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Review Article

WOUND HEALING: CURRENT UNDERSTANDING AND FUTURE PROSPECT

SHARMA AJAY KUMAR[1], SUNDER VIGHNESH[2], YASHAVARDDHAN M.H.[1,2] AND SHUKLA SANDEEP KUMAR[1*]

[1]Division of Radioprotective Drug Development Research, Institute of Nuclear Medicine and Allied Sciences, Delhi, 110 054, India
[2]School of Biotechnology, KIIT University, Bhubaneswar, Odisha, 751 024, India
*Corresponding Author: Email- sandeepshukla@inmas.drdo.in

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Abstract- Wound casualties are encountered very often in various situations including combat scenario. All these wounds need to be healed rapidly and efficiently to bring back the injured individual to an optimum level of fitness so that he can get back to his normal work schedule. So far, many strategies have been developed across the globe. But there is a no infallible solution available that can overcome the various complexities in wound healing and its management. Hence, there is a need to develop suitable technologies that could solve wound related complexities. An ideal intervention for wound care must involve components that act the different steps in the process of natural wound healing. An ideal intervention should possess blood-clotting, anti-microbial, growth promoting and analgesic properties. The present review briefly discusses the current understanding and future prospect of wound healing.

Keywords- Wound healing, Pharmacological intervention, Inflammation, Epithelization.

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Introduction

Wounds are the physical damage to the skin and underlying tissues that may be intentionally formed for surgical procedures or due to accidental exposure to excessive heat, trauma, chemicals, or microbial pathogens [1,2]. The process of wound healing starts right from the moment of injury and occurs in the form of various steps comprising hemostasis, inflammation, proliferation, re-epithelialization, and angiogenesis [3]. The management of wounds is of high clinical and socio-economic value. Wound healing occupies an important field of research in modern biomedical sciences. Many traditional as well as advanced wound healing drugs have been tested so far for faster recovery from wound damage. The present review discusses the current understanding and future perspectives in the field of wound healing.

Wounds and their classification:

Wounds can be caused by many factors that include physical, chemical, thermal, microbial and immunological insults. These insults lead to wounds that can be classified into four broad categories. They are:

- **Open wounds:**

An open wound is one in which there is clear bleeding. They can be further categorized as; Incisions, lacerations, abrasions, punctures, penetration wounds and gunshot wounds [4].

- **Closed wounds:**

Closed wounds differ from open wounds in the fact that the bleeding in closed wounds is restricted to inside the body.

- **Acute wounds:**

Acute wounds are those wounds that follow the normal process of wound healing [5]. The healing in these types of wounds is well orchestrated with defined steps.

- **Chronic wounds:**

In contrast to acute wounds, chronic wounds, as the name suggests, take abnormally long periods to heal. Chronic wounds fail to progress like normal wounds with distinct and well-defined stages [6].

Overview of the wound healing process:

Wound defines injury or disruption to the usual makeup and physiology of the skin. Wounds present clinicians around the world with a serious challenge, frequently leading to disease and death. The ideal wound healing process is classified into four different steps: Hemostasis, inflammation, proliferation, and remodeling [7].

- **Hemostasis**

This is the first stage of the wound healing process which involves constriction of blood vessels leading to reduction of blood supply at the site of injury [8]. This eventfully results into platelets aggregation that helps in closure of blood vessels walls. Clotting factors that are responsible for the cleavage of fibrinogen to fibrin, are released which help in formation of fibrin mesh to form a clot. The hemostasis stage begins instantly on detecting a break in the epithelial barrier. The first fibrin strand begins to adhere in about sixty seconds [9].

Inflammation:

The inflammation stage is activated during the hemostasis phase [10]. The main role of inflammation is to perform cleansing at the site of the wound by eliminating invading microorganisms. Inflammation is further divided into two stages. The first stage is characterized by the influx of the neutrophils to the site of the wound and late inflammatory phase involves the migration of macrophages [10].

- **Early inflammation:**

It is characterized by the production of polymorphonuclear neutrophils (PMN). Neutrophils migrate from the blood vessels to the wound facilitated by TGF-β

(Transforming growth factor- β) [robson]. They eliminate foreign material, invading pathogens and cell debris. On the completion of their role in the early inflammatory phase there is a rapid drop in numbers at the site of the wound and gradual replacement by macrophages after about 72 hours [11, 12]. The primary purpose of this stage of wound healing is the decontamination of the damaged site by phagocytosis of the invading pathogens [13].

- **Late inflammation**:

The presence of macrophages characterizes this phase. These are the most important cells in the inflammatory response [14]. They reach the wound site approximately 48-72 hours after injury to continue phagocytosis [15]. Macrophages secrete a variety of cytokines like platelet derived growth factor (PDGF) and transforming growth factor-β (TGF-β) that attract cells like fibroblasts to further assist wound healing. These macrophages perform the function of removing cell-debris, neutrophils, and bacteria [16].

- **Proliferative phase:**

In this phase, there is migration of fibroblasts to the site of the wound and formation of the extracellular matrix. After successful completion of hemostasis and the immune response, the wound healing is now focused more on tissue repair [17].

- **Fibroplasia:**

Fibroblasts migrate to the wound on the 3rd day of injury. This action is stimulated by a combination of cytokines produced initially by macrophages and lymphocytes [18]. In the wound site, the fibroblasts produce and deposit proteins that are part of the extracellular matrix. These include hyaluronan, fibronectin, type 1 and type 3 procollagen. This deposition continues till the 7th day till the matrix proteins are found in abundance and can help with cell migration and the overall repair process [19]. The fibroblasts then mature to myofibroblasts and assist with wound contraction.

- **Angiogenesis:**

Angiogenesis is one of the essential parts of wound healing progression involving the restoration of the vascular system in the damaged region to ensure influx of nutrients to the wound bed [10]. It takes places a result of the interaction between growth factors like FF, VEGF, TGF-β, endothelial cells and the extracellular matrix environment [20].

Re-epithelialization:

Re-epithelialization is the restoration of the intact epidermal barrier at the site of the wound [21]. The cells, majorly responsible for this process are the keratinocytes. A wound is not considered to be healed in the absence of the epithelialization step [22]. Epithelial cells start migrating from the edge of the wounds a few hours after formation of the wound. When epithelial cells from the different edges meet, migration stops [23].

Maturation phase:

This is also known as the remodeling stage of wound healing and is the final phase of wound healing. It is the stage where granulation tissue is gradually converted to scar tissue [24]. It starts after the 3rd week and constant alterations can last for years. Maximum tensile strength is attained after a year and at this stage the wound has 70% of the tensile strength of the original skin [25].

Factors affecting wound healing:

Overall wound healing process is also mediated through various localized and systemic factors as described below:

- **Humidity and oxygenation**:

It is important to maintain a moist wound environment for the rapid healing of wounds. Moisture helps with the epithelialization phase of wound healing [26]. Thus, occlusive dressings are used to cover wounds to provide them with a moist environment.

A high oxygen level is desirable for the healing of wounds. Partly because oxygen, a key part of ATP synthesis that prevents wound from infection, promotes angiogenesis, increases keratinocyte differentiation and migration, re-epithelialization, enhances fibroblast proliferation, and promotes collagen synthesis. These steps eventually lead to a faster rate of wound contraction [27, 28]. Oxygen is also responsible for determining the levels of superoxide dismutase [29].

- **Infection:**

Infection has the most negative effect on wound healing [30]. The likely chances of enhanced infection could be due to availability of foreign or necrotic material in the wound environment [31].

- **Age and nutrition:**

Age related impairment in wound healing is associated with a delay in wound healing due to a delayed inflammatory response [32]. This includes delayed T-cell infiltration, collagen synthesis and reduced macrophage activity. A deficiency in several key vitamins like vitamin C, vitamin K, vitamin A and vitamin E is also linked to impaired wound healing. These vitamins are important factors for clotting, collagen synthesis and epithelialization. Thus, the overall health status has a major impact on wound healing.

- **Stress:**

The level of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α which play important role in inflammatory phase of wound healing, are reduced under stress condition [33,34]. Stress is also reported to up-regulate expressions of glucocorticoids that are known to control differentiation, proliferation, gene transcription, cell adhesion molecules involved in immune cell trafficking [35].

Modern wound dressings:

Over the years, man has gained a deeper insight in to the overall process of wound healing. Topical ointments, creams and solutions are not preferred because of their tendency to lose their rheological properties [36]. This along with a deeper knowledge of new elastomeric polymers has led to the development of modern wound dressings. These dressings are often protective in nature, i.e. they prevent contamination. Along with their ability to protect, dressings should have the following characteristics [37]:

- Maintenance of humidity
- Control of exudate
- Ease of application and removal
- Allowance of gas and vapour transfer
- Thermal insulation
- Non-toxic

These properties indirectly lead to a more effective and faster re-epithelialization of wounds and control of bacterial contamination.

According to a study carried out by Thekdi et al, modern wound dressings have shown to be more efficient at healing wounds compared to conventional dressings [38]. In another study, the efficiency of hydrogel dressings was also found to be superior than the conventional dressing in the treatment of diabetic foot ulcers [39].

However, there is scope to further improve these dressings to give them additional abilities like that of hemostasis, antimicrobial activity, promotion of growth and analgesia [Fig-1].

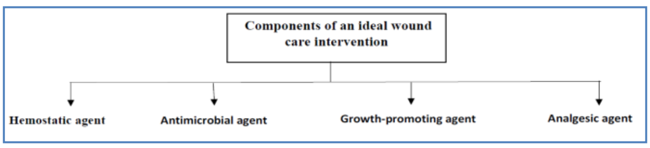

Fig-1 Chart representing the ideal properties that a wound care intervention must possess. It should have the ability to positively influence wound healing at various stages hemostasis, inflammation, proliferation and pain

Currently, there are five major classes of modern dressings. These include; hydrocolloids, hydrogels, foams, alginates and thin films. Each dressing has its advantages and disadvantages. Bacterial cellulose (BC) and Electrospun Nanofibers have also been used as advance Dressings material for wound care management [40, 41]. However, due to the mechanical and porous ability, biocompabacterial cellulose (BC) application is more preferred. Moreover, its antimicrobial could also be improved due to its interaction with any incorporated modifiers [40]. Electrospun nanofibre meshes have many advantages like high-surface area, micro-porosity and ability to load biomolecules. They have been used in chronic wound for their ability to prevent microbial infiltration and keeping a balanced moisture and gas exchange environment. In addition, these are used as scaffold in tissue engineering for many years [41].

Current approaches to wound care:

Hemostatic agents:

Hemorrhage or blood loss is the predominant cause of fatality in the combat zone [42]. The first step in the treatment of bleeding wounds is the application of pressure to the site of bleeding. Hemostatic agents are used in conjugation with this pressure. A hemostatic agent alone is far less effective without the application of pressure.

A list of hemostatic agents currently being used and their mechanism of action is listed below [Table-1]:

- **QuickClot**-

QuickClot is a hemostatic agent available in the form of a powder. These agents are called factor concentrators (based on their mechanism of action) those act by rapidly absorbing water and other fluids and thereby increasing the concentration of the several indigenous clotting factors (fibrin and platelets) produced by the body at the site of the wound [43]. This accelerates the hemostatic process by concentrating the blood clotting proteins at the wound site. This agent is made of zeolite [44], which is a microporous aluminosilicate mineral. These are often referred to as molecular sieves [45]. One major drawback of Quickclot is the heat generated by it on its application. There have been reports of Quickclot causing a burning sensation on the damaged tissue. A second generation of QuickClot based products generates lower amounts of heat. It shows a drop from 61.4 ± 10.7 °C to 40.3 ± 1.8 °C [46].

- **HemCon**-

HemCon is a hemostatic agent that is composed of chitosan. Chitosan is derived from chitin which in turn is a component of the exoskeletons of several crustaceans like shrimps, crabs, lobsters etc. [47]. Chitin is a polysaccharide and a derivative of glucose. Chitin is converted to chitosan on treatment of it by alkaline agents like Sodium hydroxide.

Chitosan-based hemostatic agents are referred to as mucoadhesive agents [48]. They act primarily because of their positive charge. On encountering a bleeding wound, they attract erythrocytes that inherently possess a negative charge, consequently causing the sealing of the wound [49]. Chitosan-based agents also exhibit antimicrobial activity according to the manufacturers of HemCon. A disadvantage of using chitin based hemostats is that there is high variability in efficacy from batch to batch, as seen in an experiment carried out in an animal model. They are also reported to work better on plane surfaces than on irregular surfaces [50].

- **Dry Fibrin Sealant dressing**-

Dry Fibrin Sealant dressing is a hemostat that falls under the category of pro-coagulant supplements. It is the first material to be approved as a hemostat by the FDA in 1998. Unlike other hemostatic agents, this dressing is itself embedded with fibrinogen, thrombin, calcium, and Factor XIII, all key intrinsic factors in blood clotting in humans. They expedite the clotting process by providing the site of the wound with the factors that are required for clotting. These factors are derived from human sources and present in highly pure forms. The new generation of products has almost negligible immune problems like viral diseases seen in the case of the older products [51].

Table-1 *List of some commercially available topical hemostatic agents*.

List of commercially available topical hemostats
QuikClot granular powder (QC)
Advanced Clotting Sponge (ACS)
QuikClot Combat Gauze™(QCG)
WoundStat™(WS)
HemCon
Advanced Clotting Sponge plus (ACS+)
QuikClot Combat Gauze X
QuikClot Combat Gauze Trauma Pad (QCTP)
QuikClot Interventional (QCI)

Antimicrobial agents:

Burn wounds are a common occurrence in the battlefield. These could rise in cases like explosions and gunshot wounds. Burn wounds turn lethal for the patient because of the growth of a wide variety of micro-organisms in the damaged region. These micro-organisms range from several strains of bacteria, fungi and viruses. It is vital to come up with topical treatments for the treatment of burn wounds due to the failure of systemically absorbed medicines like antibiotics to successfully reach the site of damage.

What makes burn wounds more susceptible to infection is the complete loss in the epidermal barrier and the denatured proteins and other bio-molecules at the site of the wound that act as nutrients for pathogens [52]. A loss in blood vessels around the wound site deters the immune response of the host to these pathogens [53]. Burn wounds also show the presence of bio-films [54], making burn wounds tougher to treat.

Infections caused by multi-drug resistant organisms remain a major problem in treating wounds suffered in the battlefield. The most commonly found multi drug resistant organisms (MDROs) in the battlefield are *Staphylococcus aureus, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter calcoaceticus-baumannii* complex [55]. A number of Gram-postive and Gram-negative bacterial strains are found to be resistant to a broad range of antibiotics [56]. Therefore, it is paramount to look screen for and test newer antimicrobial agents to treat infections caused by the above-mentioned micro-organisms.

Overview of dressings with antimicrobial agents:

There are many dressings that are commercially available which mainly consist of Silver and Honey as base [Table-2]:

Silver:

Silver is known to be effective an antimicrobial agent. However, due to the toxicity of silver ions to humans, there has been a development of silver nanoparticles. These nanoparticles exhibit a greater antimicrobial efficacy and lower toxicity [57]. Silver has a wide array of mechanisms that give it its antimicrobial activity. It is said to deactivate proteins in the cell membrane of bacteria that are important for ATP production and ion transport [58]. Another report suggests that silver binds to the 30s subunit of the ribosome and inhibits translation of bacterial proteins [59].

In the past, silver has been impregnated in dressings and tested. Ong et al designed a chitosan-based dressing impregnated with silver and a hemostatic agent. The results of this study suggested a significant reduction in mortality in a *Pseudomonas aeruginosa* infected mice model with severe cytotoxicity to fibroblasts in culture [60]. These studies indicate the potential of silver as an antimicrobial agent.

There are many dressings that are commercially available that have been incorporated with silver in different forms. Some of them are Acticoat 7, SILVERSEAL Hydrocolloid SureSkin and Silverseal.

Honey:

Honey has been used since ancient times to treat different types of wounds [61]. It is antibacterial for over 60 species of bacteria [2]. Moreover, honey is also a potent inhibitor of bio-film formation [hill], a common occurrence in burn wounds. The antibacterial characteristics of honey have been attributed to its high sugar content, presence of flavonoids and its high acidity [2].

There are commercially available honey-based wound dressings. Algivon, Medihoney and Thera Honey are some of them. Jull et al reported that topical honey successfully reduced the time taken to heal partial thickness burns by 4-5 days when compared to conventional dressings like tobramycin-impregnated gauze and other antiseptics [62].

Plant extracts:
Like honey, several plant extracts have also been in use for taking care of wounds. *Indigofera aspalathoides*, *Azadirachta indica*, *Memecylon edule*and *Myristica andamanica*are plant extracts have been investigated in wound healing [63]. Electrospinning of plant extracts has been recommended to incorporate them into a dressing [64, 65, 66].
In a study carried out by Yao et al used *Centella asiatica* as a gelatin nanofiber to test its antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Studies found that the nanofiber had a minimum inhibitory concentration of 6.25 mg/mL and 25 mg/mL for *S. aureus* and *P. aeruginosa* and *E. coli* respectively [66]. Aloe Vera is another promising plant extract with applications in wound healing. Aloe Vera is known for its antimicrobial activity [67]. Pereira et al synthesized an alginate based hydrogel incorporated with Aloe Vera gel [68].

Table-2 *Table representing commercially available topical silver/honey based antimicrobial agents [2].*

List of commercially available topical silver/honey based antimicrobial agents
Silver based:
Silverseal
Acticoat 7
Acticoat Moisture Control
SILVERSEAL Hydrocolloid
Tegaderm Ag Mesh Dressing with Silver
Urgotul SSD
Vliwaktiv Ag, Activated Charcoal Rope with Silver
Arglaes film
Restore Contact Layer with Silver
Honey based:
Manuka IG
TheraHoney
Medihoney
Algivon
Activon
Actilite

Debridement:
Wound debridement is a critical step in the treatment of wounds. It is loosely defined as the removal of dead or devitalized tissue from the site of the wound [69]. Devitalized tissue is that tissue which is dead and cannot be brought back to life. It is important to remove dead tissue because it interferes with the formation of granulation tissue. The presence of devitalized tissue also increases the risk of bacterial infections, an excessive inflammatory response and retardation of wound closure [70]. Reports suggest that debridement of wounds does indeed accelerate the wound healing process. There are several methods of wound debridement. The choice of the method to be used is dependent on the following factors [71]:

- Availability of resources
- Patients age and choice
- Part of the body that is damaged and the type of tissue
- Skills of the clinician
- Environment of the patient

The methods of debridement are described below:

- **Autolytic debridement**:

Autolytic debridement is the easiest and most preferred method of debridement. It does not heavily rely on the skills of the clinician and can be carried out with ease. This method of debridement relies on the body's natural mechanism of removal of dead tissue. This process is carried out by enzymes that manage to break down the dead tissue at the site of the wound [72]. This method is slow compared to the other forms of debridement and increases the risk of infection. TenderWet 24 is a dressing developed in Switzerland that assists autolytic debridement [73]. It functions by attracting necrotic tissue, bacteria and toxins *viz a viz* providing an optimum environment for the functioning of several lytic enzymes of the hosts defense mechanism [74].

- **Mechanical debridement:**

Mechanical debridement involves physically excising devitalized tissue from the site of the wound to prepare the wound bed for rapid recovery. However, this method of debridement is thought to be very painful [75]. Previously used methods involved placing a wet gauze on the wound and waiting for the gauze to dry. On drying, the dead skin and exudates adhere to the gauze and the gauze is then removed. This method has long been replaced by more patient-friendly alternatives. Debrisoft is one such technology that has been developed to ensure a less painful way of mechanical debridement [76]. It is known to selectively remove debris and spare newly formed granulation tissue and already established epithelial cells. In a study carried out by NICE, it was found that Debrisoft was effective in 93.4% cases involving 152 patients with 45% claiming that they experienced no pain [76].

- **Sharp debridement:**

Sharp debridement is done by removing dead tissue with instruments like scissors and scalpels. This method is described as quick and pain-free. But, this method requires highly skilled personnel as the medical practitioner should be clearly able to distinguish between healthy and dead tissue to avoid damaging healthy tissue. This makes sharp debridement highly selective [76]. It can be carried out almost anywhere, making it the most suitable method for debridement of battlefield wounds.

- **Surgical debridement**:

Surgical debridement is carried out using scissors and a scalpel by a skilled surgeon [77], almost in all cases, in an operating theatre. This form of debridement may not be suitable for treatment of wounds suffered in combat because of the lack of facilities and time. It also requires a concomitant use of anesthesia [76] to deal with the pain experienced during surgical debridement. There is also a significant loss of viable tissue. Surgical debridement is also an expensive form of treatment because of the need of a fully functioning operation theatre.

Topical Analgesia and Anesthetic agents:
Analgesia or 'pain management' is a critical step in dealing with casualties in the battlefield or in any individual who must receive treatment for wounds. In the battlefield, analgesia plays an important role in making the transport of casualties easier [78]. Pain is a factor that is often neglected when dealing with wounds and has a negative impact on the outcome of wounds. Furthermore, pain while receiving treatment makes is harder to carry out procedures like changing dressings and suturing.
Traditionally, analgesics are administered systemically to deal with pain associated with wounds, but there is a high risk of adverse effects while doing so. There have been efforts in trying to come up with an intervention that will topically and locally reduce pain [Table-3].
Dressings that are coated with drugs that have an analgesic drug are a highly recommended tool for dealing with pain associated with wounds. These include NSAID's, opioids and drugs like lidocaine. According to studies conducted by Arapoglou et al, foam dressings that are loaded with ibuprofen, a NSAID had the best analgesic effect according to patients [79].
Topical opioids are another sought after group of compounds for pain relief. Opioids target several opioids receptors. These receptors are over expressed during the time of inflammation and along with an analgesic effect, these opioids are also said to have a positive effect on the wound healing process [80, 81]. For example, according to Huptas et al, a topical morphine gel was able to significantly reduce pain in 90% of the patients [82, 83].
Topical medications like lidocaine and benzocaine are often used in pain relief. The main targets of these analgesics are the neurons. They act by blocking the

permeability of sodium ions into the neuronal membranes and as a result stabilize the electric potential of the neuron. This leads to an inhibition in the initiation and conduction of nerve impulses and leading to a numbing effect at the site of application. Reports indicate the success of a lidocaine based cream in pain reduction [84].

Table-3 *List of different types of topical analgesics used [79, 82].*

Class	Name
NSAID's	Ibuprofen, Diclofenac
Opioids	Fentanyl, morphine, diamorphine, methadone etc.
Other local anesthetics	Benzocaine, lidocaine, dibucaine, etc.

Topical growth factors:

Growth factors play a major role in the later stages of the wound healing process. These stages include the re-epithelialization, granulation tissue formation and closure of the wound. Epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet derived growth factor (PDGF) and transforming growth factor (TGF) are few of the growth factors that are a part of the normal process in wound healing. It has been reported that, chronic (non-healing) wounds have shown reduced levels of expressions of these growth factors when compared to acute wounds [85], thus, implying that growth factors play important roles in the proper progression of a wound. However, the topical use of growth factors is not that straightforward and could be lethal if not administered properly. It is of prime importance to make sure that the administered growth factors have only a local effect rather than a systemic effect. A systemic effect could lead to undesired angiogenesis [86]. The concentration and duration of growth factor interacting with the skin is also of great importance. It should sufficient enough to exhibit its effects [87]. The time administration of growth factors should be in accordance to the time at which each of them is naturally expressed as part of the normal physiologic response. For example, FGF is normally expressed at the early stages of wound healing, whereas, VEGF is expressed at the later stages [88]. Studies also suggest that combinations of growth factors are more efficient than a single growth factor alone due to their synergistic action [89]. It also important to make sure that growth factors are administered along with protease inhibitors so that to increase their half-life.

Factors to consider while topical using growth factors:

- Ensuring local effect
- Appropriate concentration and duration of exposure
- Using combination of growth factors for enhanced effect
- Choosing the right time of administration to make sure it coincides with the physiologic response

Some growth factors that have been studied are:

- Epidermal Growth Factor (EGF)-

Epidermal growth factor is responsible for the migration of epithelial cells [90]. It is also responsible for increasing the number of fibroblasts at the site of the wound [91]. Human EGF has shown success in treatment of animal excisional wound studies [92]. However, a study where EGF was used in combination with silver sulfadiazine cream did not show positive results [93]. This suggests issues with the topical delivery of growth factors. A commercial recombinant EGF is available in some countries. Positive signs for the use of topical EGF were seen in an in vivo study carried out by Ulubayramin which a dressing containing EGF was found to be more efficient than a dressing without growth factors [94].

- Fibroblast Growth Factor (FGF)-

FGF stimulates migration and proliferation of endothelial cells and increases the expression of collagen [95, 96]. Topical FGF has extensively been studied in mice and has showed promising results. bFGF (basic fibroblast growth factor), a type of FGF has also been tested in mice and has shown to stimulate angiogenesis, fibroblast proliferation and an overall acceleration in wound repair. To deal with the problem of the short half-life of FGF, it was incorporated into a chitosan film and applied by Mizuno et al and this resulted in a synergistic between chitosan and FGF and a better wound healing ability than them used individually [97]. This gives hope of incorporating growth factors in to suitable modern wound dressings.

Like the above-mentioned growth factors, there have been comprehensive studies carried out using other growth factors in both animal models and humans. There are problems associated with the half-life of growth factors when used topically. It is also important to properly select the delivery system for administering growth factors. A study where an attempt was made to treat chronic foot ulcers in diabetic patients showed no significant results owing to the use of an inappropriate delivery system which led to loss in concentration of the growth factor at the site of the wound [98].

Gene therapy can also offer a promising role in wound healing intervention strategy. Across the globe many clinical studies are underway using gene therapy some of them include trials with hepatocyte growth factor and platelet-derived growth factor A in chronic wounds (99).

Conclusion:

Wounds represent a major challenge regardless of all recent advances in wound healing interventions throughout the world. A thorough knowledge of wound biology is essential to facilitate development of various strategies for wound care management. Our better understanding of indispensable wound healing process including haemostasis, inflammation, proliferation, re-epithelialisation and angiogenesis vis-a-vis basic needs of specific wound type such as nutritional optimization, debridement, compression, management of ischemia and infections could lead to suitable wound healing agents and wound care management strategies. In brief, the compilation of advanced healing intervention should be based on the evidence that intervention facilitates its most appropriate use.

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AKS and VS have contributed equally in drafting and revision. **MHY** critically reviewed and edited the manuscript. **SKS** participated in discussion and supervision of the manuscript. All authors read and approved the final manuscript.

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