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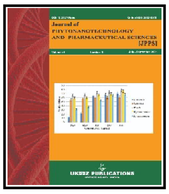

Review Article : Open Access

Wound management using phytonanoparticles: An innovative approach

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Abstract

Wound healing is a crucial physiological process where the integrity of wounded tissue is restored through a succession of events. Several natural compounds with anti-inflammatory, antibacterial, antiulcer, immunomodulatory, antiallergic effects stimulate angiogenesis and epithelial cells, fibroblasts proliferation. Various phytochemicals have cell-stimulating properties which aid in the wound healing process. Though, these phytochemicals are inexpensive, environmental friendly than modern drugs, their use is restricted due to low water solubility, poor skin penetration, less activity and stability resulting in uneven clinical effects. The novel wound care therapies are developed integrating these natural ingredients with nano-strategies. Nanotechnology can overcome the limitations of phytochemicals through exhibiting controlled release, excellent adhesion, solubility, long term stability. The phytonanomaterials show faster re-epithelialization, degradation of necrotic tissues, reduction of oxidation in the affected tissue and accelerate wound healing. Various phytonanoformulations of can result in effective distribution of phytocompounds to the wound site for successful treatment various non-healing chronic wounds.

1. Introduction

The body's first line of defence against external exposure is the skin, which performs vital activities such as vitamin D production, excretion, hydration, and thermoregulation. Any breakdown in skin integrity could result in the loss of vital processes. Minor skin injuries always result in skin contraction and cell ingrowth, which is followed by wound closure and recuperation. Severe wounds can result in infection and a longer healing time, or even non-healing of wounds. Chronic wounds are chief clinical concern affecting healthcare expenditures and quality of life of patient significantly as it affects morbidity (Bickers *et al.*,1974).

Natural products like plant-derived extracts and essential oils may be effective in the treatment and prevention of infectious wounds, especially with the counteraction to antibiotic resistance. Plant extract metal nanoparticles show promise in the treatment of bacterial and fungal skin diseases. Flavonoids have powerful antioxidant and free radical scavenging properties that are essential for wound healing. Tannins are responsible for antimicrobial activity accelerating the healing process (Johnson *et al.*, 2021).

Nanotechnology is a powerful tool for enhancing the activity of bioactive substances and amplifying their antibacterial action. Plants are increasingly being used in nanoparticle creation. For wound healing applications, phytonanoencapsulation, phytonanofibres, liposomes, nanophytosome like encapsulated phytocompounds are now being employed. Plant extracts can be easily used to make nanoparticles as they have a higher reduction potential (Gunasekaran *et al.*, 2014). The nanoparticle production takes less time and is more environmentally beneficial (Palai *et al.*, 2021). The nature of the plant extract, its quantity, salt concentration, temperature, pH, and reaction time, all influence the quality, speed, and other features of the nanoparticles formed by plant extracts. The antioxidant, antibacterial, antifungal, and cutaneous wound healing properties of the produced phytonanoparticles are all excellent with the absence of any significant toxicity.This review article will cover different plant extract metal nanoparticles which augmented the process of wound healing, owing to their free radical scavenging, anti-inflammatory, antioxidant, antimicrobial effects (Shah *et al.*, 2015).

2. Wound

Crowning the title of largest organ of the body, skin plays a key role in sensory functions, homeostasis maintenance, temperature control, and barrier against pathogens, toxins, and trauma. Wound can be defined as any interference in the skin integrity and the aetiology may be a disease, or may have an intentional or an accidental cause. It can occur as a result of surgical procedure, due to an injury, or because of other factors and conditions like pressure, shear, diabetes, or vascular diseases. Broadly, wounds can be classed as acute such as burns and surgical wounds or chronic like diabetic foot ulcers, pressure ulcers, *etc.* The term chronic is used for the wound, if it is difficult to get healed or the ulcer that is unable to regain the anatomical and physiological integrity within 3 months, and that could not be healed by a systematic and well-timed reparative method (Morton and Phillips, 2016). Prioritising the restoration of integrity and function of tissue, the wound repair procedure entails different cellular and extra-cellular pathways through superposed stages. These pathways include inflammation,

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proliferation, and re-modulation phases. In case of vascular inflammatory reaction, the blood vessel which has been damaged undergoes contraction, thus causing coagulation by an accumulation of thrombocytes in a network of fibrin. Secondly, at the time of proliferative phase, vascularization and epithelial repair take place. Thirdly, during remodelling stage, rearrangement, extracellular matrix reformation and granulation tissue reconstruction encompasses gaining of tensile strength to the maximum extent (Ganapathy *et al*., 2012).

Various growth factors along with different cytokines released at the location of wound stringently synchronize the healing process. As this process is not so simple in nature, the wound resulting process may be delayed due to interference of various factors result in increased morbidity and mortality of the patient, thus rendering to stunted cosmetic outcome, distress and serious discomfort (Xue *et al*., 2021).

At the macroscopic level, the healing protocol of wound depends on many parameters like dimension of the wound, its location, age of the patient and the concurrence of any local or systemic disease. Other components influencing wound healing include nutritional status, immunological strength of the body, stress level, smoking, obesity, increased blood pressure, diabetes, *etc.*, and also the enhanced longevity of the elderly population may cause increased prevalence of non-repairable ulcers. Because in case of aged skin, the important factors affecting wound healing like microcirculation, vasoregulation, inflammatory responses are altered and there is a smaller number of progenitor cells which delay the healing process. There is increased incidence of chronic wounds among older population influencing the quality of life (Diener and Chan, 2011). Irrespective of the cause, chronic wounds impact seriously on the physical, mental, social, and economic state of the patients along with the healthcare system. Therefore, the occurrence of chronic wounds has been entitled as 'silent epidemic'.

3. Wound infection

Control of infections plays a critical role in the handling of chronic wounds. On the other hand, bacteria are a common part of skin flora as well as wounds. About 105 numbers of bacteria have been suggested as the crucial threshold between colonization and clinical manifestation of infection. When the skin gets damaged, bacteria can easily get access to the underlying tissue resulting in inflammation subsequently leading to the release of reactive oxygen species and proteases from these inflammatory cells. Increased concentration of endotoxins released by bacteria causes elevation of pro-inflammatory cytokines level. It leads to a reduction in the production of growth factors and impairing collagen deposition in wound, thus causing delay in wound healing (Victor *et al*., 2005). As a consequence, the infection can spread from contamination stage to colonization state. This condition can be more complicated due to formation of biofilm which is an assembled consortium of bacteria ensheathed in a self-produced extracellular polymeric substance consisting of proteins, polysaccharides and deoxyribonucleic acids. In accordance to the literature, biofilm have been found in 60% and 6% of biopsy specimens obtained from chronic and acute wounds, respectively. Inside the biofilm, the microorganisms make the toughest barriers to wound healing. This happens as the biofilm shows resistance to common antibiotic therapies and to various tolerance mechanisms together with genetic as well as phenotypic resistance. Taking chronic wound management into consideration, biofilm causes severe inflammation because of enhanced and prolonged provocation of nitric oxide, free radicals and inflammatory cytokines resulting in slow down of healing process. For example, *Pseudomonas aeruginosa* manifests various resistance mechanisms like expression of efflux systems, reduced permeability, release of the enzymes having ability to inactivate the antibiotics, and modification of the target. Some other examples of notorious organisms showing multidrug-resistance include vancomycin-resistant enterococci, and *Klebsiella pneumonia* (Li and Nikaido, 2004).

Use of antibiotic in an unjustifiable way and irrational antibiotic therapies are the prime culprit of the drug resistance. Amplified risk of iatrogenic infection and extensive unfolding of microbial resistance also affect cost of treatment and the situation is further worsen due to potential hypersensitivity reactions to antibiotics. So, treatment only with antibiotic is not fruitful to encounter biofilm infection rather a multifaceted methodology should be approached involving both clinicians along with microbiologists (Hashemi *et al*., 2013).

Currently, biofilm which is inculpated in most of the non-healing wounds and in case of infections of wound has triggered remarkable interest and debate on research of wound care and management. The most common species of bacteria showing significant antibiotic resistance are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichia coli*, and *Corynebacterium* species. Association of *Staphylococcus aureus* and *Pseudomonas aeruginosa* has been commonly observed in multi-microbial infections along with cumulative antibiotic resistance to most of the antibiotics as revealed by gram-negative bacteria.

Staphylococcus aureus is generally found in infected wounds both of animals and human origin, Pseudomonas species are habitually observed in burn wounds, which are frequently specified by the existence of exudate providing moist and nutrient-rich conducive condition for bacterial multiplication. Due to the microbial attack, burns, chronic wounds, post-surgical wounds, and diabetic ulcers require extended period for complete healing and sometimes, may even fail (DeLeon *et al*., 2014).

A wound of diabetic origin is frequently correlated with production of chronic and refractory ulcers. Due to both local and systemic elements, the repair procedure does not proceed towards proliferation and maturation stages. This occurs owing to inhibition of synthesis of various cells, proteins, cytokines and growth factors which are required for augmentation and migration of keratinocytes and fibroblasts. Additionally, the skin of diabetic patients is more prone to skin infections.

An appropriate and rapid diagnosis followed by immediate proper treatment along with perfect wound dressing which can strictly prohibit bacterial penetration is highly essential to prevent the microbial growth. In this respect, novel strategies against biofilm and more research on biofilm infection as well as antimicrobial resistance are mostly needed. However, appropriate diagnostic methods involving regular microbiological methodologies and advanced clinical laboratory testing methods are also essential. Some researchers also have developed many methods of worthy novel therapies. Congruent and combined research on biofilm and development of effective therapeutics will be able to significantly treat biofilm infections (Lebeaux *et al.*, 2014).

4. Wound management

There are a number of effective treatments for the wound and burn management. A proper dressing method should imitate the extracellular ground substance and should be specified by flexibility, biological stability, and proficiency to expel the exudate from the wound, simultaneously equipping a moist environment at the site of the wound. It must also safeguard the wound from extraneous hazards and microbial infections. It should amplify epidermal migration, enhance neovascularization and regeneration of connective tissue. Advanced wound healing methodologies involving the employment of allografts, autografts, cultured epithelial autografts and wound treatment based upon biodegradable and biocompatible polymers, *viz.*, chitosan, collagen and hyaluronic acid have been permitted for dressing of wound by the Food and Drug Administration (FDA) (Bhardwaj *et al.*, 2017).

Together with traditional wound dressing, there are advanced dressing materials integrating growth factors and biological molecules for better cellular migration, extracellular matrix synthesis along with skin substitutes involving patient-derived cells. Recently, treatment of wound using antimicrobial agents has been reviewed as an effective method to control bacterial infection in wound healing (Kim *et al.*, 2019).

The main drawbacks of fruitful biofilm treatment in wound healing are the involvement of high cost and complex procedure though novel antibiofilm agents are available. This leads to enthusiasm among researchers to explore new effective choices or alternatives utilizing the vast reservoir of bioresources. Nanotechnology as a new approach can extend successful solution to prohibit drug-resistant biofilm infections. This may lead to a revolutionary approach in the field of biomedical and industrial applications. It has been observed that many of the nanoparticles as a result of their intrinsic antibacterial and antifungicidal capability can be engaged in different treatment procedures and can dramatically influence the wound healing procedure positively (Jimohand Lin, 2019). Thus, the contribution of nanoparticles in wound care and addressing adjoining biomedical problems can make the nanoparticle a potential option for invention of advanced antimicrobial agents.

5. Mechanism of action of phytonanoparticles in wound healing

Wound healing is a complicated yet well-controlled process. The steps of recuperation for all types of wounds are the same. Wound infections are characterised by microbial colonisation, particularly with harmful bacteria, resulting in chronic wounds that do not heal. As a result, the host-bacterial equilibrium is to be restored by cleaning the wound and using antimicrobial treatments. The surplus of reactive oxygen anions formed at the site of wound should be decreased since oxidative stress is considerable during the initial healing process. Bioactive phytoconstituents that encourage cell proliferation, remodelling, and maturation can be used to stimulate the wound's adjacent tissues (Shao *et al.*, 2017).

The bioactive chemical elements in plant extracts can serve as free radical scavengers, antimicrobials, anti-inflammatory agents and immunity enhancers (Palai *et al.*, 2020). These isolated compounds of plant extracts have these qualities required for normal healing. Interactions involving fibroblasts, macrophages, neutrophils, *etc.*, at the wound site, as well as collagen deposition with correct laying out surrounding the wounds are all processes in wound repair. Various interactions with multiple agents are involved in such complex processes. Concurrently, angiogenesis (the development of new blood vessels) maintains a constant supply of nutrients and healing substances. Several phytochemicals from plant extracts, either together or separately work synergistically to achieve the desired effect in all of these processes. The wound is repaired using phytochemicals extracted and combined in optimal amounts from diverse sources (Tasneem *et al.*, 2019).

Table 1: Phytonanoparticles from plant extracts used in wound healing

Sl. No.	Nanoparticle	Type of plant extract	Part used	Mechanism	Reference
1	**Silver nanoparticles (AgNPs)**	*Coptis Chinensis*	rhizome	Increased release of cytoplasmic components, particularly protein and nucleic acids, damages bacterial membrane potential and generates a high amount of intracellular reactive oxygen species.	Ahmad *et al.*, 2017
2.	**Gold nanoparticles (AuNPs)**	*Chamaecostus cuspidatus*	leaf	Anti-inflammatory and antioxidation actions extend healing ability in cut-aneous wound care.	Ponnanikajamideen *et al.*, 2019
3.	**Copper nanoparticles (CuNPs)**	*Allium saralicum*	leaf	Antioxidant, antibacterial, antifungal, and cutaneous wound healing potentials.	Tahvilian *et al.*, 2019
4.	**Titanium dioxide (TiO2) nanoparticles**	*Origanum vulgare*	leaf	Significant wound healing activity.	Sankar *et al.*, 2014
5.	**Zinc oxide (ZnO) nanoparticles**	*Aloe barbadensis*	leaf	Non-irritant, maintain skin elasticity, no inflammation and has favourable effect on skin regenerating through controlled degradation, blood clotting, platelet activation.	Batool *et al.*, 2021

Table 2: Details of various phytonanoparticles used in wound healing

Sl. No.	Nanoparticle	Type of NP	Polyphenol	Drawback of polyphenol	Mechanism	Reference
1.	**Curcumin nanoparticles**	Curcumin encapsulated into a silane-hydrogel nanoparticle vehicle	Curcumin possesses innate antimicrobial and wound healing properties	Poor aqueous solubility and rapid degradation profile	Enhance granulation, tissue formation, collagen deposition, new blood vessel formation and extends topical delivery of curcumin.	Krausz *et al.*, 2015
2.	**Resveratrol-loaded nanoparticles**	RSV-loaded cellulose acetate butyrate (CAB) NPs	RSV promotes wound healing through its antioxidant property, enhancing endothelial nitric oxide synthase and vascular endothelial growth factor expression	Chemical instability, poor oral bioavailability, low solubility	Increase drug stability, controlled release, excellent adhesion, improve the stability and solubility of RSV, increased residence, improved the reconstruction of skin.	Amanat *et al.*, 2020
3.	**Epigallocatec -hin gallate nanoparticles**	Gelatin/chitosan/epigallo-catechin gallate nanoparticle incorporated in a poly (c-glutamic acid)/gelatin hydrogel	EGCG has anti-inflammatory and immunomodulatory effects and treat dermal wounds by facilitating re-epithelialization for healing wound	Unstable in sunlight, lead to cell cytotoxicity at high concentrations	Enhance wound regeneration conditions.	Lin *et al.*, 2016
4.	**Quercetin nanoparticles**	Quercetin loaded chitosan tripolyphosphate nanoparticles	Quercetin has antiulcer, immunomodulator, anti-allergy, anti-inflammatory effects, stimulate angiogenesis and epithelial cells, fibroblasts proliferation	Low water solubility and poor skin penetration	Controlled manipulation of cytokines like TNF-α and IL-10, growth factors like VEGF and TGF-1, in the inflammatory and proliferative phases of wound healing, thus leads to better wound care.	Choudhary *et al.*, 2020
5.	**Bromelain nanoparticles**	Bromelain-loaded chitosan nanofibers	Bromelain extracted from pineapple with proteolytic enzymes for treatment of burns, wounds, inflammations	Less activity, stability and more toxicity	Faster re-epithelialization, degradation of necrotic tissues, reduction of oxidation in the affected tissue, accelerate wound healing.	Bayat *et al.*, 2019
6.	**Rutin nanoparticles**	Rutin loaded pickering emulsion	Rutin is free radical scavenger oxidizing superoxide radical species for enhancing the wound healing	Poor aqueous solubility	Exhibit long term stability due to the sustained release and synergistic effect of pickering emulsion (oleic acid, chitosan) for better healing.	Asfour *et al.*, 2017
7.	**Naringenin nanoparticles**	Naringenin-loaded chitosan-coated nanoemulsion	Possess antimicrobial, angiogenic, anti-inflammatory, antioxidant properties with cell signalling factors promoting healing	Less stability	Enhance formulation stability through repulsive interactions between scattered globules.	Akrawi *et al.*, 2020

6. Nanomaterials commonly used in wound healing

Natural substances like plant extracts and essential oils in combination with silver, gold, copper, titanium, zinc nanoparticles increase their efficacy. The ability of these NPs functionalized with plant extract and essential oils can suppress microbial colonisation and biofilm development on nanocoated wound dressings to effectively manage wounds by preventing infection without the use of antibiotics or antiseptic topical medications (Sharma *et al.*, 2020; Vasile *et al.*, 2020) (Table 1). Carboxymethyl cellulose (CMC)-based wafers incorporated with resveratrol, gelatin/chitosan/ epigallocatechin gallate nanoparticle incorporated in a poly (c-glutamic acid)/gelatin hydrogel, quercetin loaded chitosan tripolyphosphate nanoparticles, rutin loaded pickering emulsion increase drug stability, controlled release, excellent adhesion, improve the stability and solubility of phytochemcals which can be utilised to improve reconstruction of skin (Table 2). This encapsulation of nanophytocompounds overcomes the problems of phytochemicals limited bioavailability, less activity, stability and more toxicity (Monika and Chandraprabha, 2020).

7. Wound healing experiments

To extract, define, and identify the specific bioactive chemicals in the plant responsible for wound healing activity, phytochemical investigations were required. Tannins, flavonoids, alkaloids, proteins, and other essential ingredients were discovered through phytochemical screening. Experiments on wound healing can be carried out *in vitro*, *in vivo*, or both. Keratinocyte assays, fibroblast assays, and epithelial cell assays are examples of *in vitro* procedures. In contrast, *in vivo* approaches entail the use of animal models (mostly rats or mice) (Tsala *et al.*, 2013). Before beginning the treatment procedure, one of the types of wounds, such as incision/ excision/burn/dead space wounds, is made on the test animal. The phytocompound is applied topically/orally/intra-dermally to the test group after it has been converted into nanoformulation and the extent of healing is observed.

This means that the physicochemical and biological features of the unique phytoconstituent accountable or contributing to wound healing must be completely explored in order to understand the mechanism of action of the phytoconstituent (Figure 1).

Preparation of plant part extract

⬇

Preparation and synthesis of phytonanoparticles

⬇

Analysis of cell toxicity of phytonanoparticles by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay

⬇

Measurement of antioxidant activates of phytonanoparticles by DPPH (2,2-Diphenyl-1-picrylhydrazyl) assay

⬇

Preparation of fungal and bacterial species

⬇

Analysis of sensitivity of bacterial and fungal strains to phytonanoparticles

⬇

Measurement of MIC (Minimum inhibitory concentration) and MBC (Minimum Bactericidal Concentration) of phytonanoparticles

⬇

***In vivo* design**

➡ **Cutaneous wound healing potential (Findings of wound area and contractures, total cell, and blood vessel)**

➡ **Biochemical studies by determination of hydroxy proline, hexuronic acid, hexosamine (Fibroblasts synthesize some components of the primary extracellular matrix of the wound bed)**

Figure 1: Steps for wound healing experiments using phytonanoparticles.

8. Characterisation of phytonanoparticles

The characterisation of phytonanoparticles can be done through UV-Vis (Ultraviolet-visible) spectroscopy, FT IR (Fourier-trans form infrared spectroscopy), FE SEM (Field emission scanning electron microscopy), AFM (Atomic force microscopy), TEM (Transmission electron microscopy) analysis. These are easy, low cost, and non-toxic procedures (Ali *et al.*, 2016).

9. Phytonanoparticles for improved wound healing activity

Experimentation revealed extensive granulation and fibroblast aggregation in animal models treated with plant extracts. The wounds in the treated group had healed completely, with almost normal collagen and reticulin architecture. The improvement in tensile strength of the wounds in the treated group could be attributed to an increase in collagen concentration, which aids wound contraction and is aided by plant extracts. The higher rate of angiogenesis, wound contraction, and shorter period of epithelialization in animals treated with plant extracts could be related to their broad-spectrum antibacterial activity in an excision wound model (Alam *et al.*, 2011).

The effect of the plant extract on angiogenesis, epithelialization, and collagen deposition has been confirmed through electron microscopic examination. Increased collagen and protein levels result in significant increase in skin breaking strength, hydroxyproline content, and dry granulation tissue formation. Free hydroxyl proline and its peptides are liberated when collagen is broken down, and an increased quantity of hydroxyl proline is an indicator of greater collagen turnover. Enhanced wound healing includes free radical scavenging and antibacterial properties of phytoconstituents, which can operate singly or in combination to speed up wound healing (Murthy *et al.*, 2013).

The phytocompounds' antibacterial action on the wound surface could be related to the release of hydrogen peroxide and a reduction in catalase activity in the tissues or blood. Clinically, increased wound contraction and epithelialization by phytoconstituents aid in the healing of chronic wounds, as evidenced by well-designed clinical trials and electron microscopy research (Agarwal *et al.*, 2018).

10. Future perspectives

In the coming years, knowledge of the qualities of the plant's major ingredients will be required to carry out multitasking efforts in wound healing of all types of wounds. Use of phytonanoparticles necessitates more in-depth research in various topics, including the uptake potential of diverse species, the process of uptake and translocation, and phytonanoparticles activities at the cellular and molecular levels (Nowak and Barańska-Rybak, 2021). However, in order to increase the efficacy and use of nanophytocompounds in wound care, multidisciplinary efforts are required to demonstrate their safety. It's crucial to look into their precise mechanism of action and side effects, as well as to conduct properly controlled studies.

11. Conclusion

Nanotechnology-based therapy incorporating natural substances has recently been identified as a potential next-generation therapy for the treatment of chronic wounds. With present understanding and additional advancement in research focusing on important difficulties and limitations, phytonanotechnology could be a potential technique for improved wound healing activity.

Conflict of Interest

The authors declare no conflicts of interest relevant to this article.

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