Chapter

Polymeric Biomaterials for Wound Healing Incorporating Plant Extracts and Extracellular Matrix Components

Margaret O. Ilomuanya, Ibilola M. Cardoso-Daodu, Uloma N. Ubani-Ukoma and Adannaya C. Adebona

Abstract

Biomaterials are constructed to promote or stimulate the processes of wound healing. Polymeric biomaterials can be used to hydrate the wound and serve as barrier to pathogens with plant extracts, antimicrobial agents and extracellular components incorporated to stimulate the healing process. The biological and physical augmentation provided by extracellular matrix derived implants continues facilitate innovation in biomaterials utilized in management of nonhealing wounds. Tissue-processing methodologies can birth extracellular matrix-based devices with characteristic post-implantation responses ranging from the classic foreign body encapsulation of a permanent implant, to one where the implant is degraded and resorbed, to one where the processed extracellular matrix implant is populated by local fibroblasts and supporting vasculature to produce, a viable and metabolically active tissue. Extracellular matrix components and plant extracts have been shown to possesses pharmacological properties with potential for use in the treatment of skin diseases and wound healing. Antioxidant, anti-inflammatory assays, and wound healing assays have been shown to support the dermatological and wound healing usage of these medicinal plants extracts.

Keywords: Wound healing, Biomaterials, extracellular matrix, chronic wounds, plant extracts, Electrospun fibers

1. Introduction

Biomaterials are polymers that are compatible with the body system introduced into the body to correct an anomaly or used for therapeutic purposes. These materials are broadly divided into three classes – synthetic polymers (usually hydrophobic), natural polymers and inorganic polymers [1]. These polymeric materials have found usefulness in various aspects of medicine such as tissue engineering [1], drug delivery [2], gene therapies [3], wound healing etc. Wounds occur when an intact body organ or tissue is compromised. The body immediately sets off several processes to ensure healing. The successful completion of this healing process is dependent on several factors such as immune cells, infection at the wound site, external factors such as drugs and underlying conditions like diabetes, and hypoxia. Wounds can either be classed as acute where the healing period is

between 8 to 12 weeks and chronic where healing is delayed beyond 12 weeks [4] as in vascular ulcers, diabetic foot ulcers and pressure ulcers [5].

Wound healing involves four sequential but partially overlapping processes of hemostasis, inflammation, proliferation, and remodeling [3, 5]. Ideally, with proper wound care such as regular cleaning, debridement and change of dressing, the healing process should proceed uninterrupted to completion. However, due to underlying conditions, poor nutrition, possible contamination of wound site and sometimes overactive immune responses, conventional therapy is introduced to control and ensure complete healing. Wound management also involve primary close by suturing, plastering or use of adhesives at first presentation to ensure proper healing [6]. The major objectives of wound care are to prevent infection, ensure proper wound closure and reduce scar formation [7].

1.1 Biomaterials and wound healing

Conventional treatment of wounds some of which have been alluded to above include drug therapies for pain, prevention or treatment of infections and wound cleaning. Bandages and closure systems are commonly used to create an enabling environment for healing. Polymeric biomaterials, synthetic or natural are an improvement on conventional wound therapy. These polymeric materials are constructed to ensure moisture and warmth is retained at the wound site while also sealing the wound from infectious agents [4]. Some of the materials are naturally occurring such as hyaluronan, chitosan, alginates. Others include hydrocolloids, polycaprolactone (PCL), polylactide-co-glycolide (PLGA), polyethylene glycol (PEG), polyurethane (PU) etc. A major advantage of biomaterials in wound care is their biocompatibility at the site of application [1]. These materials are also biodegradable; a quality that is particularly needed when the aim is to deliver medication to a wound site. This ensures that the biomaterial will degrade after drug delivery and so does not require surgical removal. Biomaterials are constructed to promote or stimulate the processes of wound healing. For instance, hydrogels can be used to hydrate the wound and serve as barrier to pathogens; curcumin, zinc nanoparticles and antibacterial can also be incorporated to stimulate the healing process [7, 8]. Polyethylene glycol when combined with polymyxin B or alginate has antibacterial activity and promotes wound regeneration respectively [9]. Biomaterials also act as scaffolds for incorporation of growth factors and as skin substitutes using hyaluronan and collagen to mimic the extracellular matrix (ECM) [9].

Injuries or wounds are currently treated via autografting or allografting. However, due to organ rejection by the immune system in some cases and lack of donors, the use of scaffolds has become increasingly popular. These scaffolds used in tissue repair are expected to be biocompatible, biodegradable, easily sterilizable and structurally desirable [10]. They can be cell or drug loaded to enhance healing; however, the constituent materials of the scaffolds can also have innate tissue repair properties. Depending on the desired properties, scaffolds are fabricated using synthetic or natural polymers which come with their unique characteristics.

Some synthetic polymers like polyurethane are used in the fabrication of semi-permeable dressings because of its permeability to moisture and vapor while acting as barrier to bacteria [4]. Fibrous scaffolds made with Poly(lactide-co-glycolide) polymers have been employed in the regeneration of bone tissues, they are also formulated as injectable in situ scaffolds [10]. Polyethylene glycol (PEG) polymers are used as carriers for growth factors i.e., EGF for targeted delivery to the wound site [11] and electrospun scaffolds of polycaprolactone (PCL), a biocompatible and bioresorbable polymer mimics the extracellular matrix (ECM) and therefore suitable for the treatment of acute and chronic wounds [4]. Polyvinyl alcohol and eudragit polymers are also useful additions in tissue engineering.

Natural polymers employed in wound healing include collagen, gelatin, chitosan, and hyaluronic acid. Chitosan is used in burns and wound healing because of its biocompatibility, tissue repair ability and lack of side effects [12, 13]. It serves as a carrier for heavy molecules such as proteins, antigens, and peptides. Ahmad et al. [14] investigated the wound healing properties of mupirocin-loaded chitosan-based hydrogel membrane. The study showed promising reports of good wound healing potentials with controlled release and no skin irritation. Conventional treatment with topical mupirocin ointment requires multiple applications and is less acceptable because of complaints associated with soiling of patient wears. Similarly, an investigative study of high molecular weight chitosan in wound healing showed exceptionally good re-epithelialization and fast wound closure compared to fucidin-ointment treated wounds [13]. Collagen and gelatin nanofibrous scaffolds are fabricated for wound healing and cartilaginous tissue regeneration respectively [15, 16] and nanofibrous scaffolds of hyaluronic acid mimics the ECM essential in controlling cellular function [2, 17].

2. Extracellular matrix targeted for chronic wound

Extracellular Matrix (ECM) is a structural scaffold that organizes cell adhesion and migration it also controls cellular growth, metabolism, and differentiation signals. It is composed of a wide variety of dynamic macromolecules and their regulatory factors which provide structural aid and physical protection [18]. Novel research has dynamically changed our understanding of the role of the extracellular matrix in tissue regeneration. The extracellular matrix is thought to provide passive structural support for cells however it has now been discovered that the individual or fragmented Extracellular matrix can send signals vital for cell processes during wound healing through integrin reactions coupled with growth factor activation [19]. Studies have shown that the Extracellular Matrix plays an active role in chronic wound healing. In a study by Baek et al. [20], the extracellular matrix was fabricated as a porous sheet matrix derived from human adipose tissue. Its aim was to act not just as a scaffold but a tool to enhance the overall process of wound healing through its components. Application of the extra cellular matrix sheet dressing showed enhanced wound healing rate compared to the control which was foam wound dressing [20]. The extracellular matrix is a broad molecule network made up of protein glycosaminoglycan and glycoconjugate, elastin and collagen. The extracellular matrix is a non-vascular structure that controls a vast number of cellular functions. The extracellular matrix is a complex structural network and undergoes constant restructuring of its network through matrix degrading enzymes [21]. The extra cellular matrix is composed of multiple matrix proteins that make up its main part. Proteins provide structural support to cells and tissues. The proteins that make up the extracellular matrix can be structural or non-structural depending on their roles and responsibilities [22]. In a study by Hui et al. [23], growth factor re-enforced extracellular matrix was prepared, and the wound healing properties were evaluated using a mouse model. It reflected that the extra cellular matrix promotes wound healing in the early stage of adipocyte recruitment. Rapid re-epithelization, enhanced granulation, tissue growth and supported angiogenesis were also observed. Growth factor re-enforced extracellular matrix was used to treat the wounds and total wound healing was observed on day seven of wound healing [23]. To accelerate healing processes and decrease the complication occurrence various agents, growth factors, natural and synthetic antioxidants (coenzyme Q10-CoQ10), are applied. Amajuoyi et al. incorporated natural ECM matrix co-enzyme Q10 and keratin in electrospun keratin/Co Enzyme Q10/Poly vinyl alcohol nanofibrous scaffold [24]. This potential dressing for infected wounds was effective in preventing the proliferation of microorganism. Encapsulation of

CoQ10 in nanoliposomes has also been shown to enhance CoQ10 activity by accelerating wound healing process after tooth extraction [24, 25]. A reduction in inflammatory reaction and increase in collagen deposition following surgical procedure, were previously obtained in animals when CoQ10 was applied in a form of ointment resulting. The expression of IL-1β, TNF-α, NF-κB and HO-1, cytokines involved in inflammation and oxidative tissue damage, were significantly suppressed by CoQ10 application for 3 days following surgical procedure [25]. The ECM was shown to be more stimulated to facilitate wound healing when formulated with biomaterials. **Table 1** show in details the Drug delivery technologies incorporating Extracellular matrix and Plant extract targeted for management of chronic wounds.

Drug delivery Technology incorporating biomaterials	Plant extract(s)	Extracellular matrix component	Pharmacological action	Ref.
1. Hydrogels				
a. Alkyl acrylate polymer	*Aspalathus linearis*	.	Therapeutic properties of green and fermented rooibos extract loaded hydrogels have been established in vivo, with the best wound healing indices shown by the hydrogels containing fermented rooibos extract. This is possibly a result of a shorter inflammatory phase resulting in quicker wound closure and reduced fibrosis.	[26]
b. Hyaluronic acid and chitosan		Angiogenic promoting growth factor vascular endothelial growth factor	The hydrogels possessed both antibacterial and angiogenic, suggesting it might have potential as a wound healing therapeutic. The hydrogels that have incorporated hyaluronan have been shown to promote blood clotting and possess antibacterial properties	[27]
2. Electrospun scaffolds				
a. Polycaprolactone (PCL) for skin tissue engineering	*Memecylon edule*	—	PCL/ *Memecylon edule* show minimal cytotoxicity and the epidermal differentiation of adipose derived stem cells on PCL/ *Memecylon edule* scaffolds demonstrated the potential of electrospun PCL/ ME nanofibers as substrates for skin tissue engineering in chronic wound healing.	[28]
b. Chitosan nanoparticles and electrospun scaffolds	—	Novel chondrogenic growth factors (Nell-1)	Nell-1 specifically promotes inducing human bone mesemchymal cells *in vitro*, and chondrogenic differentiation by increasing expression of chondrogenic related genes and proteins. Thus enhancing its potential utility for cartilage tissue engineering	[29]

Drug delivery Technology incorporating biomaterials	Plant extract(s)	Extracellular matrix component	Pharmacological action	Ref.
3. Skin substitutes				
a. Epidermal/dermal substitute		Fibroblast	Apligraf® neonatal dermal fibroblasts grown in a matrix that consists of bovine-derived type I collagen with layers of human neonatal epidermal keratinocytes on top that have been exposed to air to promote stratification in order to mimic the stratum corneum hence facilitating chronic wound healing.	[30]
b. Allogenic dermal substitutes		Neonatal fibroblasts	TransCyte™ a collagen-coated nylon matrix with an outer silicon film seeded with human neonatal fibroblasts, has been used for both partial and full-thickness burn wounds. Dermagraft™, used both for burns and chronic wounds, consists of a bioresorbable polyglactin scaffold containing human neonatal fibroblasts	[31]
4. Nanomedicines				
a. Silver Nanoparticles	*Cassia auriculata*	—	Cassia auriculata L.-mediated silver nanoparticles were effective on both incision and excision wound models in Wistar albino rats exhibiting better performance in wound healing process rather than the extract and Povidone Iodine ointment.	[32]
b. Dual growth factor-releasing nanoparticle-in-nanofiber system		Vascular endothelial growth factor	Normal full thickness rat skin wound models demonstrated that nanofiber/nanoparticle scaffolds significantly accelerated the wound healing process by promoting angiogenesis, increasing re-epithelialization and controlling granulation tissue formation.	[33]
c. Liposomal nanocarriers	Curcumin	—	The antibacterial activity of the Curcumin-liposomal formulation was found to be like silver sulfadiazine cream 1% regarding the inhibition of the bacterial growth. At low dose of curcumin nano-liposomal formulation efficiently improved injuries and infections of burn wounds	[34]

Table 1.
Drug delivery technologies incorporating extracellular matrix and plant extract targeted for management of chronic wounds.

2.1 GAG (Glycosaminoglycans)

GAG is a lengthy linear polysaccharide chain. It is a sulphated di-saccharide formed by uronic acid and N-acetyl- glucosamine or N-acetyl -galactosamine. GAG in partnership with proteoglycans control the wound healing process, GAG is involved in the remodeling phase as it supports capillary growth, fibronectin, and collagen formation at the site of the injury so that vascular density of the wound can be restored. GAG also participates in cell to cell and cell to matrix interactions cell proliferation migration and cytokine and growth factor signaling associated with wound healing. GAG chain reflects an impressive structural diversity because of the dynamic biosynthesis that is tightly controlled in biological systems allowing modified GAG to particularly interact with various ligands in a controlled and timely manner [35]. In a study by Amaral et al. [35], Collagen-GAG scaffolds were fabricated with platelet rich protein infused in the pores of its scaffold. The composite scaffold containing collagen, GAG and platelet rich protein was observed to release key growth factors such as, TGFβ, FGF, VEGF and PDGF for vascular regeneration for 14 days. Growth factors released were enough to enhance the proliferation of major cells involved in wound healing. It also increased the angiogenic and vascularization abilities which are key indices for progress in wound healing, conclusively indicating promising results as therapy for wound healing [36].

2.2 Collagen

Collagen is the most common protein in the body. It is highly populated in the extracellular matrix of the connective tissue like the tendon, cartilage, and skin. It is the most abundant structured protein found in the extra cellular matrix. It gives tensile strength and takes part in adhesion and migration. In the extra cellular matrix collagen is aligned as fibrils to allow for support of the structural framework of the tissues. Collagen type I is in all tissues, tendon, and skin. Collagen type II is found in the cartilage and cornea. Collagen type III is found in the walls of blood vessels [18, 19]. In a study by Lei et al. [37], Collagen hydrogel was fabricated for wound dressing. It was shown to enhance the rate and quality of wound healing. It also improved the tensile strength of regenerated tissue and skin at the wound site. In the study the effect of collagen hydrogel dressing on chronic wound healing and capillary regeneration was explored in diabetic Sprague Dawley rat models. Rats treated at the wound site with collagen hydrogel showed faster healing with smaller wound areas by days seven and fourteen compared to the untreated rats [37]. In another study by Morteza et al. [38] bacterial cellulose/collagen hydrogel as wound dressing was compared to collagenase ointment and the control was an untreated wound. Bacterial Cellulose Collagen hydrogel showed better regeneration and tissue repair when applied at the wound site than the collagenase ointment or control. The study concluded that Bacterial Cellulose/Collagen hydrogel serves as a promising biologically active hydrogel dressing for skin regeneration [38, 39].

2.3 Elastin and fibronectin

It is found in the extra cellular matrix spaces of tissues and is responsible for the flexibility and distensibility of tissues. Elastin is responsible for the dermis stretching ability along with fibrillin and fibulin. The study by Kawabata et al. [40], highlighted cutaneous ulcers treated with silk elastin-based hydrogels. It was shown that silks elastin enhanced rapid wound healing in chronic ulcers of diabetic mice. Silk elastin hydrogels showed enhanced epithelialization rate compared to

conventional hydrogels in chronic ulcer models. Indicating that elastin hydrogel is a promising material for accelerating the healing of chronic ulcers [40].

Fibronectins exist in two different forms, firstly as plasma that migrates the blood, secondly as cellular protein created by fibroblast. Fibronectin is aligned into a network of fibrils. It is created in the form of a disulphide-bonded dimer that can be broken down. Fibronectin is involved in the development and response to injury. It plays an important role in enhancing and modulating cell functions in the extracellular matrix [18, 19, 40]. In a study by Norris et al. [41] an Acoustic fabrication of Collagen -Fibronectin composite gels were carried out to accelerate microtissue regeneration. The ultrasound-based fabrication altered the collagen fiber structure and arrangement this led to improvement in its bioactivity. The study investigated how the synergistic effect of collagen and fibronectin coupled with the ultrasound effect altered the protein alignment and bioactivity of composite hydrogels. Results from the investigation showed that the fibronectin can be redistributed within three-dimensional hydrogels under the influence of ultrasound to produce composite hydrogels which lead to the improvement of microtissue regeneration. Conclusively ultrasound waves can lead to protein realignment and fibronectin rearrangement which can enhance wound healing. This is a promising and novel tool and provides a less invasive treatment for chronic wounds [12].

Extra cellular matrix also plays an indirect role in the modulation of extra cellular protease production and activation it also modifies growth factor availability and activity for wound healing [42]. In a study by Riis et al. 2020, adipose derived stem cells which have the ability to deposit extracellular matrix are being investigated for novel treatment of chronic wound and enhancement of wound healing. The extracellular matrix eventually forms a scaffold which is composed of collagen I and III and fibronectin, all of which are essential for progress in wound healing processes [13]. PLA-based electrospun fibers loaded with hyaluronic acid-valsartan hydrogels have been shown to be stable and possess proven diabetic wound healing property. This was as a result of the known biomimetic effect of the fibers and increased re-epithelization facilitated by the hydrogels containing angiotensin inhibitors which is facilitated by the presence of hyaluronic acid as the ECM components [43].

3. Biomaterials and drug delivery incorporating plant extracts targeted for management of chronic wounds

Biomaterials such as biomimetic polymers have been utilized as carrier systems for plant extracts utilized in management of chronic wounds. The problems of resistance and environmental degradation associated with irrational use of orthodox medicines have increased interests in natural and safer alternatives when managing chronic of wounds. Chah et al. [44] evaluated the antibacterial and wound healing activities of methanolic extracts of *Ageratum conyzoides* L (Asteraceae), *Anthocleista djalonen*, A. Chev (Loganiaceae), *Napoleonaea imperialis*, P. *Beauv(Lecythidaceae)*, *Ocimum gratissimum*, *Briq (Lamiaceae)* and *Psidium guajava*. The antibacterial and wound healing properties of *Napoleona imperialis*, *Ocimum gratissimum* and *Ageratum conyzoides* were established however utilization of these extracts as crude portends a setback for quality control and wide utilization of these herbal products. Incorporation of herbal extracts into biomaterials have been shown to increase the stability of the herbal extracts within the biomaterial whilst ensuring that plant extract elicits its desired effect. The polyherbal antioxidant preparation containing extracts of *T. conophorum* and *O. gratissimum* was shown to exhibit excellent antioxidant and wound healing properties. The formulation served to protect the skin from reactive oxygen species created by UV

radiation and environmental toxin, thus protecting the skin from photo aging. This hence showed a migration from the work of Shah et al., where the extracts elicit wound healing activities to the instance where extracts incorporated into biomaterials could effectively be utilized as a dosage form in management of chronic wounds [44, 45]. Elegbede et al. [26] studied the therapeutic properties of green and fermented *Aspalanthus linearis* extract loaded hydrogels in surgical wound healing. The best wound healing indices shown by the hydrogels containing fermented rooibos extract due to shortening the inflammatory phase which resulted in quicker wound closure and reduced fibrosis (**Table 1**). Biomaterials have also incorporated both plant extracts and conventional medicine in management of chronic wounds.

Panax ginseng, extracted by soxhlation from the clean and dried root and incorporated into PCL (polycaprolactone nanofibers) by electrospinning for bone tissue regeneration was demonstrated to induce the expression of osteogenic genes like osteocalcin and collagen type 1 [46]. The mineralization and phosphatase activity of the ginseng extract was shown to be significantly higher due to the presence of *Panax ginseng* hence its usefulness in bone engineered scaffold development in management of surgical wounds [3, 45, 46]. Nanoscaffolds of polycaprolactone have been incorporated and electrospun with the medicinal extracts of *Tecomella undulata*, *Asparagus racemosus*, *Glycyrrhiza glabra*, and *Linum usitatissimum* to impart their wound healing properties and antimicrobial activity. Morphological examination shows that the supplement of these plant extracts did not alter the final morphology of the nanofibers, but the average diameter was increased in all the extract loaded nanofibers. The release studies using acetate buffer with a pH of 5.5 shows that the nanoscaffolds released the antibacterial extracts in a sustained manner up to a 24-hour period and also shows zones of inhibition when cultured on agar plates with growth of *S. aureus* and *K. pneumoniae* [9, 47]. The fabricated wound dressings exhibited significant moisture vapor transmission rate, which is a suitable criterion for gases permeability in facilitating wound healing. When correlated and compared with commercially accessible dressing materials, it was established that nanofiber incorporated with herbal drug was 50% more efficient [46, 47]. The plant extract from *Garcinia manostana* have been found to have usefulness as wound dressing material. Charernsriwilaiwat et al. [46–48], *in vitro* analysis using Franz's diffusion cells method and an *in vivo* analysis using Male Wistar rats shows that the plant extract fabricated with chitosan-ethylenediaminetetraacetic acid/polyvinyl alcohol composite reduces inflammation and also leads to increase in antioxidant activity. It also demonstrated antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* [48].

Curcumin is a known natural polyphenolic compound which is gotten from the rhizome of the natural plant *Curcuma longa*. It is a novel, proven treatment that facilitates faster wound healing due to its possessing antioxidant and anti-inflammatory properties. It helps in accelerating healing of wounds by contributing to the three phases of wound healing such as the inflammatory, proliferatory and the remodeling phases [49]. Curcumin has been reported to have a wide range of pharmacologic actions ranging from anti-inflammatory, anti-HIV, an antibacterial, anti-oxidant activity, anti-parasitic, anti-mutagenic and anti-cancer, with very low or no intrinsic toxicity [49, 50]. Curcumin has significant effect on the inflammatory phase during wound healing. The Inflammatory phase is one of the most important phases during wound healing, and it is often counted as the first step in optimal wound healing. Since tissue damage causes early acute inflammation, the control of inflammation can help optimize the wound healing process [49–52].

The *in vitro* analysis using myoblast cells and an *in vivo* analysis using Female mice when curcumin was electrospun with polylactic acid demonstrated greater cell mobility, early remodeling and inhibition of nitric oxide which usually impede wound healing [49, 53].

Momordica charantia is a traditional herbal commonly used for its antidiabetic, antioxidant, contraceptive, and antibacterial properties [54]. When formulated as a powder ointment, *Momordica charantia* showed a stastically significant response ($P < 0.01$), in terms of wound-contracting ability, wound closure time and period of epithelization, with increased tissue regeneration at wound bed when compared with povidone iodine which served as control [54, 55]. Hussan et al. developed biomaterial based *Momordica charantia* ointment which was evaluated as an alternative topical medication for diabetic wounds. The ointment showed intense TGF-β expression and a high level of total protein content, showing that it accelerated wound healing in diabetic rats, via enhancing TGF-β expression [55].

Utilization of medicinal plants with known wound healing activities such as *Tetracarpidium conophorum* in collaboration with known conventional medicine have been shown to increase their activity as well as shorten wound healing times. Ezealisiji *et al.* [56] reported that the n-hexane and methanol extracts of the *Tetracarpidium conophorum* seed nut established accelerated dose-dependent wound healing activity of the extracts. This was attributed to the presence of some secondary metabolites like flavonoids with repeated antioxidant and immune stimulating activities. However, Ilomuanya et al. [45, 57] utilized response surface methodology coupled with statistically designed experiments to optimize the multivariable processes in developing *Tetracarpidium conophorum* hydrogel containing gentamicin. The extract synergistically facilitated a potential wound healing activity that either active ingredient wound not have been able to achieve.

4. Conclusion and future trends

Wound healing is a complex and dynamic process of restoring cellular structures and tissue layers in damaged tissues as closely as possible to its normal state. Plant extracts and human extra cellular matrices that have been seen to possess wound healing activities have the capability of facilitating re-epithelization and tissue regeneration which accelerates the wound healing process. Utilization of appropriate biomaterials as carrier systems can enhance the activity of the plant extracts in hastening the inflammatory, proliferative and the remodeling phases of chronic wounds without the inherent problem of antibiotic resistance and hypersensitivity to the very few medications available. Increased utilization of folkloric plant extracts with proven wound healing activities will ensure an increased option and platform for management of Chronic wounds. There still exits inherent challenges in the use of extracellular matrix loaded biomaterials, cellular and extra cellular treatments options which can enable delivery of multiple molecules at the wound site without degradation is required. The cost of these technologies should also be affordable to encourage scale up.

Conflict of interest

The authors have no conflict of interest.

Author details

Margaret O. Ilomuanya[1*], Ibilola M. Cardoso-Daodu[1], Uloma N. Ubani-Ukoma[1] and Adannaya C. Adebona[2]

1 Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Lagos, Lagos, Nigeria

2 Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Federal University Oye Ekiti, Ekiti, Nigeria

*Address all correspondence to: milomuanya@unilag.edu.ng

IntechOpen

References

[1] Kohane DS, Langer R. Polymeric Biomaterials in Tissue Engineering. Paed. Research. 2008: 67, 487 – 491

[2] Samson AO, Ilomuanya MO, Gbenebor OP, Dada MO, Odili CC. Biomaterials for Drug Delivery: Sources, Classification, Synthesis, Processing and Applications. In Advanced Functional Materials. IntechOpen. 2020: 1-25 Http://dx.doi.org/10.5772/intechopen.93368

[3] Piraino F. and Selimovic S.: A Current view of Functional Biomaterials for Wound Care, Molecular and Cellular Therapies. Biomed Research International 2015: 1-11 http://dx.doi.org/10.1155/2015/403801

[4] Mir M, Ali MN, Barakullah A, Gulzar A, Arshad M, Fatima S, Asad M. Synthetic Polymeric Biomaterials for Wound Healing: A Review. Progress in Biomaterials. 2018: 7, 1-21. Https://doi.org/10.1007/s40204-018-0083-4

[5] Frykberg RG, Banks J. Challenges in the Treatment of Chronic Wounds. Advances in Wound Care. 2015: 4 (9): 560 – 582. Http://dx.doi.org/10.1089/wound.2015.0635

[6] Percival JN: Classification of Wounds and their Management. Surgery. 2002: 20(5) 114 – 117. https://doi.org/10.1383/surg.20.5.114.14626

[7] He F, Jiao H, Zhao L, Liao X, Fan Z. Facile and Large-scale Synthesis of Curcumin/PVA hydrogel: effectively kill bacteria and accelerate cutaneous wound healing in the rat. J. Biomater Sci Polym Ed. 2018; 29: 325 – 343. https://doi.org/10.1080/09205063.2017.1417002

[8] Khorasani MT, Joorabloo A, Moghaddam A, Shamsi H, MansooriMoghadam Z. Incorporation of ZnO nanoparticles into haparinised polyvinyl alcohol/chitosan hydrogels for wound dressing application. Int J Biol Macromol. 2018; 114: 1203 – 1215. https://doi.org/10.1016/j.ijbiomac.2018.04.010

[9] Murray RZ, West ZE, Cowin AJ, Farrugia BL. Development and use of biomaterials as wound healing therapies. Burns and Trauma. 2019; 1-9. https://doi.org/10.1186/s41038-018-0139-7

[10] Elkasabgy NA, Mahmoud AA. Fabrication Strategies of Scaffolds for Delivering Active Ingredients for Tissue Engineering. AAPS PharmSciTech (2019) 20: 256 https://doi.org/10.1208/s12249-019-1470-4

[11] Shahverdi S, Hajimiri M, Esfandiari MA, Larijan B, Atyabi F, Rajabiani A, Dehpour AR, Gharehaghaji AA, Dinarvand R. Fabrication and structure analysis of poly(lactide-co-glycolic acid)/silk fibroin hybrid scaffold for wound dressing applications. Int J Pharm (2014) 473:345-355. 10.1016/j.ijpharm.2014.07.021

[12] Deng C-M, He LZ, Zhao M, Yang D, Liu Y. Biological properties of the chitosan-gelatin sponge wound dressing. Carbohydrate Polym. 2007;69(3):583-589

[13] Alsarra IA. Chitosan topical gel formulation in the management of burn wounds. Int J Biol Macromol. 2009;45(1):16-21.

[14] Ahmad S, Minhas MU, Ahmad M, Sohail M, Abdullah O, Badshah SF. Preparation and Evaluation of Skin Wound Healing Chitosan-Based Hydrogel Membranes. AAPS PharmSciTech. 2018: 19(7) 3199 – 3209. Http://doi.org/10.1208/s12249-018-1131-z

[15] Yeo IS, Oh JE, Jeong L, Lee TS, Lee SJ, Park WH, et al. Collagen-based biomimetic nanofibrous scaffolds: preparation and characterization of collagen/silk fibroin bicomponent nanofibrous structures. Biomacro molecules. 2008;9(4):1106-16. 65.

[16] Aliakbarshirazi S, Talebian A. Electrospun gelatin nanofibrous scaffolds for cartilage tissue engineering. Mater Today Proc. 2017;4(7):7059-64. 66

[17] Lian Y, Yuan L, Ji L, Zhang K. Gelatin/hyaluronic acid nanofibrous scaffolds: biomimetics of extracellular matrix. Acta Biochim Biophys Sin. 2013;45(8):700-703. https://doi.org/10.1093/abbs/gmt032

[18] Jaspreet K, Shouvik B, Ram S. The extracellular matrix: Structure, composition, age-related differences, tools for analysis and applications for tissue engineering. Journal of Tissue Engineering. 2014;20(5) :2041731414557112. PMID: 25610589; PMCID: PMC4883592. https://doi.org/10.1177/2041731414557112

[19] Agren S, Werthen M. The Extracellular Matrix in Wound Healing: A Closer Look at Therapeutics for Chronic Wounds. The International Journal of Lower Extremity Wounds. 2007;6(2):82-97. doi:10.1177/1534734607301394

[20] Baek S, Lee S, Jeong Y, Kim Young K, Rhie J. Wound-healing effect of adipose stem cell-derived extracellular matrix sheet on full-thickness skin defect rat model: Histological and immunohistochemical study. Int. Wound Journal. 2019; 16: 286– 296. https://doi.org/10.1111/iwj.13030

[21] Godfrey M. Extracellular Matrix. Asthma and COPD (Second Edition), Basic Mechanisms and Clinical Management. Academic Press. 2009 274p. ISBN 9780123740014, https://doi.org/10.1016/B978-0-12-374001-4.00022-5

[22] González-Díaz, E.C.; Varghese, S. "Hydrogels as Extracellular Matrix Analogs." Gels. 2016 2(3):20. doi:10.3390/gels2030020

[23] Hui-Cong D, Jiang L, Wen-Xin G, Li J, Zhang R, Dang J, Shu M, Li L. "Growth Factor- Reinforced ECM Fabricated from Chemically Hypoxic MSC Sheet with Improved In Vivo Wound Repair Activity". BioMed Research International. 2017 11p. https://doi.org/10.1155/2017/2578017 ID 2578017

[24] Amajuoyi, J.N., Ilomuanya, M.O., Asantewaa-Osei, Y. et al. Development of electrospun keratin/coenzyme Q10/poly vinyl alcohol nanofibrous scaffold containing mupirocin as potential dressing for infected wounds. Futur J Pharm Sci 6, 25 (2020). https://doi.org/10.1186/s43094-020-00043-z

[25] Todorovic K, Jovanovic G, Todorovic A, et al. Effects of coenzyme Q10 encapsulated in nanoliposomes on wound healing processes after tooth extraction. J Dent Sci. 2018;13(2):103-108. doi:10.1016/j.jds.2017.10.004

[26] Elegbede, R.D., Ilomuanya, M. O., Sowemimo, A.A., Nneji, A., Joubert, E., De Beer, D., Koekemoer, T., van de Venter, M. (2020) Effect of fermented and green Aspalathus linearis extract loaded hydrogel on surgical wound healing in Sprague Dawley rats. Wound Medicine, 29, 100186, ISSN 2213-9095, https://doi.org/10.1016/j.wndm.2020.100186

[27] Huang J, Ren J, Chen G, Li Z, Liu Y, Wang G, et al. Tunable sequential drug delivery system based on chitosan/hyaluronic acid hydrogels and PLGA microspheres for management of non-healing infected wounds. Mater Sci Eng C. 2018;89:213-222

[28] Jin G, Prabhakaran M P, Kai D, Annamalai S K, Arunachalam K D, Ramakrishna S, Tissue engineered plant extracts as nanofibrous wound dressing, Biomaterials, 34 (3): 724-734. 2013, https://doi.org/10.1016/j.biomaterials.2012.10.026

[29] Wang C, Hou W, Guo X, Li J, Hu T, Qiu M, Liu S, Mo X, Liu X. Two-phase electrospinning to incorporate growth factors loaded chitosan nanoparticles into electrospun fibrous scaffolds for bioactivity retention and cartilage regeneration. Mater Sci Eng C Mater Biol Appl. 2017 Oct 1;79:507-515. doi: 10.1016/j.msec.2017.05.075

[30] Vig K, Chaudhari A, Tripathi S, Dixit S, Sahu R, Pillai S, et al. Advances in skin regeneration using tissue engineering. Int J Mol Sci. 2017;18:789.

[31] Shevchenko RV, James SL, James SE. A review of tissue-engineered skin bioconstructs available for skin reconstruction. J R Soc Interface. 2010;7:229-258.

[32] Kumarasamyraja D, Swamivelmanickam M. Evaluation of wound healing activity of biosynthesized silver nanoparticles from aqueous extract of Cassia Auriculata L. Int J Phytopharm. 2014;5:201-209

[33] Xie Z, Paras C B, Weng H, Punnakitikashem P, Su L-C, Vu K, Tang L, Yang J, Nguyen K T, Dual growth factor releasing multi-functional nanofibers for wound healing, Acta Biomaterialia 2013,9 (12) 9351-9359, https://doi.org/10.1016/j.actbio.2013.07.030

[34] Kianvash, N., Bahador, A., Pourhajibagher, M. et al. Evaluation of propylene glycol nanoliposomes containing curcumin on burn wound model in rat: biocompatibility, wound healing, and anti-bacterial effects. Drug Deliv. and Transl. Res. 7, 654-663 (2017). https://doi.org/10.1007/s13346-017-0405-4

[35] Amaral R, Zayed N, Pascu E, Cavanagh B, Hobbs C, Santarella F, Simpson C, Murphy C, Sridharan R, Gonzalez- Vazquez A, O Sullivan B, O Brein F, Kearney C. Functionalising Collagen-Based Scaffolds with platelet-rich plasma for enhanced skin wound healing potential. Frontiers in Bioengineering and Biotechnology. 2019; 7:371 DOI: 10.3389/fbioe.2019.00371

[36] Ghatak S, Maytin E, Vincent J, Ilia H, Ricardo A, Rodriguez M, Markwalt R, Misra S. Roles of Proteoglycans and Glycosaminoglycans in wound healing and fibrosis. International Journal of Cell Biology. 2015; 2015:834893. doi: 10.1155/2015/834893

[37] Lei J, Chen P, Li Y, Wang X, Tang S. Collagen hydrogel dressing for wound healing and angiogenesis in diabetic rat models. International Journal Clinical Experimental Medicine. 2017;10(12): 16319-16327

[38] Morteza B, Naimeh M, Moghtader M. An Introduction to Hydrogels and Some Recent Applications, Emerging Concepts in Analysis and Applications of Hydrogels. Sutapa B Majee.editor. Intech Open, DOI: 10.5772/64301

[39] Rodrigues P, Fontes de Sousa M, Saskac S, Barud H, Roncalho de Limac L, Virgínia da Conceição Amaro M, de Guzzi Plepisa A, José Lima Ribeiroc S, Minarelli Gaspara A. Bacterial Cellulose/Collagen Hydrogel for Wound Healing. Materials Research, 2016 19(1): 106-116.https://doi.org/10.1590/1980-5373-MR-2015-0249

[40] Kawabata S, Kanda N, Hirasawa Y, Noda K, Matsuura Y, Suzuki S, Kawai K. The Utility of Silk-elastin Hydrogel as a New Material for Wound Healing.

Plastic Reconstruction Surgery Global Open 2018;6: e1778 doi: 10.1097/GOX.0000000000001778

[41] Norris E, Dalecki D, Hocking D. Article Acoustic Fabrication of Collagen–Fibronectin Composite Gels Accelerates Microtissue Formation. Applied Science 2020; 10: 2907. doi:10.3390/app10082907

[42] Nicks BA, Ayello E, Woo K, Nitzki-George D, Sibbald G. Acute wound management: revisiting the approach to assessment, irrigation and closure considerations. Int J Emerg Med. 2010:3. 399 – 407. Http://dx.doi.org/10.1007/s12245-010-0217-5

[43] Ilomuanya M.O, Okafor P.S., Amajuoyi J.N., Onyejekwe J., Okubanjo O.O., Adeosun S.O., Silva B.O. (2020) Polylactic acid-based electrospun fiber and Hyaluronic acid- valsartan hydrogel scaffold for chronic wound healing. Beni Suef University J. Basic and Applied Sci. 9:31 https://doi.org/10.1186/s43088-020-00057-9

[44] Chah KF, Eze CA, Emuelosi CE, Esimone CO. Antibacterial and wound healing properties of methanolic extracts of some Nigerian medicinal plants. J Ethnopharmacol. 2006 Mar 8;104(1-2):164-167. doi: 10.1016/j.jep.2005.08.070. Epub 2005 Oct 13. PMID: 16226414

[45] Ilomuanya M.O., Akhimien T., Aghaizu C., Adeyinka O., Ajayi T. (2018) Polyherbal Antioxidant Topical Preparation Comprising Ethanol Extract of Tetracarpidium conophorum and Ocimum gratissimum: Formulation and Evaluation. Dhaka Univ. J. Pharm. Sci. 17(2): 213-219, DOI: http://dx.doi.org/10.3329/dujps.v17i2.39178

[46] Pajoumshariati S, Yavari S.K, Shokrgozar M.A, Physical and biological modification of polycaprolactone electrospun nanofiber by panax ginseng extract for bone tissue engineering application, Ann. Biomed. Eng. 44 (2016) 1808-1820

[47] Chellamani K, Vignesh Balaji R, Veerasubramanian D, Sudharsan J, Wound healing ability of herbal drug incorporated PCL (Poly (ε-caprolactone)) wound dressing, Journal of Academia and Industrial Research, April 2 (2014) 622-626

[48] Charernsriwilaiwat N, Rojanarata T, Ngawhirunpat T, Sukma M, Opanasopit P, Electrospun chitosan-based nanofiber mats loaded with Garcinia mangostana extracts, Int. J. Pharm. 452 (2013) 333-343

[49] Javadi, B., & Sahebkar, A. (2017). Natural products with anti-inflammatory and immunomodulatory activities against autoimmune myocarditis. Pharmacological Research, 124, 34-42

[50] Asefi S, Seifi M, Fard GH, Lotfi A. Innovative evaluation of local injective gel of curcumin on the orthodontic tooth movement in rats. Dent Res J (Isfahan). 2018 Jan-Feb;15(1):40-49. doi: 10.4103/1735-3327.223618

[51] Haagsma JA, Graetz N, Bolliger I et al. The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013. Inj. Prev. 22(1), 3-18 (2015).

[52] Abdollahi, E., Momtazi, A. A., Johnston, T. P., & Sahebkar, A. (2018). Therapeutic effects of curcumin in inflammatory and immune mediated diseases: A nature made jack of all trades? J. Cellular Physiology, 233(2), 830-848

[53] Nguyen T.T.T, Ghosh C, Hwang S-G, Dai Tran L, Park J.S, Characteristics of curcumin-loaded poly (lactic acid) nanofibers for wound healing, J. Mater. Sci. 48 (2013) 7125-7133.

[54] Pişkin A, Altunkaynak BZ, Tümentemur G, Kaplan S, Yazıcı OB, Hökelek M. The beneficial effects of Momordica charantia (bitter gourd) on wound healing of rabbit skin. J Dermatolog Treat. 2014 Aug;25(4):350-357. doi: 10.3109/09546634.2012.713459.

[55] Hussan F, Teoh SL, Muhamad N, Mazlan M, Latiff AA. *Momordica charantia* ointment accelerates diabetic wound healing and enhances transforming growth factor-β expression. J Wound Care. 2014 Aug;23(8):400, 402, 404-7. doi: 10.12968/jowc.2014.23.8.400

[56] Ezealisiji, K.M., Stanley, C.N. & Ekanem, E.S., 2016, 'Evaluation of anti-cholesterol activity of ethyl acetate and n-hexane extracts of Tetracarpidium conophorum (Mull. Arg.) Hutch and Dalziel (African walnut) towards hypercholesterolemic rats', Intl. J. Pharmacog. Phytochem. Res. 8(8), 1372-1376.

[57] Ilomuanya M.O., Amenaghawon N.A., Odimegwu J., Okubanjo O.O., Aghaizu C., Adeyinka O., Akhimien T., Ajayi T. (2018) Formulation and optimization of gentamicin hydrogel infused with *tetracarpidium conophorum* extract via Central composite design for topical delivery. Turkish J. Pharm. Sci. 15(3):319-327 https://doi.org/10.4274/tjps.33042