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Poly(Lactic Acid) Nano structure mats as potential wound dressings

Potansiyel yara pansuman malzemesi olarak Poli(Laktik Asit) (PLA) Nano yapı matları

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Abstract

Wound healing is a complicated procedure which necessitates laying out a suitable wound healing system or dressing which possesses key factors like a wet wound location, avoidance of microbial action and absorption of exudates. Various wound dressings can be accessible but not all can meet the particular conditions of a perfect wound healing system to complete proper wound healing process. Poly(Lactic Acid) (PLA) Nano Structure Mats are a new class of materials that possess great potential in wound healing because of biocompatibility, bio absorbability, biodegradability, absorption of exudates from the wound, physical safety of the wounded tissue and the probability to free useful molecules. Our review article gives a brief intro on the wound and skin structure and afterwards gives information about the peerless characteristics of PLA Nano Structure Mats remarkable for wound healing. Moreover, new recent investigations about PLA Nano Structure Mats usage for wound healing applications were also explored.

Keywords: Poly(Lactic Acid), PLA, Skin, Wound dressing, Nano structure, Dermis.

Öz

Yara iyileşmesi, ıslak bir yara yeri, mikrobiyal etkiden kaçınma ve eksüdaların emilmesi gibi anahtar faktörlere sahip uygun bir yara iyileştirme sisteminin veya uygun yara pansumanın yapılmasını gerektiren karmaşık bir prosedürdür. Yaralar için çeşitli yara pansuman malzemeleri kullanılabilir, ancak bunların hepsi uygun yara iyileşme sürecini tamamlamak için mükemmel bir yara iyileşme sisteminin belirli koşullarını karşılayamayabilir. Poli(Laktik Asit) (PLA) nano yapı matları, biyouyumluluk, biyo emilebilirlik, biyobozunurluk, sızıntıların yaradan emilmesi, yara dokusunun fiziksel emniyeti ve faydalı molekülleri salabilme olasılığından dolayı yara iyileşmesinde büyük potansiyele sahip yeni bir malzeme sınıfıdır. Bu derleme makalesinde, yara ve cilt yapısı hakkında kısa bir giriş yapıldıktan sonra yara iyileşmesinde dikkat çeken PLA nano yapı matlarının benzersiz özellikleri hakkında bilgi verilmektedir. Ayrıca, PLA nano yapı matlarının yara iyileşme uygulamaları için kullanımı ile ilgili son araştırmalar da ayrıntılı olarak incelenmiştir.

Anahtar kelimeler: Poli(Laktik Asit), PLA, Deri, Yara pansuman malzemesi, Nano yapı, Dermis.

1 Introduction

Wound is every damage and break in the skin surface and/or the disruption of living tissue integrity of the skin or mucosa as a result of factors such as cuts, burns, trauma, illness or other impacts etc. The most public wounds could be generated from accidents, surgical operations, underlying diseases, some undesirable skin conditions. In a wound generation, structures such as blood vessels, muscle and nerve could also be affected simultaneously. The proper protection of the wound is vital for the injured or wounded living being. Since, if the wound is not properly protected and covered, unwanted infections can generate leading to further health hazards and illnesses. Hence, wound dressings are generally utilized to protect and cover the wounds. Wound dressing is a sterile pad or compress implemented to a wound in order to support healing and mainly protect the wound from further possible harms. In this part, the introductory information about the skin, skin structure, wound, wound healing phases, wound dressing, ideal wound dressings, types of wound dressings and nano structure mats as wound dressings will be given.

1.1 Skin

Skin, one of the main human organs, works as a barricade to injurious mediums and avoids pathogens from coming into the body (Figure 1). 3 main layers named as the hypodermis, the dermis and the epidermis form the skin [1]-[3]. "Epi" part of the ***epidermis*** expression comes from the Greek language and it means "over" [4]. Epidermis is the outmost layer of the skin [5]. The epidermis could be extra sub-segmented as *strata*, granulosum, spinosum, corneum, lucidum, basale [3]. The ***dermis*** cushions the body from stress and strain and is composed of epithelial tissue and a layer of the skin underneath the epidermis [6]. The dermis which harbors many nerve endings which acquire the touch and heat senses is tightly linked to the epidermis via a basement membrane. Dermis besides comprises the hair follicles, blood vessels, apocrine glands, lymphatic vessels, sweat glands, and sebaceous glands [3], [7]. The dermis can be separated into 2 regions structurally: an external area adjoint to the epidermis, described the *papillary region*, and a unfathomable broader part recognized as the *reticular region* [4].

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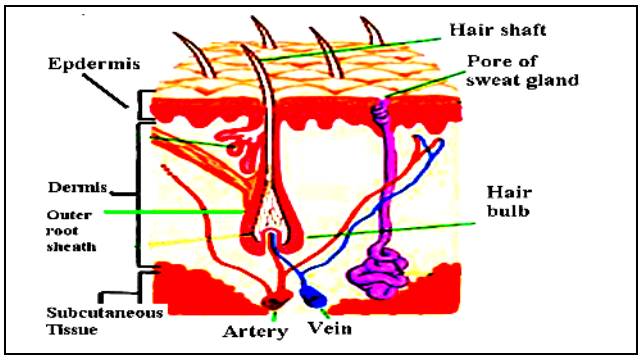

Figure 1. Schematic structure and layers of the skin [4].

1.2 Wound

Skin structure and functions of the skin can be damaged generally due to the results of hurtful events such as cuts, lacerations, surgical incisions or thermal burns etc. and chronic wounds like pressure sores or diabetic foot ulcers [8], [9]. A wound can be resulted from physical, chemical, mechanical and thermal harms (Figure 2) [10]-[12]. In another words, an interruption of normal anatomic relationship and role of the skin can also be called as wound [13],[14]. There are 2 main groups of wounds: chronic and acute wounds owing to wound healing procedures, [1],[15],[16]. Acute wounds could be resulted from traumas, yet these wounds are generally repairable in eight to twelve weeks [17]. These wounds could be resulted from mechanical damage made by sheer, dulling, and cracking act of stiff objects. Acute wounds could furthermore be generated due to exposure to high temperature, irradiation, electrical alarm, and irritated by caustic chemicals. The malice of the wounds are the real main concerns for this kind of wound [1],[2],[8].

Figure 2. Some wound examples on human skin and on animals [24]-[31].

Chronic wounds are such damages which can be generated owing to particular diseases like diabetes, tumors, and rigorous physiological contagions [6],[18],[19]. Healing period of such wounds can take over twelve weeks and recurrence of these type of wounds is not abnormal [20]. Apart from these two chief types of wound, also one could classify the wounds regarding their appearance [21],[22]. Since wounds can differ in sizes, forms, and statuses and moreover various systems can be utilized to categorize the wounds [17],[23].

1.3 Wound healing phases

Wound healing, a multipart biological procedure, engages cross-talk among various biological organizations for the suitable cell regeneration and tissue regeneration and to reinstate homeostasis and normal biological purpose [32]-[34]. Four overlying and mutually dependent periods: hemostasis and coagulation, inflammation, proliferation and re-modeling constitute the typical healing method for a wound [17],[35]-[37].

1.4 Wound dressing

The instant coverage of the wound is obligatory as soon as a great region of skin is lost [38], [39]. Wound dressings could serve an important function in the medicinal system via ensuring mechanical safety (to avoid minor diseases) and creating suitable environment for wound curing (Figure 3) [15],[40],[41]. An ideal wound dressing should supply a wet situation whilst absorbing the extreme wound exudates, making enough oxygen supply through permitting gaseous change and present low bacterial exposure with the addition of a wide-range antimicrobial agent [42],[43]. They should as well be nontraumatic and shall not stick to the wound. Furthermore, they shall not injure the granulating tissue at dressing change [40],[44],[45]. It was earlier stated in order to avoid trans-epidermal water loss and microbial disease, the urgent care of skin wounds is also essential. The original interactive dressings might stimulate action in the healing cascade and accelerate the healing route while the inert dressing fulfills quite few of the assets of an perfect dressing and possess restricted use like chief dressings [5],[23],[46].

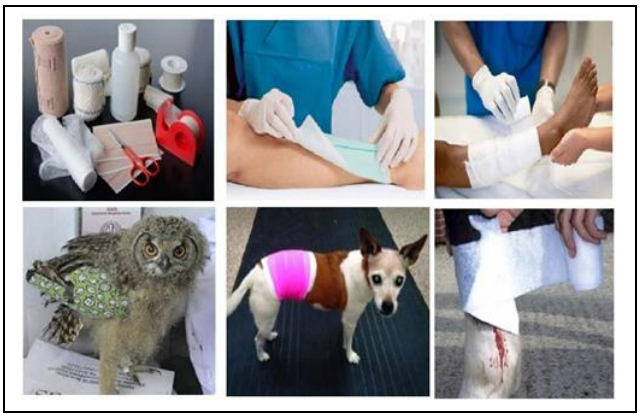

Figure 3. Some wound dressing and wound dressing application examples [47]-[53].

1.5 Ideal wound dressings

The best wound dressings should possess and fulfill following properties and performances; fluid control (the capability to absorb fluid, to provide water to a dry wound), physical barrier to evade extra physical damages, microbial control for infected wounds, odor management (a wound frequently can creates unappealing and bad odor), low adherences (appropriate dressings could aid to eliminate the adherence to a wound), space filler for deep cavity wounds, debridement by procuring the suitable moisture, T°C and pH, hemostatic (bleeding should be ceased as soon as possible to hinder loss of blood), scar reduction, metal ion metabolism (deficiency in any metal ion retards wound healing), preservation of a wet wound location, absorption of extreme exudates and drought avoidance, gaseous permeability, nontoxic, nonallergenic, sterile, avoidance of bacterial infection and disease diffusion, waterproofness, cost-effective, simple use and elimination [15],[23],[40],[44],[46],[54]-[56].

1.6 Categories of Wound Dressings

Wound dressings could be categorized vis-à-vis diversified features. There are three major wound dressing types named as passive products, interactive materials and active wound-dressing material. ***Passive products*** are common dressings like gauze and tulle. These matters simply behave as a general mantle on a wound. Therefore, the wound could recover under this wound dressing. On the other hand, ***interactive materials*** include polymeric films and foams which are transparent and permeable to water vapor and O_2. Those matters are hyaluronic acid (HA), hydrogels and foamed covers. They are high-quality barriers towards the penetration of bacteria to the wound location. Finally, ***active wound dressing materials*** are chitosan, hydrocolloids, collagens and alginates etc. [44],[57],[58].

1.7 Nano structure mats as wound dressings

Unluckily, usual wound dressings like gauze hold imperfect essential role for their malfunctioning material properties [59], [60]. In addition, special stages of the wound healing have varied pathology aspects thereby multi-functional wound dressing is necessity [61],[62]. Nano-mat based wound dressings including nanofibres, nano composites and nano structure materials are chiefly used for wound healing in the recent years because of holding up rapid and expert wound repair [6],[63]-[65]. These wound dressings gained from synthetic or natural polymers have exclusive properties for instance 3-D micro porous structure, high porosity and permeability [44],[66],[67]. These wound dressings have benefits over conservative wound dressing like gauzes, hydrogels, foams, and sponges for the healing of wounds that are [8],[68],[69]:

- Specialized replace of gases and nutrients to support cells proliferation,
- Physical safety of the wounded tissue,
- The likelihood to free useful molecules [17],[63],[70],[71].

Moreover, nanofibrous scaffolds can support hemostasis without the utilization of a hemostatic agent, pursue a rightfully moist set of surroundings for the wound with helping oxygen diffusion. Furthermore, these scaffolds can permit fluid buildup, productively defend the wound from bacterial penetration, and be basically functionalized through therapeutic complexes [10],[72]-[74]. Thus, nano structure mats are confident substances for assisting wound healing and skin regeneration [15],[63],[75].

In the next main part of this review, poly(Lactic Acid) based nano structure mats as potential wound dressings, their unique and remarkable features for wound healing, recent research studies regarding the usage of PLA Nano Structure Mats for wound healing applications were discovered.

2 PLA nano structure mats as wound dressing

Biomaterials were applied in skin wound care for several times due to their therapeutic assets, containing anti-microbial, anti-oxidant, anti-inflammatory and mitogenic activities. PLA is one of the main biopolymers applied in wound dressing and in dermal reformation [76],[77]. The major advantage of using this material is that it gradually degrades and is eventually absorbed by the skin tissue without any side effects [78]. Also researchers stated that PLA exposed bacteriostatic effects against 2 prevalent organisms. These were cultured from draining ears afterwards tympanostomy tube placement, *P. aeruginesa* and *S. aureus* [33],[75],[79]. Thus in the next part of this review, the different performances of constructs based on PLA nano structure mats for wound dressings will be emphasized and explained expansively.

2.1 Wound healing and histology

For wound dressing applications, PLA Nano Structure mats have been utilized in a vast diversity of forms like nanofibers, porous scaffolds, composite nanofibres containing drugs and additives, porous scaffolds combined with drugs or plant additives which will be reported in detail at below. In some cases after producing wound dressings, different kinds of skin cells were cultured on the mats for *in vitro* assessments. In some cases wound dressings were put on the injure wound location on the skin of the animals for *in vivo* tests. Cell cultivation, alkaline phosphatase (ALP) assay, 3-(4,5-dimethylthiazol-2-yl)-2.5-diphenyltetrazalium bromide (MTT) assay and osteocalcin assay were examined in order to estimate cellular behavior (cellular attachment, viability, proliferation, migration, differentiation and proliferation) on the mats. Furthermore, the studies of the cells' morphology on the mats were done by SEM, AFM and Fluorescence Microscopy. Also the mechanical characteristics (elasticity modulus, tensile strength) of mats were analyzed. The antimicrobial activities of the specimens were evaluated too. The results of these evaluations will also be described briefly on the following pages.

An unexpected technique for constructing PLA nanofibers is electrospinning by portable electrospinning device on hand which can be seen in Figure 4-A. The last form of PLA homogenous nanofibrous wound dressing can be observed in Figure 4-B. The nanofibrous wound dressing is removed from the skin with the usage of tweezers (Figure 4-C) [80].

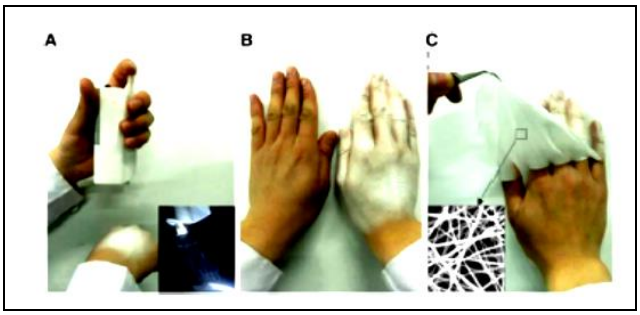

Figure 4. Novel method for preparing PLA nanofibrous wound dressing [80].

In the newest research in 2018, Yee Foong *et al.* fabricated a PLA nano-biocomposite for acute wound dressing. Dry nanofiber bacterial cellulose (BC) sheet were coated by PLA. Bacterial cellulose is a class of peerless non-plant cellulose. Bacterial cellulose can be created by a help of different bacteria types of bacteria. Some of these bacteria are *Acetobacter xylinum, Rhizobium, Aerobacter, Agrobacterium, Gluconacetobacter, Azotobacter, Achromobacter, Salmonella, Escherichia, Alcaligenes,* and *Sarcina.* Bacterial cellulose membrane was utilized for wound dressing in here. Since broad ultrafine network of bacterial cellulose eases wound healing location, advances wound exudates absorption, decreases scarring and enhances re-epithelialization simultaneously as increases healing ratios. The BC sheets can be enhanced by using a biopolymer for providing remarkable mechanical tenacity and porous surface morphology [81].

Bacterial Cellulose sheets, created with the development of nata de coco jelly, were dried. PLA has been used for the coating matters at the amount of 8%. Afterwards, the specimens loaded with antiseptic material like benzalkonium chloride (BAC). The utilization of PLA coating can develop the water resistance of the BC. The BC/8PLA bio-composite film displayed strong anti-microbial actions against two well-known bacteria (*S. aureus* and *E. coli*) [81].

PLA was blended with poly(aniline-co-ethyl3-aminobenzoate) (3EABPANI) copolymer and co-electrospun into nanofibers to explore its possibility as wound healing systems. In order to evaluate cell morphology and bio-compatibility, nano-fibrous specimens of pure polylactic acid and PLA/3EABPANI were accumulated on glass materials. The proliferation of COS-1 fibroblast cells on the nano-fibrous surfaces was controlled. Electrospinning was utilized in the manufacturing of the PLA/3EABPANI blends and resulted in better mammalian cell growth [79].

A novel interactive extracellular matrix nanofibrous wound dressings from PLA and CA (Cellulose Acetate) were manufactured in 2017 [82]. Thymoquinone (TQ) was included into the scaffolds to avoid prevalent medical infections, and for hastening the amount of wound closure and re-epithelialization and several benefits of TQ-laden Poly(lactic acid)/CA wound dressings were suggested. Mimicking the interactive extracellular matrix through the three-D nanofibrous structure, and encouragement the cell proliferation because of the hydrophilicity and bio-activity of cellulose acetate were some of these benefits. Moreover, the wound dressings stopped the bacterial infection in initial phases because of the existence of TQ, and preserved the minimum probable bacterial load in the wound area over the withstand releasement of the drug for nine days. *in vivo* valuation proved which TQ-laden PLA: CA (7:3) scaffolds encouragingly helped the wound healing procedure by ascending re- epithelialization and controlling the creation of granulation tissue [82].

Aloe-vera (AV) is a pharmaceutical herb. AV displays well-recognized spectrum of therapeutic characteristics containing anti-microbial, anti-oxidant, anti-inflammatory, and analgesic activities. Also, cell proliferation and migration of keratinocytes and fibroblast cells can be increased with AV. Biological properties of PLACL-SF-AV nanofibres demonstrated that this nano-mat can be a special biomaterial for skin tissue regeneration [83]. Salma et al. [84] created nanofibrous scaffolds based on PLA and Cellulose Acetate (CA) as an ideal biomaterial wound dressing. ***Thymoquinone*** (TQ), the dynamic component of *Nigella sativa*), was added into the nanofibers for its anti-bacterial assets and capacity to support wound healing. Its hydrophilicity and water intake capacity were advanced with the existence of cellulose acetate in the scaffolds. Besides, this resulted in a humid site for the wound. The TQ -laden CA/PLA nano composite showed strongly antibacterial performance against *gram (+)* and *gram (-) bacteria* (Figure 5) [84]. *in vivo* assays carried out on mice skin wound models revealed that thymoquinone-laden poly(lactic acid): cellulose acetate (7:3) scaffolds considerably expedites the wound healing procedure through supporting angiogenesis, augmenting reepithelialization and managing granulation tissue generation [84].

Carvacrol (CAR) is one of the best capable vital oil components with anti-microbial activity. Scaffaro *et al.* [85] studied the possibility of incorporating CAR into PLA nanofibres. PLA membranes comprising regularly dispersed CAR were effectively equipped and a series of systematic examinations containing morphomechanical characteristics, *in vitro* releasement ratio, and anti-microbial/anti-biofilm activities against *S. aureus* and *C. albicans* were approved. According to outcomes of this study, CAR displays a nice compatibility with poly(lactic acid) and performances as the plasticizer, advancing flexibility and extensibility of matrix. The graded releasement of CAR from poly(lactic acid) mats permitted a noteworthy anti-microbial activity up to one hundred forty four hours and decreased the bio-film manufacture by 92-96% and 88-95% of *S. aureus* and *C. albicens* in single and mixed cultures, respectively. A powerful decrement of cell count, biomass, metabolic activity, and vitality of established twenty-four-h and forty eight-h biofilms were also revealed [85].

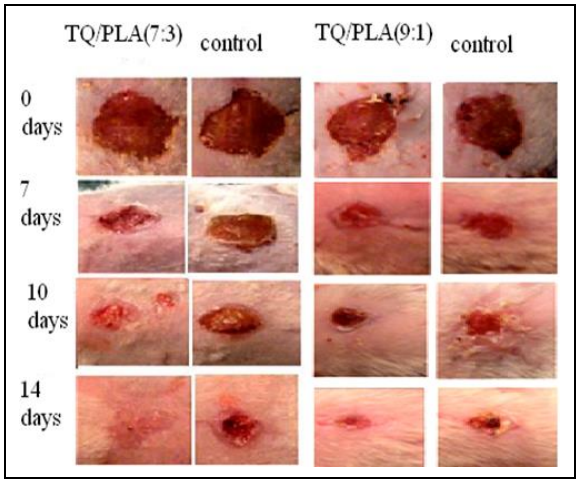

Figure 5. Digital photo evaluation of healing advancement from day zero to day fourteen for wounds applied by TQ/PLA scaffolds vs. the control [84].

Ginsenoside-Rg3 (G-Rg3) is a potent angiogenic inhibitor, derived from Red ginseng. Cui et al. [86] fabricated electrospun PLLA/G-Rg3 nanofibers for preventing scar hyperplasia of skin. The results demonstrated a potential application of G-Rg3/PLLA electrospun nanofibrous scaffolds to restore the structural and functional characteristics of wounded skin. Varshosaz *et al.* [87] prepared nanofibers through electrospinning process with different percentiles of the blends of 2 polymers of poly(methyl vinyl etherco-maleic acid) (PMVEMA) and poly(lactic-co-glycolic acid) (PLGA) load with **montelukast** that was effectual for wound curing. Li *et al.* [88] organized P(LLA-CL)/ PDEGMA nanofibrous mats. Blend fibers of PDEGMA [Poly(di(Ethylene Glycol) Methyl Ether Methacrylate] and P(LLA-CL) [Poly(L-Lactic Acid-co-ε-Caprolactone)] were constructed through electrospinning. Moreover, analogous nanofibers having CIF were made and X-ray diffraction displayed the drug to be in existence in the amorphous physical form postelectrospinning. The specimens indicate distinct thermo-sensitive characteristics and provided continued releasement of CIF higher than 20 hours *in vitro*. The nanofibers can help the proliferation of fibroblasts, and by variable the temperature cells can simply be adjoined to and separated from the nanofibers. Anti-bacterial assessments proved that nanofibers laded via Ciprofloxecin were active in preventing the growth of *E. coli* and *S. aureus. In vivo* examinations on rats specified that the P(LLA-CL)/ PDEGMA nanofibers laded with CIF possessed

more efficient wound healing characteristics in comparison with a commercially available gauze and CIF-laden nanofibers made only of P(LLA-CL) [88]. The optimized relative amount of PLGA/PMVEMA was 3:1 with the totality concentration of polymers as 37% loaded by 30% of montelukast fabricated nanofibers by a diameter of 157.6 nm, medicine loading percent of 43.7% and releasement effectivity of 75% after ten days [87]. In 2017, PLA nanofibres were utilized like a delivery system for propolis ethanolic extract (PEE) and silver nanoparticles (AgNPs) that are recognized for their famous *Antiseptic* and *Antimicrobial* activities that progressed wound healing. Electrospun PLA nanofibers with PEE sustained viability of HaCaT cells. Examination of antimicrobial activity proved the capacity of PLA/ AgNPs nano mats for decreasing the microorganism growth [89].

Lately reported that Polyaniline/PLA nanofibers let mammalian cells to adjoin and proliferate, at the same time as killing pathogenic bacteria cells. Moreover, they are new conductive substances. Polyaniline/PLA nanofibers are potentially nice fitted for utilization as scaffolds for antimicrobial wound dressings because they are capable to kill microorganisms with no antiseptic drug [90]. In the investigation by Karami *et al.* [91], electrospun poly(e-caprolactome) (PCL), PLA, and their 50/50 hybrid nanofibrous specimens holding the herbal drug thymol (1.2% v/v) fabricated for wound healing.

The electrospun 50/50 PCL/Poly(Lactic acid) specimens with thymol possessed a notable wound closure percentile of 92.5% after a time of fourteen days according to outcomes of this study [91]. In another research, nano-porous nonwoven mats of *dibutyryl chitin (DBC) /PLA* blends were fabricated for wound healing. The healing effectiveness of the *hairless mice* with DBC specimens on the 5th day was alike to the skin healing phase of control mice on the 8th day [90].

In 2013, PLA nanofibers were utilized as a carrier for *Cur* (Curcumin: The extract of the roots of *Curcuma longa* L.). Since PLA nanofibers possess a high-specific surface area and high porosity that could improve the useful characteristics of Cur [75], [92]. The features of Cur/PLA nanofibres having various quantities of Cur were checked. Curing wounds with Cur/PLA specimens considerably raised the speed of wound closure (87%) by day seven in comparison to that of PLA nanofibers (58%) [75].

In another work, nano-composite mats of poly (D,L-Lactide) nanofibers with various zinc oxide nanoparticles (nano-ZnO) concentration were constructed by 2 procedures. These methods were electrospinning of polymer/zinc-oxide solutions and integration of electrospinning of polymer solutions with electrospraying of nano-zinc-oxide dispersions. A uniform morphology with a mean porosity 55% and mean pore size almost 45 µm was determined on the poly (D,L-Lactide)/ZnO fibrous mats. Moreover, the existence of zinc-oxide nano-particles enhanced the toughness of the specimens, and the best nano- zinc-oxide concentration (3 wt%) was monitored at which the tensile strength and elasticity modulus can be enhanced [93]. Sagala et al. [94] studied on antibacterial properties of mats constructed from PLA nanofibres with *antibacterial agent* triclosan (TR) for wound dressing. TR is a basically water insoluble anti-bacterial agent. TR was added to PLA solution. The solutions were then electrospun to produce PLA nanofibres. The PLA webs tested for their antibacterial activities using agar diffusion test [94]. Cyclo-dextrins (CDs) are naturally non-toxic cyclic oligosaccharides containing α-1,4-linked glucopyranose units. TRs anti-bacterial activity could be improved by enhancing the solubility with forming CD-IC. Triclosan/Cyclodextrin inclusion complexes (TR/CD-IC) incorporated in PLA nanofibers by electrospinning and the antibacterial characteristics of the webs were examined. PLA nanofibers incorporating TR/CD-IC displayed higher antibacterial activity versus *S. aureus* and *E. coli* bacteria in comparison with PLA nano fibers comprising only TR without CD-IC [95]. *Garcinia cowa* (GC) Xanthones and their derivatives were found to be the main constituents in crude extracts of GC. These compounds were well established for their biological and pharmacological characteristics comprising anti-microbial, anti-oxidant, anti-inflammatory, and anti-malarial activities. The antimicrobial and antioxidant properties of the GC-laden PLLA nanofibrous mats were promising. It was found that mats containing 50% GC were discovered to be non-toxic to normal human dermal fibroblasts [96]. In 2010, PLA/Ag nano composite films with different silver nanoparticle weight percentiles (8, 16 and 32 wt%) were fabricated and anti-bacterial characteristics of specimens were studied. Chemical reduction process in diphase solvent was utilized for silver nanoparticles synthesis into PLA and silver nitrate and sodium borohydride were correspondingly utilized as a silver pioneer and reducing agent in the PLA. It can be concluded from the outcomes that PLA/Ag films had a surprising anti-bacterial activity with the rise in the percentile of Ag nanoparticles in the PLA [97].

Shikonin is a natural material with a testatum spectrum of wound healing, anti-tumor, anti-microbial, anti-oxidant and anti-inflammatory properties. Kontogiannopoulos *et al.* [98] constructed electrospun PLLA, PLGA and cellulose acetate nanofiber mats containing shikonin with proper release patterns for transdermal wound healing dressings. Jang *et al.* [99] estimated the influence of nonwoven mat of PLA/DBC blend nanofibers on skin wound healing in hairless mice. During a cell spreading assess in scratched human HaCaT keratinocytes, the cell spreading efficiency of DBC was validated. Scratch wound tests illustrated that DBC notably expedites the spreading ratio. The molecular aspects of the healing procedure examined by hemotoxylin & eosin staining of the healed skin. This exhibits the extents of reepithelialization and immunostaining on extracellular matrix synthesis and remodeling of the skin. DBCNFM [Nano-porous non-woven mats of electrospun DBC(DiButyryl Chitin)/PLA blend nanofibers] remarkably enhanced the expression of the type 1 collagen and filaggrin. DBC remarkably expedites the spreading ratio of HaCaT keratinocytes in a dose dependent method and topical use of DBCNFM reduced skin wound rank scores and considerably raises the skin remodeling in hairless mice [99].

Mohiti-Asli et al. [100] produced scaffolds for the treatment of acute and chronic wounds with the effective association of ibuprofen in PLA nanofibers. Nano-fibrous PLA scaffolds holding 10, 20, or 30 wt % ibuprofen were constructed. Ibuprofen releasement characteristics were measured. *in vitro* cyto-toxicity to human epidermal keratinocytes (HEK) and human dermal fibroblasts (HDF) of the scaffolds with changing ibuprofen concentrations were assessed against pure poly(lactic acid) nano-fibrous scaffolds. Afterwards, in order to support skin regeneration and/or assistance with scarless healing, scaffolds loaded with ibuprofen at the

concentration that helped human skin cell viability and proliferation (20 wt %) were considered *in vivo* in nude mice utilizing a full thickness skin incision model to control the capability of these scaffolds. A new regenerated skin on wounds applied via cell-seeded 20 wt % ibuprofen bandages showed suggestively higher blood vessel creation in relation to acellular ibuprofen bandages. Moreover, degradable anti-inflammatory scaffolds having 20 wt % ibuprofen help human skin cell viability and proliferation *in vitro*, decrease wound contraction *in vivo* [100]. Silver ion releasing PLA nanofibrous scaffolds that display outstanding anti-bacterial efficiency without the utilization of silver nano-particles were designed by Mohiti-Asli *et al.* [101] via a silver ion solution releasement (Silvadur ET) contained of silver nitrate, a proprietary polymer binder, water and ethanol. That was the first research using a polymeric coating comprising silver nitrate on nano-fibrous scaffolds. Nano-fibers coated via solutions possessing various concentrations of silver ranging from 31.25 to 250 µg/ml displayed outstanding anti-microbial characteristics versus both gram (+) and gram (-) bacteria.

On the other hand, they did not display influence on silver resistant bacteria. Biocompatibility investigations of the specimens specified that scaffolds coated with Silvadur ET solution holding silver equal to or less than 62.5 µg/ml continued viability and proliferation of both human dermal fibroblasts and human epidermal keratinocytes. These novel antimicrobial nanofibrous scaffolds were fabricated for the first time and comprise silver in a form rather than nano-particles while still displaying outstanding anti-microbial efficiency. The results show that silver could be employed in nano-fibrous bandages for wound healing treatments when provided in suitable formation as well as concentration [101].

Govindraj P et al. [102] implemented an effective association of curcumin(Cur) into a blend of PLA and hyper-branched polyglycerol (HPG). Cur concentration was optimized up to 10% in order to acquire smooth and bead free fibers. Cur concentration displayed the influence on diameter of the fiber. The existence of HPG also increases the swelling ratio, a significant characteristic needed for tissue engineering, by creating more hydrophilic structure. This greater swelling characteristic also enriched the releasement profile of the Cur, a significant treatment of a nanofibrous scaffold. In respect of the tissue-engineering parameters such as cell adhesion, cell proliferation and cell viability were concerned, the blended structure PLA/HPG/Cur fiber provided an environment profile for those characteristics [102]. In another work, researchers used silk fibroin (SF) and poly (Lactic-co-Glycolic Acid) (PLGA) for production of wound dressing. They optimized the electro-spinning process of these polymers to construct a hybrid membrane as a chronic wounds dressing. *in vitro* assessments demonstrated that the attachment and proliferation of L929 were considerably enhanced on PLGA/SF (2:1) hybrid scaffold. Also the histo-pathological evaluations proved the *in vitro* outcomes. On fifteenth day, the residual wound area in PLGA/SF (2:1) hybrid membrane group was notably less than PLGA and control groups (20). The usage of poly (lactic-co-glycalic acid) (PLGA)/collagen nanocomposite scaffolds for wound healing treatment were studied by Sadeghi et al. [103]. PLGA and collagen were dissolved in HFIP as a prevalent solvent and scaffolds were produced by electro-spinning technique. Cyto-toxicity and cell adhesion were analyzed for 2 cell line groups, human dermal fibroblast (HDF) and human keratinocyte (HaCat). Scanning electron microscope photos demonstrated suitable cell adhesion to the scaffold for both cell lines. MTT assays specified that the cell viability of HDF cells enhanced via time, nevertheless the number of HaCat cells declined after fourteen days. Its elongation was low. However, the final tensile strength was appropriate for skin substitute treatment [103].

S. Katti et al. [104] fabricated the Poly (Lactide-*co*-Glycolide) (PLAGA) nanofibers via electrospinning method for wound healing applications and determined the influence of manufacturing factors: polymer solution concentration, voltage per unit length, the morphology and diameter of nanofibers and orifice diameter (needle gauge). The outcomes specified that the diameter of nano fibers was diminished with a rise in needle gauge (decrement in orifice diameter). Moreover, it was enhanced with an increment on polymer solution concentration. The average diameter of the nano fibers diminished with a rise in voltage. Feasibility of drug association into the nano fibers was revealed via usage of cefazolin, a broad-spectrum antibiotic.

2.2 Cell viability assay

Table 1 summarizes the cell viability of different skin cells cultured on PLA nano structure mats. Table 1 displays that different research groups investigated and reported the cell viability/proliferation results of different skin cells [such as mouse myoblast cell line, HDF (Human dermal Fibroblasts), HEK (Human epidermal keratinocytes), COS-1 fibroblast (African Green Monkey Fibroblast Cells), mouse fibroblast cells and HaCaT cells (The immortalized human keratinocyte cell line) etc.] cultured on different PLA based nano structure mats [such as PLA nanofibers, PLA/Curcumin nanofibers, PLA/Ibuprofen nanofibers, PLA/3EABPANI (*Poly(aniline-co-ethyl 3-aminobenzoate) copolymer*), PLA/TQ (Thymoquinone) nanofibres, PLA/CA (Cellulose Acetate) /TQ (Thymoquinone) nanofibres, PLA/ PEE (Propolis ethanolic extract) etc.] according to the number of days (between 1 day and 2 weeks) with the utilization of different methods [such as CCK (Cell Counting Kit)-8 assay, AlamarBlue assay, Continuous fluorescence assay and MTT ((3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)) assay etc.].

3 Conclusions

It is known that wound is any damage and break in the skin surface and/or the disruption of living tissue integrity of the skin or mucosa as a consequent of factors such as cuts, burns, trauma, illness or other impacts etc. The most common wounds could be formed via accidents, surgical operations, underlying diseases, some undesirable skin conditions. In a wound generation, structures such as blood vessels, muscle and nerve could also be affected simultaneously. The proper suitable protection of the wound is vital for the injured or wounded living being. Since, if the wound is not properly protected and covered, unwanted infections can generate leading to further health hazards and illnesses. Consequently, wound dressings which are a sterile pad or compress implemented to a wound to encourage healing and protect the wound from further possible harms are used for protecting and covering the wounds. However, wound healing is a complex procedure that necessitates designing a suitable wound healing system or dressing which possesses key factors like a wet wound location, avoidance of microbial action and absorption of exudates.

Table 1. Cell viability/proliferation assay of PLA nano-fibrous specimens as wound dressings.

Type of Wound Dressings	Type of Cells	Cell Proliferation and Cell growth viability Evaluation Method	Cell Viability/Proliferation (According to Number of The Days)								Ref.
			1	2	3	4	5	7	10	14	
PLA Nanofibers	Mouse myoblast cell line	CCK (Cell Counting Kit)-8 assay	0.4	-	0.45	-	0.9	-	-	-	[75]
PLA/ 0.125 wt% Cur Nanofibers	Mouse myoblast cell line	CCK (Cell Counting Kit)-8 assay	0.45	-	0.5	-	1	-	-	-	[75]
PLA/1.250 wt% Cur Nanofibers	Mouse myoblast cell line	CCK (Cell Counting Kit)-8 assay	0.4	-	0.5	-	1.25	-	-	-	[75]
PLA/6.250 wt% Cur Nanofibers	Mouse myoblast cell line	CCK (Cell Counting Kit)-8 assay	0.4	-	0.45	-	0.55	-	-	-	[75]
PLA nanofibres	HDF (Human dermal Fibroblasts) and HEK (Human epidermal keratinocytes)	AlamarBlue assay	27%	-	-	37%	-	67%	30%	30%	[100]
PLA/ 10 wt% ibuprofen nanofibres	HDF and HEK	AlamarBlue assay	25%	-	-	35%	-	65%	32%	28%	[100]
PLA/ 20 wt% ibuprofen nanofibres	HDF and HEK	AlamarBlue assay	41%	-	-	43%	-	71%	42%	43%	[100]
PLA/ 30 wt% ibuprofen nanofibres	HDF and HEK	AlamarBlue assay	38%	-	-	40%	-	65%	39%	31%	[100]
PLA/3EABPANI 95:5 Nanofibers	COS-1 fibroblast (African Green Monkey Fibroblast Cells)	Continuous fluorescence assay	1	2.2	4.1	5.7	-	-	-	-	[79]
PLA/3EABPANI 85:15 Nanofibers	COS-1 fibroblast	Continuous fluorescence assay	1	1.5	4	5.8	-	-	-	-	[79]
PLA/3EABPANI 70:30 Nanofibers	COS-1 fibroblast	Continuous fluorescence assay	1	1.8	4.4	6.2	-	-	-	-	[79]
PLA/3EABPANI 55:45 Nanofibers	COS-1 fibroblast	Continuous fluorescence assay	1	1.7	4.5	6.5	-	-	-	-	[79]
PLA nanofibres	Mouse fibroblast cells	MTT [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)] assay	0.13	-	0.13	-	-	0.13	-	-	[82]
PLA/TQ nanofibres	Mouse fibroblast cells	MTT assay	0.11	-	0.12	-	-	0.15	-	-	[82]
PLA/CA/TQ nanofibres	Mouse fibroblast cells	MTT assay	0.15	-	0.25	-	-	0.35	-	-	[82]
PLA Nanofibers	HaCaT cells (The immortalized human keratinocyte cell line)	MTT assay	100%	-	-	-	-	-	-	-	[89]
PLA Nanofibers / 10% wt% Ethanol	HaCaT cells	MTT assay	90%	-	-	-	-	-	-	-	[89]
PLA nanofibers /10 wt% PEE	HaCaT cells	MTT assay	100%	-	-	-	-	-	-	-	[89]
TQ/ PLA Nanofibers	Mouse fibroblast cells (3T3-L1)	MTT assay	100%	-	-	-	-	-	-	-	[84]
TQ/ PLA/CA 9:1 Nanofibers	Mouse fibroblast cells (3T3-L1)	MTT assay	99.5%	-	-	-	-	-	-	-	[84]
TQ/ PLA/CA 7:3 Nanofibers	Mouse fibroblast cells (3T3-L1)	MTT assay	99.1%	-	-	-	-	-	-	-	[84]

*: Ref.: Reference number.

Various wound dressings can be accessible but not all can meet the specific conditions of a perfect wound healing system to complete proper wound healing process. Biomaterials can be applied in skin wound care for several times because of their therapeutic assets, containing anti-microbial, anti-oxidant, anti-inflammatory and mitogenic activities. PLA is one of these main biopolymers applied in wound dressing and in dermal reformation. The major advantage of using this material is that it gradually degrades and is eventually absorbed by the skin tissue without any side effects. Indeed, PLA Nano Structure Mats are a new class of materials that possess great potential in wound healing because of biocompatibility, bioabsorbability, biodegradability, absorption of exudates from the wound, physical safety of the wounded tissue and the possibility to free useful molecules. When all literatures were examined closely in detail, it is vital to point out that PLA biopolymer can be utilized in many different forms for proper wound dressing applications. For instance, PLA nano structure mats have been utilized in a vast diversity of forms like nanofibers, porous scaffolds, composite nanofibres containing drugs and additives, porous scaffolds combined with drugs or plant additives for wound dressing applications. In some cases after producing wound dressings, different kinds of skin cells were cultured on the mats for *in vitro* assessments. In some other cases wound dressings were put on the injure wound location on the skin of the animals for *in vivo* tests. Cell cultivation, alkaline phosphatase (ALP) assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and osteocalcin assay were examined in order to estimate cellular behavior (cellular attachment, viability, proliferation, migration, differentiation and proliferation) on the mats. Furthermore, the studies of the cells' morphology on the mats were done by SEM, AFM and Fluorescence Microscopy. Also the mechanical characteristics (elasticity modulus, tensile strength) of mats were analyzed. Moreover, the antimicrobial activities of the produced specimens were evaluated too. Different characteristics (such as anti-microbial, anti-inflammatory etc.) and biomedical applications of PLA nano structure mats for wound dressing applications were explored in detail. Overall, PLA biopolymer was exhibited to be a potential bio-material to be utilized in wound healing because of its anti-microbial and anti-inflammatory

nature and with many other aforementioned positive features. And moreover, PLA biopolymer finds utilization in several various forms of wound dressings. It is known that the efficient dressings should possess features optimized for exacting form of wound at a sensible low cost and with minimum problem to patients. Many different consequences of the related implemented analysis and tests of PLA biopolymer usage in wound dressing have been stated earlier. PLA nano structure mats have been used in a vast diversity of forms for wound dressing applications in many recent studies. As a result, PLA nano structure mats for wound dressing applications shows high potential for future applications with its positive properties and satisfactory performance. It is thought that the usage of PLA biopolymer nano structure mats in wound dressing will increase with the upcoming future studies and possible future commercial applications that may emerge in the light of all these scientific studies.

4 References

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