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# NANO-CARRIERS-BASED APPROACHES FOR TOPICAL WOUND THERAPY AND CARE

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## ABSTRACT

**Background:** Wound management is challenging task for researchers and also a burden on health care system. The topical infections have problems like moist condition, microbial contamination, environmental factors, forming debris etc. These conditions caught up wound into acute and chronic situations that are miserable for patients. The conventional techniques were applied but it has some limitations such as less moisture absorbent capacity, lower bioavailability and patient compliance. The modern techniques may overcome the problems of wound infections. **Main body:** The wound healing is a complex process. Basically, it has four phase, haemostasis, inflammation, proliferative phase and remodelling. Particularly, natural and synthetic sources were developed for the management of wound. There were various natural sources such as curcumin, *Aloe vera*, pomegranate, *Calendula officinalis*, alginate etc. used in the healing of wound infections. Moreover, nano-medicines plays a vital role in wound healing management. The nano-based introduced nanoparticles, polymeric nanoparticle, liposomes, niosomes, silver nanoparticles, gold nanoparticels etc, for effective healing of wound infections. In the coming years it will be anticipated that the market value of wound healing products will upraise. The regulatory bodies designed their protocol according to the patient compliance values. **Conclusion:** Overall, the management of wound is difficult. The researchers find advanced techniques for faster wound healing. The nanotechnology establish better results like faster wound healing, high bioavailability rate, low toxicity and effective therapeutic rate for management of infectious wound.

**KEYWORDS:** Nanomedicine, wound healing, nanoparticles, wound remodeling, micelles.

**Nanomedicine and Topical Wound Infection: Facts and Discussions**

The wound can be caused by an external force, which may cause cell death and tissue destruction. It disturbs the anatomical structure and functions of the body and also spread to other tissue and organ like subcutaneous tissue, tendons, vessels and including bone.[1] The skin is the largest body part and acts as the first defense mechanism in the body. Further, it has a dynamic barrier known as the acid mantle, which regulates pH and protects skin from pathogens. However, when there was an injury, automatically the body triggers the immune system, which causes bleeding and inflammation, after this the recovery phase starts with proliferation and remodeling.[2] In case of the acute wounds like minor cuts or injury can be recovered by bodies own mechanism, but when the immune system is weaker and not appropriately treated then it will convert into chronic infections. There is the growth of bacterial colonization in infectious wounds; the reason may be presence of bacteria in skin flora, other tissues and the external environment. Commonly, staphylococcus aureus and other types of staphylococci, methicillin-resistant staphylococcus aureus (MRSA), pseudomonas aeruginosa, streptococcus pyogenes and enterococci etc were noticed in patients with chronic wounds.[3]

Nanomedicine enormously participated in the research area. There are various applications available in different areas like biomedical sciences, medical devices, bioengineering, pharmaceutical science etc. Specifically, the nano-based formulations followed the particle size range under 1-100nm, that drastically improves their target efficacy. There were several diseases such as cardiovascular, neurological disorders, cancer, diabetes as well as diabetic wound healing, in which nanotechnology played an important role.

In terms of wound healing, there were various nano-based formulations such as polymeric liposomes, micelles, nanoparticles, dendrimers, liposomes etc. were developed.[4,5] They are target oriented and produce effective outcomes with fewer side effects and better patient compliance. Although, wound healing is a complicated process it has a plethora of challenges, due to moisture sensitivity, bacterial growth, and wound closure in diabetic patients.

Therefore, there are various types of dressings, hydrogels, creams, foams and gels developed for the treatment of infected wounds. Additionally, synthetic and natural moieties were also developed for targeting wounds. Natural materials such as curcumin, tulsi, honey, aloe vera etc effectively utilized in the preparation of nano-formulation.[6] The major advantages of

using natural resources are lower side effects, eco-friendly and less expensive.[7]

On the other hand, it is very important to manage the wound healing problem because it has been creating a massive financial load on the health care system. The report estimated by advanced wound care market in a period of 2021-2028 is increasing with cumulative annual growth rate (CAGR) of 6% and it is anticipated to reach USD 15,191.03 million by 2028. The wound care products covered the maximum market share, as it includes therapy devices, biological and dressing and others. Therefore, it is very essential to extend effective wound management treatments.[8]

**Main text**

**Wound healing: Pathophysiological mechanisms involved**

Wound healing is a complicated and dynamic process in which cellular and biological process interaction is involved that is taking place in tissue and organ of the body.[9] Many researchers are argued on the stages of wound healing and arbitrarily divided into four overlapping stages to understand the physiological condition of wound healing and there is haemostasis, inflammation, proliferation, remodeling.[10] Although the overlapping phase is different at a different time for acute and chronic wound healing.[11] Figure 1 represented the different phases of wound healing.

**1. Haemostasis**

After an injury or wound, this first phase has an aim to stop the bleeding and prevent loss of excessive blood through the coagulation within seconds or minutes. Firstly, platelet activated via stimulation of integrin receptors which is present in extravascular collagen and the release of soluble mediators and adhesive glycoproteins (fibrinogen, fibronectin, thrombospondins, van willebrand factor) make platelet clump and sticky.[10] After that, these clotting factors are form fibrin plug at the side of the wound and aggregated platelet get trapped within the fibrin net and this bulk of clot is not only necessary for haemostasis but it also provides extracellular matrix and protection from bacteria.[12] In this process, the growth factors (platelet-derived growth factor (PDGF), transforming growth factor (TGF) and cytokines present at the cytoplasm of platelets are released and involve in the further process (inflammation) for cleaning and healing of the wound.[13]

**2. Inflammation**

After the release of growth factors, the inflammatory cells (leukocytes, neutrophils,

monocytes, and macrophages) are activated and play a key role during inflammation. It also increases through the endothelial gap and stimulates pain receptors present on the extracellular area which are show inflammation signs like edema and erythema at the site of the wound.[14] Most cells responded in the first 24 hours or it can be often last 2 days. These activated cells act as phagocyte cells, they release pro-inflammatory cytokines and antimicrobial substances such as reactive oxygen substances (ROS), and proteasecleanse and heal the wound.[15]

**3. Proliferative phase**

This phase is mostly complete in weeks with fibroblast migration, collagen synthesis, angiogenesis, and granulation formation. The released growth factors and oxygen reach blood cells at the wound area construct new tissues with fibroblast migration.[16] After the synthesization of fibroblast, elastic tissue is formed that is collagen which is most important in this phase and makes strength to all tissues. During haemostasis many cytokines are released and they are responsible for the angiogenesis of the cell. The angiogenic factors fibroblast growth factors(FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), angiogenin, transforming growth factor (TGF-α and TGF-β) present on endothelial play a major role in the formation of granulation tissue to help the wound contraction and closure of the wound.[12]

**4. Remodeling**

The last phase of wound healing is responsible for a new epithelium layer and scar formation within over weeks or 2 years.[12] During the synthesis of the extracellular matrix collagen III is formed in the proliferative phase which is highly disorganized. The organized and tensile strength of new collagen is formed for the healing of wounds.[15]

**Natural and synthetic moieties used for wound healing: An inside story**

In today's era herbs proved to be significant in treating various acute and chronic diseases. There has been an exponential growth in the use of herbal remedies. Notably, promising results come from the benefits of phytopreparations in wound restoration. Various plants and their phytoconstituents showed an effective role in managing wounds. Moreover, herbs are not only proved to be non-toxic but they are cheap and affordable. Hence, herbs are proved to be a better medicament for healing wounds.[17] The medicinal plants that show beneficial therapeutic effects in healing wounds are Aloe vera, Azardica indica, Lantana Camara, Hypericum spp., Lantana camara, Tridax procumbens, Chromolaena odorata, Hydnocarpus

wightiana, Helianthus annus Linn., Jasminum auriculatum, Ginkgo biloba, Curcuma longa Linn., Centella asiatica, Cedrus deodara. Curcumin is found to be the most promising herb for healing wounds, which mainly acts by stimulating growth factor production.[18] These phytochemicals generally act by healing the hypersensitivity reactions in wounds by regenerating the lost tissues via various mechanisms. Various studies on animals using plant species exhibited valuable effects. For example, Leea macrophylla has healing effects. It increases the synthesis of collagen, stimulates the production of antioxidants, reduces the levels of pro-inflammatory factors, and improves cell proliferation. Wrightia tinctoria presented healing activity, with an increase in the rate of contraction of induced lesions. Pereskia aculeata accelerated the cicatricle process by increasing blood flow and collagen deposition. An ointment from Struthanthus Vulgaris stimulated the closure of lesions, stimulated the formation of granulated tissue, and stimulated the proliferation and organization of collagen fibers. Cynodon dactylon presented antioxidative activity and stimulated collagen formation and healing. Caesalpinia mimosoides stimulated reepithelialization of the epidermal layer and the contraction of lesions. Here forth it's been proved that herbs play a major and main role in wound healing.[19]

**Natural and Synthetic moieties in Wound Healing**

The severity of wounds is related to complications that need to be addressed frequently. This quick requirement to heal wounds triggers the emergence of Nanotechnology. Nanotechnology provides a sustained and controlled release of the active constituent treating not only wounds, also other diseases.[20]

Experimentally several natural and synthetic moieties derived from plants have shown prominent wound-healing effects. K.N. Chidambara Murthy et al studied that dried pomegranate (Punicagranatum) peels supported wound healing.[21] Cestrum nocturnum experiment done by Hemant Kumar Nagar et al in Wistar Albino Rats also showed a prominent effect in the healing wound.[22] Moreover, M. Maghimaa et al synthesized the metallic silver nanoparticles (AgNPs) from the aqueous extract of Curcuma longa leaf and proved their wound healing potential.[23] Moreover, In an in-vitro study, ChristophNicolauset al proved that Calendula officinalis (pot marigold) flower extracts can be used in the treatment of minor inflammation of the skin and as an aid in the healing of minor wounds.

Along with the herbal treatment as discussed earlier, nanotechnology is playing a major role in healing wounds. Nanoparticles of silver and gold are currently in use for treating wounds

developed due to diabetes.[20]

Carrageenan, a sulfated polysaccharide has the regenerative effect to heal tissues studied by RamanathanYegappan and team.[24] Nevertheless, modern medicine and drugs remain effectively unapproachable (and unaffordable) to the majority of the world's population. But, traditional medicine endures being the first line of treatment, indeed. With a greater understanding of traditional practices comes appreciation and benefit to more of the world's people. Hence, along with herbs, some synthetically derived chemicals are also capable of developing new tissues and healing wounds.[25] Polyurethane is a synthetic semi-permeable elastic polymer which when used for healing wounds provides a barrier to bacteria and exchange of gases. Other synthetic materials that is also used in wound dressing are- sodium and calcium alginate, polyesters, gelatin, pectin, or carboxymethylcellulose.[26] Further, polymeric biomaterials like Flexzan, BiopatchCrafoamsBiatainCutinova, Cultinova Gel, BiolexTegaGel have their own distinguishingtherapeuticnecessities which works on the cellular level.[27] Table 1 represented the researches of natural and synthetic materials used in wound healing.

**Conventional strategies of wound healing: Traditional approaches**

From traditional therapy to recent trends therapy or treatment of wound healing is so much challenging.[33] The recent trends of wound healing therapy and advanced dressings mainly focus on tissue debridement procedure, infection, moisture balance and epithelial management.[34] In past, for tissue debridement the new technology and techniques are developed hydro surgery, ultrasound therapy, and plasma-mediated bipolar radio-frequency ablation therapy.[35] After cleaning of damaged tissue or debridement procedure antiseptic is required for removal of the infection. Many common antiseptics (iodine, sliver sulfadiazine, polyhexanide and betaine (PHMB), sodium hypochlorite) are used in different forms Tottoli and coworkers.[34] Moreover dressing is a device that is used to protect the wound from the external environment, reduce the infection risk and easy for fast wound healing. Over the past decade, traditional dressing like natural and synthetic bandages, cotton wools were used to prevent harmful bacteria and dry the wound.[36] But nowadays advanced dressing (iodosorb, and actisorb silver) are available in the market. Nanocrystal silver coating technology and advanced dressing are also designed for the delivery of active agents like antimicrobial agents, antibacterial agents, anti-inflammatory agents for the prevention of wound surface adhesion, bacterial growth.[34]

The other skin regeneration medication is also used for wound healing this medication directly stimulates regeneration and changes the wound environment.[37] Skin regeneration products represent the most innovative branch in skin injury treatments and involve a multidisciplinary approach. Scaffolds technology is also involved in skin regeneration and the delivery of drugs to promote wound healing.[38] Cell therapy and tissue engineering are combined in scaffolds that are activated with anti-inflammatory, antibacterial active agent growth factors and overcome the limitations of current wound healing technologies and design personalized therapies for patients.[39] Table 2 represented the different types of dressings used for wound healing management.

**Nanotechnology in wound management: A newer perspective**

Many innovative studies of nanotechnology in the wound healing field show biological efficacy through the carrier circulation, direct act on the cell for repair.[47] In this field of research, nanomaterials can be used due to their effective response and superior surface-to-volume ratio. Metal nanomaterials such as silver, gold, zinc have an antimicrobial and low toxicity property for wound dressing.[48] In some literature reviews, silver nanomaterial modulates growth factors and cytokine release through inflammatory cells rapid wound healing process.[49] Gold nanomaterials have the property to decrease the microbial growth at low concentrations and heal the wound with increasing fibroblast activity and collagen formation.[50] In the case of zinc nanomaterial it shows antibacterial activity in hydrogel-based wound dressing and promotes keratinocyte migration. In addition, nanomaterial are also used in coating and scaffolds in wound dressing, which has increased porosity and their different composition provide a moist environment. This scaffold wound dressing enhances collagen synthesis and remodeling of wounds. Furthermore, polymeric nanomaterials (alginate) have high water solubility property which is easily penetrated in the skin and high improvement in wound healing through the involvement in haemostasis and inflammation phase and this nanomaterial is also used for low degradation of drugs from wound proteases and controlled release.[51] Dendrimersproperty in nonviral gene therapy is found out that enhancement of angiogenesis process and formation of granulation and control the therapeutical range of vascular endothelial growth factor (VEGF). Liposomes (deptomycin, quercetin) has antibacterial activity against bacterial infection on wound site, increased collagen synthesis and make elasticity for tissue, fibroblast proliferation and provide a moist environment at the wound site.[52] Cyclodextrin is mostly used to increase solubility, bioavailability and also increase the poor water solubility of drugs in which many

cyclodextrin-based hydrogels have the potential to improve wound healing and also show antibacterial, anti-inflammatory and angiogenesis effects.[53,54] Moreover, silica nanoparticles preparations studies in wound healing to control the blood, fast tissue repair. Nitric oxide is one of the particles involved in inflammation, angiogenesis and nitric oxide releasing silica nanoparticles antibacterial properties to protect to wound site from bacteria.[55] Another nanomaterial category is polymeric nanofibers can provide better cell attachment and cell drug interaction and also promote adherence and fibroblasts proliferation in wounds.[47] Finally, other lipid particles are useful for controlled drug release and different ways of administration of drugs.[48]

Nano-DDSs (Drug Delivery Systems) hold gigantic potential in the upgrade of medication restorative viability for their ability to forestall drug debasement and supporting medication discharge. Various nano-DDSs conveying restorative specialists are jumping up uncommonly and embraced in advancing injury mending and skin regeneration.[56,57,58] It is basic to imagine the necessities of harmed tissue and satisfy the assumption for recovery. The objective of every material firmly relies upon the injury recuperating stage yet additionally the length of the helpful impact, portion, profundity and instrument of activity. Utilizing nanomaterials can possibly advance self-mending instruments that can impersonate recovery. In any case, the heterogeneous idea of the injured tissues requires a superior comprehension of the fundamental instruments and cell falls to customize those nanomaterials for various injury mending applications.

The dissolvability, elements, and instrument of activity of atoms stacked into nanoparticles decide the choice of the nanosystem. These nanosystems may take into consideration back to back and long haul organization of lipophilic and hydrophilic medications to the objective tissue, improving their pharmacokinetics by advancing the fundamental portion for treatment. Among the gainful impacts showed by the use of various nanoparticles to wounds we can specify their anti-infection action, controlled medication discharge, cytokine guideline, and cell reinforcement action. Nanoparticles applied in the treatment of wounds may give satisfactory medication testimony and limitation, and even specifically permeabilize the layer corneum.[59] Furthermore, the consideration of both dynamic nanoparticles and nanocarriers in auxiliary vehicles to improve the application, for example, dressings, filaments, wipes, and hydrogels, is a further progression in the advancement of new medications for wound mending. The optional vehicles give corresponding advantages, for example, straightforward

and improved methods for application and measurement, auxiliary conveyance control, microenvironment insurance, co-conveyance of dynamic atoms at target locales, and tissue attachment among others. Figure 2 represented the various types of nanomaterials used in wound healing.

## Nano-Enabled Approaches for Wound Infection Management

### Polymeric nanoparticles

Polymeric NPs (Nanoparticles) are made of biodegradable polymers or copolymers, in which the drug can be dissolved, entrapped, encapsulated or attached. They can be composed of natural, synthetic, and semisynthetic polymers, like gelatin, albumin, alginate, chitosan, poly(glycolic acid) and their copolymers, PCL(Polycaprolactone), poly alkyl-cyanoacrylate, and so on. They have the advantages of controlled/sustained release, high encapsulation degree, improved bioavailability, and biocompatibility with tissues and cells.[60]

Many kinds of research focus on developing polymeric nanoparticles encapsulating antimicrobial agents. Chereddy et al.[61] reported a PLGA nanoparticle loaded with antimicrobial peptide LL37 (PLGA-LL37 NPs) could be a biodegradable drug delivery system that accelerated the healing process. It displayed antimicrobial activity on Escherichia coli and induced promoted cell migration while lifting no effect on the proliferation of keratinocytes. In the full-thickness excisional wound model, PLGA-LL37 NP treated group exhibited advanced granulation tissue formation, characterized by significantly higher collagen deposition, re-epithelialized composition and neovascularization.

To reduce the high cytotoxicity of Amphotericin B and improve the patient appliance, Sanchez et al.[62] incorporated Amphotericin B into silane-based hydrogel nanoparticles to replace the traditional intravenous injection infusion. In a murine burn model, a silane-hydrogel nanoparticle vehicle utilized to incorporate Amphotericin B resulted in equivalent or enhanced killing efficacy against Candida spp. With 72.4-91.1% reduction in comparison to untreated control and traditional formulation groups. Furthermore, the wounds treated with the Amphotericin B nanoparticles demonstrated a significant reduction of fungal biofilm metabolic activity, ranging from 80 to 95%.[63]

The performance of nanoparticles also exceeds expectations in gene therapy related to skin regeneration. To overcome the setbacks of insufficient expression of angiogenic factors and low cell viability after transplantation, biodegradable nanoparticles were developed to deliver

the hVEGF gene to human mesenchymal stem cells and human embryonic stem cell-derived cells.[64] hVEGF production, cell viability, and engraftment into target tissues of stem cells were prominently enhanced.

**Liposomes**

Liposomes are nanosized vesicular constructions comprising of an inner watery compartment encompassed with phospholipid bilayers. Liposomes offer numerous points of interest; they are protected, biodegradable, non-poisonous, biocompatible, and can embody both water-solvent and lipophilic substances. The most well-known drawbacks of liposomes emerge part of the way from helpless dependability because of potential phospholipids oxidation and hydrolysis as likewise spillage and combination of typified drug/atoms.[65] AbFGF-stacked liposome with silk fibroin hydrogel center appeared to improve the steadiness of bFGF in injury liquids and quicken the injury conclusion in mice through the advancement of granulation tissue development, collagen affidavit, angiogenesis, andre-epithelialization.[66]

In view of the medication transporter points of interest of liposomes and mechanical supporting advantages of platforms the use of liposome-framework composite frameworks comprehensively in injury mending has been as of late examined.[67] Interesting works identified with liposomes were completed by Jeschke and Pereira coworkers in different years.[68,69] The two works zeroed in on the conveyance of keratinocyte development factor (KGF) which invigorates epithelial cell separation and expansion, cycles vital in injury mending.

**Dendrimers**

Dendrimers are orchestrated from extended monomers that emerge radially from the focal core.[70] The delivery adequacy of small scale circle plasmid DNA encoding VEGF joined with arginine(Arg)- united cationic dendrimer was assessed on injuries of diabetic mice.[71] The outcomes affirmed that the infusion of the poly unpredictable brought about quick multiplying basal cells and bountiful collagen testimony and assisted injuries with recuperating the ones treated with the bare VEGF plasmid. Gelatin platforms with poly(amido amine) (PAMAM) showed generally higher cell attachment and multiplication of both keratinocytes and fibroblasts related with the expanded quality articulation of local collagen type I of fibroblasts.[72] Furthermore, the declaration of angiogenesis triggers, for example, HIF1α and VEGF were additionally higher in PAMAM mixed gelatin framework.

**Nanoemulsions**

Nanoemulsions are colloidal frameworks comprising of emulsified oil and water frameworks, where the center of the molecule is either oil or water and can be utilized as transporters of ineffectively water-dissolvable medications. The lipid stage can be made out of characteristic or engineered oils (for example Witepsol®, Myritol®, isopropyl myristate, Miglyol, and so on) and surfactants (unsaturated fats, phospholipids, polysorbate, Gelucire®, polyethyleneglycol, and so on) The watery stage can be a mix of water and co-surfactants (glycerin, ethylene glycol, and so on) if necessary.[73] High medication stacking capacity, upgraded drug dissolvability and bioavailability, generally simple planning and scale-up, controlled medication delivery, and security from enzymatic corruption are the significant preferences of nanoemulsions as medication conveyance carriers.[60] In another examination, it was assessed the injury recuperating impacts of nanoemulsion definitions of Eucalyptus fundamental oil(EEO) in correlation with unadulterated EEO and standard gentamycin. The improved nanoemulsion detailing indicated equivalent outcomes with standard gentamycin treated creatures yet introduced a huge upgrade in collagen content as contrasted and unadulterated EEO and negative control. The EEO nanoemulsion altogether improved the injury compression from day 12 to 24 as contrasted and control($P < 0.05$).[74]

Sugumar et al. (2014) built up a fascinating work containing NE stacked with eucalyptus oil by ultrasonication. Antibacterial examinations against Staphylococcus aureus indicated a total loss of feasibility inside 15 min of communication and the instrument of activity was related to the layer harm. Moreover, the skin aggravation movement and wound recuperating results (Wistar rodents) of the planned nanoemulsion, demonstrated the non-aggravation nature of the definition and higher injury constriction rate as for neomycin treated rodents.[75]

**Micelles**

Micelles have a hydrophobic internal center encircled by a hydrophilic shell in fluid arrangement, making them an ideal convey possibility for both hydrophilic and hydrophobic specialists. Polymeric micelles present great colloidal solidness, more noteworthy load limit, biocompatibility, non-harmfulness, and controlled medication discharge.[60] In a fascinating work created by Gong et al. (2013), curcumin has been stacked into polyethyleneglycol-co-polycaprolactone micelles and they were additionally scattered in a hydrogel framed by a triblock copolymer of polyethyleneglycol-polycaprolactonepolyethyleneglycol. Stacking curcumin in the hydrogel was expected on account of its ability to be a powerful cell

reinforcement and mitigating specialist, which is significant for cutaneous injury fix. Curcumin-stacked micelles with related PEG-PCL hydrogel displayed higher collagen content (22.4 ± 2.2 µg mg −1) than curcumin-stacked micelles (Cur-M) (16.9 ± 2.3 µg mg −1), clear micelles in hydrogel (M-H) (13.3 ± 1.9µgmg−1)and control group(11.3 ± 1.8µgmg−1) in both direct cut and full-thickness extraction twisted model in rodents, likewise demonstrating a fundamentally higher granulation(4.17 ± 0.41) and wound development scores(4.00 ± 0.63) versus Cur-M (3.33 ± 0.52 and 3.00 ± 0.63, separately), clear M-H(2.33±0.52 and 2.17±0.75, respectively) or control groups(2.17 ± 0.41and2.00 ± 0.63, respectively).[76]

As of late, and in vitro concentrate in diabetic rodents assessed the counter diabetic and wound mending impacts of Cur-stacked blended polymeric micelles dependent on chitosan, alginate, maltodextrin, Pluronic F127, Pluronic P123, and Tween 80. It was presumed that the created definitions with most noteworthy measures of Cur (higher than 48.74 ppm) could quicken the injury mending reaction indicating noticeable improvement in injury conclusion on the14th day and lessening the raised blood glucose level and lipid profile, unmistakably showing its potential as diabetes-controlling and wound recuperating agent.[77] Another promising model is Pluro Gel which depends on a micelle network innovation, made of a cell well disposed surfactant, and it is professed to keep up dampness in the injury and control liquid misfortune, assisting with ensuring the injury and allowing a less difficult removal.[60]

**Silver nanoparticles**

Silver nanoparticles (AgNPs) have a unique type of nanomaterial, though, it is utilized by biomedical field, cosmetics, medical devices, food industries, anti-infective agents[78]. Silver categories under broad-spectrum, therefore it is used as antibiotic, antimicrobial, and antiseptic as well as it promotes wound healing activity. For year's silver was used in the treatment of bone fractures, skin ulcers and in wound healing infections. Moreover, their use in biomedical applications showed excellent antimicrobial properties, partial anti-pathogenic resistance and greater efficacy against multidrug-resistant microorganisms.[79] Recently, the chitosan-based silver nanoparticles film (CH-AgNPs-CHF)was developed. The optimization of the formulated reported tensile strength and elongation as 1.39 ± 0.009 N/mm2 and 33.33 ± 1.634. Further, the degree of swelling was 76.66 ± 0.584 % and WVTR showed 2024.43 ± 32.78 gm.m-2 day-1 after 24 h and after 21 days it showed 1144.57 ± 13.45 gm.m-2 day-1. The antimicrobial study was performed in Escherichia coli, and it was noticed that CH-

AgNP-CHF got the highest zone of inhibition 62.22±0.91. The in-vivo studies showed faster and effective wound closure as compared to marketed SilverKind®, Nanofine gel, blank chitosan film and sterile gauze treated group (Control).Overall, result showed that it will also produce an effective results in support of wound healing management.[80]

However, silver nanoparticles are also effective in the combination with herbal formulations. One of the studies conducted in shrub Ehretia cymosa, in which Ehretia cymosa-AgNPs cream was formulated. Basically, methanol(ME), n-hexane(NE), ethylacetate(EA) were used as extraction for plant and to synthesis silver nanoparticles.Their anti-inflammatory activity was studied in carrageenan-induced rat paw edema method on albino rats, and the result showed in Methanol extract silver nanoparticle MS, N-hexane extract silver nanoparticles NE and ethyl acetate extract silver nanoparticle EA was 87.1, 90 and 100%, respectively in four hour treatment. The study sum up with the 100% healing efficacy produce by Ehretia cymosa-AgNPs cream.[81]

**Gold nanoparticles**

Gold nanoparticles(AuNPs) has also been greated progress in the field of nanotechnology. Mostly, their applications are in gene transfer and in the delivery of drug as carrier.[82] However, the colloidal form of AuNps, projected to used in biomedical applications due to its exclusive properties such as shape (rod and sphere), surface modification (neutral, cationic and anionic charged polymers), electronic arrangement and optical nature. The studies showed that AuNPs has ability to penetrate into skin layer, and enhance the absorption. Recently, AuNPs hydrogel has been formulated, in which poly ethylene glycol (PEG)-gold nanorods (AuNRs) and cationic poly allyl amine hydrochloride (PAH)-AuNRs showed excellent wound healing properties. The TEM studies showed the shape like rod and spherical, the AUNRs and AUNSs (gold-nanosheres) have diameter of 12.9 ± 0.7 nm and 29.2 ± 2.1 nm, respectively. The in-vitro studies showed the slow and prolonged release pattern. The combination showed the regeneration, collagen deposition and anti-inflammatory behavior. Over all the study proved effective nano system for wound healing.[83]

Moreover, natural products encapsulated with nanoparticles were also played an active role in wound healing management. Naraginti et.al. formulated silver and gold nanoparticles combined with Coleus forskohlii root extract applied in albino wister male rate, tried to closed full thickness excision wounds. The particles size AgNPs and AuNPs was reports as 5-

15nm and 5-18nm and the zeta potential values were 24.3 ± 0.52 mV and −48.6 ± 0.06 mV, respectively. further, the histological studies such as, Hematoxylin and Eosin staining and Van Gieson's histochemical staining were performed. They found that AuNPs have effectively suppressing inflammation and increase re-epithelialization as compares with AgNPs. The overall study showed that both the nanoparticles encapsulated with green synthesis were effective in full thickness wound closures.[84]

Furthermore, Zangeneh and his team experimented on gold nanoparticles with an aqueous extract of Falcaria Vulgaris leaves (AuNPs-F.vulgaris). The combination showed excellent cell viability and the HUVEC cell line analyzed the non-toxic nature of nanoparticles. However, AuNPs-F.vulgaris resulted in greater percentage of anti-bacterial and anti-fungal as compared to standard antibiotics, the significance value was $p \leq 0.01$. Additionally, this ointment (AuNPs-F.vulgaris) affect the growth of microorganism, at 2-8 mg/ml conc. it partially prevents and at 2-16 mg/ml concentration complete removal had been noticed. The result showed that AuNPs-F.vulgaris ointment have shown non-cytotoxicity behavior, cutaneous wound healing, antifungal and antioxidant action.[85]

**Transferosomes**

Transferosomes are specifically designed or highly elastic or deformable vesicles, it has ability to hold both hydrophilic and hydrophobic moieties like liposomes.[86] Basically, they have natural phospholipids, which enhance their penetration efficacy into the skin as well as increased entrapment efficacy of lipophilic drugs.[87] The properties also include biodegradable and biocompatible nature, therefore they smartly work as a carriers for peptides, proteins and small molecular weight compounds.[88] Recently, tocoperol acetate loaded in different concentration of polysorbates (i.e., Tween 20, 40, 60 and 80).The prepared tranferosomes were unilamellar in shape, low PDI value (≤0.27) and particle size was less than 85nm. The formulation showed 72-90% entrapment efficacy, which estimated the length of tween fatty acid chain. Further, Turbiscan™ technology was applied for testing the long term stability. The in-vitro studies in keratinocytes and fibroblasts showed effective delivery of tocopherol into the skin, that found better biocompatibility values. The transferosomes initiate cell-proliferation and migration, this process indicated the faster wound healing mechanism. It concluded that, the formulation have excellent potential for topical drug delivery as well as antioxidant activity.[89]

Ahad and his team worked on eprosartan mesylate loaded transfersomes. The transferosome

were formed while selecting different ratios of Phospholipon® 90 G and Tween® 80 (95-75: 5-25% w/w). The study revealed the spherical unicellular shape, particle size and entrapment efficacy was 71.18nm-85.66nm and 83%-88.19%, respectively. The in-vivo studies showed the trandermal flux as 1.78 μg/cm2/h to 5.02 μg/cm2/h across rat skin. The CLSM study confirmed that the formulated transferosomes were deeply penetrated into the rat skin. The formulation also cleared the skin irritation test. It was noticed that, through tween 80, eprosartan mesylate showed a better tansdermal penetration effect. Overall the study reveals that the formulated transferosome proved an effective carrier system for eprosartan mesylate for topical drug delivery.[90]

**Niosomes**

Niosomes are non-ionic surfactant-based vesicle, incorporated with cholesterol in their bilayered structure. They show non-toxic, stable and biodegradable behavior.[91] However, the Pentoxifylline (PTF), a well-known immunomodulator, is formulated as Pentoxifylline niosomes (PTF-N) for topical application. PTF-N were incorporated into base cold cream. The studies showed that the formulation F-6 and F-7 had a better penetration effect as compared to conventional cream. The reported particle size, PDI and Zeta potential of F-6 was 150.6 ± 36.3, 0.380 ± 0.097, −33.6 and the F-7 formulation was 287.0 ± 18.2, 0.309 ± 0.154, −20.0, correspondingly. Further, the entrapment efficacy of F-6 was 87.37 ± 2.73 and F-7 was 52.51 ± 4.43%. The characterization studies like, differential scanning calorimetry (DSC) confirmed the niosomal structure, FTIR indicates the peak range in between 1707 - 1659 cm−1and X-ray diffraction showed sharp and narrow peak in between 100-300, which confirmed the crystallization studies of pure drug. The ex-vivo studies reported that PTF-N formulations of F-6 and F-7 have 1.8 and 1.2 times higher penetration than PTF-conventional. Moreover, the in-vitro studies noted that there was shortened healing time than conventional. Therefore, it was concluded that the PTF-N cream significantly healed the full thickness wound while taking less time as compared to the conventional formulation.[92]

**Solid Lipid Nanoparticles**

Nanotechnology introduced several novel drug delivery technologies in the pharmaceutical field. Solid lipid nanoparticles are one of the swiftly emerging nanotechnology with numerous prospective applications in drug delivery, clinical medicine, and research, along with supplementary wide-ranging sciences.[93] SLN were first introduced in 1991 demonstrating a substitute colloidal carrier of emulsion, liposomes and polymeric micro and

nanoparticles.[94] SLN are spherical shaped formulation with diameter in 50-1000 nm range. These novel drug delivery systems are formulated using lipids (solid or liquid lipids or both), emulsifier and surfactant keeping the temperature constant for stable formulation.[95] SLNs embrace pronounced potential of targeted and sustained drug delivery in wound healing, which draws the interest of researchers worldwide.[96]

Saporito et al developed SLN loaded with rosemary and eucalyptus essential oil used in the treatment of chronic wounds and severe burns. The SLN was prepared by using high pressure homogenization technique followed by ultrasonication.[97] Likewise, Gad et al successfully prepared chamomile loaded SLN by means of hot homogenization method using 20% stearic acid. In vivo topical application in a rat model showed improved integumentary architecture, narrowing of the wound, reduced interleukin beta and MMPs 9 v/s tissue inhibitor MMP 1 ratio. Curcumin is an antioxidant used by Sandhu et al in the preparation of high drug loaded SLNs for wound healing. The method employed was hot and high pressure homogenization without consuming organic solvents and further optimized the formulation via Taguchi design followed by the central composite design.[98]

Not only herbal ingredients used in SLN formation are seen frequently, rather their application are found to be very vast. In the management of tissue repairing and healing wound, Silver sulfadiazine (AgSD) are used to or to treat or repair wound colonization. Sandri et al worked on the development of silver sulfadiazine loaded solid lipid nanoparticles for skin lesions using chondritinsulphate and sodium hyaluronate (bioactive polymer).[99] Henceforth, it's verified that nanotechnology could reduce the wound healing process to reduce treatment costs and increase the compliance of patients.[100]

**Patent and clinical trials on topical wound healing: Recent updates**

The continuous research in the field of nanomedicines has resulted into various intellectual properties and several clinical trials involving these novel formulations are being conducted worldwide. Table 3 and 4 represent the recent patents and clinical trial-based products for topical wound healing involving the nanomedicines.

**Guidelines for topical wound healing products: A regulatory perspective**

Wound healing is a complicated process, the regulatory bodies define the guidelines for some chronic ulcers like pressure ulcers, diabetic foot ulcers, venous ulcers, burns wounds. When there is a delay in the healing of wounds due to various external and internal circumstances,

then it is very important to care for and manage the wound in the proper way, otherwise, it will create complication for the patient.

The Food and Drug Administration along with the Center for Drug Evaluation and Research Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), all worked for the standardization of topical wound healing products for the treatment of cutaneous wounds.(U.S. Department of Health and Human Services, June 2006 Clinical/Medical)

For drug approval in different countries, different regulatory requirements should be followed. It is very tough that a single regulatory approach will be applicable for marketing authorization applications in various countries. Hence for each country, one should have sufficient awareness and understanding of the different marketing authorization applications. For marketing a new drug, a new drug application is submitted to the respective regulatory agency.[121]

**FGF: Fibroblast growth factor, VEGF: Vascular endothelial growth factor, PDGF: Platelet derived growth factor, Ang: Angiotensin, ROS: Reactive oxygen species, SOD: Superoxidase dismutase, CAT: Catalase, COX: Cyclooxygenase.**

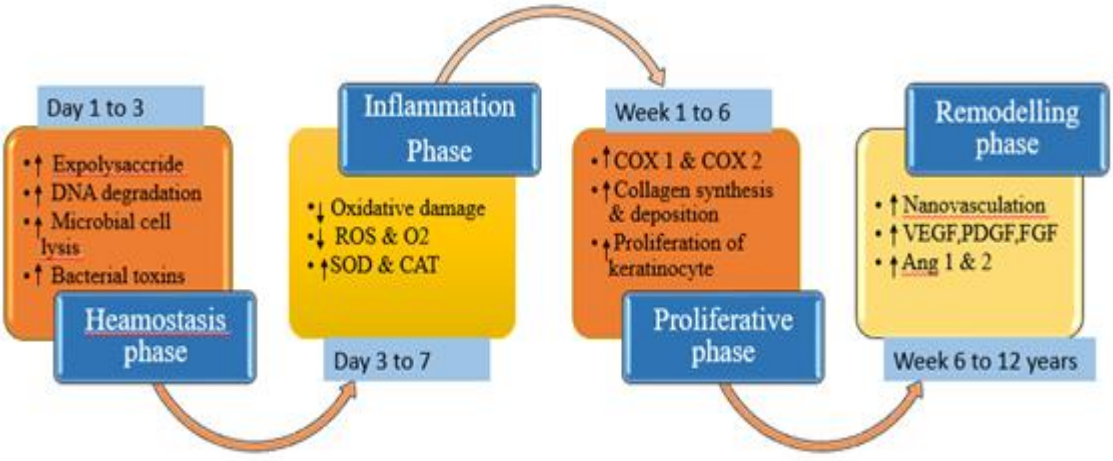


**Figure 1: Schematic representation of four phases of wound healing.**

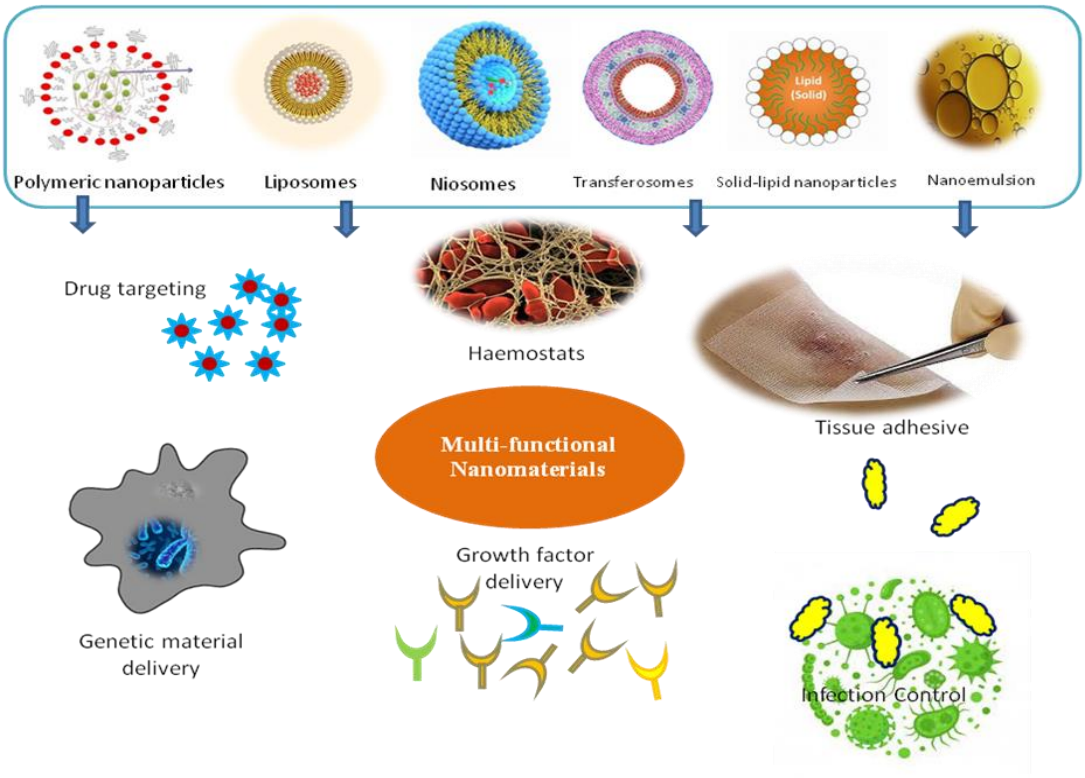


**Figure 2: Representation of the role of nanotechnology in wound healing management.**

**Table 1: Natural and synthetic polymers used in topical wound healing.**

| Polymer | Drug with polymer | Technique used for Nano formulation | Characterization studies | Models used in studies (*in-vivo/in-vitro*) | Drug loading efficacy | Results | Reference |
|---|---|---|---|---|---|---|---|
| Chitosen (CS)<br><br>Carboxymethylcellulose (CMC)<br><br>poly-lactic co-glycolic acid (PLGA) | Curcumin | Ionotropic gelation method and double emulsion solvent evaporation method | SEM:Spherical shape with the covering range of 10 nm to 112 nm.<br>DSC:found different endothermic peak at 176 °C<br><br>FTIR: Detected at 37 °C in the range of 4000–400 cm−1 | *in-vitro* studies found 74.96% for 24 h with CMC, *in-vivo* reveals the synergistic action between curcumin and chitosen which indicate the faster wound healing effect | EE % of CS NPs:91.97%, PLGANPs-92.45%, CMC NPs:90.89% | **Outcome:** Found out that at low dose of curcumin the wound healing activity faster | [28] |
| polyethylene glycol (PEG) 6000<br>Sodium dodecyl sulfate (SDS)<br>β-cyclodextrin (β-CD) | Silver and fungus *Fusarium verticillioides* | Dispersions method | TEM :<br>PEG coated with AgNPs-19.2± 3.6<br>SDS with AgNPs:13.0± 0.4<br>β-cyclodextrin with AgNPs: 14.0±4.4 | ***in-vivo* :** found out the initial growth of bacteria on wound healing | Minimum inhibitory concentrations (MICs): 0.93–7.5 µg/mL<br>Minimum bactericidal concentrations (MBCs)-: 3.75–15 µg/mL | **Outcome :** The formulation was compared with marketed (silver sulfadiazine cream) sample and it was found that it has Lower toxicity and higher tolerability. | [29] |
| Chitosan, sodium alginate and carbopol | Mupirocin | Solvent evaporation method | FTIR:Detected no interaction between drug and polymer<br><br>SEM:Detected non- | Best Formulation F-6 results: *in-vitro* studies found that have highest release rate | EE% - 93.852±3.473 | **Outcome:** The results showed that mupirocin film is more | [30] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | porous surface | *in-vivo*- studies found not irritating to skin *Ex-vivo*- Bioadhesion work $0.195 \pm 0.020$ $mJ/cm^{-2}$ | | advantageous on epithelialization, granulation tissue thickness and angiogenesis | |
| Poly(ε-caprolactone) (PCL) fibers | Silver (Ag) and cobalt (Co) | Sol-gel process, Electrospinning (ES) | FTIR:No significant changes Particle size: 32 ± 17 nm Average fiber daimater: 0.54–1.18 μm and 0.84–1.52 μm | *in-vitro* bioactivity test: In pure PCL sample no evidence of mineral found | Enhanced drug loading capacity of silver and cobalt | **Outcome:** Membrane showed great potential for soft tissue healing since cobalt and silver ions should enhance the angiogenic and antibacterial character of membranes.<br><br>-Further work needs to be carried out to understand real effect of these membranes in vivo. | [31] |
| Poly (lactide-co-glycolide) | Cefazolin, Dimethyl formamide (DMF) and tetrahydrofuran | Electrospinning process. | Maintaining the conc. of polymeric solution 0.20 g/mL, and voltage of 1 kV/cm in electro- spinning, | - | EE%: 10-30 % | **Outcome:** The study illustrated that by modifying process parameters such | [32] |

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| | (THF) | | produced the best consistency of nanofibers. | | | as orifice diameter, polymer solution concentration, and electrospinning voltage would change the fiber daimeter | |

**Table 2: Dressing types and their characteristics in recent strategies of wound healing.**

| Dressing types | Characteristic | Clinical Significance to Wound Healing | Examples | References |
|---|---|---|---|---|
| Collegen dressing hydrogel, hydrofoams, hydrocolloid, growth factors | Enhance epithilazation | Inhance keratinocytes which are maintain barrier from injury | NU-gel, Purilon gel | [40] |
| Antimicrobials, Silver impreganeted dressing, | Prevent infection: Protect the wound from bacterial invasion | Infection prolongs the inflammatory phase and delays collagen synthesis, inhibits epidermal migration and induces additional tissue damage. Infected wounds can give an unpleasant odour | Mupirocin, Actisorb Silver 200, Iodoflex, Iodosorb | [41] |
| Maggots, debridace, enzymatic agents (collagenase, papaya extract) hydrocision | Desolughing and debring agents or Debridement (wound cleansing) | Enhances migration of leucocytes into the wound bed and supports the accumulation of enzymes. Necrotic tissue, foreign bodies and particles prolong the inflammatory phase and serve as a medium for bacterial growth | Collagenase santyl, Accuzyme | [42] |
| Hydrocolloids, Hydrogels, Alleginates, | Enhance granulation formulation | Granulation tissue is produced during the repair phase. This is a complex of fibroblasts, vascular | HYCOL (Hydrolyzed Collagen Gel.), | [41] |

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| collegen granules | | endothelial cells, and macrophages within a matrix of collagen and fibrin. | Stimulen Collagen Powder, Fibracol | |
| Hydrogels, Films | Provide or maintain a moist wound environment | Prevents desiccation and cell death, enhances epidermal migration, promotes angiogenesis and connective tissue synthesis and supports autolysis by rehydration of desiccated tissue | Intrasite gel, Tegaderm | [43] |
| Hydrocolloids, alginates | Absorption. Removal of blood and excess exudate | In chronic wounds, there is excess exudate containing tissue degrading enzymes that block the proliferation and activity of cells and break down extracellular matrix materials and growth factors, thus delaying wound healing. Excess exudate can also macerate surrounding skin | Duoderm, kaltostat, algiderm | [44] |
| Hydrocolloids, hydrogels, alleginates, | Gaseous exchange (water vapour and air) | Permeability to water vapour controls the management of exudate. Low tissue oxygen levels stimulate angiogenesis. Raised tissue oxygen stimulates epithelialisation and fibroblasts | Tegagel, Sorbsan | [44] |
| Foams | Provision of thermal insulation | Normal tissue temperature improves the blood flow to the wound bed and enhances epidermal migration | Alleyn adhesive, lyofoam | [45] |
| Tulles<br><br>Textiles | Low adherence. Protects the wound from trauma | Adherent dressings may be painful and difficult to remove and cause further tissue damage | Bactigras, Jelonet, Paranet, Paratulle, Tullegras, Unitulle, Urgotul<br><br>Atrauman, Mepilex, Mepitel, Tegapore, Tricotex | [46] |
| Silver impreganeted dressing, Foam, films | Cost effective Low frequency of dressing change | Dressing comparisons based on treatment costs rather than unit or pack costs should be made (cost-benefit-ratio). Although many dressings are more expensive than traditional materials, the more rapid response to treatment may save considerably on total cost | Actisorb, 3 m Foam dressing, Opsite | [45] |

**Table 3: Clinical trials based on topical wound healing infections.**[101]

| S/n | Study title | Intervention | Condition | Phase | Date | Information provided by | Identify | Ref |
|---|---|---|---|---|---|---|---|---|
| 1 | Clinical Trial for the Efficacy and Safety of Paste Type Acellular Dermal Matrix in Chronic Wound Healing | Device: application of CG Paste+EasyFoamDevice: application of EasyFoam | Chronic Wound | not applicable | July 31, 2020 | Seoul National University Hospital | NCT04019639 | [101] |
| 2 | The Effect of Topical Agents in Cream Formations Containing Magnesium Sulfate on Wound Healing in the Rat Model | Other: placebo comparatorOther: sham comparatorOther: Experimental drug 1Other: Experimental drug 2Drug: Centella asiatica | Wound Heal | Early Phase 1 | May 14,2021 | Basaksehir Cam & Sakura Şehir Hospital | NCT04886882 | [102] |
| 3 | The Use of Autologous Amniotic Fluid at Cesarean Wound Closure to Improve Cesarean Wound Healing and Decrease Adhesion Formation; a Feasibility Study | Device: Application of Autologous Amniotic Fluid | Pregnancy Related Cesarean Wound Disruption Cesarean Section; Infection | Not applicable | February 9, 2021 | Recibio, Inc. | NCT04359472 | [104] |
| 4 | Phase 1 Study of Human Amnion Membrane Powder for Enhanced Wound Healing | Drug: Amnion Membrane PowderProcedure: SOC Wound Covering | Burns Wound of Skin Skin Wound | Early Phase 1 January 27,2021 | January 27,2021 | Wake Forest University Health Sciences | NCT03754218 | [105] |
| 5 | Controlled Comparison of a Traditional Dressing Versus a Biologic | Biological: biological dressing Other: Paraffin gauze | Split Thickness Skin Graft Wound Healing | Phase 1 Phase 2 | April 19,2021 | Nantes University Hospital | NCT03334656 | |

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| | Dressing Composed of Fetal Fibroblasts and Keratinocytes in Association With a Collagen Matrix on Skin Donor Sites | dressing | | | | | | |
| 6 | Randomized Controlled Trial Assessing a Novel Glycopolymer Compound in the Treatment of Superficial Partial-thickness Burns | Device: Catasyn™ Advanced Technology Hydrogel and SynePure™ Wound CleanserDrug: Silver Sulfadiazine | Superficial Partial Thickness Burn | Phase 4 | May25,2021 | J. Peter Rubin, MD, University of Pittsburgh | NCT04601532 | [106] |
| 7 | A Randomized Controlled Trial Evaluating Hyaluronic Acid as a Wound Healing Agent Following Alveolar Ridge Preservation | Device: Gengigel Forte© | Healing Wound | Not Applicable July 20,2020 | July 20,2020 | Vakgroep Mondgezond heidswetensc happen, University Ghent | NCT04467736 | |
| 8 | Efficacy of Preadmission Theraworx Wipe Use for Surgical Site Infection Prophylaxis in Adult Orthopaedic Surgery Patients: A Randomized Controlled Trial | Drug: Chlorhexidine Gluconate 2% WipeOther: Theraworx Bath Wipes | Surgical Site Infection | Phase 4 | April 30,2020 | Ashish Shah, University of Alabama at Birmingham | NCT03401749 | |
| 9 | Topical MRSA Bactericidal Gel to Eliminate MRSA and Promote Accelerated Healing of cSSTI of Open Wounds | Bacterial InfectionsWounds | Drug: Vancomycin 1.25-1.50% in a complex gel formulation trademarked Vancogel(R)Drug: Placebo, complex gel formulation without Vancomycin | Phase 2 | January 14,2020 | Robert S Berman MD | NCT00945152 | |

**Table 4: Recent information of patents file in wound healing management.**

| S/N | Title | Patent No. | Date Of Publication | Authority/Inventors | Applicant | Ref |
|---|---|---|---|---|---|---|
| 1 | Composition and Method for Promoting wound healing | Wo/2021/021774 | 04.02.2021 | • Minshall, Richard, D.<br>• Chen, Zhenlong | • The Board Of Trustees Of The University Of Illinois [Us]/[Us] | [110] |
| 2 | Wakeri For wound healing | Wo/2020/044368 | 05.03.2020 | • Gharpure, Milind Omkar<br>• Gulgule, Ravindra Ramakant | • Gharpure, Milind Omkar [In]/[In]<br>• Gulgule, Ravindra Ramakant [In]/[In] | [111] |
| 3 | Amniotic Fluid-Derived Extracellular Vesicles And Uses Thereof For Wound Healing | Wo/2020/176801 | 03.09.2020 | • Fagg, William, Samuel, Iv<br>• Broderick, Thomas, Christopher | • Merakris Therapeutics Llc [Us]/[Us] | [112] |
| 4 | Compositions For Skin And Wounds And Methods Of Use Thereof | Wo/2020/227642 | 12.11.2020 | • Hansson, Kenny Mikael<br>• Wagberg, Maria<br>• Bergenhem, Nils | • Modernatx, Inc. [Us]/[Us] | [113] |
| 5 | Topical Cannabinoid Compositions, Delivery Systems, And Uses For Pain Relief | Us20210015740 | 29.09.2020 | • Michael Harvey Greenspan Christopher P. Norval | • Michael Harvey Greenspan Christopher P. Norval | [114] |
| 6 | Drug Delivery Using Microneedle Arrays | Wo/2021/007344 | 14.01.2021 | • Tamayol, Ali<br>• Derakhshandeh, Hossein<br>• Mostafalu, Pooria | • Board Of Regents Of The University Of Nebraska [Us]/[Us] | [115] |
| 7 | Wound Penetrating Topical Pain Relief Compositions And Methods Of Use | Wo/2020/243352 | 03.12.2020 | • Guynn, John M. | • Tech Swerve Llc [Us]/[Us] | [116] |
| 8 | Contact Layer And Dressing For Iodine Delivery | Wo/2020/161086 | 13.08.2020 | • Dagger, Anthony<br>• Hammond, Victoria, Jody<br>• Wheldrake, Amy, Nicole | • T.J.Smith And Nephew, Limited [Gb]/[Gb] | [117] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 9 | Hermoresponsive Hydrogel Containing Polymer Microparticles For Noninvasive Ocular Biologic Delivery | Us 20190099365 | 21.03.2017 | • Morgan V. Fedorchak Steven R. Little Joel S. Schuman | • University Of Pittsburgh - Of The Commonwealth System Of Higher Education | [118] |
| 10 | Medical Hydrogel Comprising Nanofibrillar Cellulose, TailoredWound Dressing, And Methods For Preparing Thereof | Ca 3079001 | 29.01.2021 | • Raili Koivuniemi, Kari Luukko, Markus Nuopponen, Jasmi Snirvi, Marjo Yliperttula. | • Upm-Kymmene Corporation | [119] |
| 11 | Novel Cannabis Lines And Extracts For Skin Rejuvenation And Skin Protection | Wo/2020/129044 | 25.06.2020 | • Kovalchuk, Olga Li, Dongping Rodriguez-Juarez, Rocio Del Carmen Kovalchuk, AnnaHudson, Dwight Darryl, Kovalchuk, Igor | • Pathway Rx Inc. [Ca]/[Ca] | [120] |

## CONCLUSION

The complications of wound healing leads to a surplus burden on the health care system. The pathophysiological conditions of wound healing affect both internal and external factors, specifically, contamination of wounds by microorganisms, scaring, moist environment, etc. Although, chronic wounds are difficult to heal due to multidrug resistance and the formation of biofilm. However, there were various conventional techniques used like Gauzes, bandages, foams, solutions, gels, creams, etc, but they have some limitations like moist conditions, stability problems, slower effect, and patient compliance. Advanced techniques were introduced for the management of wounds. Nanotechnology opens new gateways for researchers they introduced nano-based formulations such as liposomes, niosomes, silver nanoparticles, gold nanoparticles, solid liquid nanoparticles, hydrogels, dendrimers, nanoparticles, polymeric nanoparticles etc. The outcome of the studies suggested that the advanced techniques faster the wound healing process and also resolve the patient compliance issues. The regulatory bodies also amended the advanced techniques and also supported the clinical studies for the management of wound healing.

## List of Abbreviation

AgNPs: Silver nanoparticles

AuNPs: Gold nanoparticles (AuNPs)

abFGF: Authentic human basic fibroblast growth factor

CLSM: confocal laser scanning microscopy

DDSs: Drug delivery systems

DNA: Deoxyribonucleic acid

EEO: Eucalyptus fundamental oil

FGF: Factors fibroblast growth factors

HUVECs: Human umbilical vein endothelial cells

HIF1α: Hypoxia-inducible factor 1-alpha

HUVECs: Human umbilical vein endothelial cells

NPs: Nanoparticles

PLGA: Poly(glycolic acid)

PCL: Polycaprolactone

PEG: Polyethylene glycol

PDGF: Platelet derived growth factor

PDI: Polydisperdity index

ROS: Reactive oxygen species

SLM: Solid lipid nanoparticles

TGF: Transforming growth factor

TGF-α and TGF-β: Transforming growth factor

VEGF: Vascular endothelial growth factor.

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