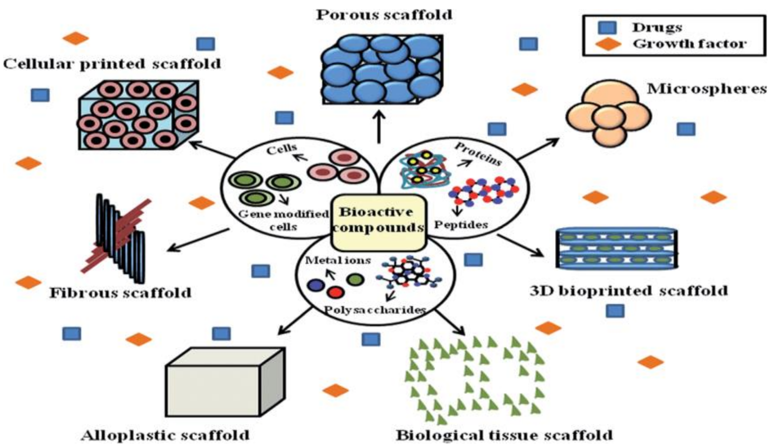

Figure 1: Design and manufacture of different types of scaffolds

Aloe Vera derived nanofibrous scaffolds

Aloe vera, which is rich in components like mannose-6-phosphate and acemannan, has been used for wounds, burns, skin inflammation, and insect stings since ancient times. Antioxidant, anti-inflammatory, anti-microbial, and immunomodulatory properties highlight its biomedical applications. It mediates the cell signaling pathway for the proliferation of fibroblasts. It promotes epithelization and collagen synthesis for effective wound healing. Silk fibroin, a natural protein obtained from silk worm (Bmnhyx rnorri) has proteins such as sericin and fibroin. Fibroin has higher elastic strength, strong mechanical properties, biocompatibility, and slow degradability, hence being used for biomedical applications. Additionally, fibroin can m1 m1c extracellular matrix X and efficiently support cell attachment and proliferation of fibroblast. Thus, aloe regulatory factors Vera and silk fibroin are attractive materials for tissue engineering. Scaffolds can be prepared by combining their unique properties using the electro-spinning technique. The nanofibrous scaffolds show a finer morphology, expressing amino and esteric groups with improved hydrophobicity and a favorable tensile strength of 11.6

percent, which is desirable for skin tissue engineering.

Biological studies show favorable fibroblast proliferation compared to control, which almost increased linearly by 34.6% on day 3 and 97.86% on day 9, with higher expression of CMFDA (5-chloromethylouroesin diacetate), collagen, and f-actin properties. Accordingly, fibroblasts adopt an elongated morphology, stimulating large disruptions in the ECM at the wound site. Human fibroblast cells adhere to and proliferate well on these matrixes owing to different components present in a layer of vera (promoting cell proliferation) and silk fibroin (providing a stable environment) and thus promote the regenerative process of human fibroblast cells, which is suitable for dermal application. Suganya et al. (2014 synthesized nanoscale fiber scaffolds using electrospinning technique with polycaprolactone (PCL) containing lyophilized powder (5% and 0%) aloe vera (AV). It is compared with the PCL/collagen blend. PCL-AVI 0% nanofibre scaffold shows finer fiber morphology with improved hydrophilic properties and tensile strength. These matrixes favor cell proliferation compared to other scaffolds [17-19].

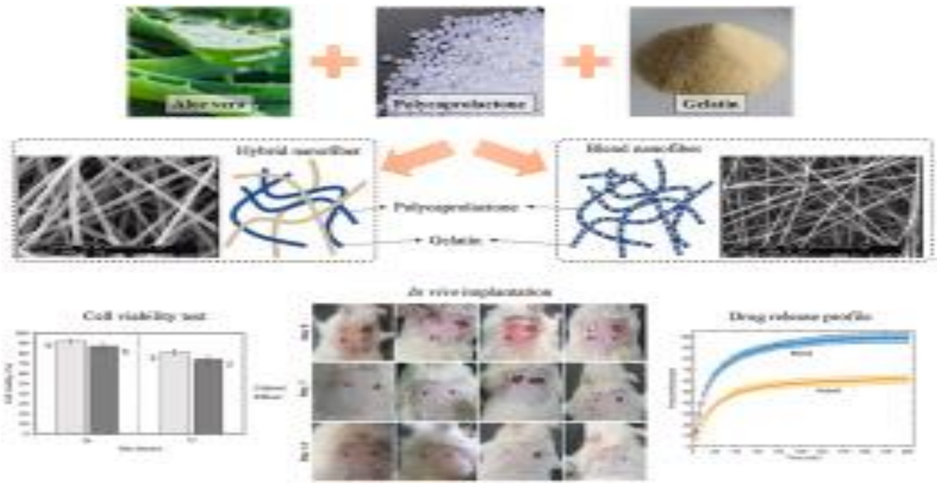

Figure 2: Aloe Vera derived nanofibrous scaffolds

CMFDA dye expression, secretion of collagen, and F-actin expression were also high. Studies conclude that PCL-AV 0% scaffold in comparison with scaffolds of PCL/collagen will serve as a better tissue engineering scaffold because of its relatively low cost, natural origin and water retention properties. Jouybar A et al. (2021) investigate the potential capacity of poly-l-lactic acid (PLLA) nanofibrous scaffolds coated with *aloe vera* gel for wound dressing applications. The electrospinning method was used for preparing PLLA nanofibers, and its influence on wound healing was investigated with and without aloe vera gel. SEM and MTT assays confirm the nanometer size and biocompatibility of nanofibrous scaffolds. Macroscopic evaluation shows that gel-coated scaffolds enhance the wound healing process compared with other groups. It can accelerate wound healing by shortening inflammatory phase, increasing fibroblast maturation, tissue proliferation, collagen formation, and epithelium productions.

Frutalin scaffolds

Plant lectins are carbohydrate-binding proteins that can interact with cell surfaces to start anti-inflammatory pathways and immune-modulatory functions. Frutalin is a tetrameric lectin isolated from *Artocarpus incisa* seeds, popularly known as breadfruit lectin. Frutalin has been proven to be most effective in fibroblast migration. Frutalin has several other biological activities. It is cytotoxic to tumor cells, chemotactic for rats and human neutrophils, and a potent mitogen of human lymphocytes. It is an inhibitor of orofacial noception in acute and chronic pain, mediated by TRPA 1, TRPV 1, and TRPM 8 receptors. It has anti-depressant like actions and protect against ethanol-induced gastric lesions.

Figure 3: Frutalin scaffolds

Polysaccharides, including galactornannans and hemicellulose, are found mainly in the endosperm of legume seeds. Galactornannans are polymers with a β-(1,4)-D mannose backbone and D galactose side units linked by α-(1,6). These polymer-containing systems are now receiving wider global interest owing to their structural features, rheology, and negligible biological toxicity" De Sousa et al., 201, incorporated frutalin into an immobilization matrix of galactomannan. These lectin scaffolds have an average membrane porosity of 0.00 µm, which is sufficient to ensure water vapor permeability. It enhances angiogenesis, fibroblast, and keratinocyte proliferation. Frutalin/galactomannan hybrid scaffold formulation can be an effective health care solution for wounds and burns in surgical patients at a lower cost than current treatment plans [20-22].

Curcumin loaded collagen scaffolds

Curcumin, also known as diferuloylmethane, is a naturally derived active agent of the perennial herb Curcuma longa. Its anti-inflammatory, antimicrobial, and antioxidant properties significantly improve wound healing and protect tissues from oxidative damage. However, low bioavailability and permeability hinders its application. Chitosan is one of the most plentiful polysaccharides existing in nature. It is a deacetylated derivative of chitin. It is biologically renewable, biodegradable, biocompatible, antimicrobial, non-antigenic, non-toxic, and bio functional. Collagen is the most abundant protein that has been extensively used for scaffold fabrication. It is degraded by the enzyme collagenase which leads to the formation of gelatinized fragments. These fragments are cleaved by several non-specific proteases. It results in the cellular infiltration of fibroblasts and can synthesize new extracellular matrix components for tissue regeneration. One of the disadvantages of collagen being utilized as a scaffold is its biological instability. Chemical cross-linking l inki ng or hybridization with natural polysaccharides are regarded as efficient methods method s to reduce the easy degradation of collagen and enhance its weak mechanical properties. Curcumin chitosan nanoparticle cs impregnated into collagen alginate scaffolds can prepared by emulsification method.

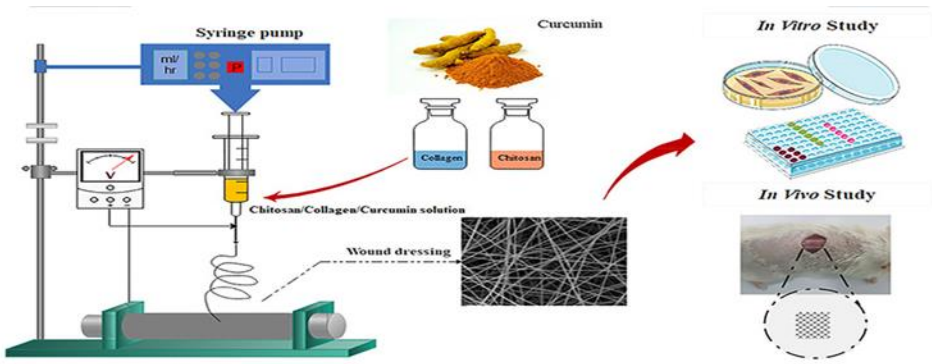

Figure 4: Curcumin loaded collagen scaffolds

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These nanofibre scaffolds show good water uptake, biocompatibility, and sustained release of drugs. In vitro wound closure analysis, anal is revealed reveals that nanohybrid scaffold-treated wounds contracted much faster and complete epithelialization with granulation occurs. Hence, synergistic combination of curcumin, chitosan, collagen, alginate have better wound healing capability. Rezaei et al., 201 8 synthesized and characterized scaffolds with curcumin nanoparticles and bio composable polymers named collagen (C) and chitosan (Ch). Research confirms that scaffolds with lower collagen content have more homogenous pore sizes. Curcumin nanoparticles incorporating C1Ch2 scaffolds demonstrate the best physiochemical characteristics. Both the lower content of collagen and the higher content of chitosan in the scaffolds are ideal parameters in the scaffolds is an ideal parameter in the wound healing process. In vivo and in vitro wound healing studies present a great closure of wounds with enhanced histological parameters in the wounds treated with C -C l Ch2 scaffolds compared to other scaffolds. Thus, the results indicate that curcumin nanoparticles incorporated into collagen/chitosan scaffolds could significantly improve wound healing.

Centella asiatica impregnate dermal scaffolds

Centella asiatica extracts are rich in tannins and phenolic derivatives and own antioxidant and wound healing properties. However, delivery of extract becomes a matter of concern due to its poor bioavailability and stability. *Centella asiatica* extract incorporated collagen scaffold ensures better work and healing by acting as a physical support for cellular proliferation. Collagen acts as a wound healing agent, possessing biodegradable and biocompatible properties. Studies on male whistar rats with 1.5% Centella *asiatica* extract incorporated collagen scaffolds reveals the high amount of hydroxyproline content as compared to marketed formulation. Histopathologic examination shows more production of collagen and rise in fibroblasts, resulting in epithelium gap reduction.

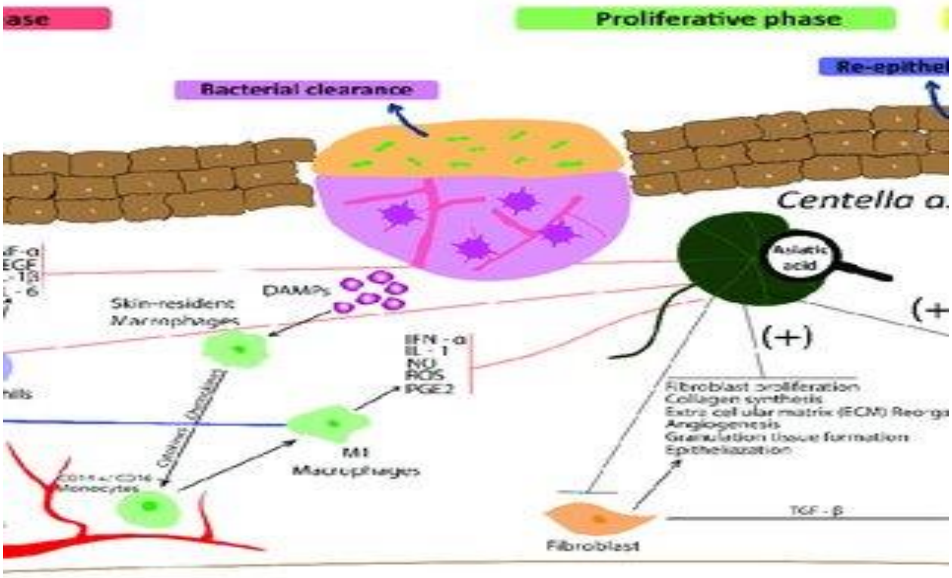

Figure 5: *Centella asiatica* impregnate dermal scaffolds

Silver nanoparticle loaded collagen scaffolds

Silver nanoparticle is an effective anti-microbial agent and is a promising method for bum treatment. Silver nanoparticle loaded collagen chitosan scaffolds enhance voltage of 20 Kv necessary for cell regeneration display optimal characteristics attachment and skin tissue wound healing by regulating fibroblast migration and macrophage activation. Combi nation of silver nanoparticles and dermal scaffolds serves as a carrier for particles to preserve their insitu functions. It empowers the scaffolds with the ability to stimulate the immune response, cell migration, and achieve rapid regeneration and high-quality repair. Wound healing studies on Sprague Dawley rats showed increased level of pro-inflammatory agents, scar-related factors, and SMA factors. On day 60, scaffold's regenerated skin has a si mi lar structure compared to normal skin.

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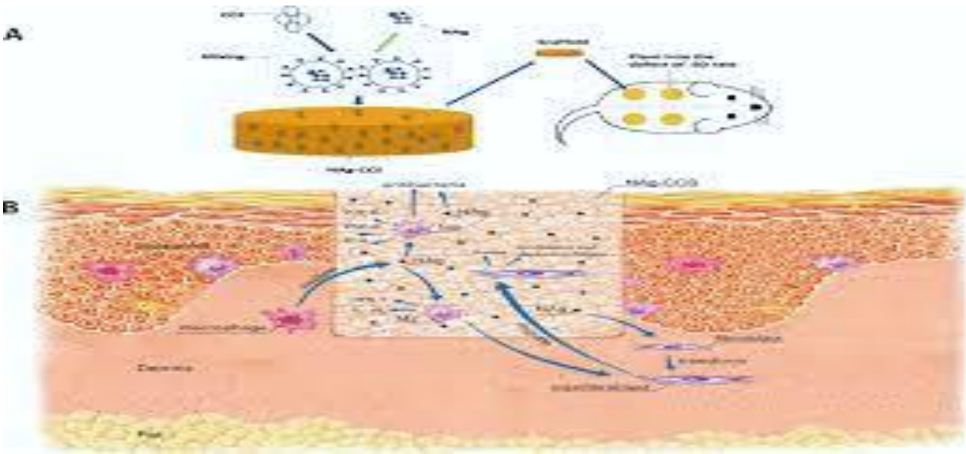

Figure 6: Silver nanoparticle loaded collagen scaffolds

Lentil seeds loaded bio scaffolds

Lentil seeds are arced in bl e legume seeds of Lens esculenta and Lens culinaris. Lentil seed has good free radical scavenging activity. Lentil seed extracts loaded chitosan/sodium alginate bio scaffolds have significant mechanical properties. Studies on albino rats confirms significant difference in antibacterial and wound healing activity when compared to blank composite scaffolds. These are applied externally on wounds without any need for removal after healing. Moreover, as the concentration of soil alginate increased, the mechanical properties of scaffolds were significantly improved.

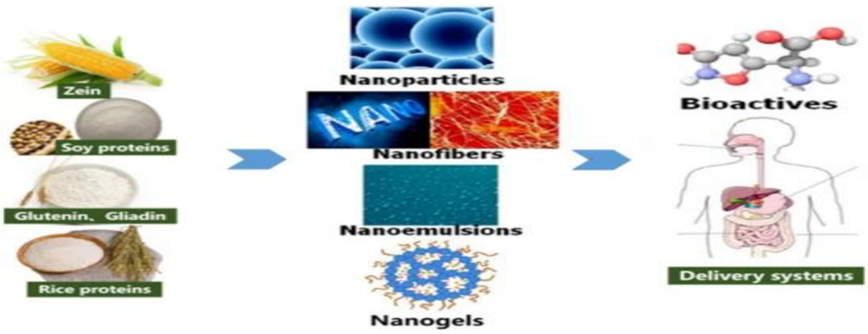

Figure 7: Lentil seeds loaded bio scaffolds

Lithospermii radix extract containing nanofibre scaffolds

Lithospermii radix (LR) extract were obtained from root of Lilhospermum erythrorhizon and have been practiced for treating wounds for hundreds of years. The main ingredients of Lithosp ermii radix (LR) extract are shikonin, isobutyl shikonin, β-hydroxyl-isovaleryl-shikon in, α-methyl-n-butyl-shikonin, and quinones. Shikonin, a derivative of naphthoquinone, has have several pharmacological properties including antibacterial, wound healing, and anti-inflammatory effects. The wound healing effects of shikon in are related to epithelial mesenchymal transition (EMT) which is a cell trans differentiate ion process important for wound healing. TG F-P signaling play an important role in EMT 34. Gelatin, a collagen derivative contains Arg-Gly-Asp-like amino acid sequences that promote cell adhesion and migration. Lithospermii radix extract was added to biocompatible gelatin solution. Various ratios of gelatin and collagen were added onto chitosan scaffolds to manufacture bilayer scaffolds. Porous chitosan scaffolds with a high swelling ratio show exudate absorption ability. In vivo wound healing studies in Sprague Daw ley rats conclude that CGF9TL bi layer scaffolds give highest wound recovery rate. CGF9 gelatin nanofibers electrospun at a constant flow rate 0. 1 ml/hour and voltage of 20Kv display optimal characteristics necessary for cell attachment and skin tissue regeneration.

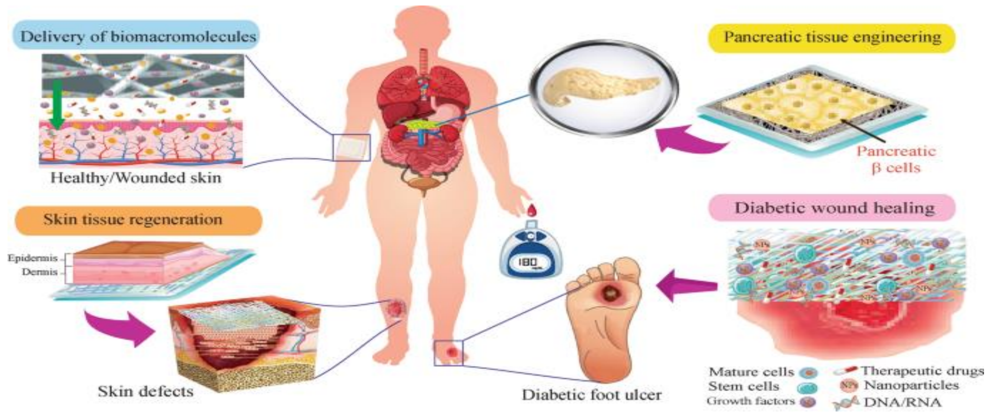

Figure 8: Lithospermii radix extract containing nanofibre scaffolds

Dual layered 3D nanofibrous scaffold

Fibrin is a good hemostatic agent that aids in the issue resolution, absorption of exudates, and act as one of the key components in biomaterial development. Keratin, an insoluble protein with higher cysteine residues, has a significant role in the physical and biological properties of biomaterial. Poly β-hydroxybutyric acid is a highly biocompatible, biocompatible polymer. Keratin, fibrin, gelatin 3 D sponge loaded with muciprocin was prepared using the freeze-drying method with naturally derived materials from bovine origin. Poly β-hydroxy butyric acid, gelatin, and solution were loaded with curcumin to get dual drug loaded dual layered nanofibrous spongy scaffold. It promotes gaseous exchange, absorption of exudates, and facilitate interaction with the host tissue. In vivo assessment using an in vivo model shows increased collagen deposition and granulation tissue formation.

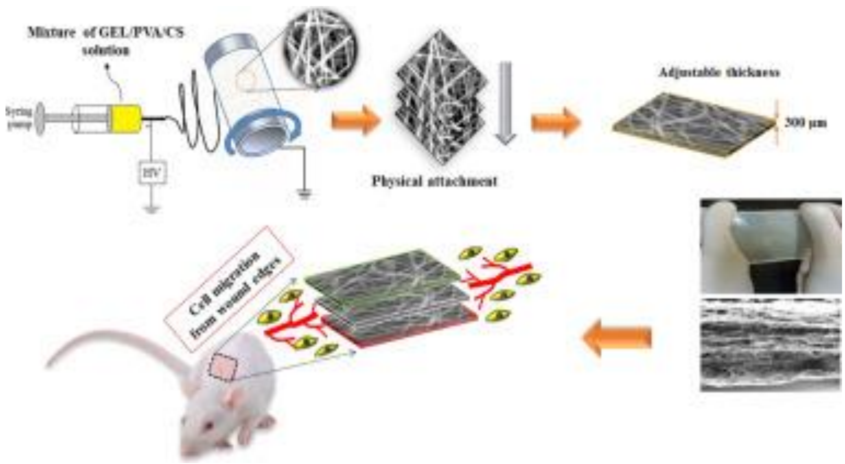

Figure 9: Dual layered 3D nanofibrous scaffold

Calendula officinalis loaded nanocomposite scaffolds

Calendula officinalis is commonly used for skin wound treatment. Among natural polymers, gum Arabic (acacia gum) is a polysaccharide that has traditionally been used for tissue engineering scaffolds. It has many advantages in repairing and regenerating the skin. Calendula officinalis is loaded PCL gum arabic nanofibrous scaffolds can be prepared by electrospinning and possess a diameter distribution in the range of 85–290 nm. Tensile strength and length were in the range of 2.13-4.41 MPa and 26.37-74.37%, respectively, making it ideal for skin t issue engineering. The scaffold's porosity was greater than 60% making it suitable for the proliferation of fibroblast cells.

Figure 10: Calendula officinalis loaded nanocomposite scaffolds

Accordingly, cell culture indicated that both Calendula officinalis and gum arabic promote cell attachment and proliferation and are well used for regenerating skin. Ronald et al.,2014) modified a collagen scaffold with polymeric microparticles and hydro glycolic extract of Calendula officinalis flowers. Subsequently loaded microparticles made of gelatin and collagen were produced by cross linking method. Invitro assessment indicate that the n corporation of gelatin-collagen macroparticles increase the resistance of scaffolds to enzymatic degradation. A sharp decrease in cytotoxicity and prolonged release of extract were attained with these scaffolds. Results support the potential of scaffolds to develop innovative skin substitutes with improved
features.

Lawsonia inermis nanofibrous scaffolds

Lawsonia inermis, which is also henna, contains several polyphenolic compounds. Recently, several pharmacological benefits have been reported for Lawsonia inermis such as immunomodulatory, antioxidant, wound healing, and anti -microbial properties. No gentotoxic inertia has been reported for Lawsonia inermis. Gelatin is one of the most commonly used polymers. But gelatin nanofibers lack the desired mechanical properties. Biocompatible polymers like polylactic acid (PLLA) have been used to fabricate tissue in engineering applications. It offers desired mechanical properties. Lawson's inermis was incorporated into gelatin, and it was electro spun with PLLA to fonn hy br id n an fibrous scaffolds. lawsoina Inermis in an ofibers scaffold can kill both gram positive and E. coli bacteria in 2 hours, and it shows good biocompatibility on fibroblast cells. PLLA/Gelatin Lawsonia il1ermis nanofibers can be used as a wound dressing to prevent infection and accelerate wound healing.

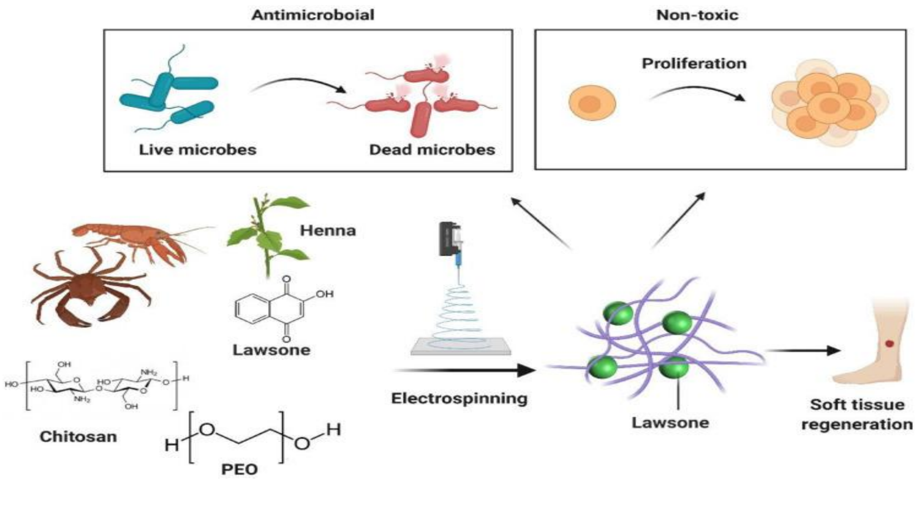

Figure 11: Lawsonia inermis nanofibrous scaffolds

Electrospun scaffold of Panchvalkal powder

Panchavalkal consists of the stem barks of five trees, namely Ficus bengalensis, Ficus lacor, and Ficus recemosa. Ficus religeosa and Thespesia populnea in equal proportions. Elcctrospun scaffold was developed by using biodegradable polymer and Panchvalkal powder (PY). Positively charged smaller particle size (40nm) is preferred red for greater penetration through epidermal barrier. In vivo studies on albino rats show better wound healing efficiency due to higher wound area contraction, less inflammation, faster epithelization, and vascularization.

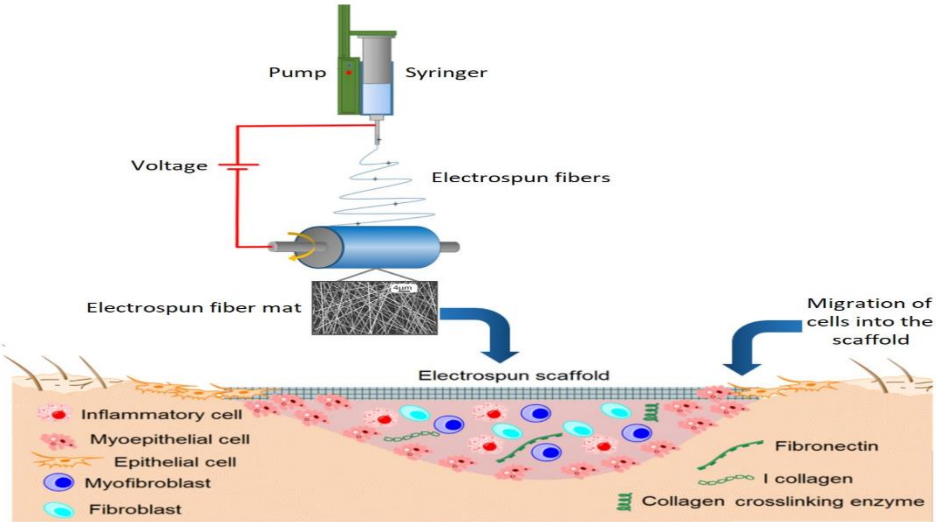

Figure 12: Electrospun scaffold of Panchvalkal powder

Complete biodegradation confirms its green nature. The elongated and spread-out morphology of PLA-PY scaffolds results in much better cell attachment in scaffolds than other systems. It has benefits over traditional systems as it is an uncontrolled dispersion. Histological analysis supports excellent epithelization and vascularization in scaffold-treated wounds as opposed to solutions and films. Clinical trials conducted demonstrate very good results when healing the developed scaffold [23-25].

Conclusion

Natural extracts have been practiced for healing since ancient times. Natural agents were loaded into scaffolds of biological polymers. Biodegradable herbal scaffolds show that they can be used as an atraumatic agent to treat different skin damage, which could be used in tissue engineering. Chemical and synthetic polymers are less preferred over biologic-based polymers due to their harmful effects on the environment and human health. Here, we reviewed scaffolds produced using completely environmentally friendly herbal extracts and biological polymers. Combinations of different natural extracts and biologically-based polymers in scaffolds help the body heal and grow new tissue. Currently, commercially available tissue-engineered scaffolds cannot be fully replacing the functional properties of native skin after wound healing. Rapid progress in tissue engineering and different approaches to design a scaffold, mainly including a natural extract is a promising one in coming years.

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