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POTENTIAL OF NANOCARRIERS FOR WOUND HEALING

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Wound in medical pathology

A wound refers to the loss in normal anatomical structure and functional integrity of the skin which is an outermost layer and first line defense of the body. It can be described by different ways based on its etiology, anatomical location, healing time, and level of contamination. In medical terminology, a wound can be defined as sharp injury that damages the epidermal tissues of the skin resulting in loss of external protective barrier to the underlying tissues making them susceptible to a variety of environmental insults, abrasions, and attack by pathogens [1]. Wounds can be broadly classified as acute if they are new and chronic if they are persistent for more than 8 weeks despite optimal medical treatment. The chronic wounds are basically acute wounds which have not progressed through the orderly well-orchestrated natural wound healing process of haemostasis, inflammation, cell proliferation and tissue re modelling or in other words wounds which have been arrested in inflammatory phase of the wound healing cascade resulting in unmanageable inflammation, continuing infection, and weakened re-epithelization [2].

Wound and accumulation of reactive oxygen species

Inflammation is a protective response of the body to tissue injury. The damaged and inflamed cells secrete cytokines and other chemical mediators which recruits circulating leucocytes to the site of injury [3]. The phagocytic leucocytes mainly neutrophils and macrophages, having potential to ingest offending agents, kill microorganism and eliminate necrotic and dead cells by phagocytosis, enters the phagocytic pathway and engulf the invading microbes and dead cells resulting in formation of phagocytic vacuole known as phagosome [4]. The phagosome with ingested microbe or dead cells then fuses with lysosome resulting in the formation of phagolysosome which triggers activation of NADPH(nicotinamide adenine dinucleotide phosphate) oxidase enzyme (also known as phagocyte oxidase) located on the membrane of the phagosome [5]. The NADPH oxidase then oxidizes the reduced NADPH resulting in formation of reactive superoxide free radical (O_2^-) which through a series of reaction gets converted into more reactive hydrogen peroxide (H_2O_2) by superoxide dismutase enzyme and even more reactive hypochlorous radical ($\text{HOCl}^\bullet$) by myeloperoxidase in the presence of halide (Cl^-) ions present abundantly within the cells and nitric oxide radical ($\text{NO}^\bullet$) by nitric oxide synthase enzyme. These highly reactive oxygen species (ROS) are powerful oxidants and antimicrobial agents which kill bacteria by their cell lysis accomplished through lipid peroxidation, oxidation of proteins and nucleic acid [6].

ROS serves defensive as well as signaling function for cell proliferation and re-

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epithelization.

Although inflammatory phase of the wound healing process helps to clear wound infection yet prolonged inflammation marked in chronic wound may wreak havoc, and injure normal and healthy tissues through excessive production of ROS, thereby delaying wound healing activity. The physiological role of inflammation pays off the price in terms of pathological consequences [7]. The ROS which eliminates microbe and dead cells in wound healing process have potential to cause destruction of normal and healthy tissues resulting in unhealed chronic wound which represents a major area of unmet clinical need resulting in increased patient morbidity and mortality, thereby necessitating wound care management which could rapidly improve wound healing and thereby patient quality of life [8].

Wound care management via nano formulations

Numerous therapeutic wound dressing materials with intrinsic antimicrobial, antifungal, anti-inflammatory, anti parasitic, and wound healing pharmacological activity have been extensively studied in wound care management. These treatment modalities help to control wound infections but do not treat the underlying cause of chronic wound that is overproduction of reactive oxygen species and hence do not efficiently improve wound healing. Further tremendous progress has been made in the identification of natural antioxidants and anti-inflammatory wound dressing materials to augment tissue repair and decline of inflammatory cells in the lesion place. Renet *al* evaluated the anti-inflammatory activity of kireinol, a biologically active compound obtained from Chinese natural herb, for wound healing potential [9].

However, these therapeutic agents suffer from low aqueous solubility, poor physicochemical stability *in vivo*, extensive hepatic and intestinal metabolism, and poor cellular uptake which constraints the applications of the therapeutic agents. Nano technological approaches can be implied for mitigating these hurdles to permit sustained, and or controlled release of the agent, to improve delivery of the therapeutic agents to the target site thus reducing degradation rate *in vivo* and enhancing bioavailability.

Mir *et al.* explored the antibacterial potential of a bioactive phenolic compound for the management of infected chronic wound. Carvacrol, an important constituent of plant essential oils was loaded into poly (caprolactone) nanoparticles and subjected to antibacterial study against *P. aeruginosa* and *S. aureus* as potential treatment option for infected wounds [10]. Doostanet *al* explored the antibacterial potential of a medium spectrum antibiotic, erythromycin, for infected wound care management. A cellulose acetate nanofibrous mat incorporated with erythromycin loaded chitosan nanoparticles was evaluated against *E. coli*, *S. aureus* and *P. aeruginosa* bacterial strains as potential dressing for infected wounds [11]. A recent study reported an increase in poor solubility of curcumin via encapsulation into a saline-hydrogel nanoparticulate vector. The results clearly demonstrated an increase in the *in vitro* efficacy against of the developed system against methicillin-resistant *S. aureus* and magnified wound termination activity [12].

Another type of nanoformulation is scaffolds, which imitates the properties of biological extracellular matrix. The possible techniques that can be used to produce them are phase separation, electrospinning and self-assembly of nano materials. Electro spinning

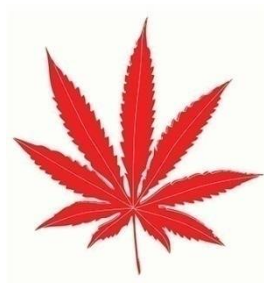
creates porous nano fibers that can be used as composite scaffolds for the adhesion and production of fibroblasts in wounds [13]. Other nano systems like dendrimers, can also form networks that can incorporate anti inflammatory and antibacterial agents for wound healing [14].

The multiple faceted implications of nanoformulations namely, the stimulation of wound healing by initiating angiogenesis, collagen synthesis/granulation, re-epithelialization, anti microbial effects, as well as their role in the mitigating abnormal scarring at the wound site presents substantial advantages compared to conventional treatment approaches and firmly positions their potential in clinical settings. More studies are needed to unearth the complete potential, as well as intricacies associated with the clinical use of nanoformulations.

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