HOSTED BY

ELSEVIER

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

الجمعية السعودية لعلوم الحياة
SAUDI BIOLOGICAL SOCIETY

Review

# Deciphering the crosstalk between inflammation and biofilm in chronic wound healing: Phytocompounds loaded bionanomaterials as therapeutics

Srivarshini Sankar, Gothandam Kodiveri Muthukaliannan *

*Department of Biotechnology, School of Bio Sciences and Technology, Vellore Institute of Technology, Vellore 632 014, Tamil Nadu, India*

ARTICLE INFO

*Keywords:*
Phytochemicals
Chronic wounds
Molecular docking
Inflammation
Quorum sensing

ABSTRACT

In terms of the economics and public health, chronic wounds exert a significant detrimental impact on the health care system. Bacterial infections, which cause the formation of highly resistant biofilms that elude standard antibiotics, are the main cause of chronic, non-healing wounds. Numerous studies have shown that phytochemicals are effective in treating a variety of diseases, and traditional medicinal plants often include important chemical groups such alkaloids, phenolics, tannins, terpenes, steroids, flavonoids, glycosides, and fatty acids. These substances are essential for scavenging free radicals which helps in reducing inflammation, fending off infections, and hastening the healing of wounds. Bacterial species can survive in chronic wound conditions because biofilms employ quorum sensing as a communication technique which regulates the expression of virulence components. Fortunately, several phytochemicals have anti-QS characteristics that efficiently block QS pathways, prevent drug-resistant strains, and reduce biofilm development in chronic wounds. This review emphasizes the potential of phytocompounds as crucial agents for alleviating bacterial infections and promoting wound healing by reducing the inflammation in chronic wounds, exhibiting potential avenues for future therapeutic approaches to mitigate the healthcare burden provided by these challenging conditions.

## 1. Introduction

The skin is a multi-layered organ that functions as an enclosure for the body's internal systems, protecting them from external stimuli as well as preventing external microorganisms from entering the body (Pereira et al., 2013). The skin is very susceptible to developing various lesions, which include burns, ulcers, as well as wounds because it remains constantly exposed to the external environment. The human epidermis is damaged by trauma in the form of a wound, which includes a variety of cellular immunological responses as well as several intrinsic metabolic processes (Wang and Windbergs, 2017). Several intermediaries, including extracellular matrix (ECM) molecules, platelets, inflammatory cells, cytokines, growth stimulants, along with chemical messengers, interact with one another during various phases of haemostasis, inflammation, migration, growth, and tissue development to carry out these events (Zahedi et al., 2010; Pereira et al., 2013). The phase of inflammatory response, proliferation, and maturation are various phases in the complicated but normal process of wound healing (Ezzati et al., 2009). Burn injuries affect over one million individuals each year (Suguna et al., 1993). There is always a demand for efficient healing medications as wound healing is often addressed in scientific and medical literature.

Normal healing of wounds entails a set of synchronized events typically starts with the occurrence of an injury and the healing process starts when the platelets gets exposed to the collagen. This results in the accumulation of platelets along with a discharge of coagulating substances, ultimately triggers the fibrin clot formation at the site of damage. According to Clark (2001), the clot made up of fibrin acts as a temporary matrix to set the stage for the processes of healing. Platelets and inflammatory cells migrate to the site of the damage and deliver vital messengers called cytokines or growth stimulants or factors (Lawrence and Diegelmann, 1994). The connective tissue, the fibroblast, is in charge of depositing the collagen required to repair tissue injury. In properly functioning healthy tissues, collagen contributes to sturdiness, integrity, as well as structure.

When tissues have been traumatized and damaged, collagen is necessary to heal the damage, restore architectural framework, along with its function (Ross, 1969; Prockop and Kivirikko, 1995). If healing

Peer review under responsibility of King Saud University.
* Corresponding author.
*E-mail addresses:* srivarshini.s@vit.ac.in (S. Sankar), k.m.gothandam@vit.ac.in (G. Kodiveri Muthukaliannan).

https://doi.org/10.1016/j.sjbs.2024.103963
Received 3 October 2023; Received in revised form 15 February 2024; Accepted 17 February 2024
Available online 23 February 2024

fails to progress normally and step by step, it may result in the persistent expansion of wounds. Furthermore, a persistently high bacterial load in wounds causes an inflow of pro-inflammatory cells and elevated inflammation, which further delays recovery (Pastar et al., 2013; Frank et al., 2009; Roche et al., 2021). Every wound has some level of colonization, and the inflammatory phase of wound healing plays a significant role in reducing the amount of microorganisms to a level that is stable enough for healthy tissues to tolerate and eliminate. This is made possible by the skin, and specifically the epidermis, which upregulates and secretes antimicrobial peptides early in reaction to microbial contact and barrier degradation (Schröder et al., 2010; Nizet et al., 2001). Additionally, individual species within these polymicrobial wound communities may modify their virulence and amount, as well as the production of a biofilm. This further obstructs the effectiveness of the "host response" and hence delays healing. Traditional and modern wound-healing treatments can be categorized into two groups based on their efficacy, clinical acceptability, and side effects. Rural people in underdeveloped nations have primarily employed traditional medicines for many years. The aforementioned therapies typically include biological organisms, silver, herbal as well as animal-derived compounds, along with traditional dressings (Bodeker et al., 1999; Vijanovic and Vujanovic, 2013). On the contrary, current remedies include the implementation of grafts, sophisticated dressings, bioengineered skin replacements, as well as growth factor therapy (Boateng et al., 2008; Gurtner et al., 2008; Groeber et al., 2011; Rustad and Gurtner, 2012).

For many years, several herbal medications and herbal mixtures have been utilized to heal wounds. The qualities of the conventional forms of wound care, particularly the herbal and various other medicines used all over the world, are still being studied scientifically. The understanding of the healing mechanism has significantly expanded over the last 35 years. New and intriguing technologies that speed up the typical healing process of wounds are now being developed. Alkaloids, tannins, flavonoids, and terpenes are just a few examples of natural products that aid in the healing process (Kumar et al., 2007). The purpose of this review is to discuss the development in basic research of electrospun nanofibers and nanogels with botanical applications, with an emphasis on the sophisticated methodology used and medical difficulties resolved throughout the wound healing process.

Classification of wounds based on cleanliness and condition of wounds

The CDC (Centers for Disease Control and Prevention) has developed classification criteria with four different categories of wound statuses in order to properly represent the cleanliness and state of wounds:

- Class 1 wounds have been regarded as clean. They are typically closed, aseptic, and non-irritable. In order to drain these wounds, an enclosed draining method is necessary. Furthermore, these wounds have no impact on the respiratory, gastrointestinal, and urinary systems.
- Class 2 wounds has low levels of contamination. Wounds in the gastrointestinal, reproductive and urinary tracts are classified as class 2 wounds. These wounds, on the other hand, travel into these tracts in a controlled environment.
- Class 3 wounds are deemed polluted wounds. Those are relatively freshly formed exposed wounds which could appear as a consequence of sterilized procedure exploitation and digestive system leaching. In addition, class 3 injuries result in either acute inflammation or the lack of infectious inflammation.
- Class 4 wounds are considered to have an unsanitary infection. These wounds are usually the consequence of serious injuries which were not dealt effectively. Class 4 wounds have weakened connective tissue and are often triggered by germs within the surgical region or burst viscera. (Onvekwelu et al., 2017).

The primary problem regarding the wound classification approach is the fact that it exhibits low reliability among healthcare professionals (Levy et al., 2013; Onvekwelu et al., 2017). Furthermore, it has been demonstrated that this wound classification technique is inadequate in neonatal surgical wounds (Herman and Bordoni, 2023).

### 1.1. Classification of wounds based on the cause of development

Acute or chronic wounds can be categorized in a variety of ways, including according to their etiology (such as pressure, trauma, venous leg ulcers, or diabetic foot ulcers), their depth of tissue involvement, or other features including closure (primary or secondary purpose).

I. Acute wounds

A newly developed wound that has not yet advanced through the various stages of wound repair is referred to as acute (Attinger et al., 2006). Acute wounds are developed as a consequence of trauma or incisions, and they heal promptly and effectively. Minor cuts and skin tears are some examples of acute wounds. An acute wound infection occurs when metabolically active planktonic microorganisms invade viable wound tissue. This leads to the induction of an inflammatory response in the host, which is a direct reaction to the pathogens' virulence expression (such as enzymes and toxins) and tissue invasion. Clinically, acute infections usually present as a distinct, visible illness. HCPs often base their diagnosis on the basic indicators of inflammation, such as tumor (swelling), rubor (redness), calor (warmth), and dolor (pain) (Castanheira and Kubes, 2019). Planktonic invaders are phagocytosed by neutrophils during acute infections, and both oxidative and non-oxidative intracellular processes destroy the invaders. NETosis is the process by which neutrophils release neutrophil extracellular traps (NETs) in addition to destroying intracellular targets. Planktonic bacteria that disperse from a mature biofilm are thought to be the main causes of recurrent acute infections, not microorganisms in biofilm form primarily accountable for acute wound infections (Bjarnsholt, 2013).

II. Chronic wounds

A condition of pathological inflammation develops in chronic wounds because they have barely proceeded through the normal healing phases. These types of wounds require an additional healing period (Attinger et al., 2006). Surgical or traumatized wounds that are non-healing or infected, venous ulcers, pressure ulcers, diabetic foot ulcers, and ischemic ulcers are a few examples of chronic wounds. Obligate bacterial colonization is a crucial pathogenic component in chronic wounds. Prolonged healing is primarily caused by common wound bacteria such *Pseudomonas aeruginosa*, *β-haemolytic streptococci*, and *Staphylococcus aureus* (Mudge, 2015). In addition to causing direct harm to the host, bacteria draw in leukocytes, which amplifies pro-inflammatory cytokines, ROS (Reactive Oxygen Species), and proteases, therefore triggering and maintaining inflammatory cascades (Schreml et al., 2010). ROS and proteases generated by hosts and bacteria break down growth factors and extracellular matrix, preventing wound closure and interfering with cell migration (Demidova-Rice et al., 2012). In fact, it has even been proposed that the established biofilm precisely manipulates the inflammatory response of the host, prolonging it to acquire an enduring supply of nutrients in the form of inflammatory exudate (Wolcott et al., 2008; Banerjee et al., 2021).

### 1.2. Healing phases for wounds

The four stages of wound healing are depicted in Fig. 1: haemostasis, inflammation, cell proliferation, as well as reorganization or remodelling.

a Haemostasis

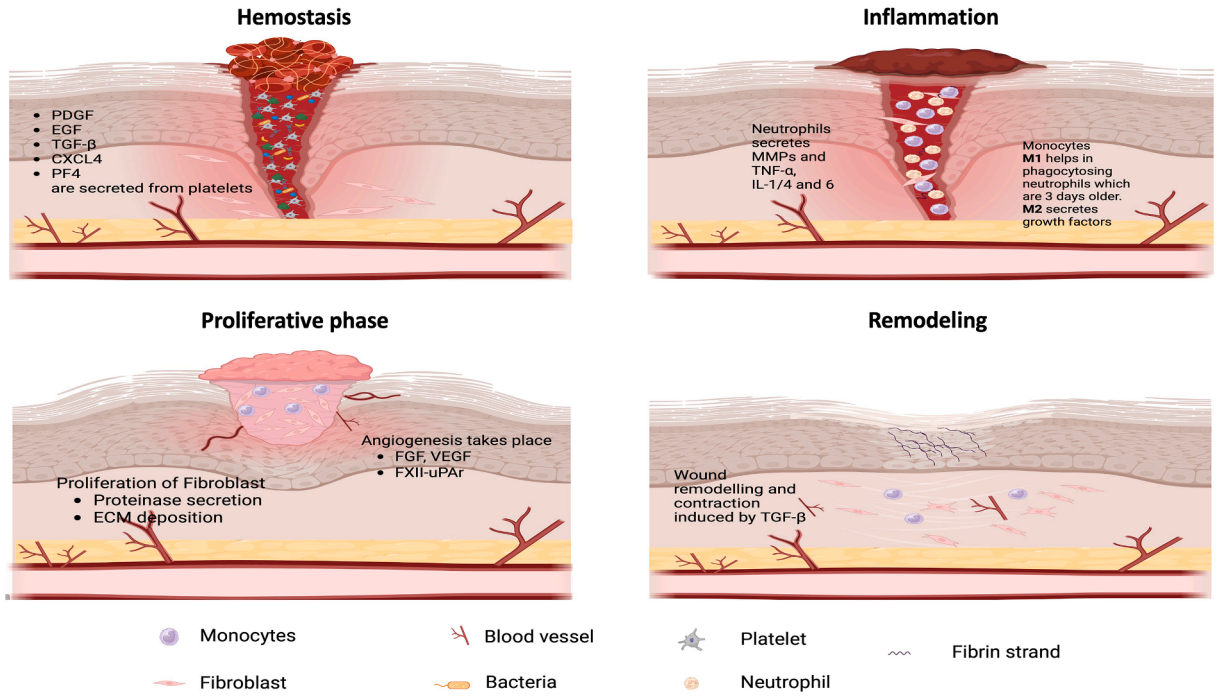


**Fig. 1.** Four phases in the wound healing process.

Haemostasis is the initial step in wound healing. Blood drains from the body during this phase to flush away microbes and antigens (Strodtbeck, 2001). The lymphatic vessels suffer damage as well during this stage. Different clotting cascades will be activated by the body, and exposed collagen will cause thrombocytes to aggregate. In addition to minimising blood loss and aggregating blood with cytokines and growth factors to bridge tissue gaps in damaged arteries, platelets also trigger vasoconstriction at the same time (Martin, 1997). It begins shortly after damage and typically concludes within the initial few hours or so. The clot is an accumulation of growth regulators or factors that stabilise blood clots and prevent bleeding. It contains proteins including fibrin, the fibronectin vitronectin, along with thrombospondin, that combine to construct a matrix that is temporary that acts as a scaffolding framework, sometimes known as a 'plug' (Kerstein, 1997).

Thromboxane A-2 and serotonin, two crucial mediators of inflammation that also promote vasoconstriction, are released by the activated platelet together with other cytokines as well as growth factors. The generated cytokines and growth factors, such as PDGF (platelet-derived growth factor) and TGF β1 (transforming growth factor), are accumulated in the clot as well (Singer and Clark, 1999). Coagulation results in haemostasis, which commences the healing process by releasing messengers that cause an inflammatory response. Clotting factor deficiencies (Factor VII, IX, XII) hinder wound healing (Beck et al., 1961).

b Inflammation

Inflammation, the second stage of wound healing, aims to sterilise the wound's surface and get it ready for the growth of new tissue. After haemostasis, the initial phase of inflammation begins (immediately up to 2–5 days later) and lasts for the first 48–72 h, however it can last up to 5–7 days (Haas, 1995). Elastase, cathepsin G, and proteinase 3 are examples of proteases that neutrophils may phagocytize and produce, both of which assist eliminate debris and kill germs from wounds.

In addition to serving many other purposes, macrophages are essential for wound healing (Kumawat et al., 2022). By phagocytosis, they eliminate debris and deceased cells in addition to functioning as antigen-presenting cells. The production of numerous effective growth factors, including PDGF, VEGF (Vascular endothelial growth factor), basic fibroblast growth factor (bFGF), and TGF- α and β, which encourage the proliferation of cells and ECM component production via localized cell populations in the skin might serve an additional substantial part in the recovery process of wounds (DiPietro and Polverini, 1993). The aforementioned factors also aid in vascular development, migration, and fibroblast activation, establishing the environment for proliferation (Witte and Barbul, 2002).

c Proliferation

The proliferation phase, which lasts between six to twenty-one days, is perhaps the most crucial stage of wound healing. The growth of new extracellular matrix tissue and collagen occurs during the proliferation stage of wound healing.

(I). Formation of granulation tissues

The third to fourth day after the injury, fibroblasts begin to show up, and during the 7–14 days, they reach their peak in quantity. Using the temporary matrix made of fibrin that was produced during the inflammatory stage of recovery, they migrate from the edges of the wound. Under the influence of bFGF, TGF- β, and PDGF secreted by macrophages, they multiply as well as synthesize glycosaminoglycans along with proteoglycans, elastins and additionally fibronectin, which function as the building blocks of the freshly formed granulation tissue's extracellular matrix, including collagen. Fibroblasts start secreting bFGF, TGF- β, and PDGF as the number of macrophages declines. In conjunction with insulin-like growth factor I, they begin to produce keratinocyte growth factor. Following secretion, collagen molecules are organized into the fibers made of, that are subsequently linked together into bundles. Furthermore, the collagen matrix laid down by fibroblasts allows cells that contribute to inflammation, blood vessel growth, and the formation of connective tissue to adhere to it, proliferate on it, and differentiate on it, providing the injured region the strength to tolerate stress (Ruszczak, 2003). Collagen deposition increases the wound's tensile strength. Initial increase in collagen levels within the wound are promptly followed by a period of equilibrium because collagenases also starts degrading collagen.

(II). Angiogenesis

Angiogenesis occurs together with fibroplasia and is required for scar development. Endothelial cells in intact venules are activated by VEGF, which is released mostly by keratinocytes along the margin of the wound but also by macrophages, fibroblasts, and platelets in reaction to hypoxia and lactic acid. The extracellular matrix, or ECM, is traversed by endothelial cells from regions of normally functioning blood vessels to the site of injury. In order to infiltrate the wound and break up the fibrin clot, agents responsible for degradation, such plasminogen activator along with the enzyme collagenase are produced after the new granulation tissue, which is composed of collagen, capillaries, as well as the extracellular matrix, has been laid (Greenhalgh, 1998).

They create new blood vessels through this process, which subsequently unite and create capillaries and initiate the flow of blood at the site of injury. When cells are sufficiently perfused, they stop generating angiogenic factors, which inhibit endothelial cell migration and proliferation. Apoptosis causes non-essential blood vessels to die, which causes the colour changes observed in tissue that is scarred as it develops.

(III). Epithelialisation

Epithelial cells that have not been completely annihilated from the wound margins migrate as the first stage of epithelialization. Within 12 to 24 h of damage, keratinocytes near the margins of the wound are stimulated by EGF (Epidermal growth factor) and TGF- β produced by stimulated platelets as well as macrophages (Lawrence and Diegelmann, 1994). The keratinocytes multiply and proceed to spread all through the injured area. The keratinocytes must be dissociated from one another and from their attachments with the cell membrane at the bottom in order to begin migrating. Migration continues as long as migratory cells from both directions of the wound comes into contact with other migrating cells, at which time it stops, a phenomenon known as contact inhibition (Garrett, 1998). Once the migration process completes, keratinocytes strengthen them by creating strong attachments between the newly formed basement membrane and each other (Clark, 1996).

All of the aforementioned modifications in the injury result in the development of granulation tissue, which is made up of inflamed cells, fibroblasts, along with new capillaries surrounded by a network of glycoproteins, Type-III collagen, as well as glycosaminoglycans, all of which are elements of a fresh, temporary ECM. The composition of the temporary ECM differs from that of normal tissue's ECM and consists of fibronectin, collagen, glycosaminoglycans, as well as proteoglycans (Ruszczak, 2003).

(IV). Contraction

After a week of healing since the injury occurred, the fibroblast transforms into myofibroblasts, which gather the borders of the wound closer and cause it to constrict (Eichler and Carlson, 2006). After the initial injury, contraction peaks 5 to 15 days later and lasts far after the wound has entirely re-epithelialized (Stadelmann et al., 1998). The contraction promotes re-epithelialization by shortening the extent that migratory keratinocytes need to travel, thereby reducing the amount of ECM necessary for covering the wound (Eriksson et al., 2022). It also shrinks the wound, reducing the quantity of ECM necessary to completely fill the incision. As the granulation phase concludes, fibroblasts begin to die, converting the tissue that has undergone granulation from a cell-rich state to a structure mostly composed of collagen (Stadelmann et al., 1998).

d Remodelling

In most medical situations, the ultimate objective of wound rehabilitation is to cure both persistent and acute wounds; nonetheless, wounds may continue to undergo remodelling or tissue development for extended periods of time (Zou et al., 2021; Eriksson et al., 2022). This final stage of wound healing decides the extent to which scarring and recurrence of the existing wound occur. The remodelling phase is characterized by a decrease in the formation of new blood vessels, periodic accumulation within the ECM, and eventually reconstruction of the granulation tissue into tissue with scarring (Xue and Jackson, 2015). Granulation tissue is mostly composed of collagen III, which is gradually replaced by the more robust collagen type I when the region of damage heals. This happens as a result of synchronous collagen I synthesis as well as lysis of collagen III, subsequently followed by ECM remodelling (Czubryt, 2012).

According to the extent and site of the wound, as well as the treatment techniques utilised, scar tissues are produced during the remodelling phase, which may take a number of years or months to fully develop. The freshly formed tissue gradually grows more durable and malleable throughout this period. Because of increased collagen production, the skin's elasticity and tear resistance are both improved. Macrophages recover their phagocytic nature after re-epithelialization. Mreg (regulatory macrophages) or M2c-like macrophages phagocytose extracellular matrix and cells which are not anymore needed to facilitate wound healing (Rodrigues et al., 2019).

### 1.3. Factors affecting wound healing

The key elements influencing wound healing includes physiological and biochemical processes, are depicted in Fig. 2:

i. Oxygenation

The metabolic functions of cells, particularly the generation of energy by means of ATP (Adenosine Tri Phosphate), require oxygen to function for the bulk of wound healing mechanisms. It prevents wounds from becoming infected, promotes vascular development, stimulates the differentiation, migration, and re-epithelialization of keratinocyte, in addition it also enhances fibroblast proliferation and collagen production, and makes wounds easier to heal (Bishop, 2008; Rodriguez et al., 2008). Due to cellular absorption by active metabolic cells, the earliest stage of wound's microenvironment is severely oxygen-depleted and hypoxic. Ageing and diabetes are two systemic disorders that can cause decreased blood flow, which will lead to lack of oxygenation to the tissue. The combination of these factors of insufficient oxygenation results in a hypoxic wound that takes time to heal. Chronic injuries are particularly hypoxic; tissue oxygenation levels ranging from 5 to 20 mm Hg were determined transcutaneously in chronic wounds, compared with normal tissue concentrations ranging from 30 to 50 mm Hg (Tandara and Mustoe, 2004).

ii. Age and chronic diseases

According to the World Health Organization, age is the main contributory factor for delayed wound rehabilitation, since the senior population (those over 60) is growing faster than any other age group. Diabetes mellitus, peripheral vascular disease, stroke, and cardiovascular disease are a few chronic conditions that may slow the healing of wounds (Gosain and DiPietro, 2004). Individuals with persistent conditions must be followed continuously throughout their therapies in order to obtain the optimal care. It is commonly known that the effects of age produce a short delay in the healing process, but not a significant decline in their ability to recover (Keylock et al., 2008).

iii. Stress

Numerous illnesses, including diabetes, malignancies, cardiovascular illness, impaired wound healing, are linked to stress. The malfunction of the neuroendocrine immune system brought on by stress is crucial for

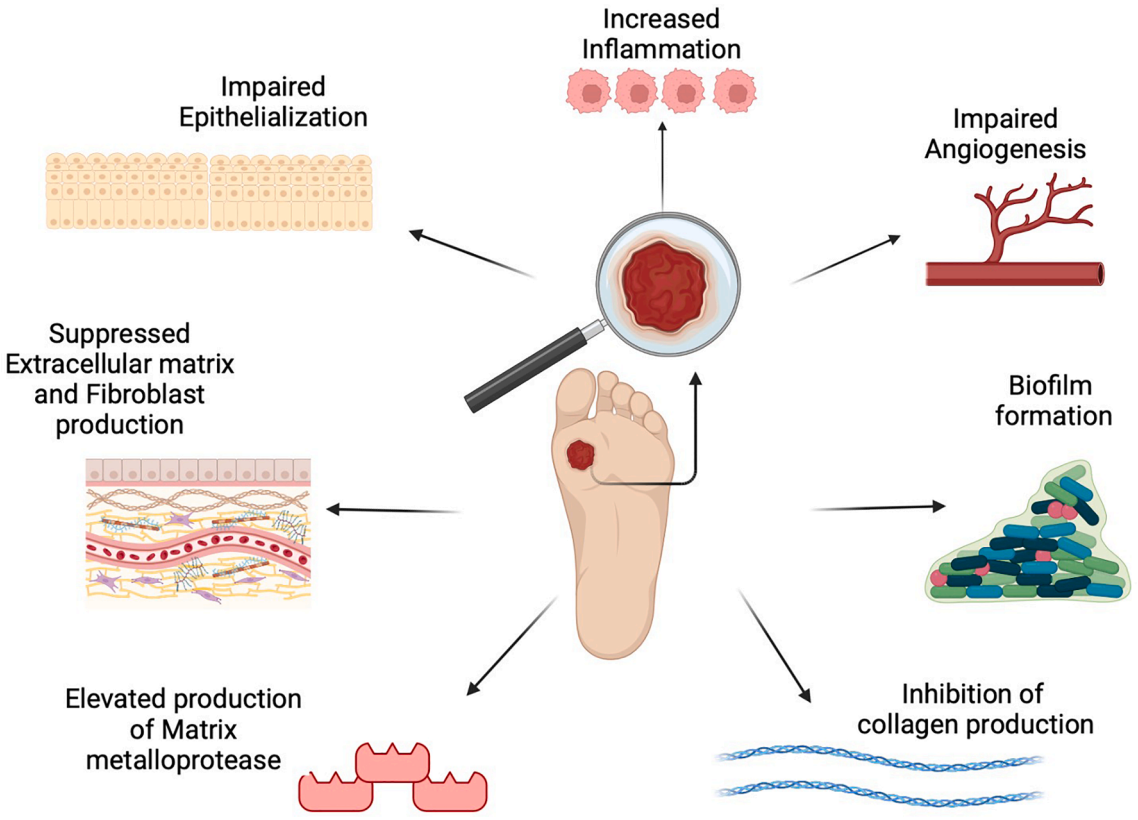


**Fig. 2.** Factors affecting the process of wound healing.

health, according to an abundance of studies. In addition to the immediate impact of depression and anxiousness upon the endocrine as well as immune systems, stressors might lead to detrimental psychological disorders like anxiety and depressive disorder, that may change the body's mechanisms as well as behavioural conduct affecting the health of individuals (Boyapati and Wang, 2007).

iv. Type of body and lack of blood supply

Body shape can also have an effect on wound healing. Because of the limited blood supply from fat tissue, an obese patient, for example, may have delayed the healing of the wound. Another obstacle to rehabilitation is protein deficiency, that is present in certain obese people (Wilson and Clark, 2004). According to Wilson and Clark (2004) obese people are more likely to experience pressure ulcers, venous ulcers, hematoma and seroma development, dehiscence, and skin wound infection. Research has indicated that obese patients undergoing bariatric and non-bariatric procedures experience a higher rate of wound complications (Anaya and Dellinger, 2006; Greco et al., 2008; Momeni et al., 2009). Patients who are obese specifically have a greater likelihood of surgical site infections. Subcutaneous adipose tissue experiences relative hypoperfusion and ischemia, which might be the cause of many of these problems. Antibiotic delivery may have diminished, which might also be the cause of this situation. Increased stress on the wound margins, which is common in obese people, also plays a role in the dehiscence of surgical wounds. Tension from the wound raises tissue pressure, which lowers microperfusion and the amount of oxygen available to the wound (Wilson and Clark, 2004; Anaya and Dellinger, 2006). On the contrary, if a patient is malnourished, the lack of nutrients as well as oxygen storage might hinder the wound healing process. Numerous lesions or ulcerations, including venous, arterial, diabetic, and pressure ulcers, can afflict the lower limbs. The absence of blood flow often causes these ulcers to form.

v. Nutrition

The influence of food on wound healing has been acknowledged over a century. The most obvious factor is that wound healing can be significantly impacted by lack of nutrition or other dietary deficiencies after trauma or surgery. Patients who have chronic wounds or wounds that are not healing, as well as those who have nutritional deficits, require special supplements. The process of healing will be influenced by how energy, carbs, fats, and proteins, as well as vitamins, and minerals are metabolised (Arnold and Barbul, 2006).

vi. Infections

Until the skin is injured, microorganisms which are normally trapped on the outermost layer of the skin get access to the tissue underneath. The condition associated with infection and stage associated with the microorganisms' development depends on whether the wound is classified to have inflammation, localised invasion, and/or spreading infection that is invasive Localised invasion is a transitional stage that includes microbial proliferation and the onset of immediate tissue response. Invasive infection in the presence of microbes that reproduce inside a wound and cause harm to the host as a result (Edwards and Harding, 2004).

Inflammation is a typical part of the recuperation process for wounds in order to get rid of contaminated disease-causing organisms. However, due to insufficient microbial elimination, inflammation might persist regardless of the absence of adequate decontamination. Interleukin-1 (IL-1) and TNF-α (Tumor necrosis factor alpha) are two cytokines associated with inflammation that are elevated over time and prolong the course of inflammatory reactions by promoting the growth of bacteria and endotoxins. If this pattern persists, the injury may become persistent and difficult to healing. This extended inflammation also causes an increase in matrix metalloproteases (MMPs), a kind of

protease that can damage the ECM. In conjunction with the elevated levels of protease content, there is a drop in the level of naturally produced inhibitors of protease.

## 2. The transition from acute wounds to chronic wounds: The role of macrophages

Healing requires and depends on inflammation since it is the immune system's reaction to external factors like bacteria or injured tissues of the host (MacLeod and Mansbridge, 2016). Early and late inflammation are the two phases of inflammation (Uluer et al., 2018; Gabriel et al., 2020). Neutrophils are drawn towards the injured site to clear it of pathogens, debris from cells and functionally inactive tissue as early inflammation is initiated (Edwards and Harding, 2004; MacLeod and Mansbridge, 2016; Uluer et al., 2018). Following neutrophils, invading monocytes undergo a process of differentiation into 'M1′ pro-inflammatory macrophages in response to PAMPs (Pathogen-associated molecular patterns), DAMPs (damage-associated molecular patterns), IL-2, IFN-β (Interferon beta), and TNF -α, associated molecular patterns. The main function of "M1″ macrophages, which have a strong phagocytic capacity, is to eliminate any potentially hazardous substances. IL-1, TNF- α, IL-6, IL-12, ROS, and MMP (Matrix metalloproteases) are among the cytokines that are released which contribute to inflammation (Edwards and Harding, 2004; Hesketh et al., 2017; Krzyszczyk et al., 2018). The production of ROS is a method for eliminating microbes, but when inflammation becomes unmanageable, it may also damage the ECM directly and hasten the senescence of cells (Dunnill et al., 2017). The process of infiltration of pro-healing cells and factors is made possible by the degradation of the damaged ECM by MMPs. In chronic wounds, it is believed that high levels of MMPs contribute to the hindering and delaying of the wound healing procedure. This is due to the intricate equilibrium that exists between tissue inhibitors of metalloproteinases (TIMPS), which act as MMPs' inhibitors (Edwards and Harding, 2004; Krzyszczyk et al., 2018).

Once the inflammation has subsided and the wound has been cleaned of contamination, healing advances onto the proliferative stage, when granulation tissue is developed. To re-epithelialize the wound, keratinocytes begin to multiply and move over the wound bed. Subsequently, they undergo a transformation into an anti-inflammatory phenotype (M2), which is required for normal wound healing to transition from proliferation to inflammation (Sharma et al., 2022). Since 'M1′ macrophages continue to exist without transitioning to the 'M2′ phenotype, pro-inflammatory cytokines generated by 'M1′ macrophages are released at a high rate, and the clearance of exhausted neutrophils slows down, and a chronic injury tends to stall at this stage (Fig. 3).

## 3. Pathophysiology of chronic wounds

The projected risks of diabetes and age-related nonhealing chronic wounds keep increasing substantially. It's significant to note that almost all chronic wounds start as small traumatic injuries. In individuals with underlying medical conditions, such as diabetes-induced neuropathy and nondiabetic neuropathies, deep wounds, bites by insects, or even just small cuts of skin that is dry which would typically recover within a matter of days or weeks, might result in the establishment of a nonhealing lesion (Shai and Halevy, 2005). Chronic wounds frequently cease healing during the inflammation stage. Even though their aetiologies differ at the molecular level, chronic wounds have some characteristics in common. These characteristics include an abundance of cytokines that promote inflammation, proteases, reactive oxygen species, the presence of chronic infection, an insufficient number of stem cells that are frequently dysfunctional, as well as a substantial number of cells that are senescent (FrykbergRobert, 2015).

The three main kinds of chronic wounds are pressure ulcers, vascular ulcers, and diabetic foot ulcers (DFU) (Piipponen et al., 2020). All four phases of skin damage recovery are impacted by diabetes (Bagheri et al., 2020). Due to the overexpression of inflammatory cytokines like TNF- α and the diminished synthesis of pro-healing mediators like IL-10 and

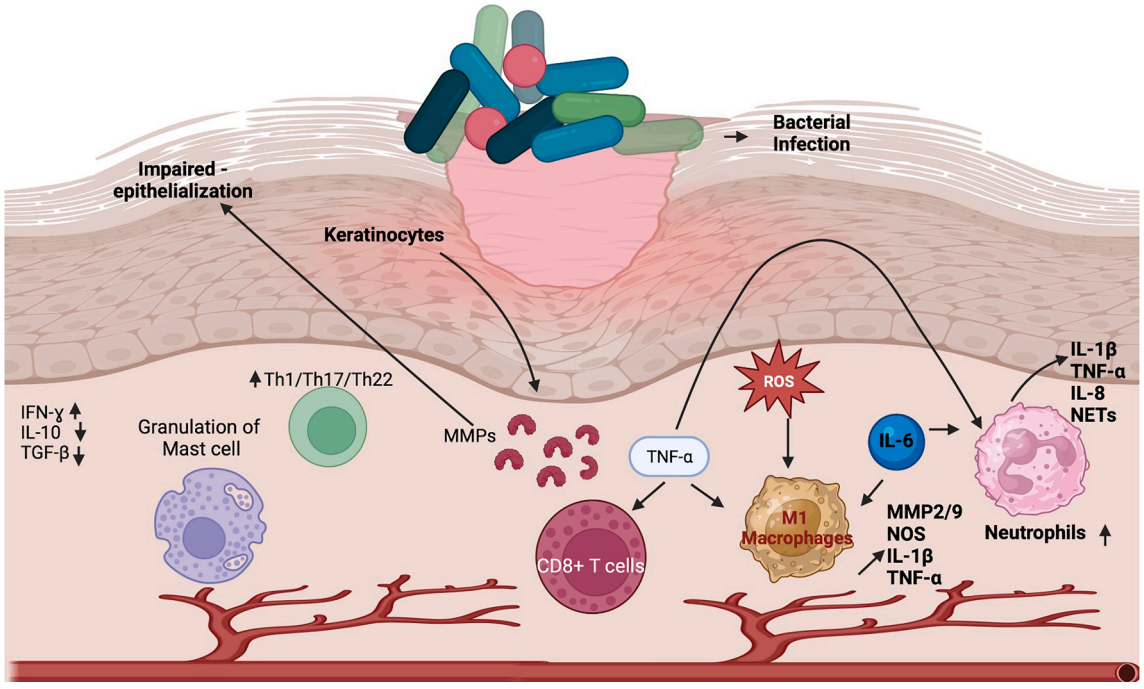


**Fig. 3.** Role of immune system in chronic wound healing. Recurrent bacterial infections, poor angiogenesis, deteriorating epithelialization, and an excess of ROS are all characteristics of chronic wounds. The extended distribution of neutrophils as well as M1 macrophages in the wound results in a highly inflammatory phenotype. Mast cell activation and CD8 + T cell activity both facilitate the process. Th1, Th17, and Th22 inflammatory T cell subtype levels are also elevated. Keratinocytes release a number of MMPs, which lead to improper re-epithelialization. Collectively, such pathological events induce tissue fibrosis, inflammation, as well as inadequate vascularization.

TGF- β, diabetic ulcers have a vehemently pro-inflammatory character which is maintained by T cells. As a result, $CD8^+$ T lymphocytes are activated and degranulate, which causes subsequent tissue necrosis as well as macrophage polarisation concerning the M1 phenotype (Seraphim et al., 2020). Myeloid cellular populations including macrophages, neutrophils, and also monocytes that are in the late stages of inflammation remain around for an extended period of time during chronic wound healing. On the other hand, as the process continues, the proportion of Langerhans cells, dermal dendritic cells, and eosinophils decreases (Joshi et al., 2020). Chronic wound formation also involves mast cells. In diabetic ulcers, epidermal mast cell populations degranulate, and the activity of these cells is downregulated, which speeds up wound healing (Dong et al., 2020). Chronic inflammation has an elevated level of expression of the CXCR3 ligand (Chemokine receptor), particularly present in Th1 (T helper) cells. Aside from that, individuals with diabetic ulcers have higher levels of inflammatory T cell subtypes such Th1, Th17, and Th22 (Strang et al., 2020).

Through the production of numerous signalling molecules, cells of the immune system constantly interact with non-hematopoietic cells, for example, keratinocytes (Piipponen et al., 2020). Keratinocytes plays a vital role in the development of chronic wounds, albeit the specific process is not entirely known. It is well established that keratinocytes' defective regulation of certain miRNAs, including miR-34a/c, miR-203, miR-19a/b, and miR-20a, affects immunological processes and delays the healing of cutaneous wounds (Yuan et al., 2019; Wu et al., 2020; Li et al., 2021). Accordingly, the activation of the NF- κB pathway caused a delay in wound healing and an elevated level of inflammation in mice, which led to an upregulation of chemokines and cytokines that promote inflammation in keratinocytes (Li et al., 2021). The development of chronic wounds is also controlled epigenetically by miRNAs that govern inflammatory responses by modulating signalling pathways such as Wnt/-catenin, NFκ-B, PI3K/Akt/mTOR, TGF-/Smad, and VEGF (Nie et al., 2020). Due to increased IL-36, TGF- β, as well as CXCL1 (chemokine (C-X-C motif) ligand 1) production, excessive neutrophil including macrophage rate of infiltration and abnormal tissue granulation growth and development, mice lacking the IL-36 receptor antagonist exhibited delayed wound healing (Saito et al., 2020). Furthermore, diabetes mellitus-related chronic wounds are adversely impacted by the chemokine receptor CCR4. IL-6, IL-12, IL-1, TNF- α, and IL-10 expression were decreased in CCR4-depleted diabetic mice, and these cytokines all aid in wound healing (Barros et al., 2019). In a different investigation, it was shown that DFU (diabetic foot ulcer) patients had poor control over the transcription factors FOXM1(forkhead box protein M1) and STAT3 (Signal transducer and activator of transcription). The growth of neutrophils and macrophages as well as their migration to the microenvironments of diabetic wounds are mediated by FOXM1 and STAT3. MMP is yet another aspect that promotes a prolongation of wound healing (Dissemond et al., 2020). MMPs are secreted by cells in the wounded region throughout the course of normal wound healing, including fibroblasts, keratinocytes, and immune cells. TGF- β, VEGF, EGF, interleukins, and interferons are a few of the growth factors as well as cytokines that play a role in wound healing among these mediators (Goldberg and Diegelmann, 2020). MMPs are essential for appropriate epithelization and cell proliferation and are often only needed in minimal amounts. Their abnormal functioning, impairs epithelialization and is significantly linked to wounds that are difficult to heal (Kaur et al., 2020). As a result, delayed ulcer healing in diabetic patients has been associated with elevated MMP-9 production by activated neutrophils (Nguyen et al., 2018).

Microbes and platelet-derived substances, including transforming growth factor (TGF) or Extra Cellular Matrix fragment molecules, promote the continuous inflow of cells from the immune system as a result of constant tissue damage; as a consequence, the chain of cytokines that promote inflammation, intensifies and lasts for a long time, resulting in increased amounts of proteases. Protease levels in chronic injuries are higher than those of their corresponding inhibitors, which causes ECM degradation and the breakdown of growth mediators including its receptors. In addition to preventing the wound from progressing towards the phase of proliferation, the breakdown of proteins in ECM also draws additional inflammatory cells into the area, hence accelerating the inflammation cycle (McCarty and Percival, 2013). However, the inflammatory factors and insufficient supply of oxygen in chronic wounds promotes the production of ROS, endangering proteins in the ECM therefore results in cell damage. Proteases and cytokines that cause inflammation are subsequently activated by this series of events (Schreml et al., 2010). Mesenchymal stem cells (MSCs) have been demonstrated to be crucial for wound healing (Ennis et al., 2013). When there has been a wound, these stem cells may be drawn towards the bloodstream, then integrate onto the remodelling microvasculature. The deficiency and dysfunction of stem cells have been demonstrated in human beings as well as animals with diabetes and chronic wounds. For these individuals to get around this limitation and accomplish the healing of their wounds, the immediate transfer of functional MSCs from donors who are healthy might be recommended (Rodriguez-Menocal et al., 2012; Cianfarani et al., 2013; Shil and Peterson, 2013). In general, chronic wound healing happens when the body's immune system is unable to undergo the regular healing process, leading to an extended accumulation of neutrophils as well as pro-inflammatory macrophages within the wounded area, that encourages inflammation, tissue fibrosis, and inadequate blood flow.

## 4. Biofilms in chronic wound

Chronic wound treatment is still a challenge since it is extremely complicated to reduce the persistent inflammation in chronic wounds. After a skin injury, microorganisms that are typically only present on the skin's surface may enter the deeper tissues. Infection within the incision is the root of persistent inflammation. Invasive infection is the presence of organisms that may proliferate inside a wound and cause harm to the host, and this infection has a significant role in the leisure recovery of chronic wounds (Schilrreff and Alexiev, 2022). A condition that is moist and nutrient-rich for bacterial colonisation and growth is provided by the high levels of discharge that are present in chronic wounds. Additionally, the presence of germs and endotoxins worsens the inflammatory response (Versey et al., 2021). Gram-positive bacteria, like *Staphylococcus aureus*, prevail in the initial stages of chronic wounds, while Gram-negative bacteria, such as *Pseudomonas aeruginosa,* dominate in the later stages (Cardona and Wilson, 2015). Additionally, the bacteria that are present in the site of the injury and the captivated inflammatory cells both create a variety of proteases, especially MMPs, which break down the growth factors and ECM that are present (James et al., 2008). Despite the fact that chronic skin wounds receive a lot of oxygen, anaerobic bacteria are nonetheless prevalent in the wound area. Curiously, the conventional commensal bacteria *Corynebacterium* is found in high concentrations in chronic injuries.

A biofilm may develop in the event that the bacterial infection fails to be promptly managed. Exopolysaccharide matrix is secreted during biofilm development and has the ability to safeguard bacteria against antibiotics as well as the body's immune system. The number of inflammatory mediators disproportionately rises in the existence of bacteria as well as endotoxins, leading the wound into an endless cycle of inflammation (Malone-Povolny et al., 2019; Xu et al., 2021). Inflammatory cytokines including TNF- α and IL-6, as well as MMPs, are accumulated as a result of biofilms' activation of pro-inflammatory macrophages and neutrophils and their interaction with the immune system of the host (Fig. 4). This promotes persistent inflammation (Wu et al., 2019).

The fact that there are numerous species of microbes (polymicrobial biofilm) present, limited permeability of antimicrobial agent, especially the quick emergence of resistance to antibiotics within biofilm bacteria, among other difficulties, make it exceedingly difficult to effectively eradicate biofilms (Omar et al., 2017). Antibiotic resistance, which

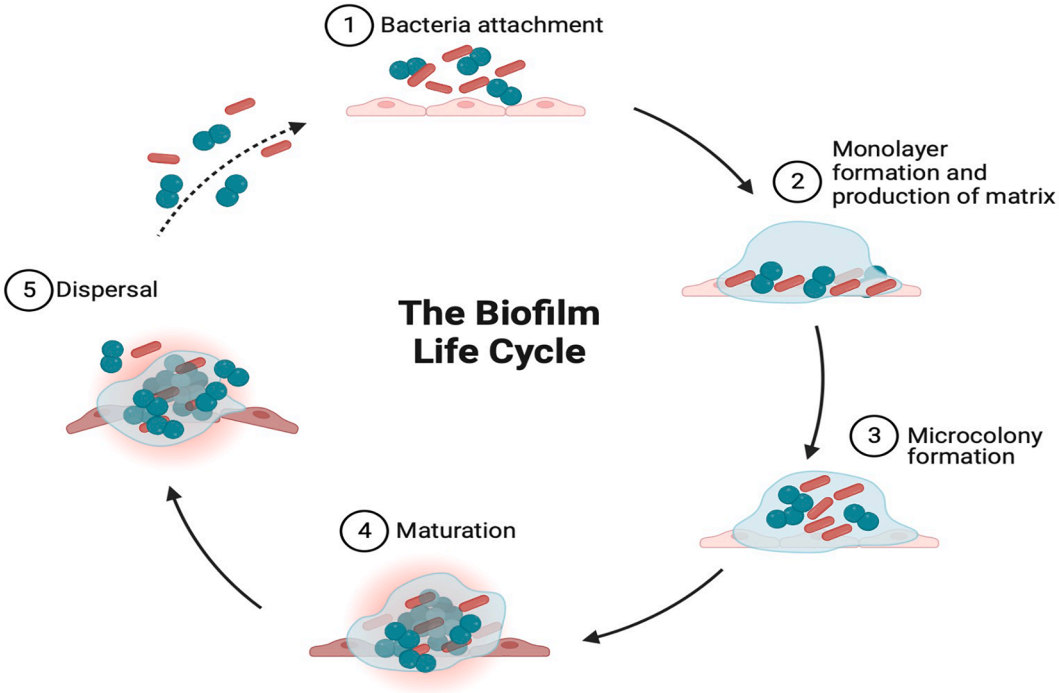


**Fig. 4.** The formation and growth of biofilms.

becomes a significant public health concern, is particularly facilitated by the presence of a variety of microorganisms in biofilms, particularly in chronic wounds. A variety of techniques utilizing bioactive substances have been proposed to accelerate the recovery process for persistent wounds, and preclinical experiments have shown encouraging results (Raziveva et al., 2021).

### 4.1. *Quorum sensing*

A crucial step in the development of biofilms and the display of their unique characteristics is quorum sensing (QS). Numerous bacterial species have been shown to possess quorum sensing molecules known as autoinducers (AIs), having different molecules acting as quorum sensors according to the individual species. AIs may be categorised into a wide variety of groups. N-acylhomoserine lactones (AHLs) released from Gram-negative bacteria have received the greatest attention (Diggle et al., 2002). Additionally, it appears that most Gram-positive bacteria develop short peptides and a group of compounds known as AI-2, the structures of which have remained unknown (Antunes and Ferreira, 2009; Kleerebezem et al., 1997). These AIs are tiny compounds that are generated at a constant rate in bacterial cells, irrespective of their kind. Several of the aforementioned AIs may effortlessly pass through the membranes of bacteria, in which instance their internal concentration is similar to the ambient level. The effective concentration of AI rises as the population of bacteria in a region (microcolony) increases. A multitude of alterations in gene expression are induced by AIs once their intracellular concentration reaches a threshold level. Along with other modifications, this causes the characteristics of a biofilm.

*Staphylococcus aureus* and *Pseudomonas aeruginosa* are two of the bacterial species that have been the subject of the most extensive research into quorum sensing; they are also frequently found in chronic wounds. The quorum sensing method used by *S. aureus* and other Gram-positive bacteria has been used as a paradigm for peptide-based quorum sensing (Novick and Geisinger, 2008). Autoinducing peptides (AIPs), which are encoded by the agr locus, are responsible for this species' quorum sensing. Several other virulence factors, like as biofilm development, are also regulated by the same locus (Kong et al., 2006; Vuong et al., 2000). Similar to this, *P. aeruginosa's* quorum sensing systems have also received an enormous amount of attention. It has also been shown that several of the virulence components associated with this chronic wound coloniser, which includes released virulence factors like proteases, factors that are attached to the cells like lipopolysaccharide, as well as biofilm development, are regulated by quorum sensing pathways (Fig. 5) (Lyczak et al., 2000). In this organism, quorum sensing affects the formation of biofilms very early on, since quorum sensing mutants are unable to produce biofilms with the expected structural characteristics. Investigators have examined the QS system in vivo and discovered that cystic fibrosis patients who had *P. aeruginosa* colonisation had significantly increased amount of autoinducer molecules (Keays et al., 2009).

There are several factors that contribute to biofilms' resistance to antimicrobial treatment. The penetration of antibiotics in biofilms has decreased, and certain negatively charged antimicrobial chemicals are repelled by the negatively charged exopolymer. The treatment of chronic wounds with biofilm is challenging because certain bacteria also emit antibiotic sequestering compounds. Due to their extremely organised and condensely packed structure, biofilms enhance the likelihood that bacteria of the same species or other species would horizontally transfer genes associated with antibiotic resistance to one another. Acquiring these genes causes the bacteria to undergo permanent genotypic alterations, which raises the risk of severe and chronic infections. Once the antibiotic medication is stopped, the biofilm might start growing again and can even renew itself, as was shown by the cell population which survived in extreme conditions (James et al., 2008; Clinton and Carter, 2015).

### 4.2. *Pseudomonas aeruginosa and Staphylococcus aureus in chronic wounds*

*Staphylococcus aureus, Pseudomonas aeruginosa, E. coli, Acinetobacter spp.*, coagulase-negative *Staphylococcus epidermidis*, and *Staphylococcus lugdunensis* are typically the organisms that are causing skin infections. In addition to hemolysins, metalloproteases, and hyaluronidase, these bacteria also generate several other virulence-related factors. Patients with chronic wounds that tested positive for *Staphylococcus aureus* and *Pseudomonas aeruginosa* have respective infection rates of 93.5 % and

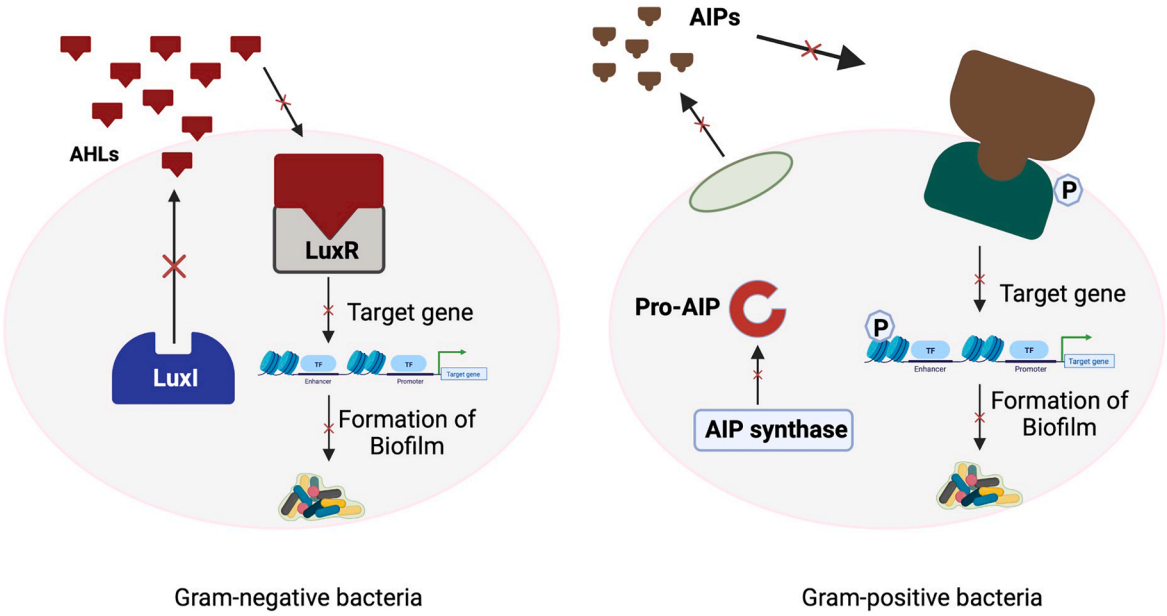


**Fig. 5.** Quorum sensing system/mechanism of Gram positive bacteria and Gram negative bacteria.

52.2 % (Gui et al., 2014; Serra et al., 2015; Jeyanthi and Velusamy, 2016). *Pseudomonas aeruginosa* is discovered to be connected with deeper parts of the wound, whereas *Staphylococcus aureus* is mainly seen invading the top layer (Serra et al., 2015). The release of inflammatory cytokines results in tissue damage when the bacterial threshold of $10^5$ bacteria per gram of tissue is reached (Arya et al., 2014; Haji Zaine et al., 2014). In this approach, bacterial infections lead to the chronic condition of the wound. *Staphylococcus aureus* cannot produce robust biofilms on its own, but when it co-infects with *Pseudomonas aeruginosa*, a robust infectious cluster is formed that worsens the lesion and slows the process of healing (Das and Singh, 2018).

MMPs, or matrix metalloproteases, are thought to be crucial in the process of healing wounds because they play a significant role in inflammatory reactions. The ECM is degraded by MMPs, which facilitates the movement of cells from the immune system from the circulation to the site of inflammation. MMPs are initially released as zymogen, an inactive form that is eventually changed into an active form (Serra et al., 2015). The activation of many MMPs that induce damage to tissues due to haemorrhage and cell death in the area of the wound as a result of *Pseudomonas aeruginosa* synthesising the enzyme elastase, however, increases the degree of severity of the wound and delays healing. Nevertheless, *Pseudomonas aeruginosa* generates an enzyme called elastase, that changes MMPs from their inactive form zymogen, to their active form. The resulting activation of MMPs causes damage to the tissues due to haemorrhage and cellular death in the area of injury, aggravating the wound and hindering the healing process. Laminin and type IV collagen are broken down by overactive MMPs, which damages tissue by altering capillaries, destroying membranes, and laminin (Beaufort et al., 2013). Additionally, *Staphylococcus aureus* exacerbates the stimulation of many MMPs and results in swollen lesions that are brought on by infiltration of neutrophil. In order to break the cell membrane connections of the host and cause necrosis of both the epidermal and dermal layers of the skin, *Staphylococcus aureus* secretes alpha-hemolysin, which communicates with disintegrin along with the metalloproteinase region of protein-10 (Nishifuii et al., 2008; Wilke and Wardenburg, 2010; Kim et al., 2014).

### 4.3. Quorum sensing system impediment and drawbacks

Antibiotics are administered together with rigorous tissue debridement to remove biofilms from chronic wounds. Anti-biofilm treatment is being used more often to treat chronic wounds (Omar et al., 2017). To undermine the integrity of the biofilm and speed up the healing process of wounds, a number of targets were specifically targeted. The bacterial QS system is crucial for the development of biofilms in chronic wounds and hence offers a key target for anti-biofilm treatment (Kalia and Kumar, 2014; Kumar et al., 2014). Since the QS system depends on autoinducer chemicals for signalling, preventing them would prevent synchronised virulence action. Both Gram-positive as well as Gram-negative bacteria have different QS systems. Autoinducer-1 as well as furanone-based signalling systems are found in Gram-negative bacteria, whereas oligopeptide as well as furanone-based systems are found in Gram-positive bacteria. In addition to these, bacteria also have the Pseudomonas quinolone signal (PQS), diffusible signal factor (DSF), and autoinducer-3 (AI-3) systems. Although the essential supply of signal and response phases have been retained in all QS systems, there are two primary kinds of QS inhibitors (QSI): those that block signal supply and those that block signal response (Rutherford and Bassler, 2012; LaSarre and Federle, 2013). Enzymatically cleaving QS signal molecules in order to prevent them from functioning is a process known as quorum quenching. AHL acylases as well as lactonases, which break the homoserine lactone rings and amide bonds of the AHL molecule, are two examples of how AHL may be degraded. AHL oxidase and AHL reductase are two more enzymes that alter the activity of the AHL molecule rather than cleaving it. Bacterial species, such as *P. aeruginosa*, *Acinetobacter spp*., as well as *Klebsiella pneumonia*, are mostly found in bacterial biofilms around persistent wounds, produce and release AHL-degrading enzymes (Koul et al., 2016; Koul and Kalia, 2017). Antibiotic-resistant bacteria can be found in biofilms, hence QS inhibition can be used as a replacement for antibiotics. QSIs prevent the generation of virulence factors that are controlled by sensing without impeding the growth of bacteria. Therefore, microorganisms that do not exhibit resistance to antibiotics can be eliminated by the immune system (Brackman and Coenye, 2015).

According to Abbas and Shaldam (2016), Glyceryl trinitrate (GTN), an FDA-approved drug, was tested for its capacity to prevent the development of QS-based biofilms in *P. aeruginosa* burn infections. Pyocyanin and protease synthesis were decreased in conjunction with the formation of the QS molecule violacein. Inhibiting the development and functioning of biofilms is made possible by the fact that it prevents autoinducers from attaching to their receptors. When QS is inhibited, it can sometimes enhance the colonisation of more virulent wild type bacteria while eliminating the less virulent mutant strains, leading to an

increase in the predominance of pathogenic genotypes in infections that occur in hospitals. Therefore, QS inhibitors need to be utilised with caution, since their inappropriate usage might result in the generation of QS inhibitor resistance bacteria, worsening biofilm induced pathogenicity (Kalia, 2013; Garcia-Contreras, 2016).

## 5. Utilization of natural therapeutics for mending wounds

The healing process for wounds requires an intricate hierarchy of structured biochemical and cellular processes in order to repair the structural integrity of the epidermis as well as the tissue beneath. Despite the fact that numerous synthetic compounds are being explored and assessed for their ability to speed up the recovery process, they have inevitable downsides, such as increased toxicity to cells and greater likelihood of bacterial tolerance. Plant extracts and plant-based ingredients have been recognized as potential substitutes for commercial wound rehabilitation treatments because they include a wide range of active components that are easily accessible and have fewer negative effects. Natural substances with antioxidant, anti-inflammatory, antimicrobial, and pro-collagen production activities have been shown in various investigations to have a potential to promote healing of wounds (Thakur et al., 2011) (Fig. 6). The impact of each biologically active substance on wound healing may vary. The following part emphasizes the use of a number of meticulously selected natural compounds that have been effectively managed wound care for many years in the wound healing process.

### 5.1. Honey

Honey is a carbohydrate-oversaturated fluid formed immediately following the digestion of nectar that was gathered from flowers and then retained in the hive's cells. It is a naturally occurring antibiotic effective against biofilms of bacteria as well as resistant pathogens (Minden and Bowlin, 2018). Honey's high osmolality, acid content, along with glucose oxidase concentration account for its antibacterial properties (Hixon et al., 2019). Furthermore, it was recently discovered that honey works well against the bacterial biofilm, which is characterized as an accumulation of colonies of bacteria at the site of injury that jeopardize the normal process of healing since the bacteria evolve into 1000 times harder to eradicate (Majtan et al., 2020). Due to its ability to reduce inflammation and function as an antioxidant, honey is a potential therapy for wounds (Iacopetti et al., 2020). As a result of scavenging free radicals and acting as a vasoconstrictor, it suppresses the production of prostaglandin and minimizes inflammation, and fluid exudate in wounds (Cushine and Lamb, 2005). Honey improves epithelial development, which speeds up the process of healing as well as regeneration of tissue (Jull et al., 2013).

### 5.2. Aloe vera

The ancient Egyptians, Romans, and native peoples of Africa, Asia, along with the Americans have all utilized aloe vera as a primary treatment for burns, ulcers, and surgical injuries for more than 5000 years (Garcia-Orue et al., 2017). The various natural bioactive compounds included in this plant include phytol, pyrocatechol, saponins, acemannan, anthraquinones, glycosides, oleic acid, along with simple and complex water-soluble polysaccharides (Salehi et al., 2018). In accordance with (Nejatzadeh-Barandozi, 2013), acetone extracts of aloe vera leaves have more antibacterial activity than alcohol and aqueous extracts. According to (Lawrence et al., 2009), Gram-positive bacteria seem to be more susceptible than Gram-negative bacteria. The chemicals that give the extract its antibacterial actions include saponins, acemannan, dihydroxy-anthraquinones, and anthraquinone derivatives (Martinez-Romero et al., 2006).

Furthermore, the bioactive ingredients like aloe and aloe-emodin present in the gel are in charge of the beneficial anti-inflammatory properties, they also have an impact on FGF by promoting the growth and development of different kinds of cells, improve wound shrinkage and production of collagen, favours transport of oxygen, and improve the blood flow of the skin, and subsequently promote healing of wounds through numerous along with epithelial cell remodelling (Lordani et al., 2018).

### 5.3. Curcuma longa

Curcumin, a conventional alternative medicine with anti-

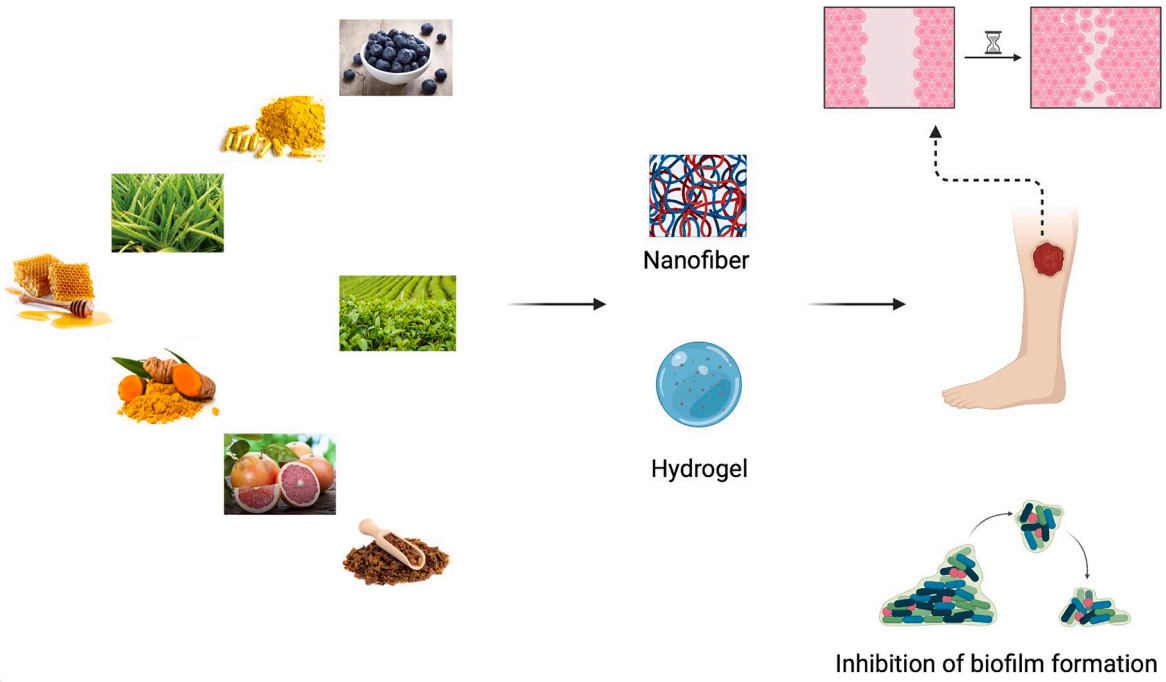


**Fig. 6.** Diagrammatic representation of the phytocompounds, that may result in enhanced wound healing and inhibits the formation of biofilm.

inflammatory and free-radical scavenging properties, has been shown to be an unique approach to promote quicker healing of wounds (Sidhu et al., 1998&1999). It is a naturally occurring polyphenolic antioxidant substance that was isolated from the rhizome of Curcuma longa, a plant in the ginger family that may have the ability to aid in the healing of wounds (Mohanty et al., 2012). Mohanty et al. (2012) formulated a polymeric bandage loaded with curcumin and oleic acid to increase the effectiveness of curcumin. Due to the effective free radical scavenging characteristics of curcumin and oleic acid bandages, biochemical metrics and histological analyses showed greater wound reduction and enhanced proliferation of cells by inhibiting inflammation via down-regulation of NF- κB pathway.

According to research by Joe et al. (2004) administration of polymeric bandages containing curcumin to rats drastically decreased the expression of antioxidant enzymes. This was due to a finding that curcumin decreased lipid peroxidation and hence decreased the need for antioxidant enzymes. Collagen with a high aldehyde content increased significantly. In addition to a rise in collagen levels, Panchatcharam et al. (2006) also noted an earlier maturity of collagen fibres. The two o-methoxyphenolic groups along with the ß-diketone moiety in the curcumin molecule facilitate the potent antioxidant action to diminish ROS throughout the inflammatory phase (Priyadharshini, 2014). Curcumin is the antioxidant that has been most extensively explored for use in wound healing because of its potent antioxidant activity. It was previously demonstrated that curcumin increases growth factor expression, particularly TGF-β1 expression, which encourages VEGF expression by activating the TGF- β pathway (Rujirachotiwal and Suttamanatwong, 2021). Additionally, curcumin can reduce inflammation by altering the levels of cytokines, specifically by stimulating IL-10 or suppressing IL-1 β, TNF- α, as well as MMP-9 (Shah and Amini-Nik, 2017; Makuch et al., 2021). A new curcumin-loaded hydrogel was recently described by (Liu et al., 2018) which was found to lessen oxidative damage and speed up the wound healing process.

### 5.4. Naringenin

A polyphenol known as naringenin, which is mostly present in citrus fruits, has remarkable biological effects including anti-inflammatory, antioxidant, cholesterol-lowering, and anticancer (Gattuso et al., 2007; Patel et al., 2018). Naringenin's impact on inflammatory reactions and the oxidative stress brought on by thermal burn-induced in rats was examined by (Al-Roujayee, 2017). The findings demonstrated that the activities of antioxidant enzymes are increased followed by the application of naringenin to the burn. In order to enhance the potential for wound healing, naringenin was also combined with other substances (such as chitosan).

After 14 days of therapy, Akrawi and colleagues demonstrated that Wistar rats' wound contraction was greatly accelerated by a nano emulsion, which is a combination of both naringenin and chitosan, and that naringenin also induced anti-inflammatory along with antioxidant benefits (Akrawi et al., 2020). These findings point to the possibility of using naringenin for the treatment of burn injuries considering its antioxidant properties.

### 5.5. Propolis

The bees' salivation of natural resins, particularly gathered from leaf shoots and fissures in the bark, results in propolis, a strong sticky resinous material (Martinotti and Ranzato, 2015). Propolis's composition varies substantially depending on the time of year and the type of flower it comes from, but it mostly consists of resins (about 50 %), wax (30 %), essential aromatic compounds (10 %), pollen (5 %), and miscellaneous materials (5 %) (Nina et al., 2015). The flavonoid composition of propolis—including, but not limited to, pinocembrin, galangin, and pinobanksin—gives it antimicrobial effects against Gram (+) and Gram(-) bacteria, protozoa, fungi, and viruses (Majtan et al., 2020). Quercetin and naringenin, two of the most common propolis components, increase the permeability of the membrane while decreasing the membrane's potential, making bacteria less susceptible to antibacterial treatments (Ibrahim and Alqurashi, 2022). Additionally, flavonoids in propolis decrease bacterial motility by inhibiting RNA polymerase (Cushnie et al., 2005).

One way that propolis uses its antioxidant potential is by trapping free radicals (Eriksson et al., 2022). Additionally, propolis demonstrated anti-inflammatory properties in both chronic and acute inflammation models. According to (Rossi et al., 2002), the abundance of carvacrol in propolis causes it to inhibit cyclooxygenase activity by acting in a concentration-dependent way. Through the modulation of ECM components, the production of collagen, and the regulation of transforming growth factor (TGF), propolis enhances skin cell proliferation, remodelling capacity, and induces re-epithelialization (Toreti et al., 2013).

### 5.6. Epigallocatechin gallate

In vitro studies have shown that catechins, which naturally occur as polyphenolic chemicals, have antioxidant, anti-inflammatory, and free radical scavenging activities. Epigallocatechin gallate (EGCG), among the main catechin isoforms, has been demonstrated to suppress infiltration of leukocyte, activity of myeloperoxidase, and also to minimise UV-B triggered erythema (Kapoor et al., 2004).

In order to better understand how the catechin epicatechin gallate (ECG) influences the development of scars, Kapoor and his colleagues used a wound healing rat model. The degree of scar formation, as measured by the collagen fibres' maturity and orientation, significantly improved, according to the ECG. The group that had ECG treatment showed increased iNOS and COX-2 levels, which also resulted in the rise of formation of new blood vessels. This corresponded with VEGF protein levels, the most influential protein responsible for angiogenesis.

### 5.7. Berberine

In a study carried out by Zhou et al. (2021), it was determined how berberine, affected diabetic wounds in streptozotocin induced diabetic rat models and a hyperglycaemia promoted cell model. It was also determined how berberine affected TrxR1 (thioredoxin reductase 1). Berberine therapy significantly decreased hyperglycaemia induced HaCaT cell damage, improved extracellular matrix formation, and considerably expedited the healing process. Additional research revealed that berberine stimulated TrxR1, inhibited subsequent JNK signalling, which prevented the development of oxidative stress and cell death, supported proliferation of cells, suppressed matrix metalloproteinase 9, elevated the transforming growth factor-β1, and tissue-associated inhibitors of MMP 1, which expedited up the healing process.

### 5.8. Gallic acid

Gallic acid (GA) is a phenolic acid which is found in most of the plants. In human keratinocytes and fibroblasts, (Yang et al., 2016) investigated the effects of gallic acid on the healing of wounds in healthy and hyperglucidic circumstances to imitate diabetes. As a result of their investigation, it is possible that GA functions as an antioxidant by enhancing the level of expression of genes related to antioxidant. In both healthy and hyperglucidic situations, GA accelerated the spread of keratinocytes and fibroblasts. The positive effects of GA on wound repair are further supported by the activation of molecules known to be essential for wound healing, including focal adhesion kinases (FAK), c-Jun N-terminal kinases (JNK), as well as extracellular signal-regulated kinases (Erk).

### 5.9. Resveratrol

The dietary polyphenol resveratrol, which is abundant in red wine

and grapes, is renowned for exhibiting anti-oxidant properties. In a research conducted by Zhou et al. (2021), they showed that oxidative stress had an impact on HUVEC proliferation as well as migration and that resveratrol pre-treatment assisted in reversing this effect. The expression of Nrf2 (nuclear factor erythroid 2–related factor 2) and Mn-SOD (Manganese Superoxide Dismutase) was increased in *in vivo* wound healing experiment, which further demonstrated improved wound healing by reducing oxidative stress damage.

Liu et al. (2021) revealed that Resveratrol reduced the decreased viability and increased apoptosis caused by LPS (Lipopolysaccharides), while simultaneously increasing the expression of miR-212, which is important for cell proliferation. The miR-212/CASP8 axis was controlled by resveratrol in a mouse model to accelerate wound healing.

## 6. Difficulties in the delivery of traditional herbal remedies for wound healing

The herbal medicines, as described in conventional or complementary therapies aimed at promoting the healing, primarily consists of plant components or unprocessed extracts of plant-based substances, in which the chemical compounds that are present in the plant might function effectively together or may have unclaimed effects on consumers. The availability of treatments for many ailments, cheap expenditure, as well as lack of harmful side effects of these products are all factors contributing to the current rise of herbal-based research. Additionally, the profitable marketing techniques draw consumers of all ages to utilize herbal medications as alternatives to prescription drugs (Ekor, 2014).

The widespread belief that herbal products are generally safe and won't have any negative side effects isn't always accurate. Several herbal ingredients have been demonstrated to induce significant adverse effects that might result in fatal illnesses, according to a considerable amount of literature (Cosyns et al., 1999; Ernst, 2002; Phua et al., 2009; Oyedepo and Palai, 2021). Tachypnoea, vomiting, tinnitus, and the characteristic acid/base imbalance were the symptoms of salicylism in cases caused by transcutaneous penetration and absorption of methyl salicylate from the herbal product following topical treatment at atypical patches of skin (Bell and Duggin, 2002). Additionally, it has been documented that topical use of ancient Chinese medicines can lead to toxic exposure to heavy metals (Wu et al., 2013). Unreported medications in the herbal supplement may potentially be to blame for toxic symptoms in alongside hazardous heavy metals (Ernst, 2002). As a result, research on polyherbal compounds is carried out over the globe and emphasizes the safety issues (Ishtiaq et al., 2017; Chen et al., 2018; Kumar et al., 2018b; Liyanagamage et al., 2020). In this regard, it is crucial to isolate the medicinal plant extract's pure constituent that is contributing to its curative potential and assess its effectiveness.

The effectiveness of herbal treatments, on the contrary, relies on when they get to the area of action. Whereas lower doses may not be beneficial and larger concentrations may result in hazardous symptoms, the ideal medication concentration might offer the most therapeutic benefit. When a medicinal substance is administered orally, many of its ingredients either degrade within the gastrointestinal conditions or go through a breaking down process while being absorbed via the portal vein. Additionally, for the potential use of therapeutics, improved delivery tools are required due to the lack of solubility of medicinal plant components, the requirement for a substantial dosage for efficiency, generalized delivery, and failure to comply with patients due to elevated dosage and inadequate effectiveness (Ansari et al., 2012). There is an increasing need for a multidisciplinary strategy in distributing medicinal products from plant origin to the illness target for higher efficacy in order to minimize these negative effects of herbal components. Additionally, new technologies are being developed for herbal therapeutics that regulate pharmacokinetic characteristics in order to enhance bioavailability, target delivery to maximize therapeutic effect, strengthen their stability as well as protection towards chemical and physical declination, have a extended or regulated release, and have diminished immunogenicity and non-specific toxicity alongside enhanced bio-recognition and potency (Devi et al., 2010). The restrictions could potentially be circumvented by adapting multidisciplinary delivery methods for the distribution of herbal compounds. The unique methods for administering the above mentioned natural compounds to improve wound healing as well as to eradicate the bacterial biofilms are covered in the part of the article that follows.

### 6.1. Novel therapeutic delivery techniques for enhancing wound healing

To enhance therapeutic outcomes, patient adherence, and reduce side effects, advanced medication delivery techniques are being used to treat wounds. The plant-based compounds can be nanosized or included in nanostructures to increase the effectiveness of plant-based therapies for managing chronic wounds (Madhyastha et al., 2023). According to (Mordorski and Prow, 2016), nanomaterials have the distinctive properties of being small at the nanoscale and having an elevated area of surface to volume ratio.

While the controlled release properties of the nanocarriers would deliver the therapies for an extended amount of time, the nanoscaled size promotes intracellular absorption as well as the penetration of drugs into the wounded site (Hamdan et al., 2017). For effective administration of phytochemicals, a variety of cutting-edge drug delivery technologies have been developed, including nanofibers, nanoparticles, nanoemulsion, as well as nanogels.

### 6.2. Limitations of various methods in preparing nanofibers

Nanofibers are precisely developed fibers possessing a diameter of no more than one micron. Nanofiber made up of biopolymer compositions might be used as cell growth scaffolds. Furthermore, other biologically active materials, including as growth stimulating factors (Sahoo et al., 2010; Xie et al., 2013), can be included during the fabrication of nanofiber scaffolds. Drawing, template synthesis, freeze drying, phase separation, self-assembly, and electrospinning are all possible methods for developing 3D permeable scaffolds that replicate the composition and biological effects of natural ECM (Nune et al., 2017).

Drawing

It only works with materials that are viscoelastic and is dependent on the ejection mould's aperture size, making it challenging to develop fibres with diameters less than 100 nm.

Template synthesis

It is incapable of synthesizing lengthy uninterrupted nanofibers.

Freeze drying

It is impossible to achieve homogeneous porosity in the material.

Self-assembly

Due to its limits, that are confined to a few polymers, long uninterrupted fibres are incapable of being generated. The expensive cost of biomaterial manufacturing has limited their applicability; optimized peptide nanofibers can be disintegrated making them susceptible to endocytosis.

Phase separation

Extended uninterrupted fibres cannot be developed; only a few polymers are obtainable.

Electrospinning

It can be challenging to develop an enormous amount of scaffold.

### 6.3. Limitations in preparing nanogels

Hydrogels are innovative delivery systems for drugs that have been under consideration since the beginning of the 1960 s. The first type of hydrophobic gel proposed by Wichterle and Lim consisted of cross-linked hydroxyethyl methacrylate (HEMA) hydrogels, which were designed for biological purposes (Hoffman, 2002; Hamidi et al., 2008). The potential for biological compatibility, hydrophilicity, controlled release of drugs, sophisticated drug delivery, and other benefits of hydrogels are only a few of their numerous benefits. Each type of polymer that is used to make hydrogels may have advantages and disadvantages, thus it is important to choose the right one for the application and intended location of drug administration. There are some limitations of hydrogels as drug delivery systems and they are mentioned below (Ghasemiyeh et al., 2019):

- When hydrogels expand, there is a sudden burst of drug release, and large porous hydrogels release drugs rapidly.
- In diffusion-controlled release hydrogels, the drug releasing mechanism is non-specific.
- Injecting hydrogels that are both temperature and pH sensitive might cause needle obstruction.
- Inadequacy and appropriateness as a carrier for small molecular weight as well as hydrophobic active medications.
- Limited capacity for transgenic expression for the primary purpose of delivering genes along with inadequate DNA or RNA loading capacity in hydrogel networks.

### 6.4. Administration and delivery of nanofibers for wound healing

Nanofibers have gained increased importance in today's society as a result of their widespread application in the medical sector, tissue engineering, and other drug delivery systems (Kapahi et al., 2015). According to (Jeckson et al., 2021b; Kenry and Lim, 2017), the dimensions of nanofibers range from a few 10 to 1000 nm. Biodegradable hydrophobic, hydrophilic, as well as amphiphilic polymers are among the distinctive polymers employed in the manufacture of nanofibers. Gelatin, dextran, nylon, polystyrene, polyacrylonitrile, poly(vinyl pyrrolidone), poly(-caprolactone), polycarbonate, polyimides, polyvinyl alcohol (PVA), polybenzimidazole, and others are among the most commonly utilized polymers for the production of nanofibers.

To achieve immediate drug release, a suitable polymer with a higher surface-to-volume proportion and nanofiber network with larger porosity is used (Jeckson et al., 2021a). To increase the amount of drug release from the manufactured nanofibers, swollen or biodegradable polymers are also used (Kajdic et al., 2019). Therefore, altering the chemical composition of the polymer has a big impact on how quickly drugs are delivered using a comparable delivery mechanism (Kajdic et al., 2019). Molecular assembly, thermally induced phase separation, as well as electrospinning technologies may all be utilized to generate delivery systems for nanofiber formulations, with the latter way being the most popular (Kapahi et al., 2015).

Isfandiary et al. (2017) investigated the application of aloe vera nanofiber within chitosan-collagen scaffolding, where it has demonstrated its efficacy and safety in the treatment of burn wounds. Elnaz et al. (2022) synthesized a nanofiber of polycaprolactone and polyethylene glycol 3:1 in ratio by incorporation naringenin using electrospinning, where the naringenin encapsulated nanofiber showed enhanced wound healing when compared to the nanofiber control group.

Due to their enhanced ability to heal wounds by combining the structural advantages of nanofibers with honey, honey-incorporated nanofibers are becoming more and more popular. In a research conducted by Arslan et al. (2014), different concentrations of polyethylene terephthalate (PET), PET/chitosan, PET/honey, and PET/chitosan/honey solutions were electrospun to produce fibrous mats. The findings demonstrated that HTCs-capsaicin as well as HTCs (honey/tripolyphosphate/chitosan)-Au-NPs were efficient in suppressing growth of bacteria when compared to HTCs, HTCs-capsaicin/Au-NP NFs, and antibiotics. MTT assay revealed that the mats made from nanofibrous increased cell growth above that of the untreated comparison group. Animal experiments demonstrated that the synthesized mats encouraged wound closure more efficiently compared to those in the control samples.

Electrospinning was used by Tang and colleagues to develop a honey/alginate/PVA nanofibrous membrane (Tang et al., 2019). In order to formulate an effective dressing for wounds, honey was added into an nanofibrous network made of alginate and PVA. They found that the honey content in the nanofibrous membranes' has a potential to control the excessive generation of reactive oxygen species and they were also demonstrated to possess6 antibacterial effect towards Gram-positive bacteria *S. aureus* and against Gram-negative *E. coli* bacteria utilizing a disc diffusion experiment and a dynamic contact analysis.

In 2021, Ghorbani et al. (2021) came up with gum tragacanth (GT) Nanofibers with honey incorporation for using it as a wound dressing mat. Additionally, the potential of the NFs to degrade was enhanced by increasing the honey content in the honey/ethylcellulose/gum tragacanth (EGH) Nanofibers. Additionally, the EGH Nanofiber mat with an increased honey concentration had improved mechanical properties, optimal cell growth, attachment, as well as proliferation, enhanced antioxidant capacity, and antibacterial activities. A series of cellulose acetate-hyaluronic acid (CA/HA) electrospun fibers infused with berberine (BBR) were developed using the electrospinning technique in a research by Ghorbani et al., to test their antibacterial effectiveness and potential for use as in vivo skin wound dressings. Rat in vivo tests revealed that the CA/HA/BBR dressing reduced the size of the wound as well as enhanced the healing capacity (>95 %) and collagen production with extended therapy. According to these findings, adding BBR to the dressing increased its bioactivity without impairing its physical attributes. As a result, nanostructured dressing consisting of CA/HA/BBR electrospun fibers is very effective at promoting tissue healing.

In a research conducted by Samadian et al. (2020), they developed a Cellulose Acetate/Gelatin (CA/Gel) electrically spun mat filled with berberine as a specifically designed dressing for diabetic foot ulcers. The wound healing efficiency of prefabricated dressings was tested and compared in diabetic rats treated with streptozotocin. In accordance with the antibacterial research, the dressings have a high antibacterial impact. In the animal studies, the thickness of collagen was $88.8 \pm 6.7$ % along with the angiogenic score of $19.8 \pm 3.8$ clearly indicated normal wound healing. These findings indicated that incorporating berberine did not impact the dressing's mechanical characteristics while improving its biological effects. In a study conducted by Cheng et al. (2020), they synthesized resveratrol-loaded hydroxypropyl-cyclodextrin (HPBCD) and polyvinylpyrrolidone (PVP) nanofibers using electrospinning. Results revealed that resveratrol nanofibers had a significantly higher (more than 20,000-fold) water solubility than the pure substance. Additionally, resveratrol nanofibers demonstrated strong antioxidant activity. Resveratrol found in nanofiber compositions permeated the skin more effectively than pure resveratrol. Additionally, in HaCaT keratinocytes, resveratrol nanofibers reduced the production of inflammation-associated proteins (COX-2 and MMP-9). As a result, resveratrol-loaded nanofibers can significantly increase both the solubility as well as physicochemical characteristics of resveratrol and could potentially be used as an anti-inflammatory and antioxidant product to apply topically.

### 6.5. Delivery of drug incorporated nanogels for healing of wounds

Nanogels are three-dimensional hydrogel substances in the nanoscale range of sizes that have a great capacity to retain water while actually releasing when exposed to the aqueous media. They are made of crosslinked swellable polymer networks. Nanohydrogels are hydrogels that release pharmaceuticals into organs, tissues, as well as cells via meshes that range in size from 5 nm to 100 nm while offering treatments that are between the sizes of 10 and 100 nm (Ozkan et al., 2019). A wide range of naturally existing polymers, manufactured polymers, or a combination of both can be encountered in nanogels. Researchers are interested in nanogels as drug carriers, particularly to assist the site- or time-dependent dispersion of pharmacological drugs. Nanogel preparations are accessible in a variety of useful forms due to the wide variety of polymer system types as well as the simple modification of their physical and chemical characteristics. Nanogels exhibit high degrees of stability, pharmaceutical integration potential, physiological reliability, permeability, and response to environmental signals (Soni et al., 2016).

The components of propolis have been effectively incorporated onto AgNP's surface by Patil et al. (2015). When evaluated against Staphylococcus aureus, the addition of propolis and AgNP together dramatically reduced the minimum inhibitory concentration of AgNP alone. When PLSN gel was compared to commercial silver sulfadiazine gel, burn wound repair in wistar rats exhibited similar findings. In an investigation conducted by Eskandarinia et al. (2020), a thick membrane made of polyurethane as well as an ethanol-based extract of propolis (PU/EEP) was electrospun with a polycaprolactone/gelatin (PCL/Gel) scaffolding. The PCL/Gel scaffold was employed as the sublayer to promote cell attachment as well as proliferation, while the PU/EEP membrane was utilized as the topmost layer to shield the wound region from contamination from outside and dryness. According to the zone of inhibition conducted, *Staphylococcus aureus* (5.4 ± 0.3 mm), *Escherichia coli* (1.9 ± 0.4 mm), and *Staphylococcus epidermidis* (1.0 ± 0.2 mm) all showed substantial anti-bacterial effect. Exceptional levels of biodegradable properties biological compatibility, as well as hydrophilicity (51.1 ± 4.9°) were displayed by the bilayer wound dressing. The wound healing process and the accumulation of collagen in the Wistar rat skin wound model may be greatly sped up by the PU/EEP-PCL/Gel bilayer wound dressing. The freezing-thawing cyclic technique was used to develop bio-nanocomposite hydrogel dressings for wounds made from egg white, poly (vinyl alcohol), along with clay nanoparticles infused with honey, and the dressings was assessed *in vitro* as well as in vivo. Overall in vivo results demonstrated honey-loaded bio-nanocomposite hydrogel wound dressings' exceptional capacity to establish and sustain a moist zone on the outermost layer of both infected and non-infected wounds, as well as their ability to speed up the wound healing process (Rafati et al., 2020).

The work conducted by Fathollahipour et al. (2020) focuses on the development and characterisation of thermally cross-linked PVA-based hydrogels incorporating honey as well as sucrose for erythromycin distribution and the findings suggest that these hybrid hydrogels might be used as therapeutic wound dressings to control the degree of antibiotic delivery within the wound site and prevent infections caused by the development of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Gong et al. (2013) have developed curcumin-loaded micelles encapsulated in a temperature-sensitive hydrogel polymer for epidermal wound repair. Curcumin encapsulation and loading efficiency in micelles have been proved to be extraordinarily high. With quick gel conversion, the sedentary hydrogel was tenacious and efficiently covered the wound. The wound that had been treated with hydrogel had a thicker, stronger dermis with more collagen. The study conducted by Chakraborty et al. (2021) looked at the possibility of producing an Aloe vera topical gel composition with insulin-loaded nanoemulsion and evaluating its efficacy for wound repair in diabetes induced rats. The wound healing effect indicated by more substantial contraction of the wound using the insulin and Aloe vera gel composition. Histopathological study indicated that the histological morphology of the skin of the groups receiving treatment had improved significantly. The skin irritation testing indicates that the prepared gel is non-irritant and appropriate for application to the skin.

In a work done by Park et al. (2021), hexanoyl glycol chitosan which is thermosensitive (HGC) was conjugated with gallic acid (GA) to develop a unique synthetic tissue adhesive material capable of closing wounds. The self-repairing, high tensile strength, firmer tissue adhesion, and biological degradation of the GA-HGC hydrogels were all tunable in accordance with the GA content. Unlike to the control group, GA-HGC hydrogels considerably enhanced the closure of wounds and the regeneration of tissue, by upregulating collagen, EGF, VEGF and TGF- β and by activating fibroblasts. The construction of temperature-controlled hydrogel using GA and lysozyme was described in a study by (Gong et al., 2022). This hydrogel demonstrated excellent antibacterial activity and improved chronic wound healing properties against an *E. coli*-infected wound model by suppressing the expression of pro-inflammatory genes HIF-1α (Hypoxia inducible factor −1 alpha), TGF-β and MCP-1(Monocyte chemoattractant protein-1). A peptide-hydrogel that is loaded with resveratrol (Pep/RES) was conceptualised and synthesised by Zhao et al. (2020) to be utilised as a dressing for the skin wound. Resveratrol that has been released in situ from the hydrogel has an anti-inflammatory impact both *in vitro* as well as in vivo. The Pep/RES dressing demonstrated increased wound healing rate, decreased inflammation, structured accumulation of collagen, and ultimately reduced incidence of scar formation.

## 7. Future directions and conclusion

Despite researchers' efforts, there has been minimal progress towards obtaining therapeutic approval for bionanomaterials based on plant compounds. The intricate nature of the process of wound healing, the undetermined equilibrium and durability of newly developed bionanomaterials, constraints in study simulations, particularly persistent wound models, a lack of knowledge regarding toxicity resulting from prolonged exposition to novel therapies, as well as, the implications of these newly developed therapies on the emergence of microbial resistance, these are the factors that accounts for the challenges of using bionanomaterials.

The latest advances in technology work in harmony to promote the development, manufacture, characterisation, along with the *in vitro* and in vivo assessment of bionanomaterials, with a strong preference for plant-based compounds. These plant-based bionanomaterials seek optimum properties that function at every point of wound healing for both acute and chronic wounds. A more effective treatment strategy is hindered by the shortcomings of these invite models. For instance, a number of research have demonstrated encouraging results in animal models, but failed in a clinical trials context. This failure is likely attributable to the disparities between the wound-related microbial environments of humans and animal models. Additional investigations into more complicated models that represent human skin is needed in this area. A polymicrobial biofilm is a good model for studying antibacterial action. It is recommended to utilize primary cultures of fibroblasts from wounds or donor skin with chronic diseases to assess cytotoxicity. We found that polyvinyl alcohol, chitosan, and glycerol are among the most widely utilized polymeric scaffolds mainly because of their outstanding biocompatibility, low level of toxicity, and chemical properties. Obtaining an appropriate equilibrium between physicochemical-mechanical-biological characteristics, on the other hand, remains to be one of the earliest and most challenging difficulties in developing novel nanometric biomaterials.

In order to better comprehend the molecular processes associated with novel multilayer, biodegradable, biocompatible, as well as biologically replicated bionanomaterials loaded with natural compounds that improve approaches with supplemental mechanisms as well as are preferably effortless to utilize in a practical setting, thorough

investigations are necessary. These attempts to use novel procedures and evaluate beneficial models or methods are anticipated to facilitate the path towards wound healing bionanomaterial therapy in the healthcare setting. Furthermore, the formulations' sustained-release features may lead to a more prolonged period of effect and an improved safety profile. Multiple formulations aid in the healing process by providing moist conditions for the wound to heal. Furthermore, the simplicity of fabrication and cheap maintenance expenses suggest that these improved drug delivery systems, in conjunction with plant compounds, are conceivably useful method for more effective chronic wound management than traditional and conventional dressings for patients.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

The authors acknowledge Vellore Institute of Technology management for providing the necessary facilities to carry out this work.

### *Authors' contributions*

SS contributed to the conception and design, drafting of the article, and final approval of the manuscript. KMG contributed to the critical revision of the manuscript content, and final approval of the manuscript.

## References

Abbas, H.A., Shaldam, M.A., 2016. Glyceryl trinitrate is a novel inhibitor of quorum sensing in *Pseudomonas aeruginosa*. Afr. Health Sci. 16,1109-1117. https://doi: 10.4314/ahs.v16i4.29.

Akrawi, S.H., Gorain, B., Nair, A.B., Choudhury, H., Pandey, M., Shah, J.N., Venugopala, K.N., 2020. Development and optimization of naringenin-loaded chitosan-coated nanoemulsion for topical therapy in wound healing. Pharmaceutics 12, 893. https://doi.org/10.3390/pharmaceutics12090893.

Al-Roujayee, A.S., 2017. Naringenin improves the healing process of thermally-induced skin damage in rats. Int. J. Med. Res. 45, 570–582. https://doi.org/10.1177/0300060517692483.

Anaya, D.A., Dellinger, E.P., 2006. The obese surgical patient: a susceptible host for infection. Surg. Infec. 7, 473–480.

Ansari, S.H., Islam, F. and Sameem, M., 2012. Influence of nanotechnology on herbal drugs: A Review. J. Adv. Pharm. Technol. Res. 3, 142. https://doi: 10.4103/2231-4040.101006.

Antunes, L.C.M., Ferreira, R.B., 2009. Intercellular communication in bacteria. Crit. Rev. Microbiol. 35, 69–80. https://doi.org/10.1080/10408410902733946.

Arnold, M., Barbul, A., 2006. Nutrition and wound healing. Plast. Reconst. Surg. 117, 42S–58S. https://doi.org/10.1097/01.prs.0000225432.17501.6c.

Arslan, A., Şimşek, M., Aldemir, S.D., Kazaroğlu, N.M., Gümüşderelioğlu, M., 2014. Honey-based PET or PET/chitosan fibrous wound dressings: effect of honey on electrospinning process. J. Biomater. Sci. Polym. Ed. 25, 999–1012. https://doi.org/10.1080/09205063.2014.918455.

Arya, A.K., Tripathi, R., Kumar, S., Tripathi, K., 2014. Recent advances on the association of apoptosis in chronic non healing diabetic wound. World J. Diabetes 5, 756. https://doi.org/10.4239/wjd.v5.i6.756.

Attinger, C.E., Janis, J.E., Steinberg, J., Schwartz, J., Al-Attar, A., Couch, K., 2006. Clinical approach to wounds: debridement and wound bed preparation including the use of dressings and wound-healing adjuvants. Plast. Reconst. Surg. 117, 72S–109S. https://doi.org/10.1097/01.prs.0000225470.42514.8f.

Bagheri, M., Mostafavinia, A., Abdollahifar, M.A., Amini, A., Ghoreishi, S.K., Chien, S., Hamblin, M.R., Bayat, S., Bayat, M., 2020. Combined effects of metformin and photobiomodulation improve the proliferation phase of wound healing in type 2 diabetic rats. Biomed. Pharmacother. 123, 109776 https://doi.org/10.1016/j.biopha.2019.109776.

Banerjee, K., Madhyastha, R., Nakajima, Y., Maruyama, M., Madhyastha, H., 2021. Nanoceutical adjuvants as wound healing material: precepts and prospects. Int. J. Mol. Sci. 22, 4748. https://doi.org/10.3390/ijms22094748.

Barros, J.F., Waclawiak, I., Pecli, C., Borges, P.A., Georgii, J.L., Ramos-Junior, E.S., Canetti, C., Courau, T., Klatzmann, D., Kunkel, S.L., Penido, C., 2019. Role of chemokine receptor CCR4 and regulatory T cells in wound healing of diabetic mice. J. Invest. Dermatol. 139, 1161–1170. https://doi.org/10.1016/j.jid.2018.10.039.

Beaufort, N., Corvazier, E., Mlanaoindrou, S., De Bentzmann, S., Pidard, D., 2013. Disruption of the endothelial barrier by proteases from the bacterial pathogen *Pseudomonas aeruginosa*: implication of matrilysis and receptor cleavage. PLoS One 8, e75708. https://doi.org/10.1371/journal.pone.0075708.

Beck, E., Duckert, F. and Ernst, M., 1961. The influence of fibrin stabilizing factor on the growth of fibroblats in vitro and wound healing. Thromb. Haemost. 6, 485-491. https://doi: 10.1055/s-0038-1654579.

Bell, A.J., Duggin, G., 2002. Acute methyl salicylate toxicity complicating herbal skin treatment for psoriasis. Emerg Med J. 14, 188–190. https://doi.org/10.1046/j.1442-2026.2002.00316.x.

Bishop, A., 2008. Role of oxygen in wound healing. J. Wound Care 17, 399–402. https://doi.org/10.12968/jowc.2008.17.9.30937.

Bjarnsholt, T., 2013. The role of bacterial biofilms in chronic infections. APMIS 121, 1–58.

Boateng, J.S., Matthews, K.H., Stevens, H.N., Eccleston, G.M., 2008. Wound healing dressings and drug delivery systems: a review. J. Pharm. Sci. 97, 2892–2923. https://doi.org/10.1002/jps.21210.

Bodeker, G., Ryan, T., Ong, C.K., 1999. Traditional approaches to wound healing. Clin. Dermatol. 17, 93–98. https://doi.org/10.1016/S0738-081X(98)00056-X.

Boyapati, L., Wang, H.L., 2007. The role of stress in periodontal disease and wound healing. Periodontology 2000 (44), 195–210. https://doi.org/10.1111/j.1600-0757.2007.00211.x.

Brackman, G., Coenye, T., 2015. Quorum sensing inhibitors as anti-biofilm agents. Curr. Pharm. Des. 21, 5–11. https://doi.org/10.2174/1381612820666140905114627.

Cardona, A.F., Wilson, S.E., 2015. Skin and soft-tissue infections: a critical review and the role of telavancin in their treatment. Clin. Infect. Dis. 61, S69–S78. https://doi.org/10.1093/cid/civ528.

Castanheira, F.V., Kubes, P., 2019. Neutrophils and NETs in modulating acute and chronic inflammation. Blood 133, 2178–2185.

Chakraborty, T., Gupta, S., Nair, A., Chauhan, S., Saini, V., 2021. Wound healing potential of insulin-loaded nanoemulsion with Aloe vera gel in diabetic rats. J. Drug Deliv. Sci. Technol. 64, 102601 https://doi.org/10.1016/j.jddst.2021.102601.

Chen, Y., Guo, D.J., Deng, H., Wu, M.F., Zhang, Y.N., Li, S., Xu, R., Chen, J., Jin, X.X., Li, B., Xu, Q., 2018. Acute and chronic toxicity of a polyherbal preparation–Jueyin granules. BMC Complement Altern. Med. 18, 1–13. https://doi.org/10.1186/S12906-018-2211-Z.

Cianfarani, F., Toietta, G., Di Rocco, G., Cesareo, E., Zambruno, G., Odorisio, T., 2013. Diabetes impairs adipose tissue–derived stem cell function and efficiency in promoting wound healing. Wound Repair. Regen. 21, 545–553. https://doi.org/10.1111/wrr.12051.

Clark, R.A., 1996. Wound repair: overview and general considerations. Mol. Cell. Biol. Wound Repair 3–50. https://doi.org/10.1007/978-1-4899-0185-9_1.

Clark, R.A., 2001. Fibrin and wound healing. Ann. N. Y. Acad. Sci. 936, 355-367. https://doi: 10.1111/j.1749-6632.2001.tb03522.x.

Clinton, A., Carter, T., 2015. Chronic wound biofilms: pathogenesis and potential therapies. Lab. Med. 46, 277–284. https://doi.org/10.1309/LMBNSWKUI4JPN7SO.

Cosyns, J.P., Jadoul, M., Squifflet, J.P., Wese, F.X., de Strihou, C.V.Y., 1999. Urothelial lesions in Chinese-herb nephropathy. Am. J. Kidney Dis. 33, 1011–1017. https://doi.org/10.1016/S0272-6386(99)70136-8.

Cushnie, T.T., Lamb, A.J., 2005. Detection of galangin-induced cytoplasmic membrane damage in Staphylococcus aureus by measuring potassium loss. J. Ethnopharmacol. 101, 243–248. https://doi.org/10.1016/j.jep.2005.04.014.

Czubryt, M.P., 2012. Common threads in cardiac fibrosis, infarct scar formation, and wound healing. Fibrogenesis Tissue Repair 5, 1–11. https://doi.org/10.1186/1755-1536-5-19.

Das, L., Singh, Y., 2018. Quorum Sensing Inhibition: A Target for Treating Chronic Wounds. In: Kalia, V. (Ed.), Biotechnological Applications of Quorum Sensing Inhibitors. Springer, Singapore, pp. 111–126.

Demidova-Rice, T.N., Hamblin, M.R., Herman, I.M., 2012. Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care. Adv. Skin Wound Care 25, 304. https://doi.org/10.1097/01.ASW.0000416006.55218.d0.

Devi, V.K., Jain, N. and Valli, K.S., 2010. Importance of novel drug delivery systems in herbal medicines. Pharmacogn Rev . 4, 27. https://doi: 10.4103/0973-7847.65322.

Diggle, S.P., Winzer, K., Lazdunski, A., Williams, P., Cámara, M., 2002. Advancing the quorum in *Pseudomonas aeruginosa*: MvaT and the regulation of N-acylhomoserine lactone production and virulence gene expression. J. Bacteriol. 184, 2576–2586. https://doi.org/10.1128/jb.184.10.2576-2586.2002.

DiPietro, L.A., Polverini, P.J., 1993. Role of the macrophage in the positive and negative regulation of wound neovascularization. Behring Inst. Mitt. 92, 238–247.

Dissemond, J., Augustin, M., Dietlein, M., Faust, U., Keuthage, W., Lobmann, R., Münter, K.C., Strohal, R., Stücker, M., Traber, J., Vanscheidt, W., 2020. Efficacy of MMP-inhibiting wound dressings in the treatment of chronic wounds: a systematic review. J. Wound Care 29, 102–118. https://doi.org/10.12968/jowc.2020.29.2.102.

Dong, J., Chen, L., Zhang, Y., Jayaswal, N., Mezghani, I., Zhang, W. and Veves, A., 2020. Mast cells in diabetes and diabetic wound healing. Adv. Ther. 37, 4519-4537. https://doi: 10.1007/s12325-020-01499-4.

Dunnill, C., Patton, T., Brennan, J., Barrett, J., Dryden, M., Cooke, J., Leaper, D., Georgopoulos, N.T., 2017. Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. Int. Wound J. 14, 89–96. https://doi.org/10.1111/iwj.12557.

Edwards, R., Harding, K.G., 2004. Bacteria and wound healing. Curr. Opin. Infect. Dis. 17, 91–96.

Eichler, M.J., Carlson, M.A., 2006. Modeling dermal granulation tissue with the linear fibroblast-populated collagen matrix: a comparison with the round matrix model. J. Dermatol. Sci. 41, 97–108. https://doi.org/10.1016/j.jdermsci.2005.09.002.

Ekor, M., 2014. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front. Pharmacol. 4, 177. https://doi.org/10.3389/fphar.2013.00177.

Ennis, W.J., Sui, A., Bartholomew, A., 2013. Stem cells and healing: impact on inflammation. Adv. Wound Care 2, 369–378. https://doi.org/10.1089/wound.2013.0449.
Eriksson, E., Liu, P.Y., Schultz, G.S., Martins-Green, M.M., Tanaka, R., Weir, D., Gould, L. J., Armstrong, D.G., Gibbons, G.W., Wolcott, R., Olutoye, O.O., 2022. Chronic wounds: Treatment consensus. Wound Repair Regen. 30, 156–171. https://doi.org/10.1111/wrr.12994.
Ernst, E., 2002. Toxic heavy metals and undeclared drugs in Asian herbal medicines. Trends Pharmacol. Sci. 23, 136–139. https://doi.org/10.1016/S0165-6147(00)01972-6.
Eskandarinia, A., Kefayat, A., Agheb, M., Rafienia, M., Amini Baghbadorani, M., Navid, S., Ebrahimpour, K., Khodabakhshi, D., Ghahremani, F., 2020. A novel bilayer wound dressing composed of a dense polyurethane/propolis membrane and a biodegradable polycaprolactone/gelatin nanofibrous scaffold. Sci. Rep. 10, 3063. https://doi.org/10.1038/s41598-020-59931-2.
Ezzati, A., Bayat, M., Taheri, S., Mohsenifar, Z., 2009. Low-level laser therapy with pulsed infrared laser accelerates third-degree burn healing process in rats. J. Rehabil. Res. Dev. 46 https://doi.org/10.1682/jrrd.2008.09.0121.
Fathollahipour, S., Koosha, M., Tavakoli, J., Maziarfar, S., Mehrabadi, J.F., 2020. Erythromycin releasing PVA/sucrose and PVA/honey hydrogels as wound dressings with antibacterial activity and enhanced bio-adhesion. Iran. J. Pharm. Res. 19, 448. https://doi.org/10.22037/ijpr.2019.1101002.
Frank, D.N., Wysocki, A., Specht-Glick, D.D., Rooney, A., Feldman, R.A., St. Amand, A.L., Pace, N.R. and Trent, J.D., 2009. Microbial diversity in chronic open wounds. Wound. Repair. Regen.*17*, 163-172. https://doi.org/10.1111/j.1524-475X.2009.00472.x.
FrykbergRobert, G., Jaminelli, B., 2015. Challenges in the treatment of chronic wounds. Adv. Wound Care 4, 560–582. https://doi.org/10.1089/wound.2015.0635.
Gabriel, A., Barrett, C., Cullen, B., Hodges, D., Lee, W., Snyder, R., Speyrer, M., Suski, M., Dick, S., Thomason, H.A., Treadwell, T., 2020. Infection and inflammation in the wound environment: Addressing issues of delayed wound healing with advanced wound dressings. Wounds: Compendium Clin. Res. Pract. 32, S1–S17.
García-Contreras, R., 2016. Is quorum sensing interference a viable alternative to treat *Pseudomonas aeruginosa* infections? Front. Microbiol. 7, 1454. https://doi.org/10.3389/fmicb.2016.01454.
Garcia-Orue, I., Gainza, G., Gutierrez, F.B., Aguirre, J.J., Evora, C., Pedraz, J.L., Hernandez, R.M., Delgado, A., Igartua, M., 2017. Novel nanofibrous dressings containing rhEGF and Aloe vera for wound healing applications. Int. J. Pharm. 523, 556–566. https://doi.org/10.1016/j.ijpharm.2016.11.006.
Garrett, B., 1998. Re-epithelialisation. J. Wound Care 7, 358–359. https://doi.org/10.12968/jowc.1998.7.7.358.
Gattuso, G., Barreca, D., Gargiulli, C., Leuzzi, U., Caristi, C., 2007. Flavonoid composition of citrus juices. Molecules 12, 1641–1673. https://doi.org/10.3390/12081641.
Ghasemiyeh, P., Mohammadi-Samani, S., 2019. Hydrogels as drug delivery systems; pros and cons. Trends Pharmacol. Sci. 5, 7-24. https://doi: 10.30476/TIPS.2019.81604.1002.
Ghorbani, M., Ramezani, S., Rashidi, M.R., 2021. Fabrication of honey-loaded ethylcellulose/gum tragacanth nanofibers as an effective antibacterial wound dressing. Colloids Surf. A Physicochem. Eng. Asp. 621, 126615 https://doi.org/10.1016/j.colsurfa.2021.126615.
Goldberg, S.R., Diegelmann, R.F., 2020. What makes wounds chronic. Surg. Oncol. Clin. N. Am. 100, 681–693. https://doi.org/10.1016/j.suc.2020.05.001.
Gong, W., Huang, H.B., Wang, X.C., He, W.Y., Hou, Y.Y., Hu, J.N., 2022. Construction of a sustained-release hydrogel using gallic acid and lysozyme with antimicrobial properties for wound treatment. Biomater. Sci. 10, 6836–6849. https://doi.org/10.1039/D2BM00658H.
Gong, C., Wu, Q., Wang, Y., Zhang, D., Luo, F., Zhao, X., Wei, Y., Qian, Z., 2013. A biodegradable hydrogel system containing curcumin encapsulated in micelles for cutaneous wound healing. Biomater. 34, 6377–6387. https://doi.org/10.1016/j.biomaterials.2013.05.005.
Gosain, A., DiPietro, L.A., 2004. Aging and wound healing. World J. Surg. 28, 321–326. https://doi.org/10.1007/s00268-003-7397-6.
Greco 3rd, J.A., Castaldo, E.T., Nanney, L.B., Wendel, J.J., Summitt, J.B., Kelly, K.J., et al., 2008. The effect of weight loss surgery and body mass index on wound complications after abdominal contouring operations. Ann. Plast. Surg. 61, 235–242. https://doi.org/10.1089/sur.2006.7.473.
Greenhalgh, D.G., 1998. The role of apoptosis in wound healing. Int. J. Biochem. Cell Biol. 30, 1019–1030. https://doi.org/10.1016/S1357-2725(98)00058-2.
Groeber, F., Holeiter, M., Hampel, M., Hinderer, S., Schenke-Layland, K., 2011. Skin tissue engineering—in vivo and in vitro applications. Adv. Drug Deliv. Rev. 63, 352–366. https://doi.org/10.1016/j.addr.2011.01.005.
Gui, Z., Wang, H., Ding, T., Zhu, W., Zhuang, X., Chu, W., 2014. Azithromycin reduces the production of α-hemolysin and biofilm formation in Staphylococcus aureus. Indian J. Microbiol. 54, 114–117. https://doi.org/10.1007/s12088-013-0438-4.
Gurtner, G.C., Werner, S., Barrandon, Y., Longaker, M.T., 2008. Wound repair and regeneration. Nature 453, 314–321. https://doi.org/10.1038/nature07039.
Haas, A.F., 1995. Wound healing. Dermatol. Nurs. 7, 28–34.
Haji Zaine, N., Burns, J., Vicaretti, M., Fletcher, J.P., Begg, L., Hitos, K., 2014. Characteristics of diabetic foot ulcers in Western Sydney, Australia. J. Foot Ankle Res. 7, 1–7. https://doi.org/10.1186/s13047-014-0039-4.
Hamdan, S., Pastar, I., Drakulich, S., Dikici, E., Tomic-Canic, M., Deo, S., Daunert, S., 2017. Nanotechnology-driven therapeutic interventions in wound healing: potential uses and applications. ACS Cent. Sci. 3, 163–175. https://doi.org/10.1021/acscentsci.6b00371.
Hamidi, M., Azadi, A., Rafiei, P., 2008. Hydrogel nanoparticles in drug delivery. Adv. Drug Deliv. Rev. 60, 1638-1649. https://doi: 10.1016/j. addr.2008.08.002.
Herman, TF., Bordoni B., Wound Classification. [Updated 2023 Apr 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554456/ (accessed on 21 August 2023).
Hesketh, M., Sahin, K.B., West, Z.E., Murray, R.Z., 2017. Macrophage phenotypes regulate scar formation and chronic wound healing. Int. J. Mol. Sci. 18, 1545. https://doi.org/10.3390/ijms18071545.
Hixon, K.R., Klein, R.C., Eberlin, C.T., Linder, H.R., Ona, W.J., Gonzalez, H., Sell, S.A., 2019. A critical review and perspective of honey in tissue engineering and clinical wound healing. Adv. Wound Care. 8, 403-415. https://doi: 10.1089/wound.2018.0848.
Hoffman, A.S., 2002. Hydrogels for biomedical applications. Adv. Drug Deliv. Rev. 54, 3–12. https://doi.org/10.1016/s0169-409x(01)00239-3.
Iacopetti, I., Perazzi, A., Martinello, T., Gemignani, F., Patruno, M., 2020. Hyaluronic acid, Manuka honey and Acemannan gel: Wound-specific applications for skin lesions. Res.Vet. Sci. 129, 82-89. https://doi: 10.1016/j.rvsc.2020.01.009.
Ibrahim, M.E.E.D., Alqurashi, R.M., 2022. Anti-fungal and antioxidant properties of propolis (bee glue) extracts. Int. J. Food Microbiol. 361, 109463. https://doi: 10.1016/j.ijfoodmicro.2021.109463.
Isfandiary, A., Widiyanti, P., Hikmawati, D., 2017. Composite of chitosan-collagen-aloe vera for scaffolds application on skin tissue. J. Biomimetics Biomater. Biomed. Eng. 32, 82–89. https://doi.org/10.4028/www.scientific.net/JBBBE.32.82.
Ishtiaq, S., Akram, M., Kamran, S.H., Hanif, U., Afridi, M.S.K., Afzal, A., Asif, A., Younus, M., Akbar, S., 2017. Acute and sub-acute toxicity study of a Pakistani polyherbal formulation. BMC Complement Altern. Med. 17, 1–13. https://doi.org/10.1186/s12906-017-1889-7.
James, G. A., Swogger, E., Wolcott, R., Pulcini, E.d, Secor, P., Sestrich, J., Costerton, J. W., Stewart, P. S., 2008. Biofilms in chronic wounds. Wound Repair Regen. 16, 37–44. https://doi:10.1111/j.1524-475X.2007.00321.x.
Jeckson, T.A., Neo, Y.P., Sisinthy, S.P., Gorain, B., 2021a. Delivery of therapeutics from layer-by-layer electrospun nanofiber matrix for wound healing: An update. J. Pharm. Sci. 110, 635–653. https://doi.org/10.1016/j.xphs.2020.10.003.
Jeckson, T.A., Neo, Y.P., Sisinthy, S.P., Foo, J.B., Choudhury, H., Gorain, B., 2021b. Formulation and characterisation of deferoxamine nanofiber as potential wound dressing for the treatment of diabetic foot ulcer. J. Drug Deliv. Sci. Technol. 66, 102751 https://doi.org/10.1016/j.jddst.2021.102751.
Jeyanthi, V., Velusamy, P., 2016. Anti-methicillin resistant Staphylococcus aureus compound isolation from halophilic Bacillus amyloliquefaciens MHB1 and determination of its mode of action using electron microscope and flow cytometry analysis. Indian J. Microbiol. 56, 148–157. https://doi.org/10.1007/s12088-016-0566-8.
Joe, B., Vijaykumar, M., Lokesh, B.R., 2004. Biological properties of curcumin-cellular and molecular mechanisms of action. Crit. Rev. Food Sci. Nutr. 44, 97–111. https://doi.org/10.1080/10408690490424702.
Joshi, N., Pohlmeier, L., Ben-Yehuda Greenwald, M., Haertel, E., Hiebert, P., Kopf, M., Werner, S., 2020. Comprehensive characterization of myeloid cells during wound healing in healthy and healing-impaired diabetic mice. Eur. J. Immunol. 50, 1335-1349. https://doi: 10.1002/eji.201948438.
Kajdič, S., Planinšek, O., Gašperlin, M., Kocbek, P., 2019. Electrospun nanofibers for customized drug-delivery systems. J. Drug Deliv. Sci. Technol. 51, 672–681. https://doi.org/10.1016/j.jddst.2019.03.038.
Kalia, V.C., 2013. Quorum sensing inhibitors: an overview. Biotechnol. Adv. 31, 224–245. https://doi.org/10.1016/j.biotechadv.2012.10.004.
Kalia, V.C. and Kumar, P., 2014. The battle: quorum-sensing inhibitors versus evolution of bacterial resistance. In: Kalia, V. (Eds.), Quorum sensing vs quorum quenching: a battle with no end in sight, New Delhi: Springer India,pp.385-391. https://doi: 10.1007/978-81-322-1982-8_31.
Kapahi, H., Mansoor Khan, N., Bhardwaj, A., Mishra, N., 2015. Implication of nanofibers in oral drug delivery. Curr. Pharm. Des. 21, 2021–2036.
Kapoor, M., Howard, R., Hall, I., Appleton, I., 2004. Effects of epicatechin gallate on wound healing and scar formation in a full thickness incisional wound healing model in rats. Am. J. Pathol. 165, 299–307. https://doi.org/10.1016/S0002-9440(10)63297-X.
Kaur, K., Singh, A., Attri, S., Malhotra, D., Verma, A., Bedi, N., Bedi, P.M.S., 2020. Matrix metalloproteinases (MMPs) and diabetic foot: Pathophysiological findings and recent developments in their inhibitors of natural as well as synthetic origin. The eye and foot in diabetes. IntechOpen; London, UK.
Keays, T., Ferris, W., Vandemheen, K.L., Chan, F., Yeung, S.W., Mah, T.F., Ramotar, K., Saginur, R., Aaron, S.D., 2009. A retrospective analysis of biofilm antibiotic susceptibility testing: a better predictor of clinical response in cystic fibrosis exacerbations. J. Cyst. Fibros. 8, 122–127. https://doi.org/10.1016/j.jcf.2008.10.005.
Kenry, Lim, C.T., 2017. Nanofiber technology: current status and emerging developments. Prog. Polym. Sci. 70, 1-17. https://doi.org/10.1016/j.progpolymsci.2017.03.002.
Kerstein, M.D., 1997. The scientific basis of healing. Adv. Wound Care. 10, 30–36.
Keylock, K.T., Vieira, V.J., Wallig, M.A., DiPietro, L.A., Schrementi, M., Woods, J.A., 2008. Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 294, R179-R184. https://doi: 10.1152/ajpregu.00177.2007.
Kim, H.K., Missiakas, D., Schneewind, O., 2014. Mouse models for infectious diseases caused by Staphylococcus aureus. J. Immunol. Methods 410, 88–99. https://doi.org/10.1016/j.jim.2014.04.007.
Kleerebezem, M., Quadri, L.E., Kuipers, O.P., De Vos, W.M., 1997. Quorum sensing by peptide pheromones and two-component signal-transduction systems in Gram-positive bacteria. Mol. Microbiol. 24, 895–904. https://doi.org/10.1046/j.1365-2958.1997.4251782.x.

Kong, K.F., Vuong, C., Otto, M., 2006. Staphylococcus quorum sensing in biofilm formation and infection. Int. J. Med. Microbiol. 296, 133–139. https://doi.org/10.1016/j.ijmm.2006.01.042.
Koul, S., Kalia, V.C., 2017. Multiplicity of quorum quenching enzymes: a potential mechanism to limit quorum sensing bacterial population. Indian J. Microbiol. 57, 100–108. https://doi.org/10.1007/s12088-016-0633-1.
Koul, S., Prakash, J., Mishra, A., Kalia, V.C., 2016. Potential emergence of multi-quorum sensing inhibitor resistant (MQSIR) bacteria. Indian J. Microbiol. 56, 1–18. https://doi.org/10.1007/s12088-015-0558-0.
Krzyszczyk, P., Schloss, R., Palmer, A., Berthiaume, F., 2018. The role of macrophages in acute and chronic wound healing and interventions to promote pro-wound healing phenotypes. Front. Physiol. 9, 419. https://doi.org/10.3389/fphys.2018.00419.
Kumar, P., Koul, S., Patel, S.K., Lee, J.K., Kalia, V.C., 2014. Heterologous expression of quorum sensing inhibitory genes in diverse organisms. In: Kalia, V. (Eds.), Quorum sensing vs quorum quenching: a battle with no end in sight, New Delhi: Springer India, pp. 343-356. https://doi:10.1007/978-81-322-1982-8_28.
Kumar, B., Vijayakumar, M., Govindarajan, R., Pushpangadan, P., 2007. Ethnopharmacological approaches to wound healing—exploring medicinal plants of India. J. Ethnopharmacol. 114, 103–113. https://doi.org/10.1016/j.jep.2007.08.010.
Kumawat, M., Madhyastha, H., Singh, M., Jain, D., Daima, H.K., 2022. Functional silver nanozymes regulate cell inflammatory cytokines expression in mouse macrophages. Colloids Surf. A: Physicochem. Eng. Asp. 650, 129294 https://doi.org/10.1016/j.colsurfa.2022.129294.
LaSarre, B., Federle, M.J., 2013. Exploiting quorum sensing to confuse bacterial pathogens. Microbiol. Mol. Biol. Rev. 77, 73–111. https://doi.org/10.1128/mmbr.00046-12.
Lawrence, W.T., Diegelmann, R.F., 1994. Growth factors in wound healing. Clin. Dermatol. 12, 157–169. https://doi.org/10.1016/0738-081X(94)90266-6.
Lawrence, R., Tripathi, P., Jeyakumar, E., 2009. Isolation, purification and evaluation of antibacterial agents from Aloe vera. Braz. J. Microbiol. 40, 906–915. https://doi.org/10.1590/S1517-83822009000400023.
Levy, S.M., Holzmann-Pazgal, G., Lally, K.P., Davis, K., Kao, L.S., Tsao, K., 2013. Quality check of a quality measure: surgical wound classification discrepancies impact risk-stratified surgical site infection rates in pediatric appendicitis. J. Am. Coll. Surg. 217, 969–973. https://doi.org/10.1016/j.jamcollsurg.2013.07.398.
Li, D., Peng, H., Qu, L.E., Sommar, P., Wang, A., Chu, T., Li, X., Bi, X., Liu, Q., Sérézal, I. G., Rollman, O., 2021. miR-19a/b and miR-20a promote wound healing by regulating the inflammatory response of keratinocytes. J. Invest. Dermatol. 141, 659–671. https://doi.org/10.1016/j.jid.2020.06.037.
Liu, J., Chen, Z., Wang, J., Li, R., Li, T., Chang, M., Yan, F., Wang, Y., 2018. Encapsulation of curcumin nanoparticles with MMP9-responsive and thermos-sensitive hydrogel improves diabetic wound healing. ACS Appl. Mater. Interfaces 10, 16315–16326. https://doi.org/10.1021/acsami.8b03868.
Liu, Y., Xiong, W., Wang, C.W., Shi, J.P., Shi, Z.Q., Zhou, J.D., 2021. Resveratrol promotes skin wound healing by regulating the miR-212/CASP8 axis. Lab. Invest. 101, 1363–1370. https://doi.org/10.1038/s41374-021-00621-6.
Liyanagamage, D.S.N.K., Jayasinghe, S., Attanayake, A.P., Karunaratne, V., 2020. Acute and subchronic toxicity profile of a polyherbal drug used in Sri Lankan traditional medicine. Evid. Based Complementary Altern. Med. 2020. https://doi:10.1155/2020/2189189.
Lordani, T.V.A., de Lara, C.E., Ferreira, F.B.P., de Souza Terron Monich, M., Mesquita da Silva, C., Felicetti Lordani, C.R., Giacomini Bueno, F., Vieira Teixeira, J.J., Lonardoni, M.V.C., 2018. Therapeutic effects of medicinal plants on cutaneous wound healing in humans: a systematic review. Mediat. Inflamm. 2018. https://doi: 10.1155/2018/7354250.
Lyczak, J.B., Cannon, C.L., Pier, G.B., 2000. Establishment of *Pseudomonas aeruginosa* infection: lessons from a versatile opportunist. Microbes Infect. 2, 1051–1060. https://doi.org/10.1016/S1286-4579(00)01259-4.
MacLeod, A.S., Mansbridge, J.N., 2016. The innate immune system in acute and chronic wounds. Adv. Wound Care 5, 65–78. https://doi.org/10.1089/wound.2014.0608.
Madhyastha, H., Madhyastha, R., Chakraborty, E., Banerjee, K., Shah, K., Nakajima, Y., Chauhan, N.S., Sudhakaran, S.L., Ohe, K., Muthukaliannan, G.K. and Gopalakrishnan, A.V., 2023. Fluro-Protein C-Phycocyanin Docked Silver Nanocomposite Accelerates Cell Migration through NFκB Signaling Pathway. Int. J. Mol. Sci. 24, 3184. https://doi: 10.3390/ijms24043184.
Majtan, J., Sojka, M., Palenikova, H., Bucekova, M., Majtan, V., 2020. Vitamin C enhances the antibacterial activity of honey against planktonic and biofilm-embedded bacteria. Molecules 25, 992. https://doi.org/10.3390/molecules25040992.
Makuch, S., Więcek, K., Woźniak, M., 2021. The immunomodulatory and anti-inflammatory effect of curcumin on immune cell populations, cytokines, and in vivo models of rheumatoid arthritis. Pharmaceuticals 14, 309. https://doi.org/10.3390/ph14040309.
Malone-Povolny, M.J., Maloney, S.E., Schoenfisch, M.H., 2019. Nitric oxide therapy for diabetic wound healing. Adv. Healthc. Mater. 8, 1801210. https://doi.org/10.1002/adhm.201801210.
Martin, P., 1997. Wound healing–aiming for perfect skin regeneration. Science 276, 75–81. https://doi.org/10.1126/science.276.5309.75.
Martínez-Romero, D., Alburquerque, N., Valverde, J.M., Guillén, F., Castillo, S., Valero, D., Serrano, M., 2006. Postharvest sweet cherry quality and safety maintenance by Aloe vera treatment: a new edible coating. Postharvest Biol. Technol. 39, 93–100. https://doi.org/10.1016/j.postharvbio.2005.09.006.
Martinotti, S. and Ranzato, E., 2015. Propolis: a new frontier for wound healing?. Burns Trauma. 3, 1-7. https://doi: 10.1186/s41038-015-0010-z.
McCarty, S.M., Percival, S.L., 2013. Proteases and delayed wound healing. Adv. Wound Care 2, 438–447. https://doi.org/10.1089/wound.2012.0370.
Minden-Birkenmaier, B.A., Bowlin, G.L., 2018. Honey-based templates in wound healing and tissue engineering. Bioengineering 5, 46. https://doi.org/10.3390/bioengineering5020046.
Mohanty, C., Das, M., Sahoo, S.K., 2012. Emerging role of nanocarriers to increase the solubility and bioavailability of curcumin. Expert Opin. Drug Deliv. 9, 1347–1364. https://doi.org/10.1517/17425247.2012.724676.
Momeni, A., Heier, M., Bannasch, H., Stark, G.B., 2009. Complications in abdominoplasty: a risk factor analysis. J. Plast. Reconstr. Aesthet. Surg. 62, 1250–1254. https://doi.org/10.1016/j.bjps.2008.03.043.
Mordorski, B., Prow, T., 2016. Nanomaterials for wound healing. Curr. Dermatol. Rep. 5, 278–286. https://doi.org/10.1007/s13671-016-0159-0.
E.J. Mudge Recent accomplishments in wound healing Int. Wound J. 2015 12,4–9 https://doi: 10.1111/iwj.12230.
Nejatzadeh-Barandozi, F., 2013. Antibacterial activities and antioxidant capacity of Aloe vera. Org. Med. Chem. Lett. 3, 1–8. https://doi.org/10.1186/2191-2858-3-5.
Nguyen, T.T., Ding, D., Wolter, W.R., Pérez, R.L., Champion, M.M., Mahasenan, K.V., Hesek, D., Lee, M., Schroeder, V.A., Jones, J.I., Lastochkin, E., 2018. Validation of matrix metalloproteinase-9 (MMP-9) as a novel target for treatment of diabetic foot ulcers in humans and discovery of a potent and selective small-molecule MMP-9 inhibitor that accelerates healing. J. Med. Chem. 61, 8825–8837. https://doi.org/10.1021/acs.jmedchem.8b01005.
Nie, X., Zhao, J., Ling, H., Deng, Y., Li, X., He, Y., 2020. Exploring microRNAs in diabetic chronic cutaneous ulcers: Regulatory mechanisms and therapeutic potential. Br. J. Pharmacol. 177, 4077–4095. https://doi.org/10.1111/bph.15139.
Nina, N., Quispe, C., Jiménez-Aspee, F., Theoduloz, C., Feresín, G.E., Lima, B., Leiva, E. and Schmeda-Hirschmann, G., 2015. Antibacterial activity, antioxidant effect and chemical composition of propolis from the Región del Maule, Central Chile. Molecules. 20, 18144-18167. https://doi: 10.3390/molecules201018144.
Nizet, V., Ohtake, T., Lauth, X., Trowbridge, J., Rudisill, J., Dorschner, R.A., Pestonjamasp, V., Piraino, J., Huttner, K., Gallo, R.L., 2001. Innate antimicrobial peptide protects the skin from invasive bacterial infection. Nature 414, 454–457. https://doi.org/10.1038/35106587.
Novick, R.P., Geisinger, E., 2008. Quorum sensing in staphylococci. Annu. Rev. Genet. 42, 541–564. https://doi.org/10.1146/annurev.genet.42.110807.091640.
Nune, S.K., Rama, K.S., Dirisala, V.R., Chavali, M.Y., 2017. Electrospinning of collagen nanofiber scaffolds for tissue repair and regeneration. Nanostruct. Novel Ther. Elsevier 281–311. https://doi.org/10.1016/B978-0-323-46142-9.00011-6.
Omar, A., Wright, J.B., Schultz, G., Burrell, R., Nadworny, P., 2017. Microbial biofilms and chronic wounds. Microorganisms 5, 9. https://doi.org/10.3390/microorganisms5010009.
Oyedepo, T.A., Palai, S., 2021. Preparation of phytopharmaceuticals for the management of disorders. Acad. Press Herb. Remed. Toxicity Regulations 89–127. https://doi.org/10.1016/B978-0-12-820284-5.00014-9.
Özkan, S.A., Dedeoğlu, A., Bakirhan, N.K., Özkan, Y., 2019. Nanocarriers used most in drug delivery and drug release: nanohydrogel, chitosan, graphene, and solid lipid. Turk. J. Pharm. Sci. 16, 481. https://doi.org/10.4274/tjps.galenos.2019.48751.
Panchatcharam, M., Miriyala, S., Gayathri, V.S., Suguna, L., 2006. Curcumin improves wound healing by modulating collagen and decreasing reactive oxygen species. Mol. Cell. Biochem. 290, 87–96. https://doi.org/10.1007/s11010-006-9170-2.
Park, S.G., Li, M.X., Cho, W.K., Joung, Y.K., Huh, K.M., 2021. Thermosensitive gallic acid-conjugated hexanoyl glycol chitosan as a novel wound healing biomaterial. Carbohydr. Polym. 260, 117808 https://doi.org/10.1016/j.carbpol.2021.117808.
Pastar, I., Nusbaum, A.G., Gil, J., Patel, S.B., Chen, J., Valdes, J., Stojadinovic, O., Plano, L.R., Tomic-Canic, M., Davis, S.C., 2013. Interactions of methicillin resistant Staphylococcus aureus USA300 and *Pseudomonas aeruginosa* in polymicrobial wound infection. PLoS One 8, e56846.
Patel, K., Singh, G.K., Patel, D.K., 2018. A review on pharmacological and analytical aspects of naringenin. Chin. J. Integr. Med. 24, 551–560. https://doi.org/10.1007/s11655-014-1960-x.
Patil, S., Desai, N., Mahadik, K., Paradkar, A., 2015. Can green synthesized propolis loaded silver nanoparticulate gel enhance wound healing caused by burns? Eur. J. Integr. Med. 7, 243–250. https://doi.org/10.1016/j.eujim.2015.03.002.
Pereira, R.F., Barrias, C.C., Granja, P.L., Bartolo, P.J., 2013. Advanced biofabrication strategies for skin regeneration and repair. Nanomedicine 8, 603–621. https://doi.org/10.2217/nnm.13.50.
Phua, D.H., Zosel, A. and Heard, K., 2009. Dietary supplements and herbal medicine toxicities—when to anticipate them and how to manage them. Int. J. Emerg. Med. 2, 69-76. https://doi: 10.1007/S12245-009-0105-Z.
Piipponen, M., Li, D. and Landén, N.X., 2020. The immune functions of keratinocytes in skin wound healing. Int. J. Mol. Sci. 21, 8790. https://doi: 10.3390/ijms21228790.
Priyadarsini, K.I., 2014. The chemistry of curcumin: from extraction to therapeutic agent. Molecules 19, 20091–20112. https://doi.org/10.3390/molecules191220091.
Prockop DJ, Kivirikko KI.1995. Collagens: molecular biology, diseases and potentials for therapy. Annu Rev Biochem. 64:403–434. https://doi:10.1146/annurev.bi.64.070195.002155.
Rafati, Z., Sirousazar, M., Hassan, Z.M., Kheiri, F., 2020. Honey-loaded egg white/poly (vinyl alcohol)/clay bionanocomposite hydrogel wound dressings: in vitro and in vivo evaluations. J. Polym. Environ. 28, 32–46. https://doi.org/10.1007/s10924-019-01586-w.
Rodrigues, M., Kosaric, N., Bonham, C.A. and Gurtner, G.C., 2019. Wound healing: a cellular perspective. Physiol. Rev. 99, 665-706. https://doi: 10.1152/physrev.00067.2017.

Rodriguez, P.G., Felix, F.N., Woodley, D.T., Shim, E.K., 2008. The role of oxygen in wound healing: a review of the literature. Dermatol. Surg. 34, 1159–1169. https://doi.org/10.1111/j.1524-4725.2008.34254.x.

Rodriguez-Menocal, L., Salgado, M., Ford, D., Van Badiavas, E., 2012. Stimulation of skin and wound fibroblast migration by mesenchymal stem cells derived from normal donors and chronic wound patients. Stem Cells Transl. Med. 1, 221–229. https://doi.org/10.5966/sctm.2011-0029.

Ross, R., 1969. Wound healing. Sci. Am. 220, 40–50. https://doi.org/10.1038/scientificamerican0669-40.

Rossi, A., Longo, R., Russo, A., Borrelli, F. and Sautebin, L., 2002. The role of the phenethyl ester of caffeic acid (CAPE) in the inhibition of rat lung cyclooxygenase activity by propolis. Fitoterapia. 73, S30-S37. https://doi: 10.1016/S0367-326X(02)00188-0.

Rustad, K.C. and Gurtner, G.C., 2012. Mesenchymal stem cells home to sites of injury and inflammation. Adv. Wound Care. 1,147-152.https://doi:10.1089/wound.2011.0314.

Ruszczak, Z., 2003. Effect of collagen matrices on dermal wound healing. Adv. Drug Deliv. Rev. 55, 1595–1611. https://doi.org/10.1016/j.addr.2003.08.003.

Rutherford, S.T. and Bassler, B.L., 2012. Bacterial quorum sensing: its role in virulence and possibilities for its control. Cold Spring Harb. perspect. med. 2, a012427. https://doi: 10.1101/cshperspect.a012427.

Sahoo, S., Ang, L.T., Goh, J.C.H., Toh, S.L., 2010. Growth factor delivery through electrospun nanofibers in scaffolds for tissue engineering applications. J. Biomed. Mater. Res. 93, 1539–1550. https://doi.org/10.1002/jbm.a.32645.

K. Saito Y. Iwata H. Fukushima S. Watanabe Y. Tanaka Y. Hasegawa M. Akiyama K. Sugiura IL-36 receptor antagonist deficiency resulted in delayed wound healing due to excessive recruitment of immune cells Sci. Rep. 10, 14772.https://doi 2020 10.1038/s41598-020-71256-8.

Salehi, B., Albayrak, S., Antolak, H., Kręgiel, D., Pawlikowska, E., Sharifi-Rad, M., Uprety, Y., Tsouh Fokou, P.V., Yousef, Z., Amiruddin Zakaria, Z., Varoni, E.M., 2018. Aloe genus plants: from farm to food applications and phytopharmacotherapy. Int. J. Mol. Sci. 19, 2843. https://doi.org/10.3390/ijms19092843.

Samadian, H., Zamiri, S., Ehterami, A., Farzamfar, S., Vaez, A., Khastar, H., Alam, M., Ai, A., Derakhshankhah, H., Allahyari, Z., Goodarzi, A., 2020. Electrospun cellulose acetate/gelatin nanofibrous wound dressing containing berberine for diabetic foot ulcer healing: In vitro and in vivo studies. Sci. Rep. 10, 8312. https://doi.org/10.1038/s41598-020-65268-7.

Schilrreff, P., Alexiev, U., 2022. Chronic inflammation in non-healing skin wounds and promising natural bioactive compounds treatment. Int. J. Mol. Sci. 23, 4928. https://doi.org/10.3390/ijms23094928.

Schreml, S., Szeimies, R.M., Prantl, L., Karrer, S., Landthaler, M., Babilas, P., 2010. Oxygen in acute and chronic wound healing. Br. J. Dermatol. 163, 257–268. https://doi.org/10.1111/j.1365-2133.2010.09804.x.

Schröder, J.M., 2010. The role of keratinocytes in defense against infection. Curr. Opin. Infect. Dis. 23, 106–110. https://doi.org/10.1097/QCO.0b013e328335b004.

Seraphim, P.M., Leal, E.C., Moura, J., Gonçalves, P., Gonçalves, J.P. and Carvalho, E., 2020. Lack of lymphocytes impairs macrophage polarization and angiogenesis in diabetic wound healing. Life Sci. 254, 117813. https://doi: 10.1016/j.lfs.2020.117813.

Serra, R., Grande, R., Butrico, L., Rossi, A., Settimio, U.F., Caroleo, B., Amato, B., Gallelli, L., De Franciscis, S., 2015. Chronic wound infections: the role of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Expert Rev. Anti-Infect. Ther. 13, 605–613. https://doi.org/10.1586/14787210.2015.1023291.

Shah, A., Amini-Nik, S., 2017. The role of phytochemicals in the inflammatory phase of wound healing. Int. J. Mol. Sci. 18, 1068. https://doi.org/10.3390/ijms18051068.

Shai, A., Halevy, S., 2005. Direct triggers for ulceration in patients with venous insufficiency. Int. J. Dermatol. 44, 1006–1009. https://doi.org/10.1111/j.1365-4632.2005.02317.x.

Sharma, S., Madhyastha, H., Kirwale, S.S., Sakai, K., Katakia, Y.T., Majumder, S., Roy, A., 2022. Dual antibacterial and anti-inflammatory efficacy of a chitosan-chondroitin sulfate-based in-situ forming wound dressing. Carbohydr. Polym. 298, 120126 https://doi.org/10.1016/j.carbpol.2022.120126.

Sidhu, G.S., Singh, A.K., Thaloor, D., Banaudha, K.K., Patnaik, G.K., Srimal, R.C., Maheshwari, R.K., 1998. Enhancement of wound healing by curcumin in animals. Wound Repair Regen. 6, 167–177. https://doi.org/10.1046/j.1524-475X.1998.60211.x.

Sidhu, G.S., Mani, H., Gaddipati, J.P., Singh, A.K., Seth, P., Banaudha, K.K., Patnaik, G. K., Maheshwari, R.K., 1999. Curcumin enhances wound healing in streptozotocin induced diabetic rats and genetically diabetic mice. Wound Repair Regen. 7, 362–374. https://doi.org/10.1046/j.1524-475X.1999.00362.x.

Singer, A.J., Clark, R.A., 1999. Cutaneous wound healing. N. Engl. J. Med. 341, 738–746. https://doi.org/10.1056/NEJM199909023411006.

Soni, K.S., Desale, S.S., Bronich, T.K., 2016. Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation. J. Control. Release. 240, 109–126. https://doi.org/10.1016/j.jconrel.2015.11.009.

Stadelmann, W.K., Digenis, A.G., Tobin, G.R., 1998. Physiology and healing dynamics of chronic cutaneous wounds. Am. J. Surg. 176, 26S–38S. https://doi.org/10.1016/S0002-9610(98)00183-4.

Strang H., Kaul A., Parikh U., Masri L., Saravanan S., Li H., Miao Q., Balaji S. 2020. Role of cytokines and chemokines in wound healing. In: Bagchi D., Das A., Roy S., (Eds.), Wound Healing, Tissue Repair, and Regeneration in Diabetes. Elsevier; Amsterdam, The Netherlands: pp. 197–235. https://doi.org/10.1016/B978-0-12-816413-6.00011-3.

Strodtbeck, F., 2001. Physiology of wound healing. Newborn Infant Nurs. Rev. 1, 43–52. https://doi.org/10.1053/nbin.2001.23176.

Suguna, L., Chandrakasan, G., Ramamoorthy, U., Joseph, K.T., 1993. Influence of honey on biochemical and biophysical parameters of wounds in rats. J. Clin. Biochem. Nutr. 14, 91–99. https://doi.org/10.3164/jcbn.14.91.

Tandara, A.A. and Mustoe, T.A., 2004. Oxygen in wound healing—more than a nutrient. World J. Surg. 28, 294-300. https://doi: 10.1007/s00268-003-7400-2.

Tang, Y., Lan, X., Liang, C., Zhong, Z., Xie, R., Zhou, Y., Miao, X., Wang, H. and Wang, W., 2019. Honey loaded alginate/PVA nanofibrous membrane as potential bioactive wound dressing. Carbohydr. Polym. 219, 113-120. https://doi: 10.1016/j.carbpol.2019.05.004.

Thakur, R., Jain, N., Pathak, R. and Sandhu, S.S., 2011. Practices in wound healing studies of plants. Evid. Based Complementary Altern. Med. 2011. https://doi: 10.1155/2011/438056.

Toreti, V.C., Sato, H.H., Pastore, G.M. and Park, Y.K., 2013. Recent progress of propolis for its biological and chemical compositions and its botanical origin. Evid. Based Complementary Altern. Med. 2013. https://doi: 10.1155/2013/697390.

Uluer, Elgin Türköz, Hafize Seda Vatansever, and Feyzan Özdal Kurt., 2018.Wound healing and microenvironment. Wound Healing: Stem Cells Repair and Restorations, Basic and Clinical Aspects; pp. 67-77.

Versey, Z., da Cruz Nizer, W.S., Russell, E., Zigic, S., DeZeeuw, K.G., Marek, J.E., Overhage, J., Cassol, E., 2021. Biofilm-innate immune interface: contribution to chronic wound formation. Front. Immunol. 12 (648554) https://doi.org/10.3389/fimmu.2021.648554.

Vujanovic, S., Vujanovic, J., 2013. Bioresources in the pharmacotherapy and healing of burns: a mini-review. Burns 39, 1031–1038. https://doi.org/10.1016/j.burns.2013.03.016.

Vuong, C., Saenz, H.L., Götz, F., Otto, M., 2000. Impact of the agr quorum-sensing system on adherence to polystyrene in *Staphylococcus aureus*. J. Infect. Dis. 182, 1688–1693. https://doi.org/10.1086/317606.

Wang, J., Windbergs, M., 2017. Functional electrospun fibers for the treatment of human skin wounds. Eur. J. Pharm. Biopharm. 119, 283–299. https://doi.org/10.1016/j.ejpb.2017.07.001.

Wilke, G.A., Wardenburg, J.B., 2010. Role of a disintegrin and metalloprotease 10 in *Staphylococcus aureus* α-hemolysin–mediated cellular injury. Proc. Natl. Acad. Sci. 107, 13473–13478. https://doi.org/10.1073/pnas.100181510.

Wilson, J.A., Clark, J.J., 2004. Obesity: impediment to postsurgical wound healing. Adv. Skin Wound Care 17, 426–432.

Witte, M.B., Barbul, A., 2002. Role of nitric oxide in wound repair. Am. J. Surg. 183 (4), 406–412. https://doi.org/10.1016/S0002-9610(02)00815-2.

Wolcott, R.D., Rhoads, D.D. and Dowd, S.E., 2008. Biofilms and chronic wound inflammation. J. Wound Care. 17,333-341. https://doi: 10.12968/jowc.2008.17.8.30796.

Wu, Y.K., Cheng, N.C., Cheng, C.M., 2019. Biofilms in chronic wounds: pathogenesis and diagnosis. Trends Biotechnol. 37, 505–517. https://doi.org/10.1016/j.tibtech.2018.10.011.

Wu, M.L., Deng, J.F., Lin, K.P., Tsai, W.J., 2013. Lead, mercury, and arsenic poisoning due to topical use of traditional Chinese medicines. Am. J. Med. 126, 451–454. https://doi.org/10.1016/j.amjmed.2013.01.001.

Wu, J., Li, X., Li, D., Ren, X., Li, Y., Herter, E.K., Qian, M., Toma, M.A., Wintler, A.M., Sérézal, I.G. and Rollman, O., 2020. MicroRNA-34 family enhances wound inflammation by targeting LGR4. J. Investig. Dermatol. 140, 465-476. https://doi: 10.1016/j.jid.2019.07.694.

Xie, Z., Paras, C.B., Weng, H., Punnakitikashem, P., Su, L.C., Vu, K., Tang, L., Yang, J., Nguyen, K.T., 2013. Dual growth factor releasing multi-functional nanofibers for wound healing. Acta Biomater. 9, 9351–9359. https://doi.org/10.1016/j.actbio.2013.07.030.

Xu, Z., Liang, B., Tian, J., Wu, J., 2021. Anti-inflammation biomaterial platforms for chronic wound healing. Biomater. Sci. 9, 4388–4409. https://doi.org/10.1039/D1BM00637A.

Xue, M., Jackson, C.J., 2015. Extracellular matrix reorganization during wound healing and its impact on abnormal scarring. Adv. Wound Care 4, 119–136. https://doi.org/10.1089/wound.2013.0485.

Yang, D.J., Moh, S.H., Son, D.H., You, S., Kinyua, A.W., Ko, C.M., Song, M., Yeo, J., Choi, Y.H., Kim, K.W., 2016. Gallic acid promotes wound healing in normal and hyperglucidic conditions. Molecules 21, 899. https://doi.org/10.3390/molecules21070899.

Yuan, L., Sun, Y., Xu, M., Zeng, F. and Xiong, X., 2019. miR-203 acts as an inhibitor for epithelial-mesenchymal transition process in diabetic foot ulcers via targeting interleukin-8. Neuroimmunomodulation. 26, 239-249. https://doi: 10.1159/000503087.

Zahedi, P., Rezaeian, I., Ranaei-Siadat, S.O., Jafari, S.H., Supaphol, P., 2010. A review on wound dressings with an emphasis on electrospun nanofibrous polymeric bandages. Polym. Adv. Technol. 21, 77–95. https://doi.org/10.1002/pat.1625.

Zhao, C.C., Zhu, L., Wu, Z., Yang, R., Xu, N. and Liang, L., 2020. Resveratrol-loaded peptide-hydrogels inhibit scar formation in wound healing through suppressing inflammation. Regen. Biomater. 7, 99-107. https://doi: 10.1093/rb/rbz041.

Zhou, X., Ruan, Q., Ye, Z., Chu, Z., Xi, M., Li, M., Hu, W., Guo, X., Yao, P., Xie, W., 2021. Resveratrol accelerates wound healing by attenuating oxidative stress-induced impairment of cell proliferation and migration. Burns 47, 133–139. https://doi.org/10.1016/j.burns.2020.10.016.

Zhou, R., Xiang, C., Cao, G., Xu, H., Zhang, Y., Yang, H., Zhang, J., 2021. Berberine accelerated wound healing by restoring TrxR1/JNK in diabetes. Clin. Sci. 135, 613–627. https://doi.org/10.1042/CS20201145.

Zou, M.L., Teng, Y.Y., Wu, J.J., Liu, S.Y., Tang, X.Y., Jia, Y., Chen, Z.H., Zhang, K.W., Sun, Z.L., Li, X., Ye, J.X., 2021. Fibroblasts: heterogeneous cells with potential in regenerative therapy for scarless wound healing. Front. Cell Dev. Biol. 9, 713605 https://doi.org/10.3389/fcell.2021.713605.