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An Overview On The Application Of Nanotechnology In Burn Wound Management

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Abstract: Burn injuries represent a significant global health concern, and the effective burn management approaches are crucial in addressing this challenge. This review article specifically sums up the application of different and modern nanotechnology techniques that can be used in burn management. The review sections involve the pathogenesis of burn, the main strategies that are employed in burn management, the different nano-formulations that can be used in burn management, as well as the advantages of utilizing nanotechnology in this context. Nanotechnology offers unique properties and capabilities which contribute to efficient drug delivery, enhanced wound healing, and the development of advanced dressings with antimicrobial properties. Nanoparticles also enable targeted drug delivery and the potential for personalized burn treatments. The application of nanotechnology in delivering antimicrobial treatments has also contributed to the reduction in bacterial resistance. Overall, the application of nanotechnology in burn management holds significant promise in improving outcomes, reducing complications, and enhancing the quality of life for burn patients.

Keywords: Burn management; burns; microorganism resistance; nanotechnology

1. Introduction

A double action is played by the skin in the course of defending the body against pathogens. Skin represents a physical barrier protecting internal organs against drastic environmental conditions. It also provides a guard against microorganisms and harmful environmental agents by innate and acquired immunity. [1].

A heat source getting in contact with the skin results in a burn injury. Burn injuries can be caused by several factors such as high temperature, friction, electrical current, radiation and various chemicals. The degree of seriousness of burns is defined by the surface area of the body burnt, which affects morbidity and patient mortality. Also the severity of burn injury is affected by the burn location, the temperature that caused the burn, the exposure time to the causative agent, where time and temperature play a synergistic role [2]. Since long ago, the burns and their management have represented an important problem. Prehistoric paintings on Egyptian papyri and old Chinese art describe the care employed in burn care. Ointments, dressings and treatment regimens have been recorded in the old writings of Celsus, Galen and Hippocrates [3]. A major development in the field of burn care especially in the case of fluid loss, hypermetabolic response to burns, control of infection, topical antimicrobial development, removal of burnt tissue, skin grafting, culture of keratinocytes, response to burns, resuscitation and artificial skin substitutes since the twentieth century [4]. Efforts are being done to[1] improve survival rates and the quality of life in burn patients [5].

Skin injury is usually associated by damage in its immune mechanism, which renders the site of wound susceptible to germ infection. This may be associated with many complications upon invasion of the microbes throughout the body. A biofilm can be formed by these microbes which could be resistant to antibiotics and hence delay healing and could have life threatening effects. [6]. These Multidrug-resistant (MRD) pathogens post a serious issue in treatment as they require longer healing times. Long healing durations may be associated with a greater risk of adverse consequences as loss of organ, limb amputation or possibly death [7]. Hence, illnesses associated by infection characterized by antimicrobial-resistance (AMR) and MDR possess higher death incidences compared to all cancer forms as reported by the Centers for Disease Control and Prevention (CDCP) [8].

The severity of burn wounds (superficial, deep or complete wounds) determines their healing time. Thus, the healing time may extend from few weeks to a long time especially if wound infection took place [9].

Recently, many centers have been established to provide

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specialist care for burn treatment in order to minimize mortality rates. Burn treatment is usually associated with long hospital stays. Burn patients need in most cases special care as post-traumatic care, management of scars, dealing with psychological problems, where patients suffer post-traumatic stress disorder (PTSD)[10].

Within the last twenty years, nanomaterials (NMs) have been utilized in infection management to promote wound healing [11]. An advanced dressing has been developed as a targeted approach by formulation of nanoparticles into scaffolds. Antimicrobials have been formulated as NMs using polymers, lipids, mesoporous silica, and various other carriers as illustrated in figure 1 [12, 13].

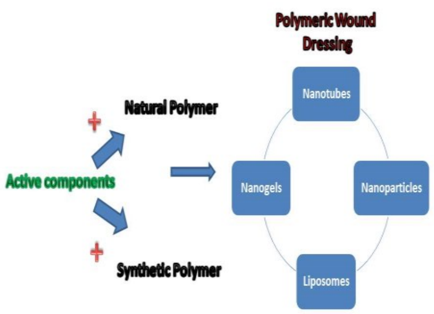

Figure 1: The loading of active components into carriers representing polymeric wound dressing

The concept of nano-antibiotics (nanobots) is dated to ten years ago. These have been evaluated for their antimicrobial and antiseptic effects. However, few articles have been published which studied the wound healing capabilities of these nanobots [14].

In this review we will demonstrate the various aspects concerned with burns and their associated complications, the possible approached for burn management, the application of nanotechnology in burn management, as well as the different nano-formulations utilized in such management.

2. Burn Classification:

Burns can be classified based on their degree of deep penetration into the skin layers [15]. Those which involve only the epidermis are classified as "Superficial" or "First degree" burns. They are characterized by reddening of skin, with moderate pain sensation and absence of blisters. Usually, they heal without scar formation within 5 to 10 days [16]. Second degree burns are "superficial partial thickness" burns. They are characterized by a deeper damage to the dermal layer of the skin. Such burns are characterized by the presence of blisters, whose underlying layers are reddened. Pain is a common symptom in such cases. Healing usually occurs within 2- 3 weeks with minimal scaring [16].
The third degree burns or "full-thickness" burns show a deeper penetration involving the subcutaneous tissue. The damage extends to the nerves, and hence the patient experiences no pain sensation. Theses burns require more than 8 weeks to heal and may require surgical intervention [15].

3. Burn Aggravation variables:

The main variables that contribute to aggravating burn wounds include reduced levels of expression of several growth factors, excessive inflammatory response, and bacterial infection.
Some growth factors (GFs) are involved in initiation of inflammation and differentiation of monocytes to macrophages. Others are also involved in reversal of inflammation. Other GFs promote angiogenesis for the growth of granulation tissue [17]. GFs promote the proliferation, differentiation and migration of the keratinocytes, fibroblasts and vascular endothelial cells which are involved in the tissue repair process. They are also involved in the remodeling of damaged tissue [18].
Prolongation of the inflammatory stage in wound healing delays the healing process. Wound infection prevents the disposal of neutrophiles, which delays the release of GFs by macrophages. Hence, the initiation of tissue regeneration and apoptosis of damaged tissue are delayed [19].
The most dangerous among them is a bacterial infection [20]. Table 1 lists the microorganisms that have the potential to infect invasive burn wounds [21].

Table 1: Microorganism list infecting burn wounds

Group	Species
Fungi	Aspergillus spp., Candida spp.
Viruses	Varicella-zoster virus, Herpes simplex, Cytomegalovirus
Gram-positive organisms	Methicillin-resistant Staph. Aureus, Coagulase-negative Staphylococci, Enterococcus spp., Vancomycin-resistant enterococci
Gram-negative organisms	Pseudomonas weruginosa, E. coli, Klebsiella pneumoniae, Enterobacter spp., Proteus spp., Actinobacter spp., Bacteroides spp.

4. Burn Management:

Management and treatment of burn injuries is based on anti-infection, stem cell therapy, and growth factor (GF) administration. Those approaches help decrease infection rates and quicken the healing process [22, 23]. During healing, the burn site is a dynamic living habitat that changes in response to extrinsic (such as dehydration, systemic hypotension, and cooling), as well as intrinsic (like the release of inflammatory mediators and bacterial proliferation) factors [24, 25]. Intactness of the basement membrane promotes gradual and normal epidermal growth without scar formation [26]. However, sometimes skin pigmentation occurs as a result of an over-activity of melanocytes in superficial burns [27]. Partial injury of the dermis and the basement membrane of the epidermis develop non-hypertrophic scars during healing [25]. Hypertrophic scarring is common in deep dermal and full-thickness burns that heal on their own for longer than 21 days or that require extensive wound care [28].

Three therapeutic approaches are typically used to treat a burn wound: dressing-free treatment, dressing-covered care, early surgical removal of dead tissues and rebuilding [26]. Due to susceptibility of burned skin infection, burn wounds require mainly antibiotics and other antibacterial agents to eradicate microorganisms from the surface [29]. Systemically administered antibiotics may not provide full therapeutic reach to the infection site. Prolonged antibiotic administration may increase antibiotic resistance [23]. The drop in systemic medication exposure by local administration is considered a good strategy to overcome the risk of bacterial resistance [30]. That concept encourages the use of local therapy in burn treatment.

Compared to conventional medicine, advances in nanotechnology may provide solutions for serious medical issues like inflammatory [31], neurological, and dermatological disorders [32]. Nano-systems were initially thought to be carriers for drug delivery and targeting. Recently, beneficial characteristics were found in nanomaterials themselves [33]. The degree of interaction between nanoparticles and the skin, and nanoparticle residence at the site of action are affected by the extent of skin damage, the kind and size of nanoparticles. Irritated or damaged skin displays a reduced ability to act as a barrier, hence, increases the likelihood of nanoparticle absorption into the bloodstream [34]. Variable categories of nano-formulations are used to treat skin burns, as organic nanostructures (polymer nanoparticles, nano-emulsions, nano-gels, liposomes, and lipid nanoparticles) and inorganic nanostructures (gold, copper, or silver nanoparticles) [35].

5. Benefits and drawbacks of nanotechnology

The advancement in nano-medicine and nanotechnology resulted in the recent development of novel nano-materials. [36]. These nanomaterials differ significantly compared to ordinary state due to both their increased relative surface area and their quantum size effect. That is the main reason for researchers' interest all over the world in nanotechnology [37]. There is a lot of promise in using nanomaterials, particularly noble metal nanoparticles, in the field of biomedicine. Noble metals, which have many uses, are non-reactive and are not liable to complex formation with other elements [38].

Nanotechnology led to the development of materials sized between 1- 100 nm [39]. Although nanoparticles have been previously used in drug delivery and targeting, nanoparticles individually, have recently displayed a lot of medicinal potential. The application of nanomedicine can improve the treatment of bad prognosis illnesses, as cancer, neurological disorders, and infections [40]. In addition, novel wound healing medical techniques were developed based on nanotechnology. Also, new treatment approaches, based on nanosystems, can be created to treat a range of illnesses, in specific infections in burn wounds. Because of the significant drawbacks of the current burn wound infection treatment modalities, including inadequate permeability, adverse medication reactions, and enzymatic degradation, nanotechnology may be a suitable substitute [41].

Despite the numerous benefits offered by nanotechnology, they exhibit several drawbacks and challenges. Several nanoparticles possess potential toxicity to humans and to the environment, due to their biological effects, when compared to their large sized counterparts. Additionally, the details of interactions existing between the biological systems and nanoparticles are not completely elaborated. Hence, the consequences of their use on human health and ecosystems are not fully estimated. [42].

6. Reasons for utilizing nanotechnology in the control of burning

The infection is one of the biggest obstacles in treating burns because it prolongs the inflammatory phase, which slows down the healing process [43]. Antibiotics, through nanotechnology, have been introduced as nanoparticles to treat wounds locally without exposing the patient to the medicine systemically [44].

The main problem facing burn patients is Multidrug-Resistant Organisms-microorganisms (MDROs), which is caused by extensive systemic antibiotic exposure. It was possible to overcome such problem by the administration of anti-infective agents in a nano-form. For example, the viability of antibiotic-resistant bacteria can be decreased by the use of nanocrystalline silver [10]. Unlike conventional $AgNO_3$ which exhibits the lowest inhibitory activity, nanocrystalline silver exhibits the highest efficiency with a fast inhibition rate and a broader activity against a variety of microorganisms [45]. Silver nanocrystals possess effective antibacterial activity, cytokine modulation, and inflammation inhibition capabilities, resulting in their usefulness in treating wounds in both emergency and cosmetic fields [46]. Similarly, they are recommended for other skin injuries, such as minor cuts, abrasion cuts, laceration cuts, and first- and second-degree burns [47].

7. Different types of Nanoparticles used in burn management

Various kinds of nano-delivery technologies have been employed in burn treatment like nano-emulsions (NEs) [43]. NEs are made up of two immiscible liquids stabilized by a suitable surfactant, forming a heterogeneous system. Typically, a droplet diameter ranging from 50 to 200 nm produce transparent dispersion. However, a droplet size exceeding 500 nm results in a milky cloudy dispersion. [48]. NEs possess many benefits including long term physical stability, their possible inclusion into parenteral and non- parenteral routes as well as the possibility to solubilization of many drugs [49].

Polymeric nanoparticles are particles having a size range of 10–1000 nm, which can be prepared from natural, semi-synthetic, or synthetic polymers. Nanoparticle matrix can encapsulate drugs (dissolved or disseminated) or the drug can be chemically bonded to its surface, depending on the type of polymer [50]. The chemical nature, size, and viscosity of the formulation of polymeric nanoparticles affect their capacity to penetrate epidermal layers. Polymeric nanoparticles have many advantages as ease of manufacture, chemical and physical stability, variety of sizes and shapes, high drug loading capacity, and potential for targeted and controlled drug release [51].

Metallic nanoparticles (MNPs), thanks to their unique characteristics have recently drawn particular attention. These include copper, zinc oxide, gold, silver, and titanium dioxide [52]. MNPs' are characterized by their huge surface area-to-volume ratio, which enhances their therapeutic and pharmacological efficacy. Additionally, upon using the magnetic field-controlled release, MNPs may enhance the accumulation of antimicrobial compounds at the sites of infection. The use of MNPs to treat multi-drug resistant organism (MDR) infections has increased over the past ten years, and studies revealed that these very potent nanoparticles can effectively prevent and treat wound infections [53]. Metal ions exhibit a wide range of antimicrobial activities, including disruption of electron transport chains, formation of reactive oxygen species (ROS), damage to cell membranes, and malfunctioning of proteins [54]. They represent a good option for treating resistant infections and promoting the healing of burn wounds due to their broad-range activity against many bacteria. Zinc oxide NPs, could repair damaged skin by lowering necrosis, regulating infection, collagen fiber deposition, and re-epithelialization, which promotes wound healing [55]. Gold nanoparticles are used in wound healing despite their expensive costs due to their exceptional qualities being antioxidant, anti-inflammatory, antibacterial, and especially scaffold-enhancing characteristics [56]. Additionally, titanium dioxide nanoparticles can effectively prevent skin infections caused by both gram-positive and gram-negative bacteria. Hence, they have been licensed as wound healer agents [57]. Similarly, copper NPs exhibit strong antimicrobial properties [58].

Additionally, liposomes are high-performance nanocarriers in the drug delivery which are of natural origin, often phospholipids. The low toxicity, biocompatibility, stability, sustaining drug release, prolongation of systemic circulation and long residence in targeted site of liposomes renders them great candidates for eliminating resistant microorganisms in burn wounds [59]. Liposomes can also transport antimicrobial medications to bacteria. Furthermore, it is possible to increase liposome efficacy against resistant infections of wounds by modifying their composition and utilizing different materials in the formulation [60]. Also, research demonstrated the effectiveness of a liposome formulation, into which was incorporated epidermal growth factor, in the course of burn treatment [61].

Hydrogels are the perfect nanostructures for wound healing and infection control. This is due to the three-dimensional soft polymers made of nanoscale particles with a variety of characteristics. These characteristics include a high water content, ideal stability, and appropriate mechanical and chemical qualities [62]. Increasing the bioavailability of antimicrobial drugs in the infection sites is a crucial strategy for combating MDR bacteria. Enhanced antimicrobial drug bioavailability was brought about using hydrogels, with a pronounced reduction in adverse effect. [63].

Nanogels represent another nano-formulation that can be used in treatment of wound burns. Aqueous and oil phases are stabilized by surfactants and occasionally additional surfactants are combined to form nanoemulsions, that have been previously discussed. Large interphase spacing and extremely tiny dispersed phase droplets (20–500 nm) are their defining characteristics like surface tension and low interphase [64]. These characteristics allow nanoemulsion to improve absorption rate, remove variability in absorption, aid in the solubilization of lipophilic medications, and ultimately boost bioavailability. Nevertheless, because nanoemulsions have a low viscosity, their direct topical application is inconvenient and alters the skin's penetration profile. Such drawback can be managed by adding the nanodispersion to the polymer solution, to create an in situ nanoemulgel (NEGs). Hydrophobic medications are incorporated into the oily cores of the nanoemulgel within the gel cross-linked structure [65]. Nananoemulgels increase the topical effectiveness of many poorly permeable medications [66]. It manages also the issue of hydrogels' hydrophilicity, which restricts their use to the delivery of hydrophobic drugs. The facile administration and sustained/controlled medication delivery offered by the combination of hydrogel and nanoemulsion improve patient compliance. As a technique of prolonged release, a nanoemulgel permits the maintanence of the drug concentration within the therapeutic range, even at low levels of the active ingredient. The active ingredient contained in the internal phase of the nanoemulsion is released into the skin by the dispersion phase, which is cross-linked. This cross-linked structure allow the gradual relase of drug paricles. As a result, prolongation of skin exposure to the medication is insured [67].
Nanogels have been developed using chitosan as a carrier containing silver sulphadiazin cubosomes for burn treatment [68]. Also, it was possible to load metal or metal oxide antimicrobial agents (e.g. Ag or ZnO NPs) onto nanogels to avoid infection and promote burn wound healing. Loading of metallic antimicrobials onto nanogels enhanced their antimicrobial action against both Gram- positive and –negative bacteria [23].

Carbon Quantum Dots (CQDs) are carbon-based nanoparticles, having a diameter of less than 10 nanometers [69]. They are suitable for antibacterial applications due to their low toxicity, remarkable water solubility, great chemical stability, good biocompatibility, and photoelectric capability. On the other hand, photo-thermal and photodynamic therapies are very effective ways to combat MDR infections and could be combined with CQDs and other nanostructures that can absorb light radiation [70]. The membrane, proteins, and DNA of a bacterial cell can be destroyed by light radiation in these therapeutic techniques. In photo-thermal and photodynamic therapy, respectively, increasing the temperature and reactive oxygen species generation by the released waves results in the death of bacteria. In addition to eliminating microorganisms, photo-thermal therapy's heat creation could significantly lower the risk [71].

Nano fibers are also among the nano-structures that can be employed in the management of skin burns. They are fibers having a diameter in the order of a billionths of a meter. These fibers may be as small in diameter as down to 1.5 and 1.75 nanometers [72]. They are prepared using natural, synthetic or semisynthetic polymers by several techniques including template-based synthesis [73], electrospinning [74], interfacial polymerization [75], self-assembly [76] and sonochemical synthesis [77]. The nanofiber mat is so flexible that it can fit properly to uneven burn wounds within any body part. The naofiber mat promotes cell adhesion, differntiation, proliferation and growth. Accordingly, naonfibers are employed in skin tissue engineering through using natural and sysnthetic polymers for embedding skin stem cells, which promotes skin regeneration at the site of the burn [78].

8. Using Nanostructures as an Appropriate Platform to Combat MDR Pathogens in Burn Wounds

The main problems for burn patients are MDR microorganisms, which are brought on by extensive systemic antibiotic exposure [79]. Furthermore, topical antibiotic treatment was not likely to be an effective wound-healing technique because of the breakdown of the epidermal barrier after a burn [44]. Nanostructures can increase the possibility of topical administration and decrease systemic drug dosage [30]. However, the kinetics and dynamics of nanostructures rely on several variables, including the extent of skin damage, the existence of infection in the burn wound, and the characteristics of nanoparticles (such as size, kind, and half-life) [34]. Furthermore, a perfect nanoparticle for topical application on burn wounds needs to have properties like nonimmunologic, nontoxicity, biodegradability, and appropriate release profile [41].

Additionally, the organic or inorganic component source of the nanoparticles plays a significant role in minimizing any negative effects that should be taken into consideration for advancements in wound healing [21].

Among the treatments for burn wound infections, Silver Sulfadiazin (SSD) in particular has become well-known and is considered the standard treatment for burns [80]. It has been employed in the form of ointments and wound dressings due to its wide antimicrobial activity against Gram-positive and Gram-negative microorganisms [81]. SSD has also the advantage of promoting epithelialization. Moreover, the use of SSD is devoid of pain upon application, of high patient compliance, and can be used easily with or without dressing [82]. Today, The high surface to volume ratio of nanometer-sized silver particles rendered silver effective at very low concentrations and with minimal tissue toxicity [83].

9. Polymeric nanotherapeutics (PNs) for the management of burn Wounds

NPs, including nanosheets, nanoemulsions, liposomes, nanogels, and nanofibres have been used to treat burn injuries [84]. The following figure 2 represents the different nanotherapeutics used in burn injury management.

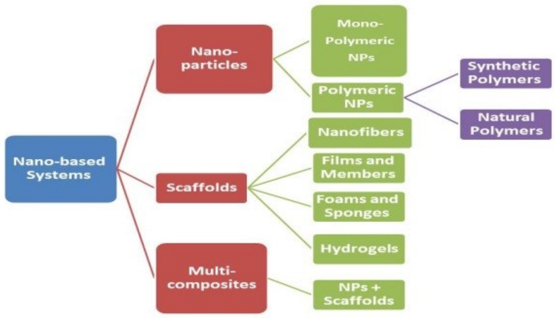

Figure 2: Nanotherapeutics used in burn injury management

To create a variety of nanotherapeutics, medications can be encapsulated within polymeric nanoparticles for delivery via several routes of administration as oral, transdermal, parenteral, mucosal, occular and implantation [85]. Several carriers have been used in preparation of nanotherapeutics to encapsulate medication. For example, Hyaluronic acid (HA) was used to load curcumin and quercetin to produce an appropriate drug localization in epidermis and dermis as well as a 98% wound closure within 28 days [86]. Also, Chitosan with its hydrogel-like properties served as wound dressing which promoted hemostasis, reduction of inflammation and granular tissue proliferation in wound repair [87].

10. Conclusion

The most serious problems associated with wound burns is the infection. The inclusion of anti-infective agents in nanoformulation to prepare wound dressings promotes proper wound healing. The incidence of bacterial resistance development in greatly reduced with the topical application of anti-infectives. The nano-particles show enhanced drug tissue penetration and improved healing properties.

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