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A STUDY OF THERAPEUTIC DRUG DELIVERY FOR WOUND HEALING APPLICATIONS

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ABSTRACT

More goods with ideal therapeutic properties have recently hit the market thanks to the development of pharmaceutical technology, polymer science, and Nanotechnology. The unique mechanical qualities and similarity to the extracellular matrix make fibers (nano or micro), hydrogels, and transdermal films excellent candidates for skin dressing. In addition to its potential therapeutic value, this carrier system's ease of processing and development makes it a prospective option for application in wound dressing. This is because it requires the creation of a unique carrier system, which may include fibers and may be formed from a broad range of polymers derived from either natural or synthetic sources. Biological and naturally generated wound dressing material might be a more secure alternative for wound care in this context. The current study's goals need the development of a biological haemostat that is both biodegradable and provides controlled releasing of encapsulated medications to increase wound healing rates; this haemostat would include a broad range of antimicrobial agents. All of the used carrier systems were suitable for use as wound dressings.

KEYWORDS: Therapeutic, Drug Delivery, Wound Healing Applications, Nanotechnology, pharmaceutical technology.

INTRODUCTION

After cardiovascular disease and cancer, the healing process itself is the third greatest cause of mortality in the world in 2020 (Okonkwo et al., 2020). Acute and chronic skin injuries affect several million people annually. About 300,000 individuals each year die from chronic disease and burn accidents in low- and middle-income countries (Stokes et al., 2017). Accidents and infections are the leading causes of severe trauma. Infections caused by bacteria that grow in a wound are called wound infections. (Rahim et al., 2017) This infection causes tissue destruction at the wound site by inducing immune system inflammation (Lafuse et al., 2021). Additionally, it causes wounds to take longer to heal,

which may lead to potentially fatal infections. Cancer, arthritis, chronic infections, and diabetes are all on the rise (Lipsky et al., 2012), as are other immune suppressive disorders and auto immune diseases. In addition to the aforementioned, the development of bacteria resistance to antimicrobials effectively eliminates any hope of boosting regeneration capability. Antimicrobial effects on wounds are often intended to be confined when using traditional wound care treatments. The therapy of wounds is complicated greatly by the presence of these bacterial infections (Allahyerdiyey et al., 2011). Active in microorganisms from the earliest stages of infection were gram-positive Staphylococcus aureus and Streptococcus pyogenes bacteria. Gram-negative bacteria like Escherichia coli and Pseudomonas aeruginosa etc. are implicated in the latter stages of the infectious process, when a chronic wound is formed (Cisek et al., 2017). Patients with wound infections often exhibit pus formation, redness and swelling, increased pain or swelling, and fever (Enbiale et al. 2021). The antibacterial activities of the medication form and wound are crucial to the therapeutic efficacy of these treatments, and it is generally agreed that they are useless in wounds caused by pathological disorders (Oliver et al. 2021). Traditional solutions' inability to monitor drug release results in increased dosing frequency, increased risk of adverse reactions, and worse patient compliance (Pons et al., 2019). Polymeric formulations, including chitosan, alginate, collagen, gelatin, etc., have been shown to be beneficial for rapidly halting bleeding and are particularly appropriate for significant trauma (Heher et al., 2018). This problem may be resolved by covering the wound with appropriate antibacterial wound dressing materials (Alavi et al., 2020). There are many types of dressings on the market, but the vast majority of them have shortcomings in one or more key areas, such as weak mechanical characteristics, blood clotting capacity, swelling ability, or antimicrobial activity. That's why it's crucial to develop innovative dressing materials (Patil et al., 2021). The biological origin of biomaterials makes the development of biomaterial-based antibacterial dressings an essential area of research (El- Assar et al. 2021). According to the published literature study, the most promising wound dressing materials are composite materials based on biomaterials.

Wound healing

Human skin provides a barrier against pathogens, particles, and evaporation, and it also provides immunity (biochemical and adaptive immunity) (Gizaw et al., 2018). Anatomically, skin is composed of three layers: the stratified keratinized epidermis (SKE), the collagen-rich

dermis (CED) where glands, hair follicles, capillaries, and nerves all have their origins, and the hypodermis (HDE), which is mostly composed of blood vessels and adipose tissues. A cut is an abnormality in behavior that alters the normal anatomical structure of the skin. The epidermis and dermis are often the most damaged layers in skin wounds (Moeini et al., 2020). However, only a select few severe wounds really affect the hypodermis, muscles, viscera, and bones. Acute and chronic wounds are the two main types of wounds. Burns and abrasions, among other types of trauma-caused wounds, fall within the category of "acute wounds" (Chen et al., 2019). Patients with limited mobility often develop chronic wounds, which may cause serious complications such as infection of the muscle, tendon, or bone (osteomyelitis) and even death. Sen et al. (2009) state that early discovery is crucial for successful wound care and management.

WOUND HEALING CYCLE

Inflammation, tissue proliferation, and tissue remodeling are the three main components of the wound-healing pathway seen in Figure 1.1. Acute inflammatory responses are part of the inflammation process, and elements such signaling pathways, macrophages, antigens, monocytes, neutrophils, and cytokines (which inhibit bacterial development) are needed to attract inflammation to the location. During the inflammation phase of the proliferation process, an inflammatory response is formed, activating the recruitment of keratinocytes, fibroblasts, and endothelial cells, which in turn leads to cell migration and cell proliferation. Tissue granulation, cell proliferation, and ECM secretion are further outcomes of this process (Kuna et al., 2017). Scar tissue forms as a result of an epithelial-mesenchymal transition during the remodeling process, which is characterized by the emergence of cell migration, the disruption of tissue repair, and the constriction of the wound (Schultz et al., 2005). As can be seen in Figure 1, cell proliferation results in the development of new blood vessels and then of nerve sprouts.

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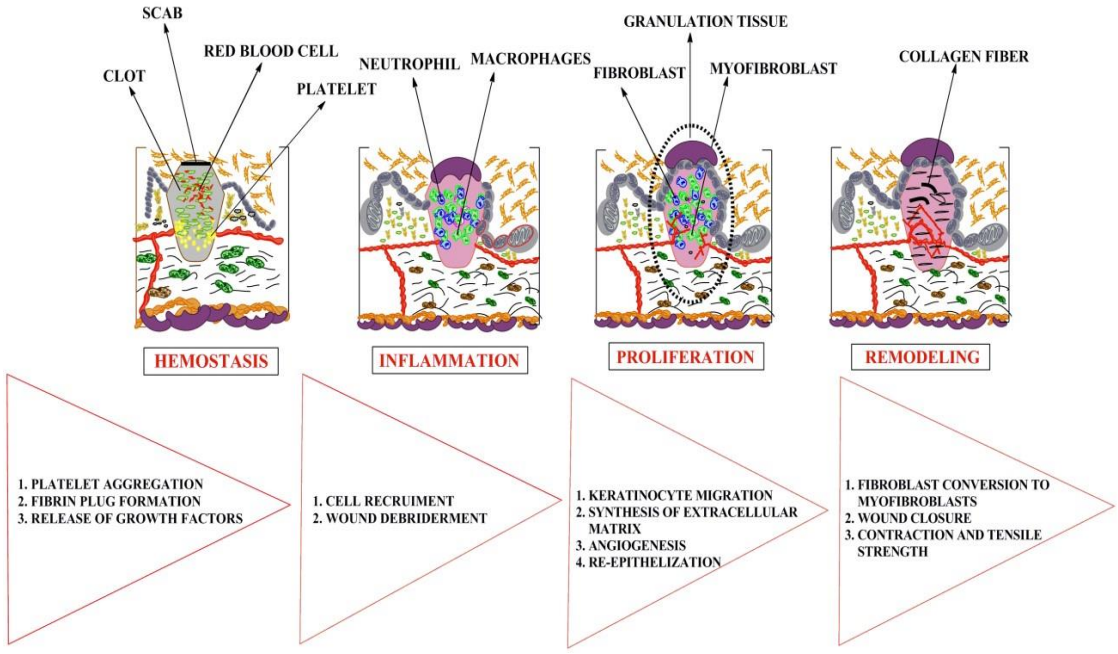

Figure 1. Cascades in wound healing process

WOUNDS AND ITS CLASSIFICATION

According to the definition provided by Quain et al. (2015), a skin wound is an abnormal process that disrupts the normal, biological structure and functional aspects of the skin. Epidermis and dermis, two of the skin's three outer layers, are primarily impacted by the disease (Kruse et al., 2016). The skin's anatomical structure also includes the hypodermis, blood vessels, sweat glands, connective tissue, etc. Two distinct kinds of skin wounds exist:

- Acute wounds (trauma based)
- Chronic wounds (can cause septicaemia, osteomyelitis and even death).

Chronic wounds are prevalent yet immobile wounds that may affect more than just the skin and can even cause damage to the surrounding muscles (Guo et al., 2010). In order to effectively treat, prevent, and manage wounds, early diagnosis is essential. Dermal disturbances in the skin's essential sections are what cause acute wounds (Fedakar et al., 2008).

FACTORS AFFECTING WOUND HEALING

Several different things may slow wound healing. In broad strokes, as shown in Figure 2, the variables influencing repair may be classified as either local or systemic. Wound healing is

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affected by both local (those things that happen at the site of the injury) and systemic (the person's overall health and wellbeing) aspects. As can be seen in Figure 2, a number of these reasons are interconnected and influenced by both regional and global variables.

Two factors influencing wound healing are classified as

i. Local factors
ii. Systemic factors

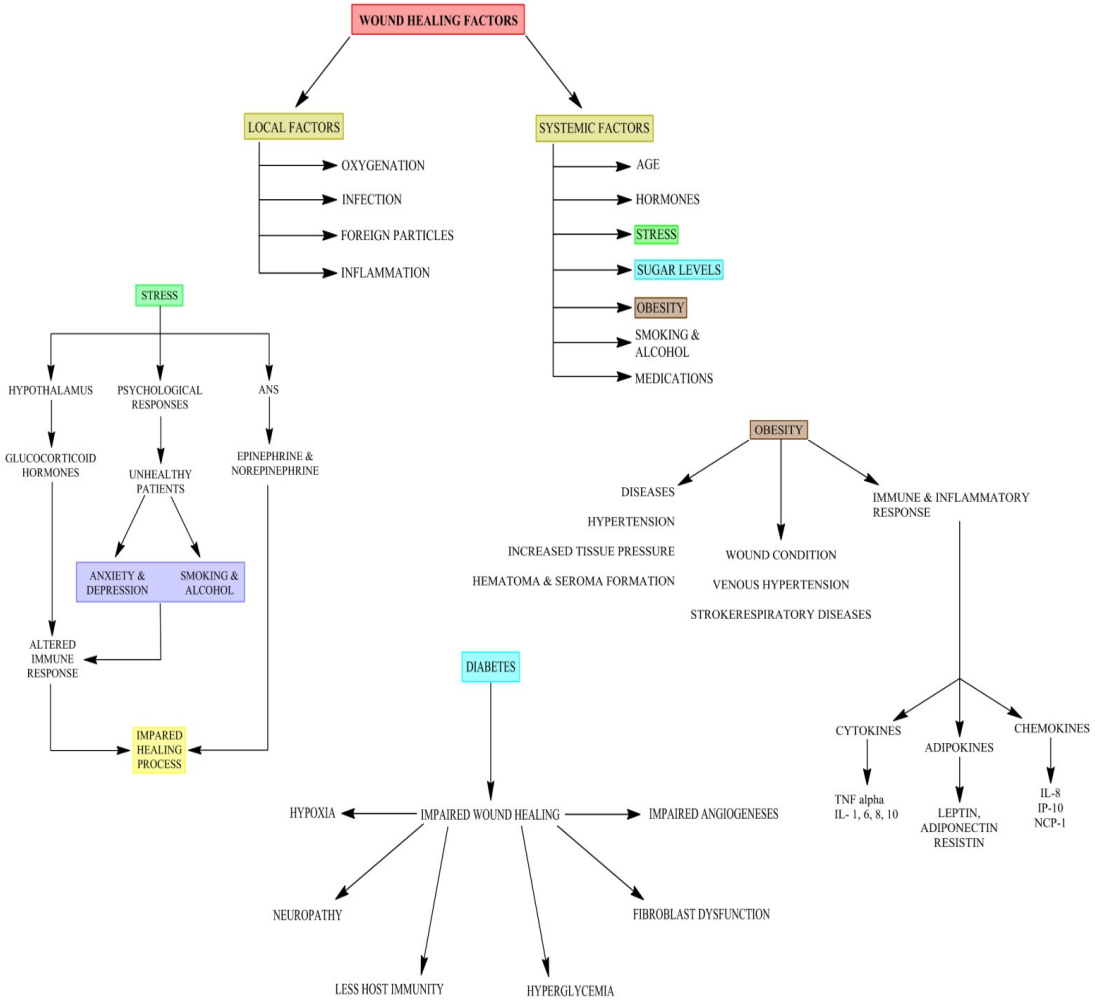

Figure 2. Various factors affecting wound healing

Local factors

1. Oxygenation

Oxygen is required for practically all wound healing processes and is vital for cellular metabolism, especially the creation of energy via ATP. Its antimicrobial and angiogenic effects, increased keratinocyte differentiation, migration, aid wound closure and re-epithelialization, enhanced fibroblast proliferation and collagen production, and decreased inflammation (Wongkanya et al., 2017). Wounds that lose oxygen supply heal more slowly. Wound healing is accelerated by short-term hypoxia after an infection, but slowed by long-term or chronic hypoxia. Certain aspects of the wound-healing process are triggered by hypoxia in acute wounds (Behm et al., 2012). Hypoxia may trigger the production of cytokines and growth factors by macrophages, keratinocytes, and fibroblasts.

Key regulators of cell proliferation, migration and chemotaxis, and angiogenesis in the wound healing process include cytokines generated in hypoxia, such as PDGF, TGF-, VEGF, tumour necrosis factor-alpha (TNF-alpha), and endothelin-1 (Behm et al., 2012).

2. Infections

It is not until the skin is broken that the microorganisms that are normally kept on the skin's surface may invade the deeper tissues. If inflammation is noted for the wound, the infection and replication status of the microorganisms are either colonization, local invasion/critical colonization, or spreading invasive infection. The presence of nonreplicating germs on a wound is called contamination, whereas the presence of replicating microorganisms on a lesion without tissue damage is called colonization. The local infection/critical colonization phase occurs in between the onset of systemic symptoms and the resolution of the infection itself. Invasive infection is defined as the presence of reproducing organisms inside a wound, leading to further host harm (Sakarya et al., 2014).

3. Inflammation

It's an inevitable byproduct of the body's wound-healing process and crucial for getting rid of any infectious microbes. However, insufficient microbial clearance might lead to chronic inflammation if cleaning is unsuccessful. Interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-alpha) are pro-inflammatory cytokines that, when elevated for an extended period of

time, aid germs and endotoxins and lengthen the inflammatory response (Guo et al., 2010). If this continues, the wound may become chronic and resistant to treatment. Matrix metalloproteases (MMPs) are a class of proteases that may degrade the extracellular matrix (ECM), and their levels tend to rise with persistent inflammation. Increased protease activity is accompanied by a reduction in endogenous protease inhibitors. Rapid breakdown of growth factors is seen in chronic wounds due to a shift in the protease balance (Edward et al., 2004).

Systemic factors

1. Age

People over the age of 60 make up the fastest-growing segment of the population, and advanced age is a major risk factor for tissue regeneration and wound healing impairment (World Health Organization [WHO]). Multiple human and animal investigations have investigated age-related wound healing improvements and delays at the cellular and molecular level. It is generally believed that healthy elderly persons have a temporary delay in wound healing as a result of the effects of aging, but not a true impairment in regards to the quality of healing. The aging body has a higher challenge to inadequate wound healing due to the varying impairments in inflammatory mechanism, epithelial tissue, collagen formation, and angiogenesis as studied in mice (Emery et al., 2005).

2. Hormones

Sex hormones contribute to the impaired ability to repair wounds that comes with aging. It has been discovered that older men recover from acute wounds more slowly than older women do (Gilliver et al., 2007). This may be due in part to the fact that the steroid precursor dehydroepiandrosterone (DHEA) interacts strongly with the female and male hormones androgens (testosterone and 5-alpha-dihydrotestosterone, DHT) and estrogens (estrogen and 17 beta-estradiol). Regeneration, protease inhibition, matrix synthesis, epidermal function, and inflammation are just a few examples of how hormones like female estrogen and male androgens regulate genes (Hardman et al., 2008).

3. Stress

Reduced cell proliferation, differentiation, cellular molecular adhesion, and the significance of gene controlling the transcription process are all results of tightly regulating the stress response, which in turn affects and limits the inflammatory aspect of wound healing (Glaser et al., 2005).

4. Sugar levels

Diabetes or hyperglycemia, which causes high blood glucose levels, disrupts and reverts the wound healing process that results in diabetic foot ulcers. As a result of the incorrect angiogenesis and subsequent inflammatory response, these abnormalities are responsible for roughly 80% of lower limb amputations (Vileikyte, 2007). Oxidative stress, advanced reactive species, and a raised amount of matrix metalloproteinases (60 times more than acute wounds) are all impeded by the high quantity of oxygen radicals in DMU. Significant declines in neuropeptides, short-chained polypeptide neuropeptides, and cell chemotaxis, all of which are essential for growth and proliferation, have an adverse effect on wound healing (Woo et al., 2007).

5. Obesity

More than thirty percent of American adults and fifteen percent of children and adolescents are obese, according to a recent research by the Centers for Disease Control and Prevention (CDC). It is generally recognized that growing obesity is linked to an increase in the prevalence of a wide range of diseases and health conditions, such as cardiovascular disease, type 2 diabetes, cancer (malignant), heart attack, sleep difficulties, respiratory issues including asthma, and slow wound healing (Sibbald et al., 2008). Pressure ulcers, venous ulcers, and hematomas and seromas are among wound complications that are more common in obese people (Greco et al., 2008). Obesity increases the likelihood of several diseases, health issues, and surgical infections during both bariatric and non-bariatric treatments. As a result, the subcutaneous membrane of adipose tissue might become hypoperfused (Momeni et al., 2009).

6. Smoking and alcoholic consumption

Tobacco smoke has components and chemicals that counteract the positive benefits of smoking on the body. Even while nicotine stimulates and speeds up the healing process at moderate dosages, it causes vasoconstriction and poor blood flow when used in large quantities. In addition, the presence of carbon monoxide (CO) is evidence of oxygen use. Clinical and experimental evidence suggests that alcohol poisoning weakens the body's defenses, leaving the host more susceptible to infections and lowering the rate of blood vessel growth (Ahn et al., 2008).

7. Medications

The healing process is greatly aided by medications such nonsteroidal anti-inflammatory drugs (NSAIDS) and glucocorticoids (GC). In addition to their widespread anti-inflammatory actions, such as the reduction of cellular wound reactivity, fibroblast proliferation, and collagen production, GCs are also known to impede the healing of wounds. Wounds may heal with the use of systemic steroids (Franz et al., 2007) despite inadequate granulation tissue and reduced wound contraction. Wound healing's master transcription factor hypoxia-inducible factor-1 (HIF-1) is likewise suppressed by glucocorticoids. Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen are often used for the treatment of pain and the prevention of asthma and rheumatoid arthritis. Because of its anti-platelet activity, low-dose aspirin is commonly used as a preventative therapy for cardiovascular disease (Wagner et al., 2008). There is no proof that using NSAIDs for short periods of time improves recovery. However, it is still unclear if long-term use of NSAIDs interferes with wound healing. In animal models, ibuprofen's systemic administration has an antiproliferative impact on human health (wound healing), resulting in fewer fibroblasts, impaired cellular lysis, delayed wound closure, and slowed epithelialization (Hofman et al., 2007).

CONCLUSION

More goods with ideal therapeutic properties have recently hit the market thanks to the development of pharmaceutical technology, polymer science, and Nanotechnology. The unique mechanical qualities and similarity to the extracellular matrix make fibers (nano or micro), hydrogels, and transdermal films excellent candidates for skin dressing. In addition to its potential therapeutic value, this carrier system's ease of processing and development makes it a prospective option for application in wound dressing. This is because it requires

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