EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 12
67-77
Year: 2019

HISTORICAL AND FUTURE DIRECTIONS IN WOUND HEALING THERAPY

Mohamed Raouf Mohamed*[1], Khaled Aly Khaled[2], Hamza Abdel Raouf[3] and Usama Farghaly Aly[4]

[1]Pharmacist One in Critical Care Pharmacy of King Faisal Specialist Hospital and Research Center-Jeddah-KSA Faculty of Pharmacy, Minia University.
[2]Professor of Pharmaceutics, Department of Pharmaceutics, Faculty of Pharmacy, Minia University.
[3]Professor of Dermatology and Andrology, Department of Dermatology, Faculty of Medicine, Minia University.
[4]Associate Professor of Pharmaceutics, Department of Pharmaceutics, Faculty of Pharmacy, Minia University.

***Corresponding Author: Mohamed Raouf Mohamed**
Pharmacist One in Critical Care Pharmacy of King Faisal Specialist Hospital and Research Center-Jeddah-KSA Faculty of Pharmacy, Minia University.

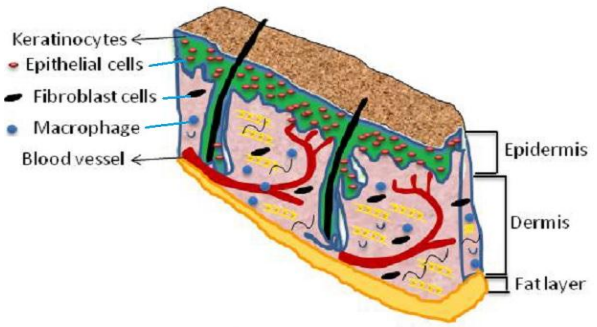
Article Received on 09/09/2019 **Article Revised on 30/09/2019** **Article Accepted on 20/10/2019**

ABSTRACT
Wounds can be classified based on the time at which it heals as acute and chronic. An acute wound is an injury that causes a break in the skin and it occurs suddenly, last a short time, and may heal on its own. A chronic wound is a wound that does not heal in orderly set of stages and in a predictable time the way most wounds do. Chronic wound remain one of the most common and serious consequences of diabetes. Wound healing may be delayed due to abnormal cell function, hyperglycemia, peripheral neuropathy, peripheral vascular disease, susceptibility to infections and abnormal planter foot pressures. Delayed wound healing causes prolong morbidity and may ultimately end up in loss of part or whole of the foot. Treatment of chronic wound represents a significant and growing challenge. The wound-healing process consists of four integrated and overlapping phases: homeostasis, inflammation, proliferation, and tissue remodeling or resolution. Impaired wound healing is a major complication of diabetes. Many topical therapeutic agents have been used to enhance wound healing. Development of new generation wound care products is an evolving field. One of the most common agents used for wound care are topical preparations.

INTRODUCTION
A wound can have a significant impact on a person life. Wounds can lead to prolonged periods of disability in addition to suffering pain and discomfort. It may even prevent a person from performing everyday activities such as walking and bathing. This inactivity may in itself lead to further health problems. Some wounds are associated with odour and excessive drainage and require frequent attention as they may impede social interactions. A non-healing wound may prevent a return to work which can have psychological as well as economic ramifications.

Development of new generation wound care products is an evolving field. To find clinical and commercial wound management products, there is a need to have proper understanding of processes involved in wound healing and treatment in more advanced way.

1.1 Wounds
Wound is a reversible or irreversible outcome of injury in which the part effected is torn, cut or punctured. This may be due to trauma, surgery or health disorders. The wounds are generally classified according to the depth of tissue loss. The classification is as follows; wounds with tissue loss or without tissue loss. The wounds with tissue loss include burn wound (second and third degree burn wounds) and diabetic foot ulcer. The wounds without tissue loss include laceration and first degree burn wound. The wounds are classified, also, according to its depth into the skin, which indicates whether it is a superficial, partial thickness or a full thickness wound. A superficial wound involves epidermis of the skin only whereas partial thickness wound include epidermis and dermis of the skin. A full thickness wound consisted of epidermis, dermis and subcutaneous tissue of the skin.



Schematic Representation of Structure of Skin (Kanitakis, 2002).

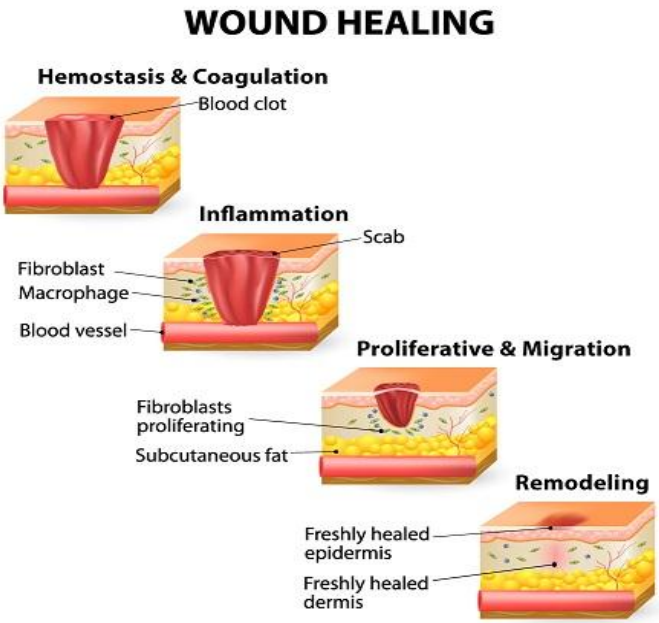
Wounds can even be classified based on the time at which it heals as acute and chronic. An acute wound is an injury that causes a break in the skin and it can happen suddenly, lasts a short time, and may heal on its own. For example, a puncture wound is usually made by a sharp, round, and pointed object, such as a needle or nail. There are principally two types of acute wounds; traumatic wounds and surgical wounds. A traumatic wound such as a minor cut, leads to extensive tissue injuries when a force exceeds the strength of the skin or the underlying supporting tissues. A traumatic wound is classified by whether or not it is tidy or untidy. A surgical wound is either incised and sutured or lay open to heal by a surgeon. The wound breaks the integrity of the skin including the epidermis and dermis. Surgical wounds are classified in relation to the potential for infection in the wound: they are considered to be either clean, clean contaminated or contaminated (dirty).

The majority of acute wounds heal without any complication. However, chronic non-healing wounds involving progressively more tissue loss, give rise to the biggest challenge to wound-care product researchers. Unlike surgical incisions, where there is very little tissue loss and are easy to heal, chronic wound disrupt normal process of healing. Delayed healing is a result of compromised wound physiology and occurs with venous stasis, diabetes, or prolonged local pressure. Second major challenge is the prevention of scarring, keloid formation or contractures to obtain cosmetically acceptable healing (Kim SK, 2013).

Wound infection is the major difficulty in the field of wound care management. This is because such infections can cause exudate formation, delay the wound healing, facilitate improper collagen deposition, etc. Microbes are the major reason for infection and their prevalence is high in and around us.

1.2 Phases of Wound Healing

Wound healing, is a normal biological process in the human body and it is achieved through four precisely and highly programmed phases: hemostasis, inflammation, proliferation, and remodeling (Jespersen J, 1988). For a wound to heal successfully, all four phases must occur in the proper sequence and time frame. Many factors can interfere with one or more phases of this process, thus causing improper or impaired wound healing. The different phases of wound healing are illustrated below.



Schematic representation of different phases of wound healing (Gaur M, 2017).

1.2.1 Hemostasis

Hemostasis occurs immediately after initial injury. Platelet is the key cell responsible for this function, in which body forms a clot to prevent further bleeding. The coagulation cascade is activated through extrinsic and intrinsic pathways, leading to platelet aggregation and clot formation in order to limit blood loss (Robson MC, 2001). As blood spills into the site of injury, the blood components and platelets come in contact with exposed collagen and other extracellular matrix components. This contact triggers the release of clotting factors from the platelets and the formation of a blood clot composed of fibronectin, fibrin, vitronectin and thrombospondin (Broughton et al, 2006). The blood clot and platelets trapped within it are not only important for haemostasis, as the clot also provides a provisional matrix for cell migration in the subsequent phases of haemostatic and inflammatory phases. The cytoplasm of platelets contains α-granules filled with growth factors and cytokines, such as Platelet Derived Growth Factor (PDGF),

Transforming Growth Factor-β (TGF-β), Epidermal Growth Factor (EGF) and Insulin-Like Growth Factor (IGF). These molecules act as promoters in wound healing cascade by activating and attracting neutrophils and later macrophages, endothelial cells and fibroblasts (Richardson, 2004). Platelets also contain vasoactive amines, such as serotonin, that are stored in dense bodies and cause vasodilation and increased vascular permeability, leading to fluid extravasations in the tissue that result in edema which in turn potentiates itself during the following inflammatory phase (Hart, 2002).

1.2.2 Inflammation

The humoral and cellular inflammatory phase follows two separate phases, an early inflammatory phase and a late inflammatory phase (Hunt, 1998).

Early inflammatory phase

It activates the complement cascade and initiates molecular events, leading to infiltration of the wound site by neutrophils, whose main function is phagocytosis in order to destroy and remove bacteria, foreign particles and damaged tissue. The neutrophils begin to be attracted to the wound site within 24 - 36 h of injury by various chemoattractive agents including TGF-β.

Late inflammatory phase

As part of the late inflammatory phase, 48 - 72 h after injury, macrophages appear in the wound and continue the process of phagocytosis (Pierce et al, 1991). These cells are originally blood monocytes that undergo phenotypic changes on arrival into the wound to become tissue macrophages attracted to the wound site by a myriad of chemoattractive agents, including clotting factors, complement components, cytokines such as PDGF, TGF-β, leukotriene B4 and platelet factor IV as well as elastin and collagen breakdown products. Macrophages have longer lifespan than neutrophils and continue to work at a lower pH (Glat, 1997). These cells act as key regulatory cells and providing an abundant reservoir of potent tissue growth factors, particularly TGF-β, as well as other mediator activating keratinocytes (TGF-α, heparin binding epidermal growth factor, Fibroblast Growth Factor (FGF), collagenase), fibroblasts and endothelial cells (Goldman, 2004).

1.2.3 Proliferation

The proliferative phase starts on the third day after wounding and lasts for about 2 weeks thereafter. It is characterized by fibroblast migration, deposition of newly synthesized extracellular matrix and abundant formation of granulation tissue.

Fibroblast migration

Following injury, fibroblasts and myofibroblasts in the surrounding tissue are stimulated to proliferate for the first 3 days. Then, they migrate into the wound, being attracted by factors such as TGF-β and PDGF which are released by inflammatory cells and platelets (Servold, 1991). Once in the wound, they proliferate profusely and produce matrix proteins hyaluronan, fibronectin, proteoglycans, type 1 and type 3 procollagen. By the end of the first week, abundant extracellular matrix accumulates which further supports cell migration and is essential for the repair process. Fibroblasts, then, change to their myofibroblast phenotype. At this stage, they contain thick actin bundles below the plasma membrane and actively extend pseudopodia, attaching to fibronectin and collagen in the extracellular matrix. Wound contraction, which is an important event in the reparative process helps to approximate the wound edges and then takes place as these cell extensions retract. Having accomplished this task, redundant fibroblasts are eliminated by apoptosis (Clark, 1993).

Collagen synthesis

Collagens are an important component in all phases of wound healing. Synthesized by fibroblasts, they impart integrity and strength to all tissues. They play a key role especially in the proliferative and remodelling phases of repair (Folkman J, 1987). Collagens act as a foundation for the intracellular matrix formation within the wound. Unwounded dermis contains 80 % type I and 25 % type III collagen whereas wound granulation tissue expresses 40 % type III collagen.

Angiogenesis and granulation tissue formation

Modeling and establishment of new blood vessels is critical in wound healing and takes place concurrently during all phases of the reparative process. Resident endothelial cells are responsive to a number of angiogenic factors, including FGF, Vascular Endothelial Growth Factor (VEGF), PDGF, angiogenin, TGF-α and TGF-β. A fine balance is kept by the action of inhibitory factors, such as angiostatin and steroids. Inhibitory and stimulatory agents act on proliferating endothelial cells directly as well as indirectly by activating mitosis, promoting locomotion and by stimulating host cells to release endothelial growth factors (Takeshita et al, 1994). Under hypoxic conditions, molecules are secreted from the surrounding tissue, promoting proliferation and growth of endothelial cells. In response, a four-step process takes place: (i) production of proteases by endothelial cells for degradation of the basal lamina in the parent vessel in order to crawl through the extracellular matrix (ii) chemotaxis (iii) proliferation (iv) remodeling and differentiation. Fibroblast Growth Factor and VEGF play central regulatory roles in all of the processes (Mulder, 2002).

Initially, there is no vascular supply in the wound center. So, the viable tissue which is limited to the wound margins is perfused by uninjured vessels and by diffusion through undamaged interstitium. Capillary sprouts from the surrounding edges invade the wound clot and within a few days, microvascular networks composed of many new capillaries are formed.

Epithelialization

Migration of epithelial cells starts from the wound edges within a few hours of wounding. A single layer of cell initially forms over the defect, accompanied by a marked increase in epithelial cell mitotic activity around the wound edges. Cells migrating across them attach to the provisional matrix below. When the advancing epithelial cells meet, migration stops and the basement membrane start to form (Field CK, 1994).

1.2.4 Remodeling

As the final phase of wound healing, the remodeling phase is responsible for the development of new epithelium and final scar tissue formation. Synthesis of the extracellular matrix in the proliferative and remodeling phase is initiated contemporarily with granulation tissue development. This phase may last up to 1 or 2 years or sometimes for an even more prolonged period of time. Remodeling of an acute wound is tightly controlled by regulatory mechanisms with the aim of maintaining a delicate balance between degradation and synthesis, leading to normal healing. Along with intracellular matrix maturation, collagen bundles increase in diameter and hyaluronic acid and fibronectin are degraded. The tensile strength of the wound increases progressively in parallel with collagen collection. Collagen fibers may regain approximately 80 % of the original strength compared with unwounded tissue. The acquired final strength depends on the localization of repair and its duration. The original strength of the tissue can never be regained.

Synthesis and breakdown of collagen as well as extracellular matrix remodeling takes place continuously and both tend to equilibrate to a steady state about 3 weeks after injury. Matrix metalloproteinase enzymes produced by neutrophils, macrophages and fibroblasts in the wound are responsible for the degradation of collagen. Their activity is tightly regulated and synchronized by inhibitory factors. Gradually, the activity of tissue inhibitors of metalloproteinase increases, culminating in a drop in activity of metalloproteinase enzymes, thereby promoting new matrix accumulation (Falanga V, 1998).

Its subsequent organization is achieved during final stages of the remodeling phase, to a greater extent by the wound contraction that has already begun in the proliferative phase. The underlying connective tissue shrinks in size and brings the wound margins closer together, owing to fibroblast interactions with the extracellular matrix. The process is regulated by a number of factors in which PDGF, TGF-β and FGF being the most important. As wound heals, the density of fibroblasts and macrophages are further reduced by apoptosis. With time, the growth of capillaries stops, blood flow to the area declines and metabolic activity at the wound site decreases. The end result is a fully matured scar with a decreased number of cells and blood vessels and a high tensile strength (Kerstein MD, 2007).

1.3. FACTORS AFFECTING WOUND HEALING

Wound healing is a normal biological process in the human body. Many factors can adversely affect this process and lead to improper and impaired wound healing. Understanding of these systemic and local factors and their influence on wound healing is essential for better therapeutic opportunity for wound treatment (Albrition, 1991).

Systemic factors

1. Nutrition

Several macro and micro nutrients play a vital role in wound healing. Relevant macronutrients include proteins, carbohydrates, fats and water. Protein is essential for collagen and protein synthesis on wound site. A state of malnutrition may provide an inadequate amount of protein and this can decrease the rate of collagen synthesis, wound tensile strength or increased chance of infection (Franz et al, 2007). Carbohydrate aids cell proliferation and phagocytic activity of leucocytes to prepare wounds for fibroplasia and its deficiency decreases resistance to infection and impairs collagen synthesis. Relevant micronutrients include vitamins A, B-complex, C, E and K and minerals such as copper, iron and zinc.

2. Medication

Many drugs are known to impair wound healing. Chemotherapeutic agents used in cancer are well known to delay wound repair (Sherman RA, 1997). Systemic glucocorticoids interfere with normal healing process by reducing collagen synthesis and fibroblast proliferation.

3. Old Age

Elderly age is found to associate with delayed wound healing. It is reported that the fibroblast growth and activity diminishes. Collagen production and wound contraction is slow in older individuals (Greenhalgh, 2003).

4. Diabetes and other disease conditions

Diabetic patients are more susceptible to wound healing (Cuzzell JZ, 1990). Acute and chronic liver diseases are also associated with delay in wound healing. Patients with altered immune function have an increased susceptibility to wound infection (Riou et al, 1992).

5. Venous sufficiency

Adequate blood supply and tissue perfusion is extremely important for wound healing. Excessive pain, cold and anxiety can cause local vasoconstriction and increased healing time. Smoking decreases tissue perfusion and oxygen tension in wound (Lazarus et al, 1998).

Local Factors

1. Infection

Wound infection is probably the most common reason of impaired wound healing. *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are the

primary causes of delayed healing and infection in both acute and chronic wounds (Menke et al, 2007).

2. Skin maceration
If the peri-wound area is exposed to excess moisture from exudates, perspiration or incontinence, maceration and damage to the surrounding tissue can occur. This may predispose to infection, skin sensitivities, further skin breakdown and impede wound healing (Cutting KF, 2002).

3. Pressure, friction and shear
Mechanical forces such as pressure, friction and shear significantly impair wound healing by prolonging tissue damage. When pressure at the wound site is excessive or sustained, blood supply to the capillary network may be disrupted. This impedes blood flow to the surrounding tissue and delays healing (Pieper B, 2000).

4. Trauma and oedema
Wounds heal slowly and may not heal at all in an environment in which they are repeatedly traumatized or deprived of local blood supply by oedema. Oedema interferes with the transportation of oxygen and cellular nutrition to the wound (Dong et al, 1993).

5. Oxygen tension
Inadequate oxygen perfusion results in the formation of unstable collagen with low tensile strength and lower tissue resistance to infection by decreasing the phagocytic activity of leucocytes (Greif et al, 2000).

6. Foreign body
Unnecessary sutures, fragments of steel, glass, even bone can impede the healing.

7. Size, location and type of wound
Wound in richly vascularised area heals faster than those in poorly vascularised area.
A small incision wound heals faster than larger ones caused by trauma.

8. Radiotherapy
Local irradiation impairs wound healing by depleting dermal fibroblasts and decreasing the proliferative potential of endothelium. High dose may lead to vessel narrowing and reduced blood flow causing delay in wound healing (Devalia HL, 2008).

1.4 CLASSIFICATION OF WOUNDS
Based on the basis of physiology of wound healing
Wounds are popularly categorized by their level of chronicity as either an acute or a chronic wound.

Acute Wounds
Acute wound is a tissue injury that normally proceeds through an orderly and timely reparative process that results in sustained restoration of anatomic and functional integrity. Acute wounds are usually caused by cuts or surgical incisions and complete the wound healing process within the expected time frame (Menke et al, 2007).

Chronic Wounds
Chronic wounds are wounds that have failed to progress through the normal stages of healing and therefore enter a state of pathologic inflammation. Chronic wounds either require a prolonged time to heal or recur frequently. Local infection, hypoxia, trauma, foreign bodies and systemic problems such as diabetes mellitus, malnutrition, immune deficiency or medications are the most frequent causes of chronic wounds (Davies et al, 2007).

1.5 Wound healing therapies
Wound management requires careful and accurate assessment of the wound with the use of proper wound care products. Over the years the market has moved from traditional (gauze based) products to advanced (moist wound healing) products to actives (antimicrobials, mechanical devices) (LeBlanc et al, 2008).

The ultimate goal of wound management is the prevention of wounds, or the halting of wound deterioration to achieve more rapid healing. This goal can only be accomplished by intervening with appropriate quality care, in a timely manner with appropriate wound management (LeBlanc et al, 2008).

There are three basic principles which underlie wound healing:
1. Identify and control as best as possible the underlying causes
2. Support patient centered concerns
3. Optimize local wound care
There are many wound healing therapies available currently and the details of them are given below:

1.5.1 Hyperbaric oxygen therapy
Hyperbaric oxygen therapy (HBOT) is breathing 100% oxygen while under increased atmospheric pressure. Hyperbaric oxygen therapy can be done in single-person chambers or chambers that can hold more than a dozen people at a time. Chamber pressures typically rise to 2.5 times the normal atmospheric pressure. At the end of the session, which can last from thirty minutes to two hours, technicians slowly depressurize the chamber. In people with foot ulcers due to diabetes, HBOT significantly improved the ulcers healed in the short term but not the long term and the trials had various flaws in design and/or reporting that means we are not confident in the results (Kranke et al, 2004).

1.5.2 Vacuum assisted closure
Vacuum assisted closure (also called vacuum therapy, vacuum sealing or topical negative pressure therapy) is a sophisticated development of a standard surgical procedure, the use of vacuum assisted drainage to remove blood or serous fluid from a wound or operation site. The technique will help to remove chronic edema,

leading to increased localized blood flow, and the applied forces result in the enhanced formation of granulation tissue. However, the technique is appeared costly and inconvenient for patients (Blume et al, 2008).

1.5.3 Skin graft

A skin graft is a section of epidermis and dermis which has been completely separated from its blood supply in one part of the body, the donor site, before being transplanted to another area of the body, its recipient site. A skin graft is used to permanently replace damaged or missing skin or to provide a temporary wound covering. Skin that is damaged extensively by burns or non-healing wounds can compromise the health and well-being of the patient. Skin grafts can be classified as partial, full-thickness grafts and pedicle skin grafts (Milcheski et al, 2014).

Chronic wounds are a common problem faced by health care professionals. They are a difficult condition to manage, and as the name implies, take a long time to heal. These wounds are a cause of distress to the patient and a conundrum to the treating professional. They cause a financial burden not only to the patient in terms of lost man hours of work and reduced productivity, but also to the health services in terms of the cost of caring for the patient.

1.6 Topical Wound Treatments

When it comes to wound care, the challenge is to strike a balance between keeping the wound clean and moist, while at the same time fighting off the bacteria and microorganisms that threaten the body's natural ability to heal itself. A moist environment provides a perfect breeding ground for infectious microorganisms that can make the healing process painful and malodorous. Infection that occurs in a healing wound can cause complications and become costly to treat. Researchers and physicians have tried many number of topical treatments for wound care, including antibiotics, chlorohexidine, phenytoin, hydrogen peroxide, iodine and even honey (Sorg et al, 2017).

1.6.1 Topical Antimicrobial Therapy

Chronic skin wounds affect 3% of persons aged 60 years (Drosou et al, 2003) and are usually related to neuropathy (eg, diabetic foot or pressure ulcers), vasculopathy (venous stasis or arterial insufficiency ulcers), or trauma. Patients with chronic wounds are frequently treated with either systemic or topical antimicrobial therapy (Lipsky BA, 2009).

Disinfectants and *Antiseptics*

Disinfectant are agents with activity against virtually all disease-causing microorganisms, including spores; they are used primarily for sterilizing spelling surfaces and may be toxic to tissues.

Antiseptics are disinfectants that can be used on intact skin and some open wounds to kill or inhibit microorganisms. They often have multiple microbial targets, a broad antimicrobial spectrum, and residual anti-infective activity but are often toxic to host tissues (eg, fibroblasts, keratinocytes, and possibly leukocytes). These compounds have antibacterial and desloughing actions and are generally safe when applied to intact skin (Fonder et al, 2008). Commonly used antiseptics include hydrogen peroxide, which has limited bactericidal and debriding activity; chlorhexidine, which has long-acting activity against a wide range of both gram-negative and gram-positive bacteria; and iodophors, which release free iodides but may be cytotoxic (Lipsky BA, 2009).

Newer formulations, such as cadexomer iodine, offer sustained delivery of bactericidal concentrations to moist wounds without apparent tissue damage. Silver compounds (metallic, nanocrystalline, and ionic) have a broad bactericidal spectrum and have been used as topical antiseptics in various types of wound dressings (Patel et al, 2008). Because they are rapidly inactivated in the wound environment, they require a sustained delivery formulation. Silver has proven efficacy against several common wound pathogens, including methicillin-resistant *Staphylococcusaureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum b-lactamase producers. Resistance is rare but has been reported, mostly with gram-negative species (Paul, 2008). Silver compounds in various wound products differ in the manner and speed with which they release the bactericidal silver ions (Castellano et al, 2007).

Antibiotics

They usually act on one specific cell target, have a narrower spectrum of activity, are relatively nontoxic and are more susceptible to losing their effectiveness to bacterial resistance. The first topical antibiotics were derived from agents developed for systemic use (ie, sulfonamides in the mid-1930s), followed in the next decade by topical penicillins, bacitracin, gramicidin, aminoglycosides (including neomycin), polymixin, tetracyclines, and choloramphenicol. Agents introduced later include fusidic acid, clindamycin, metronidazole, mupirocin. Neomycin is active against most aerobic gram-negative rods (excluding most *Pseudomonas* species) and staphylococci (but not most other gram-positive cocci); resistance develops relatively frequently, as does contact dermatitis. Polymixin is active against some gram-negative rods (including *Pseudomonas* species) but not gram-positive cocci; systemic absorption is uncommon, and dermatitis is rare. Bacitracin is active against most gram-positive organisms, and resistance and toxicity are uncommon. These three antibiotics are combined in a nonprescription ointment commonly used to wounds by patients. It is best to avoid using topical antibiotics that are available for systemic therapy when treating wound infections, because they can provoke delayed hypersensitivity reactions, favor superinfections, and select for resistant pathogens. One exception is metronidazole, which can reduce the fetid odor of

(presumably) anaerobically colonized wounds (Terpenning et al, 1994). Antibiotics used only in topical formulations may be appropriate for treating some infected wounds. Mupirocin is active against aerobic gram-positive cocci (except enterococci) and has minimal toxicity, and cross-resistance is uncommon (Cooper R, 2004). Available data make it difficult to assess the efficacy of topical antimicrobials for chronic wounds (Lipsky BA, 2009).

1.6.2 Topical honey for Treating Chronic Wounds

Honey was considered one of the oldest wound dressing therapy (Lusby et al, 2002). Its use on skin wounds has been documented on skin grafts, trauma wounds, necrotizing fasciitis, pilonidal sinuses, pressure ulcers, lacerations, burns, surgical wounds, herpetic lesions, atopic dermatitis, animal bites, and rheumatoid ulcers (Namias, 2003). The use of honey had been forgotten with the discovery of antibiotics however, with antibiotic resistance on the rise in recent years, honey has been rediscovered and its uses once again are investigated.

The enzymes found in honey, play an important role in its antibiotic properties. Invertase produced by the bee converts sucrose to glucose and fructose, amylase breaks down starch, glucose oxidase converts glucose to gluconolactone which in turn yields gluconic acid and hydrogen peroxide (Pieper, 2009). Trace amounts of vitamin B, calcium, iron, zinc, potassium, phosphorus, magnesium, selenium, and chromium are also found in the composition of honey.

Honey with its supersaturated mixture of sugars with small quantities of enzymes, amino acids, vitamins, minerals and organic acids holds many desired properties for an impressive antibacterial dressing for wounds. Previous study has reported that, honey inhibits over 60 species of bacteria including, anaerobes, gram-positive and gram-negative bacteria (Molan, 1998) and even some yeast species of *Aspergillus*, and *Penicillium*.

Another factor associated with the antibiotic effect of honey its content of phytochemicals. The phytochemicals found in honey mostly consist of complex phenol and organic acids that further serve an antibacterial function (Lusby et al, 2002). They also aid in reducing the risk of oxidative damage in the tissue.

The third antimicrobial property of honey is due to glucose oxidase converting glucose to gluconic acid which gives honey its low pH. The low pH of honey comes also from the organic acids acetic, butanoic, formic, citric, succinic, lactic malic, pyroglutamic, and gluconic acid (Molan, 1992). Honey has an acidic composition with a pH between 3.2-4.5, which is acidic enough to inhibit many pathogens. The more acidic the pH, the more the pathogen growth is inhibited. In addition to decreasing the pathogens in the wound, the acidic environment is beneficial to epithelialization. The acid environment increases the amount of oxygen released from the hemoglobin in the wound bed, which, in turn, increase the rate of granulation (Kaufman et al, 1985).

The honey is sterilized with γ radiation to remove the spores but retain its biologic properties (Cooper et al, 2002). Manuka honey has a high level of phytochemical components and has been found to be very effective in clearing wounds (Hasamnis et al, 2010). It is known that honey's antibacterial activities are slower than those of traditional antiseptics which decrease bacteria count in minutes but balancing the speed against honey's other properties is the question. Honey is a well accepted natural regimen and people are open to the idea of using it as a medical treatment.

Future directions

1.6.3 Topical Phenytoin for Treating Chronic Wounds

Phenytoin is an anticonvulsant drug. It acts by blocking neuronal excitation by binding to sodium channels at rest, preventing them from becoming functional and generating excitatory action potentials (Arya R and Gulati S, 2012). A clinical study demonstrated that phenytoin sodium accelerates gingival wound healing compared with controls (Simpson et al, 1965). The first double blind, placebo controlled clinical study involving the use of phenytoin in leg ulcers demonstrated that, when compared with controls, the use of phenytoin promoted wound healing (Muthukumarasamy et al, 1991).A number of other studies have been conducted that have demonstrated the effectiveness of phenytoin in the treatment of a variety of wounds including diabetic ulcers (Bansal NK and Mukul, 1993), trophic ulcers in leprosy (Carneiro PM et al, 2003), chronic leg ulcers (Carneiro and Nyawawa ET, 2002), and superficial burn wounds (Shaw J et al, 2007). A published systematic review identifying, summarising and critically appraising the clinical evidence regarding the effects of phenytoin on wound healing was cited (Shaw J et al, 2007). The possible mechanism of action by which phenytoin promotes wound healing has been investigated (Shaw J et al, 2007).Various animal *in vitro* and clinical studies have indicated that phenytoin has actions that contribute to:

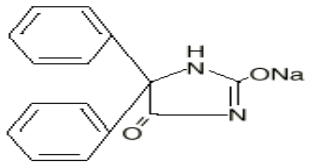
- An increase in the proliferation of fibroblasts (Moy et al, 1985).
- An increase in the deposition of collagen (Rhodes et al, 2001).
- A decrease in the action of collagenase (Moy et al, 1985).
- A decrease in bacterial contamination in wounds (El Zayat, 1989).

The precise mechanism of phenytoin decreasing bacterial contamination of wounds is not known. It has been reported that phenytoin has contributed to the removal of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* spp, *Pseudomonas* spp (Modaghegh et al, 1989) and Gram-negative organisms from wounds. It is not known if this effect is due to a primary antibacterial effect of phenytoin or if it is due to a secondary effect of

phenytoin, such as neovascularisation and/or collagenisation.
The side effects of oral phenytoin have not been reported in the topical application of phenytoin in wound healing due to minimal systemic absorption of phenytoin. Side effects of topical phenytoin include a transient burning sensation when it is first applied to a wound and hypertrophic granulation. The latter was found to be avoidable by ceasing therapy once granulation tissue covers the total wound area (Pai et al, 2001).

Topical application of phenytoin has been used successfully in the management of diabetic foot ulcers. It stimulates the development of granulation tissue formation within 2 to 7 days after beginning treatment (Shaw et al, 2011). Biopsies of Phenytoin treated wounds show neovascularization, collagenization and decreased polymorphnuclear and eosinophil cell infiltration (Hauer-Jensen et al, 2006).

Phenytoin Sodium is an antiepileptic drug. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5,5-diphenyl-2, 4-imidazolidinedione.



Structure of Phenytoin sodium

The drug is available as Oral Capsule contains 100 mg phenytoin sodium.

Statins
Statins have been shown to have a number of beneficial effects that are not related to lipid lowering. Statins have anticoagulant, immunosuppressive, and antiproliferative effects that could conceivably affect wound healing or the risk of wound complications after surgery or injury. Studies also showed that local atorvastatin therapy may be useful for healing the wounds in diabetic rats. More encouraging, the safety profile of statins is excellent and the major side effects are rare and mostly reversible (Toker et al, 2009).

Statins as inhibitors of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, have revolutionized the treatment of hypercholesterolemia. They are the most efficient agents for reducing plasma cholesterol, being also appreciated for their good tolerance. Angiographic studies have demonstrated that these compounds reduce the progression and may induce the regression of atherosclerosis (Vaughan et al, 2000).They have been divided into two categories, involving: directly lipids, or intracellular signaling pathways (Meier et al, 2000).

Classification of statins
There are a number of classification criteria for statins. These include: How they are obtained, liver metabolism, physico-chimical properties and specific activity.

Some of the statins are obtained after fungal fermentation: lovastatin (Mevacor), pravastatin (Lipostat, Pravachol) and simvastatin (Zocor), others by synthesis: fluvastatin (Lescol), atorvastatin (Sortis, Lipitor), and cerivastatin (Baycol, Lipobay). Only six statins are, at this moment, in clinical use: lovastatin, simvastatin, pravastatin, atorvastatin, Rosuvastatin and fluvastatin.

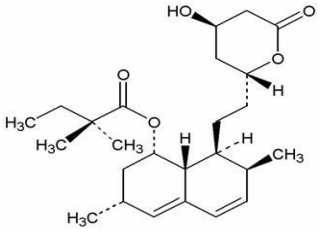
All statins have the liver as target organ and subjected to liver metabolism (Lennernas H., 1997). Pravastatin is extremely hydrophilic, fluvastatin has intermediar characteristics, lovastatin, simvastatin, atorvastatin and cerivastatin are hydrophobic (Blumenthal RS., 2000). Atorvastatin, cerivastatin, fluvastatin and pravastatin are administered as active compounds (acid form). Lovastatin and simvastatin are administered as inactive forms (lactone), which have to be enzymatically hydrolized to generate active forms (Blumenthal RS., 2000). Statins are generally well tolerated. The most important adverse effects are liver and muscle toxicity (Maron et al, 2000).

Atorvastatin has been used before as topical gel for diabetic wound healing in rats. All treated groups of rats showed a time dependant increase in % wound contractions higher than that produced by the control group. These contractions were statistically significant (Aly, 2012).

Simvastatin
Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-(2-(tetrahydro-4 hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl)-1naphthalenylester.

The empirical formula of simvastatin is C25H38O5 and its molecular weight is 418.57.



Structure of simvastatin

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and

CONTRAINDICATIONS

Simvastatin is contraindicated in the following conditions:

- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).
- Concomitant administration of gemfibrozil, cyclosporine, or danazol.
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.

WHY CONSIDER TOPICAL SIMVASTATIN THERAPY FOR WOUND HEALING DISORDERS?

Potential advantages of using topical simvastatin therapy for wound healing:

- High and sustained concentration of simvastatin at the site of wound.
- Limited potential for systemic absorption and toxicity.
- May enable avoidance of using systemic medications.
- Easily applied as outpatient, by patient or caregiver, potentially reducing the need for institutional care.
- Often better adherence to treatment.

CONCLUSIONS

This review details different therapies that have been used for treatment of acute and chronic wounds. The capacity of statins as a topical agent to accelerate wound healing was reported more than thirteen years ago but it has not been marketed as a topical formulation yet.

ACKNOWLEDGEMENT

I convey my sincere expression of thanks to Dr Mostafa Abdel Fattah lecturer of vascular surgery, Department of vascular surgery, Faculty of medicine, Minia University for his valuable advice, helpful suggestions, comments and encouragement.

REFERENCES

1. Albrition JS. Complications of wound repair. Clinics in Podiatric Medicine and Surgery, 1991; 8: 773-785.
2. Aly UF. Preparation and evaluation of novel topical gel preparations for wound healing in diabetics. Int J Pharm Pharm Sci., 2012; 4(4): 76.
3. Arya R, Gulati S. Phenytoin-induced gingival overgrowth. Acta Neurologica Scandinavica, Mar, 2012; 125(3): 149-55.
4. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes care, Apr 1, 2008; 31(4): 631-6.
5. Blumenthal RS. Statins: effective antiatherosclerotic therapy. American heart journal, Apr 1, 2000; 139(4): 577-83.
6. Carneiro PM, Nyawawa ET. Topical phenytoin versus EUSOL in the treatment of non-malignant chronic leg ulcers. East African medical Journal, 2003; 80(3): 124-9.
7. Carneiro PM, Rwanyuma LR & Mkony CA. A comparison of topical Phenytoin with Silverex in the treatment of superficial dermal burn wounds. Cent Afr J Med., 2002; 48(9-10): 105-8.
8. Castellano JJ, Shafii SM, Ko F, Donate G, Wright TE, Mannari RJ, Payne WG, Smith DJ, Robson MC. Comparative evaluation of silver-containing antimicrobial dressings and drugs. International wound journal, Jun, 2007; 4(2): 114-22.
9. Clark RA. Regulation of fibroplasia in cutaneous wound repair. American Journal of the Medical Sciences, 1993; 306: 42–48.
10. Cooper R. A review of the evidence for the use of topical antimicrobial agents in wound care. World wide wounds, Feb, 2004; 1: 1-8.
11. Cooper RA, Halas E, Molan PC. The Efficacy of Honey in Inhibiting Strains of Pseudomonas Aeruginosa From Infected Burns. J Burn Care Rehabil, November/December, 2002; 23(6): 366-370.
12. Cutting KF, White RJ. Maceration of the skin and wound bed 1: its nature and causes. Journal of wound care, Jul, 2002; 11(7): 275-8.
13. Cuzzell JZ, Stotts NA. Wound care: Trial and error yield to knowledge. American Journal of Nursing, 1990; 90: 50-63.
14. Davies CE, Hill KE, Newcombe RG, et al. A prospective study of the 2.microbiology of chronic venous leg ulcers to reevaluate the clinical predictive value of tissue biopsies and swabs. Wound Repair Regen, 2007; 15: 17–22.
15. Devalia HL, Mansfield L. Radiotherapy and wound healing. International wound journal, Mar, 2008; 5(1): 40-4.
16. Dong YL, Fleming RY, Yan TZ, Herndon DN, Waymack JP. Effect of ibuprofen on the inflammatory response to surgical wounds. The Journal of trauma, Sep, 1993; 35(3): 340-3.
17. Drosou A, Kirsner RS, Welsh E, Sullivan TP, Kerdel FA. Use of infliximab, an anti-tumor necrosis alpha antibody, for inflammatory

dermatoses. Journal of cutaneous medicine and surgery, Sep, 2003; 7(5): 382-6.
18. El Zayat SG. Preliminary experience with topical phenytoin in wound healing in a war zone. Mil Med., 1989; 28: 347-50.
19. Falanga V. Wound healing and chronic wounds. Journal of cutaneous medicine and surgery, Dec, 1998; 3: S1-1.
20. Field CK, Kerstein MD. Overview of wound healing in a moist environment. The American journal of surgery, Jan 1, 1994; 167(1): S2-6.
21. Folkman J, Klagsbrun M. Angiogenic factors. Science, Jan 23, 1987; 235(4787): 442-7.
22. Franz MG, Steed DL, Robson MC. Optimizing healing of acute wound by minimizing complications. Current Problems in Surgery, 2007; 44(11): 691-763.
23. Gaur M, Dobke M, Lunyak V. Mesenchymal stem cells from adipose tissue in clinical applications for dermatological indications and skin aging. International journal of molecular sciences, Jan, 2017; 18(1): 208.
24. George Broughton II, Janis JE, Attinger CE. The basic science of wound healing. Plastic and reconstructive surgery, Jun 1, 2006; 117(7S): 12S-34S.
25. Glat PM, Longaker MT. Wound healing. In: Aston SJ, Beasley RW, Thorne CH, editors. Grabb and Smith's Plastic Surgery. 5th ed. Philadelphia: Lippincott–Raven, 1997; 3–12.
26. Goldman R. Growth factors and chronic wound healing: past, present, and future. Advances in skin & wound care, Jan 1, 2004; 17(1): 24-35.
27. Greenhalgh DG. The role of apoptosis in wound healing. The international journal of biochemistry & cell biology, Sep 1, 1998; 30(9): 1019-30.
28. Greif R, Akça O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. New England Journal of Medicine, Jan 20, 2000; 342(3): 161-7.
29. Hart J. Inflammation 2: its role in the healing of chronic wounds. Journal of wound care, Jul, 2002; 11(7): 245-9.
30. Hasamnis AA, Mohanty BK, Patil S. Evaluation of wound healing effect of topical phenytoin on excisional wound in albino rats. Journal of Young Pharmacists, Jan 1, 2010; 2(1): 59-62.
31. Hauer-Jensen MC, Fort JL, Fink LM. Influence of Statins on Postoperative Wound Complications after Inguinal or Ventral Herniorrhaphy. Hernia, 2006; 10: 48–52.
32. Hunt TK. The physiology of wound healing. Annals of emergency medicine, Dec 1, 1988; 17(12): 1265-73.
33. Jespersen J. Pathophysiology and clinical aspects of fibrinolysis and inhibition of coagulation. Experimental and clinical studies with special reference to women on oral contraceptives and selected groups of thrombosis prone patients. Danish medical bulletin, Feb, 1988; 35(1): 1-33.
34. Kanitakis J. Anatomy, histology and immunohistochemistry of normal human skin. European journal of dermatology: EJD, 2002; 12(4): 390-9.
35. Kaufman T, Eichenlaub EH, Angel MF, Levin M, Futrell JW. Topical acidification promotes healing of experimental deep partial thickness skin burns: a randomized double-blind preliminary study. Burns, Dec 1, 1985; 12(2): 84-90.
36. Kerstein MD. Factors affecting wound healing. Adv. wound care, 2007; 10: 30-6.
37. Kim SK. Chitin and chitosan derivatives: advances in drug discovery and developments. CRC press, 2013 Dec 4.
38. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database of Systematic Reviews, 2015; 6.
39. Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Pecoraro RE, Rodeheaver G, Robson MC. Definition and guidelines for assessment of wounds and evaluation of healing. Archives of Dermatology, 1998; 130(4): 489-493.
40. LeBlanc K, Christensen D, Orsted HL, Keast D. Prevention and treatment of skin tears. Wound Care Canada, 2008; 6(1): 14-30.
41. Lennernas, Hans, and Gunnar Fager. "Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors." *Clinical pharmacokinetics*, 1997; 32.5: 403-425.
42. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clinical infectious diseases, Nov 15, 2009; 49(10): 1541-9.
43. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clinical infectious diseases, Nov 15, 2009; 49(10): 1541-9.
44. Lusby PE, Coombes A, Wilkinson JM. Honey: a potent agent for wound healing? J Wound Ostomy Continence Nurs, 2002; 29: 295-300.
45. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation, Jan 18, 2000; 101(2): 207-13.
46. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. Jama, Jun 28, 2000; 283(24): 3205-10.
47. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. Clinics in dermatology, Jan 1, 2007; 25(1): 19-25.
48. Milcheski DA, Chang AA, Lobato RC, Nakamoto HA, Tuma Jr P, Ferreira MC. Coverage of deep cutaneous wounds using dermal template in combination with negative-pressure therapy and subsequent skin graft. Plastic and Reconstructive Surgery Global Open, Jun, 2014; 2(6).
49. Modaghegh S, Salehian B, Tavassoli M, Djamshidi A, Rezai AS. Use of phenytoin in healing of war and non-war wounds: a pilot study of 25 cases. International journal of dermatology, Jun, 1989; 28(5): 347-51.

50. Molan PC. The antibacterial activity of honey: 1. The nature of the antibacterial activity. Bee world. Jan 1, 1992; 73(1): 5-28.
51. Moy LS, Tan EM, Holness R, Uitto J. Phenytoin modulates connective tissue metabolism and cell proliferation in human skin fibroblast cultures. Archives of dermatology, Jan 1, 1985; 121(1): 79-83.
52. Mulder GD, Vande Berg JS. Cellular senescence and matrix metalloproteinase activity in chronic wounds: relevance to debridement and new technologies. Journal of the American Podiatric Medical Association, Jan, 2002; 92(1): 34-7.
53. Muthukumarasamy MG, Sivakumar G, Manoharan G. Topical phenytoin in diabetic foot ulcers. Diabetes Care, Oct 1, 1991; 14(10): 909-11.
54. Namias N. Honey in the Management of infections. Surg Infect, 2003; 4: 219-226.
55. Pai MR, Sitaraman N & Kotian MS. Topical phenytoin in diabetic ulcers: a double blind controlled trial. Indian J Med Sci., 2001; 55(11): 593-9.
56. Patel PP, Vasquez SA, Granick MS, Rhee ST. Topical antimicrobials in pediatric burn wound management. J Craniofac Surg, 2008; 19: 913–22.
57. Pieper B. Honey-Based Dressings and Wound Care. J Wound Ostomy Continence Nurs. January/February, 2009; 36(1): 60-66.
58. Pieper B. Mechanical forces: pressure, shear, and friction. Bryant, RA (Ed.) Acute and Chronic Wounds. Nursing Management, 2000; 221-64.
59. Pierce GF, Mustoe TA, Altrock BW, Deuel TF, Thomason A. Role of platelet-derived growth factor in wound healing. Journal of Cellular Biochemistry, 1991; 45: 319–326.
60. Rhodes RS, Heyneman CA, Culbertson VL, Wilson SE, Phatak HM. Topical phenytoin treatment of stage II decubitus ulcers in the elderly. Annals of Pharmacotherapy, Jun, 2001; 35(6): 675-81.
61. Richardson M. Acute wounds: an overview of the physiological healing process. Nursing times, 2004; 100(4): 50-3.
62. Riou JP, Cohen JR, Johnson Jr H. Factors influencing wound dehiscence. The American journal of surgery, Mar 1, 1992; 163(3): 324-30.
63. Robson MC, Steed DL, Franz MG. Wound healing: biologic features and approaches to maximize healing trajectories. Current problems in surgery, 2001; 2(38): 72-140.
64. Servold SA. Growth factor impact on wound healing. Clinics in Podiatric Medicine and Surgery, 1991; 8: 937–953.
65. Shaw J, Hughes CM, Lagan KM & Bell PM. The clinical effect of topical phenytoin on wound healing: a systematic review. Br J Dermatol, 2007; 157(5): 997-1004.
66. Sherman RA. A new dressing design for treating pressure ulcers with maggot therapy. Plastic and Reconstructive Surgery, 1997; 100(2): 451-456.
67. Simpson GM, Kunz E & Slafta J. Use of diphenylhydantoin in treatment of leg ulcers. NY State J Med., 1965; 65: 886-8.
68. Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin wound healing: an update on the current knowledge and concepts. European surgical research, 2017; 58(1-2): 81-94.
69. Takeshita S, Zheng LP, Brogi E, Kearney M, Pu LQ, Bunting S, Ferrara N, Symes JF, Isner JM. Therapeutic angiogenesis. A single intraarterial bolus of vascular endothelial growth factor augments revascularization in a rabbit ischemic hind limb model. The Journal of clinical investigation, Feb 1, 1994; 93(2): 662-70.
70. Terpenning, Margaret S., et al. "Colonization and infection with antibiotic-resistant bacteria in a long-term care facility." *Journal of the American Geriatrics Society*, 1994; 42.10: 1062-1069.
71. Toker S, Gulcan E, Cayc MK, Olgun EG, Erbilen E, Ozay Y. Topical Atorvastatin in The Treatment Of Diabetic Wounds. Am J Med Sci., 2009; 338(3): 201-4.
72. Vaughan C.J., Gotto A.M., Basson C.T., The evolving role of statins in the management of atherosclerosis, J. Am. Coll. Cardiol., 2000; 35: 1-10.