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Research Article

WOUND HEALING: ROLE OF TRADITIONAL HERBAL MEDICINE TREATMENT

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ABSTRACT

This review paper highlights about wound healing, a vital physiological process of tissue repair or remodelling, which still remains a challenge in the Indian healthcare system. Different wound dressings containing antibiotics and antibacterial agents, nanoparticle based wound dressings prevent bacterial infection and bio film formation in the wound bed. However, the use of antibiotics, allopathic drugs and antibacterial nanoparticles in wound healing has some limitations since most of these antibacterial agents have side effects such as cytotoxicity. Furthermore, there is no efficient evidence-based therapy available for specific chronic wounds. Another problem is wound healing and wound management is very expensive health care, which poor people cannot afford to bear expenditure. There are a variety of herbal plants that have wound healing properties. Plant-based constituents have been extensively used for the treatment and management of different types of wounds. Folklore cultures employ a significant number of plants to treat cuts, wounds, and burns. Therefore, the use of Complementary and Alternative herbal Medicines (CAMs) is a promising approach to improvising clinical and medical challenges faced by non-healing chronic wounds. In addition to this, the use of natural plant derived substances are considered safe compared to synthetic molecules and can be much cheaper than conventional therapies.

Keywords: Acute wound, chronic wound, antibiotics, nanomedicine, wound dressings, wound infection, herbal medicine, India, wound healing.

INTRODUCTION

A wound is defined as the breakage in the continuity of the skin (1-26, 31-42 46, 47, 79-84, 96-102, 138). A wound may also be defined as an interruption within the continuity of the epithelial lining of the skin or mucosa that occurs as a result of physical or thermal damage (1-26, 31-42 46, 47, 79-84, 96-102, 138). In general, wound healing is classified with four specific stages of hemostasis, inflammation, proliferation, and maturation (1-26, 31-42 46, 47, 79-84, 96-102). Wound healing is a vital natural physiological response to tissue damage consisting of the collaboration of many cell strains and their products (1-26, 31-42 46, 47, 79-84, 96-102). **Wound healing** is one of the most complex and essential treatments in the human body and still remains a challenge in the healthcare system (1-26, 31-42 46, 47, 79-84, 96-102). In general, antimicrobial action is a current focus in wound healing and biomedical devices (1-26, 31-42 46, 47, 79-84, 96-102). The **antimicrobial wound dressing** can be intrinsic, with the dressing material itself, or can be engineered with antimicrobial molecules by adding an antibiotic agent to a polymer backbone or in the form of **nanoparticles** or chemicals linked to a polymer surface (1-26, 31-42 46, 47, 79-84, 96-102).

Conventional **wound dressing** materials seem to be insufficient to facilitate and support wound healing mechanism (1-26, 31-42 46, 47, 79-84, 96-102). As an alternative for conventional wound dressing, polysaccharide-based biopolymers such as chitosan and alginate are promising because of their biocompatibility, biodegradability, antimicrobial activity, and ability to accelerate wound healing (34). Thus, they are considered as promising materials for wound dressing applications (1-26, 31-42 46, 47, 79-84, 96-102).

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Nanotechnology has increasingly revolutionized medical care, and its potential has also been investigated for the formulation of wound dressings (1-26, 31-42 46, 47, 79-84, 96-102). An ideal wound dressing should be adherent to the wound surface and not to the wound bed, it should also be non-antigenic, biocompatible, semi-permeable, biodegradable, elastic but resistant, and cost-effective (1-26, 31-42, 46, 47, 79-84, 96-102). It has to give protection against bacterial, infectious, mechanical, and thermal agents, to modulate the level of wound moisture, to entrap and deliver drugs or other molecules (1-26, 31-42 46, 47, 79-84, 96-102).

Wound healing may be a complicated and unique process, with the changing wound environment in response to the overall health status of an individual (1-26, 31-42 46, 47, 79-84, 96-102). After the certain circumstances such as trauma, either by accident or by surgery wound healing play an important role in preserves the integrity of skin (1-26, 31-42 46, 47, 79-84, 96-102). None of the **wound dressings** currently used clinically can mimic all the properties of normal and healthy skin (1-26, 31-42 46, 47, 79-84, 96-102). Electro spinning has gained remarkable attention in wound healing applications because of its excellent ability to form nanostructures similar to natural extracellular matrix (ECM) (1-26, 31-42 46, 47, 79-84, 96-102). **Electro spun** dressing accelerates the wound healing process by transferring drugs or active agents to the wound site sooner (1-26, 34, 35, 42).

Skin injury

Skin plays an essential role in protecting our body against any physical, chemical injury, water loss, and contributes to the maintenance of bodily homeostasis (1-26, 31-42 46, 47, 79-84, 96-102). **Skin injury** also occurs in daily life, where the skin loses its protective action, leading to the formation of a wound in the skin (1-26, 31-42 46, 47, 79-84, 96-102). Skin plays a key role in protecting our internal environment from the external environment, maintaining

homeostasis, and regulating temperature (1-26, 31-42 46, 47, 79-84, 96-102). After damage, the skin should restore its integrity to maintain its functions (42). The anatomy of human skin consists of outer epidermis, dermis layers and lower subcutaneous layer permeated by a complex vascular and nervous network (1-27, 31-42 46, 47, 79-84, 96-102). On the outer side is the epidermis that consists predominantly of keratinocytes, which form a tight seal for protection along with melanocytes, Langerhan and Merkel cells (1, 27, 35). Below this is the dermis, which is attached to the epidermis by the basement membrane, a thin layer of extracellular matrix (ECM) consisting mostly of laminins, integrins, perlecan, nidogen, and collagen IV (1, 27, 35). The composition of the dermis is complex and differs quite dramatically from the epidermis (1-27, 31-42 46, 47, 79-84, 96-102). It consists of thin layer of extracellular matrix (ECM), which acts as a **scaffold** for fibroblasts and other mesenchymal cells, blood vessels, hair follicles, and sweat glands. It also houses molecules, such as growth factors and enzymes, that regulate the local environment (1-26, 31-42 46, 47, 79-84, 96-102). The dermis has several sub-layers, with the papillary layer closest to the basement membrane consisting of poorly ordered thin collagen fibres housing a high density of fibroblasts (1-26, 31-42 46, 47, 79-84, 96-102). This complex nature of the skin makes it particularly difficult to replicate in the laboratory (1-26, 31-42 46, 47, 79-84, 96-102). Since skin is the largest organ of the human body, any obstruction in its continuity, such as a wound or a cut, compromises health and immunity (1-26, 31-42 46, 47, 79-84, 96-102). As a result, the wound must be treated as soon as possible with suitable treatment (26).

Therapies used in wound healing

Tissue engineering and regenerative medicines are the futuristic view of technologies for developing wound healing systems (1-26, 31-42 46, 47, 79-84, 96-102). Several therapies are available for the wound-healing process (1-26, 31, 34, 35, 46-96). These therapies include both conventional and modern treatments. Some examples of modern and currently used treatments are stem cell therapy, oxygen therapy, nitric oxide therapy, artificial dressing, and growth factor therapy (1-26, 31-42 46, 47, 79-84, 96-102). Comparatively, conventional treatments include using natural substances such as plant extracts, honey, larvae, etc (1-26, 31-42 46, 47, 79-84, 96-102). The treatments are effective when the healing materials are fabricated with excellent wound-healing potential (1-26, 31-42 46, 47, 79-84, 96-102). An ideal wound dressing should improve the healing process by eliminating excessive exudates, promoting autolytic debridement, retaining adequate moisture for healing, and providing the least inconvenience for the patient (1-26, 31-42 46, 47, 79-84, 96-102). A **wound dressing** should allow faster healing without being too expensive (1-26, 31-42 46, 47, 79-84, 96-102). However, conventional dressings are mostly dry and challenging to apply (1-26, 35). To overcome these drawbacks, active wound dressing has been developed by incorporating active agents in wound dressing materials to prevent microorganisms from infecting the wound (1-27, 31-42 46, 47, 79-84, 96-102).

Complementary and Alternative Herbal Medicines (CAMs)

Use of Complementary and Alternative herbal Medicines (CAMs) in **Indian health care sector** is increasing and its applications in wound management remains a cost effective treatment (1-26, 31-42 46, 47, 79-84, 96-102, 103-137). Use of **natural medicine** and principles for healing is one of the fundamental principles of traditional medicine (1-26, 31-42 46, 47, 79-84, 96-102, 103-137). This is mainly due to unique ability of natural molecules to interact with different bio-molecules (1-26, 31-42 46, 47, 79-84, 96-137). Therefore, there is a huge potential for the development of safe, sustainable and effective treatment module using alternate medicine from plant or other natural sources (1-26, 31-42 46, 47, 79-84, 96-137). This will help to scientifically promote several traditional herbal medicines for healing different category of wounds (1-26, 31-42 46, 47, 79-84, 96-137).

Current options for wound healing which includes, use of anti-microbial agents, healing promoters along with application of herbal and natural products (1-26, 31-42 46, 47, 79-84, 96-102, 103-137). Traditional approaches are often ineffective on a variety of chronic wounds, such as venous ulcers or the diabetic foot ulcer (1-26, 31-42 46, 47, 79-84, 96-137). There is a strong evidence that naturally derived bioactive compounds have pro-healing properties, raising a great interest in their potential use for wound healing (1-26, 30-34, 35,103-137). **Plant-derived** compounds, such as curcumin and essential oils, are widely used to modify materials applied as wound dressings. Moreover, dressing materials are more often enriched with vitamins (e.g., L-ascorbic acid, tocopherol) and drugs (e.g., antibiotics, inhibitors of proteases) to improve the skin healing rate (1-26,34, 40, 103-137). Accurate wound valuation including estimation of the wound size, color, type, location, and exudates level determines the most suitable type of the wound dressing to be used (1-26, 31-42 46, 47, 79-84, 96-102).

Types of wound

Wound is defined as an anatomical and functional disruption of the skin following an injury (1-26). In response to the injury, wound healing is a complex process of tissue repair or remodelling (1-26, 31-42 46, 47, 79-84, 96-102). In general, there are different types of wounds such as **Acute wounds**, closed wounds, open wounds, incised wounds, tear or laceration wounds, puncture wounds, abrasive or superficial wounds, penetration wounds, gunshot wounds and chronic wounds (1-26, 31-42 46, 47, 79-84, 96-102). Open wounds are usually accompanied by bleeding and are associated with rupturing layers of the skin (1-26, 34, 35-40). Closed wounds resulted from bruising or dead blood and crashes (1-26, 31-42 46, 47, 79-84, 96-102).

Acute wound

In terms of clinical features, wounds are divided into acute and chronic wounds (1-26, 31-42 46, 47, 79-84, 96-102). Therefore, wounds can be classified into two broad types, acute wounds, and chronic wounds (1-26, 31-42 46, 47, 79-84, 96-102). Acute wounds heal normally in a very orderly and efficient manner (1-26, 31-42 46, 47, 79-84, 96-102). They are characterized by four distinct, but overlapping phases: haemostasis, inflammation, proliferation and re-modeling (1-26, 31-42, 46, 47, 79-84, 96-107). These wounds progress through the normal stages of wound healing such as inflammation, proliferation, re-modeling and showed definite signs of healing within 2– 4 weeks (1-26, 31-42 46, 47, 79-84, 96-102). During normal physiological processes such as acute wound healing inflammatory cells are recruited to the site of injury and help in tissue repair through secretion of cytokines and growth factors that promote tissue re-modeling and angiogenesis (1-26, 31-42 46, 47, 79-84, 96-102). In normal wound healing, inflammation subsides once the tissue repair is completed (1-26, 31-42 46, 47, 79-84, 96-102).

Chronic wound

In chronic wounds, due to the high level of **inflammation**, healing is longer than acute wounds. However, many chronic wounds undergo a natural healing process, but the tissue lacks normal structural and functional properties (138). **Chronic wounds** are characterized by a persistent inflammation, hard re-epithelialization, impaired angiogenesis, dysregulated levels of cytokines/growth factors and/or increased protease activity (1-26, 31-42 46, 47, 79-84, 96-102). Chronic wound often characterized by infection/ biofilm

elevates the production of inflammatory and pro-inflammatory cytokines that resulted in an increased production of matrix metalloproteases and a reduction in their inhibitors (1-26, 31-42 46, 47, 79-84, 96-102). Biofilms are composed of multimicrobial communities that attached to each other (138). **Biofilm** formation is one of the most important barriers in the process of chronic wound healing and consequently increases the risk of wound infection (138). Other signs of wound infection include increased exudates, delayed healing, bleeding during manipulation or contact with the wound, unpleasant odour, and abnormal granulation tissue (138). Unpleasant **odour of the wound** can be due to infection or the presence of necrotic tissue (138).

Chronic wounds are often characterized by pathologic responses resulting in fibrosis and non-healing chronic ulcers (1-26, 31-42 46, 47, 79-84, 96-102). This clinical condition is a result of undiagnosed or untreated wounds (1-26, 31-42 46, 47, 79-84, 96-102). Chronic wounds caused by infections, diabetes, and radiation exposures are becoming a worldwide growing medical burden (1-26, 31-42 46, 47, 79-84, 96-102). Chronic wounds are due to tumours, bed wounds, and diabetic wounds, which lead to extended inflammation and a more prolonged healing time (1-26, 31-42 46, 47, 79-84, 96-102). Further, **Chronic wound** inflammation favours exudates persistence (1-26). The bacterial film has a special importance in the dynamics of chronic inflammation in wounds that do not heal (1-26, 31-42 46, 47, 79-84, 96-102). Chronic skin lesions are more common in older people due to diabetes and circulatory disorders, physical disability, and inactivity (138). Failure to treat such patients in a timely manner will eventually lead to amputation of their lower limbs (138).

Recent progress highlighted the physical signals determining stem cell fates and bacterial resistance, which holds potential to achieve a better wound regeneration *in situ*. **Nanoparticles** (NPs) would benefit chronic wound healing (1-26, 31-42 46, 47, 79-84, 96-102). However, the cytotoxicity of the silver NPs (AgNPs) has aroused many concerns (98). Biofilm on the skin surface of chronic wounds is an important factor in the pathology, inhibiting wound healing (1-26, 31-42 46, 47, 79-84, 96-102). The major clinical signs and symptoms of a patient with a chronic wound are pain, erythema, edema, heat, purulence with high wound **bioburden** (1-26, 31-42 46, 47, 79-84, 96-102). **Chronic wounds** represented a major public health issue, with an extremely high cost worldwide (1-26, 31-42 46, 47, 79-84, 96-102). Clinical studies showed that over 60% of chronic wounds presented a **biofilm** (1-26, 31-42 46, 47, 79-84, 96-102). These wound-dressings should act by removing the **biofilm** pathogenic bacteria and modulating the inflammation (1-26, 31-42 46, 47, 79-84, 96-102). Angiogenesis is impaired in all chronic wounds leading to further tissue damage resulting in chronic hypoxia and impaired micronutrient delivery (1-26). Of all the angiogenic stimulators, VEGF plays a crucial role in wound healing (1-26, 31-42 46, 47, 79-84, 96-102).

Chronic inflammation, a hallmark of the non-healing wound, may ultimately predispose these wound sites to potential malignant change (1-26, 31-42 46, 47, 79-84, 96-102). In contrast, chronic wounds do not follow the sequential stages of healing and failed to show evidence of healing within 4 weeks. Chronic wounds are greatest burden to health care (1-26, 31-42 46, 47, 79-84, 96-102). These cause burden through, prolonged hospitalization, loss of mobility, compromising quality of life, requirement of support and sometime increase the risk of **nosocomial** infection causing burden to health care workers and other patients visiting hospital (1-26, 31-42 46, 47, 79-84, 96-102). Chronic wounds represent a major health care burden including financial expenses and have a devastating impact on morbidity (1-26, 31-42 46, 47, 79-84, 96-102). Furthermore, signs and symptoms specific to secondary **wounds** often observed in proliferative phase include (1-26, 31-42 46, 47, 79-84, 96-102), (1) wound breakdown (2) serous drainage with concurrent inflammation, (3) foul odour (4) pocketing at the base of the wound (5) discoloration of granulation tissue, (6) friable granulation tissue, (7) delayed healing (3).

The **chronic wound** associated fibroblasts showed fibroblast senescence (1-26, 31-42 46, 47, 79-84, 96-102). Chronic wound environment impairs angiogenesis and stalls epithelialization (1-26, 34, 35). These characteristics represent chronic wound environment that cause delayed healing (1-26, 31-42 46, 47, 79-84, 96-102). **Wound** associated with chronic diseases such as diabetes and cancer pose a greater challenge to treat and manage, which is mainly due to molecular complexity (1-26, 31-42 46, 47, 79-84, 96-102). Most of the chronic wounds are characterized by **bacterial contamination** and further biofilm formation which creates complications during the treatment (1-26, 31-42 46, 47, 79-84, 96-102). In addition to elevated inflammatory cells and the production of pro-inflammatory cytokines, a bacterial infection is very common (1-26, 31-42 46, 47, 79-84, 96-102). Systemic infections are usually treated using systemic antibiotics (1-26, 31-42 46, 47, 79-84, 96-102). However, once there is a control in bacterial balance, the use of topical antibiotics should be discontinued, as prolonged courses of antibiotics may hamper wound healing and lead to antimicrobial resistance (1-26, 31-42 46, 47, 79-84, 96-102). Another major problem is that **chronic wounds** remain unresponsive to conventional wound care treatments such as topical agents, wound dressings, and skin grafts (1-26, 31-42 46, 47, 79-84, 96-102).

Wound healing: Bacterial infections

Bacterial infections can delay **wound healing** and in some cases cause the wound to not heal (1-26, 31-42 46, 47, 79-84, 96-102, 103-137, 138). Therefore, the presence of bacteria in the wound bed is one of the biggest challenges in the wound healing process. In fact, the bacteria cause inflammation and disrupt the wound healing process (1-26, 31-42 46, 47, 79-84, 96-102, 103-137, 138). Adhesion of **bacteria** onto a wound surface gradually leads to the formation of biofilms that protect the bacteria against the immune system and antibiotics, then the liberation of **endotoxins** can cause sepsis and eventually death (1-26, 31-42 46, 47, 79-84, 96-102, 103-138). **Antibiotic resistance** of bacteria is a growing problem with the overuse of antibiotics (138). Antimicrobial resistance can lead to extended infection, delayed healing, and long hospital admissions (138). Following are the common bacteria found in the wounds (138).

Gram-positive bacteria: Staphylococcus aureus (S. aureus), Streptococcus pyogenes (S. pyogenes), Bacillus subtilis (B. subtilis), Candida albicans (C. albicans), Staphylococcus epidermidis (S. epidermidis), Staphylococcus haemolyticus (S. hemolyticus), Staphylococcus saprophyticus (S. saprophyticus), Bacillus pumilus (B. pumilus), Listeria monocytogenes (L. monocytogenes), Bacillus cereus (B. cereus), Streptococcus pneumoniae (S. pneumoniae), Streptococcus mutans (S. mutans), Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus faecalis (VRE) (138)

Gram-negative bacteria: Escherichia coli (E. coli), Pseudomonas aeruginosa (P. aeruginosa), Pseudomonas fluorescens (P. fluorescens), Klebsiella aerogenes (K. aerogenes), Salmonella typhimurium (S. typhimurium), Klebsiella pneumoniae (K. pneumoniae). Both gram-positive and gram-negative: Saccharomyces cerevisiae (S. cerevisiae) (138).

Factors influencing wound healing

The structure of the **skin** is complex and wound biology is influenced by many factors particularly local physiological environment (1-26, 31-42 46, 47, 79-84, 96-102). Many local

conditions influence wound occurrence, persistence, and healing (1-26, 31-42 46, 47, 79-84, 96-102). Many factors can impair the healing process. Specific biological markers characterize the non-healing of chronic wounds (3-30, 34, 35-83). Both local and systemic factors contribute to delayed healing (1-26, 31-42 46, 47, 79-84, 96-102). Local factors include the presence of tissue maceration, foreign bodies, biofilm, hypoxia, ischemia, and wound infection (1-26, 28-35, 36-83). Systemic factors include diabetes, advanced age, malnutrition, and other chronic organ diseases (1-26, 31-42 46, 47, 79-84, 96-102). There are a variety of systemic and local factors that influence wound healing, including oxygenation, inflammation, age, stress, diabetes, nutrition, and nicotine (1-26, 31-42 46, 47, 79-84, 96-102).

Hemostasis, inflammation, proliferation or granulation, **remodeling** or maturation are the principle phases of wound healing (1-26, 31-42 46, 47, 79-84, 96-102). The most common condition that is representative of a wound is microbial infection and inflammation (1-26, 31-42 46, 47, 79-84, 96-102). Exposed skin surface which comprises of subcutaneous tissue helps wide range of microorganisms to colonize on the **substratum** (1-26, 30-34, 35-83). Both aerobic and anaerobic microorganisms are present in acute and chronic wounds (1-26, 31-42 46, 47, 79-84, 96-102). Further, the prevalence of contamination by microorganisms also depends on a person's immunity or body-host defence (1-26, 30-34, 35-83). If the host immune response is compromised, involved tissue is devitalized by ischemic, hypoxic, or necrotic conditions that favour microbial growth (1-26, 31-42 46, 47, 79-84, 96-102). **Wound healing** can be hampered by a variety of circumstances (1-26, 30-35, 35-83). The elements that affect repair are frequently divided into two categories: **local and systemic** (1-26, 31-42 46, 47, 79-84, 96-102). Local factors have a direct impact on the wound's features, whereas systemic factors have an impact on the individual's overall health or disease state, which influences their ability to heal (1-26, 31-42 46, 47, 79-84, 96-102). Because many of these elements are interconnected, systemic variables influence wound healing via local consequences (1-26, 31-42 46, 47, 79-84, 96-102).

1. Oxygenation: For wound healing, oxygen is a very essential component (1-26, 30-34, 35-83). It is a complicated procedure that involves several biological processes like cell proliferation, angiogenesis, and protein synthesis, all of which are required for tissue function and integrity to be restored (1-26, 30-34, 35-83). Appropriate wound tissue oxygenation can affect healing responses (1-26, 31-42 46, 47, 79-84, 96-102).

2. Role of the macrophage in wound healing: (Inflammation): In wounds, macrophages perform slightly different functions, such as host defence, promoting and determining inflammation, removing apoptotic cells, and so supporting cell proliferation and tissue regeneration after injury (1-26, 30-34, 35-83). The macrophage, on the other hand, is essential for the repair of regularly healing wounds. As **wounds heal**, the local macrophage populace transitions primarily on pro-inflammatory (M1-like phenotypes) followed by anti-inflammatory (M2-like phenotypes) (1-26, 31-42 46, 47, 79-84, 96-102). Thus, macrophages keep pro-inflammatory characteristics during wound healing (1-26, 30-34, 35-83).

3. Age: In healthy people, ageing causes epithelialization to be delayed (1-26, 34, 35-83). Collagen synthesis is unaffected by ageing; However, wound non-collagenous protein deposition is reduced. In older people, this decline may compromise the mechanical qualities of scarring (1-26, 31-42 46, 47, 79-84, 96-102).

4. Stress: Physiological stress responses can directly influence wound healing processes (1-26). The sources of stress include pain, odor, work stress, staying alone, financial stress, poverty, and social isolation (1-26, 31-42 46, 47, 79-84, 96-102). Uncontrollable stress has been shown in clinical studies to boost the risk of a non-healing, lower standard of life, and lead to the adoption of unhealthy habits, highlighting the significance of a multidisciplinary approach to wound healing (1-26, 34, 35-84). **Psychological stress** can also cause many health issues influencing wound healing:**1**) Feelings of fear, anger, sadness, worry, numbness, or frustration, **2**) Changes in appetite, energy, desires, and interests, **3**) Difficulty concentrating and making decisions, **4**) Difficulty in sleeping or nightmares, **5**) Physical reactions, such as headaches, body pains, stomach problems, and skin rashes, **6**) Worsening of chronic health problems, **7**) Worsening of mental health conditions (1-26, 31-42 46, 47, 79-84, 96-102).

5. Diabetes : Diabetes mellitus is a complicated metabolic condition with several direct and indirect consequences on wound healing (26-29). Hyperglycemia or uncontrolled glycemic levels in diabetes mellitus affect white blood cell function and increase the risk of infection (28-29). Controlling diabetes, maintaining nutrition, and treating a systemic illness are important factors in promoting wound healing (1-29). **Diabetes** affects **wound healing** through the decreased inflammatory responses, loss of protective sensations due to neuropathy, the development of ischemia, and increased risk of infection (1, 2, 3-26, 34, 35-83).

6. Diet and Nutrition: Nutritional therapy is an essential component for the successful treatment of wound healing (1-26, 34, 35-83). Acute malnutrition would be associated with increased loss in muscle mass and weakening of immune defences prompted in the severity of the wound healing (1-26, 34, 35-83). People suffering from wounds required an intensive care unit admission often requires nutrition therapy as part of supportive care (1-26, 34, 35-83). There is a direct correlation among nutrition, immune system, and wound healing (1-26, 31-42 46, 47, 79-84, 96-102). The nutrients and bioactive molecules such as **melatonin,** vitamins, proteins, carbohydrates in the diet (foodstuffs) influences the immunity and wound healing (1-26, 34, 35-83). Therefore, nutritional therapy appears as the first-line treatment and should be implemented into standard practice (1-26, 34, 35-83). Optimal intake of all nutrients, mainly those playing crucial roles in immune system, should be the top priority of the well-balanced diet system (1-26, 34, 35-83).

Natural plant bioactive compounds can also reduce the inflammatory response induced by chronic wounds (1-26, 34, 35-84, 103-137). High biological value proteins, fatty acids (omega 3), **melatonin**, vitamins A and C, dietary fibre, selenium and copper present anti-inflammatory effects; polar lipids have an anti-thrombotic effect; vitamins A, C and D protect against respiratory infections; vitamin E, iron, and zinc improve the immune function; and vitamins C, A and E, and omega 3 fatty acids present antioxidant effects (1-26, 34, 35-84, 103-137). Consumption of **carbohydrates** with a higher glycaemic index should be avoided since this contributes to inflammation (1-26). Natural bioactive compounds found in **plants** and sea food, namely revesterol, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), **melatonin**, capsaicin, and curcumin, among others, have been associated with anti-inflammatory effects (1-26, 34, 35-84, 103-137).

7. Cancer patients: Wound healing may proceed in a relatively unimpeded manner for many patients with cancer, due to malnutrition, nature and effects of the oncologic disease process and its treatment methods (1, 2, 3, 4-26). Thus, the best strategy to win the war on cancer is to restore the functionality of chemosurveillance, increase nutritive food uptake and prevent the loss of wound healing metabolites that ultimately results in enhanced wound healing (1-26, 31-42 46, 47, 79-84, 96-102).

8. Burn injury-patients: Non-healing chronic wounds are also characterized by myofibroblasts activity that persists and drives tissue alterations, which is particularly evident in hypertrophic scars developing after **burn injury** and in the fibrotic phase of scleroderma (1, 2, 3-26, 34, 35-83). Myofibroblasts-generated contractions are

also typical for fibrosis, affecting vital organs such as the liver, heart, lung and kidney 1-26, 31-42 46, 47, 79-84, 96-102).

The phases of wound healing

Wound healing is a complex dynamic process involving several sequential steps, including induction of inflammatory process, regeneration of parenchyma tissue, migration and proliferation of parenchymal tissue cells, production of extracellular matrix proteins, remodeling of tissue and gaining wound strength (1-26, 38-40, 47, 83, 84, 103-137). **Healing of a wound** involves different cell types, secreted growth factors, cytokines, the extracellular matrix and various enzymes (1, 2, 3-80, 103-137). Various cells such as platelets, neutrophils, monocytes, macrophages, fibroblasts, keratinocytes, endothelial cells, epithelial cell and myofibroblasts are involved in wound healing process (1-26, 30, 35, 40-84). Among all cells, **fibroblasts** have long been recognized as key cells in wound healing as they play a major role in all the three phases (1-94).

Wound healing is divided into following different phases.

1. Hemostasis- The first healing stage is **hemostasis**, which begins with the cessation of bleeding (1-26, 30-35, 40-83). When a part of the body bleeds, the first step is to start the hemostasis phase, and the blood vessels contract, which reduces the bleeding (1-26, 30, 35-89). In this situation, platelets then stick together to cover the damaged vascular wall, and coagulation occurs (1-26, 34, 35-84). Many platelets stick together with fibrin glue, which traps red blood cells like a net and stops bleeding (1-26, 30, 34-83). The process of homeostasis occurs very quickly (1,2,3-26, 34-83). After that, the first fibrin scaffold is formed in 60 s with fibrin glue, which turns from a liquid to jelly to form a blood clot and releases prothrombin (1-26, 31-42 46, 47, 79-84, 96-102). The thrombus retains platelets, clots, or blood cells in the wound area (1,2,3-26, 34-83). Platelets emit vaso-constrictive chemicals, but their primary function is to form a stable clot that seals the injured vessel (1,2,3-26, 34-83). **Platelets** also release substances influences the synthesis of fibrin from fibrinogen (1-26, 31-42 46, 47, 79-84, 96-102). If there are no underlying clotting abnormalities, hemostasis occurs within minutes of the original injury 1-26, 31-42 46, 47, 79-84, 96-102, 138).

2. Inflammation- Inflammation is the second phase in wound healing and occurs right after the blood vessels are damaged and blood is leaking (1, 2, 3, 4-26, 34-83). Inflammation both controls bleeding and prevents infection (1-26, 31-42 46, 47, 79-84, 96-102). During this phase, white blood cells, growth factors, nutrients, and enzymes move toward the injured area, which leads to swelling, redness, pain, and various inflammatory stages (1-26, 31-42 46, 47, 79-84, 96-102). **Inflammation** is a natural part of the wound-healing process and only extends the healing process of the wound (1-26, 31-42 46, 47, 79-84, 96-102). Neutrophils are the first line of defense against infection, phagocytizing debris, and bacteria. The macrophage is a cell that aids with wound healing by acting as a contractor (1-26, 31-42 46, 47, 79-84, 96-102). Blood-borne cells—neutrophils, macrophages, and **platelets**—play crucial roles during the coagulation and inflammatory phases (2) of the healing. These cells provide the growth factors and interim matrices required for the recruitment into the wound bed of epidermal and dermal cells (1-26, 31-42 46, 47, 79-84, 96-102).

3. Proliferation or granulation- The next stage is proliferation, which begins when new tissue regenerates in the wound (1, 2 3, 4-26, 34-83). In this step, the new tissue is formed with **extracellular matrix** (ECM) and collagen (1-26, 31-42 46, 47, 79-84, 96-102). A new network of blood vessels and healthy granular tissue is fabricated with adequate oxygen supply and proper nutrition (1, 2 3, 4-26, 34-83). Throughout the process of proliferation, the injury is reassembling with advanced granulation tissue (1-26, 31-42 46, 47, 79-84, 96-102). This granulation tissue is consisting of collagen and extracellular matrix and a modern set of blood vessels develop this activity is said to be angiogenesis (1, 2 3, 4-26, 34-83). The **proliferative process** (2) starts around 3 days after injury and is characterized by increased rates of proliferation, migration, and extracellular matrix (ECM) synthesis of keratinocytes and fibroblasts in response to autocrine, juxtracrine, and paracrine growth factors (1-26, 31-42 46, 47, 79-84, 96-102). In this process, angiogenesis/neovascularization occurs too (3-26). The tissue has a granular texture (granulation tissue), due to the involvement of blood vessels (1-26, 31-42 46, 47, 79-84, 96-102).

4. Remodeling or Maturation- The last phase is remodeling, which occurs by converting collagen type III to collagen type I when the wound is completely closed (1, 2 3, 4-26, 34-83). In this stage, collagen is reabsorbed along the squeezing lines, which leads to the attachment of collagen fibers and an improvement in the new tissue's tensile strength (1-26, 31-42 46, 47, 79-84, 96-102). **Remodeling** is the ultimate stage of healing, which begins two to three weeks after the commencement of the lesion and can last a year or longer (1-26, 31-42 46, 47, 79-84, 96-102). Eventually, inside the granulation tissue, differentiated fibroblastic cells (myofibroblasts) begin to remodel the extracellular matrix at about 1 to 2 weeks after injury (1-26, 31-42 46, 47, 79-84, 96-102). Extracellular matrix remodeling accompanied by resident cell apoptosis leads to an a cellular scar formation (1-26, 31-42 46, 47, 79-84, 96-102).

Different wound healing technique:

The most frequent wound healing treatments include

1. Hyperbaric oxygen therapy (HBOT).
2. Negative pressure therapy (NPT).
3. Platelet-rich plasma therapy (PRP).
4. Stem Cell Therapy (SCT)- Skin and composite equivalents derived from embryonic stem cells in addition to application of bone marrow-derived stem cells may serve as possible options in near future (1, 3).
5. Biosurgery.
6. Cell-based dressings (1, 26) -The use of adult and/or mesenchymal stromal cells (MSCs)- included in dressings is growing rapidly and reinventing itself (1, 26). Thus, these cell-based strategies aimed to reduce the continuous inflammatory state, normalize the impaired inter-cellular communication and promote the regeneration of chronic wounds (1-26).
7. Nanoparticle based wound dressings (1-26, 30-35, 83-137).
8. Natural **plant gums** used in wound dressings (30).
9. Biocompatible Nanomaterials (1-84)

Wound healing process

The **wound healing** and repair bring an immense burden economically and socially to the patient (1-21, 26, 34, 38-40, 47, 83, 84 103-139). Although conventional gauzes and bandages are known as common treatments for wound closure, however, they are susceptible to bacterial infection and cannot accelerate the wound healing process (1-83, 103-137). **Wound healing** is a complex mechanism that can be categorized as an allergic response, propagation, and re-modeling in three parallel phases (1-39, 83, 84). Angiogenesis plays a critical role in wound healing (1-26, 31-42 46, 47, 79-84, 96-102). The inflammatory process initiates a proliferative wound repair response further characterized by vascular responses like **blood coagulation and hemostasis** (1-36, 38-40, 47, 83, 84, 103-139). Cellular activities include leukocyte infiltration with the release of antimicrobials and cytokines (1-80, 139). During the proliferative process, the epithelium is formed to coat the wound surface with the subsequent growth of granulation tissue to fill the

wound space (1-84). The re-modeling process begins to restore structural integrity and functional competence to the tissue when the new tissue is established inside the wound (1-36, 38-40, 47, 83, 84, 103-137).

Wound healing in burn patients

For **burns patients**, the ability to collect skin for autografts can be limited by the area of the burn and the sites that containing healthy skin (1-35, 38-83). Hair follicles are easily accessed and contain stem cells capable of differentiating into and restoring skin after grafting (1-35, 40-83). When the dermis and epidermis are lost due to a burn injury, some of the structures typically found in these areas are more often not replaced during the repair process (1-26, 35, 40-83). This includes hair follicles and sweat glands (35). This means that the skin that regenerates is generally hairless and does not sweat properly (1-26, 31-42 46, 47, 79-84, 96-102). No **epidermal/dermal** substitute has been developed yet that contains structures such as hair follicles or sweat glands (1-26, 31-42 46, 47, 79-84, 96-102). Also missing from scar tissue are melanocytes, the cells that produce pigments that give the skin its color (1-26, 35, 40-83, 139). No skin substitutes to date contain these cells (35). Incorporation of adipose-derived stem cells into a recombinant collagen scaffold demonstrated superior **wound healing** when compared to the recombinant protein **scaffold** alone (1-26, 31-42 46, 47, 79-84, 96-102, 139). However, the lack of a dermis in some burns, has led to skin substitutes being designed around scaffolds that contain both keratinocytes and fibroblasts (1-26, 35, 37-83, 103-139).

Wound healing: Nanomaterial polymers

Nanotechnology could provide the biochemically involved biological reactions needed to promote the wound healing process (1-30, 34, 83, 84). **Wound healing** refers to the replacement of damaged tissue through coordinated cellular events (1-21, 34, 83, 84). Nanomaterials are useful agents for accelerating the wound-healing process and drug delivery capability (1-30, 34, 83, 84). Conventional **wound healing** materials seem to be insufficient to facilitate and support this mechanism (1-21, 26, 34, 83). The improvement of wound healing process using nanotechnology has been inspired by the lack of adequate physicochemical properties and specific biological responses of classical materials for wound treatment (1-21, 34, 83, 84). **Nanotechnology** consists of manipulating materials at nanoscale levels and is widely employed in various fields of medicine, engineering, and electronics (1-27, 34, 83, 84). In wound healing process, nanomaterials can influence the collagen deposition and skin tissue regeneration (1-25, 34, 83, 84**). Nanotechnology** has become known as an exciting wound treatment tool (1-25, 34, 83, 84, 98). Multiple kinds of macroscopic nanobiomaterials (e.g., electrospinning nanofibers, nanosheets, nanoemulsions, carbon nanotubes-based, or graphene-based nanocomposites) and nano-sized biomaterials (e.g., NPs, ions, molecules, nucleic acids, functional peptides, proteins, oligosaccharides, or polysaccharides) have exhibited great potential capabilities of modulating vascularization, bacterial resistance, and inflammation during wound healing (1-25, 34, 83, 84, 98).

Natural biopolymers have recently been used as wound healing materials because of their biocompatibility, and biodegradability (1-21, 26, 31, 34, 83, 84). Unique polymer-based biomaterials can be used as a novel drug delivery systems, providing a new treatment strategy of non-healing chronic wounds (3-21, 26, 34, 40-84, 98). In general, bio-nanomaterials influenced the wound-healing process in terms of antibacterial, anti-inflammatory actions, capability to influence extracellular matrix (ECM) synthesis, stem cell proliferation, differentiation, and growth factors (1-28, 34, 83, 84, 98). **Natural biopolymers** can be promising for replacing conventional wound healing materials because of their remarkable biocompatibility, biodegradability, and good physicochemical properties (1-21, 26, 34, 83, 84). It can be a strategy to promote wound healing by intervening in the healing phases (1-21, 34, 83, 84). For **nanoparticulate** wound healing design, growing interest has been focused on natural biopolymers due to their biocompatibility and good adaptability to technological needs (1-21, 34, 83, 84). Recent studies highlighted that several natural plant-derived molecules can influence healing stages (34). In particular, **plant essential oils** showed excellent antibacterial, antifungal, antioxidant, and anti-inflammatory properties that can be amplified by combining them with nano technological strategies (1-21, 34, 83, 84). Recently, natural materials have gained much attention in biomedical production because of their high biocompatibility and environmentally friendly properties (36, 98). **Polysaccharides** are the most common natural biopolymers used for wound-healing materials (1-21, 34, 83, 84). In particular, alginate and chitosan polymers exhibited intrinsic antibacterial and anti-inflammatory effects, useful for guaranteeing efficient treatment (1-21, 34, 83, 84, 98). **Polyhydroxyalkanoates** (PHAs) are one of the new natural polymers that are synthesized by microorganisms using waste as a carbon source (36). They have good mechanical properties and biocompatibility, leading to their use in wound dressing production (1-21, 26, 34, 36, 83, 84, 98). However, there is a concern that their purity and chemical composition might induce an inflammatory reaction (1-21, 26, 34, 36, 83, 84).

For wound healing materials, natural and synthetic polymers are commonly used as the dressing material, in the form of films, **hydrogels**, and **scaffolds** (1-21, 34, 36, 83, 84). The natural agents such as agarose, alginate, and carrageenan are polysaccharides that are also used in wound healing process (1-21, 26, 34, 36, 83, 84). **Agarose** is generally extracted from seaweed (36). Because of its biocompatibility, transparency, and neutral charge, it is used in many biomaterial applications, including wound healing and tissue engineering (36). Moreover, an **agarose scaffold** has shown excellent mechanical properties and a suitable porous structure for drug delivery (1-21, 26, 34, 36, 83, 84). Because of the high porosity and non-adhesive properties of alginate dressing, it requires a secondary dressing to fix them (36). Moreover, the alginate dressing was reported to be difficult to remove from the wound (1-21, 26, 34, 36, 83, 84). **Carrageenan** also have limitations in processability and reactivity, so modification of their chemical and physical properties, such as blending with other polymers, is required to improve their properties (1-21, 26, 34, 36, 83, 84, 139).

The incorporation of **nanomaterials** with biocompatible polymers has been an emerging area for wound-healing application (31, 34, 83, 84, 139). Biopolymers are mainly naturally occurring polymers, usually obtained from microorganisms or by extraction from plants (83, 84-95). Some **biopolymers** can also be obtained by chemical synthesis from basic biological systems (83, 84-95). The main advantage compared to synthetic polymers is biocompatibility and used in the production of biodegradable plastics for food packaging and surgical applications (1-30, 83, 84-95). On the other hand, their disadvantages are poor mechanical properties, lower productibility, and dependency on many environmental factors (1-28, 34, 83, 84). The common biopolymers for wound healing applications are proteins, collagen, gelatin, silk fibroin, alginate, hyaluronic acid, chitosan, and fucoidan poly-Nacetyl glucosamine (1-21, 34, 83, 84).

Commonly, two types of approaches are used where nanomaterials either act as drug or vehicle to deliver the drug (1-21, 26, 31, 34, 83, 84, 139). Materials such as silver, gold, zinc, gold copper, titanium, and terbium are used in the form of nanoparticles to act as a drug (1-21, 26, 31, 34, 83, 84). **Nanomaterials** (NM) are classified into four classes: carbon-based NM, inorganic-based NM, organic-based NM, and composite-based NM (1-21, 26, 31, 32, 34,

83, 84). Whereas, in another approach, nanomaterials are used to deliver antibiotics, growth factors, nucleic acids, and antioxidants (1-21, 26, 31, 34, 83, 84).

Antibacterial Nanoparticles

Due to the growing resistance of bacteria to antibiotics, biomaterial experts have focused their researches on the use of **antibacterial nanoparticles** such as silver (Ag), copper (Cu), and zinc oxide (ZnO) in biomedical applications (138). **Silver (Ag)** nanoparticles are similar to pharmaceutical nanoparticles in that the active agent is the product of particle degradation (138). **Silver (**Ag) has low permeability and is considered safe when used in skin treatments. Long-term studies on burn dressings containing Ag nanoparticles and ions have proven their very low toxicity in this application (138). Silver (Ag) reduces the infection, at the same time slows the healing processes (138). **Copper *(*Cu*)*:** Cu is one of the essential and rare elements in the human body. Cu has strong antibacterial effect and less cytotoxicity than Ag nanoparticles which can play an effective role in wound healing (138). **Zinc oxide (ZnO*)*:** The use of ZnO antibacterial nanoparticles in nanomedicine and wound healing has had promising results (138). ZnO is widely used in antibacterial products due to its low cost, non-toxicity, good biocompatibility, minimal environmental effects, and ease of synthesis by various methods (138).

Carbon nanotubes (CNTs) in wound healing

The combination of hydrogels and **Carbon nanotubes** (CNTs) was very effective in wound healing and antibacterial treatment (1-21, 26, 31, 34, 83, 84). Nanomaterials-based **hydrogels** are considered as an attractive platform for wound-healing applications (1-21, 26, 31, 34, 83, 84). These hydrogels demonstrated superior mechanical strength, antioxidant, antibacterial, electrical, and tissue regeneration potentials (31). However, few obstacles, including low drug resistance, low antibacterial properties, toxicity, and low physical strength, are associated with the **hydrogel** composites (1-21, 26, 31, 34, 83, 84, 139).

Biocompatible **nanomaterials** have attracted enormous interest for biomedical applications. (1-21, 26, 31, 34, 83, 84). Carbonaceous materials, including carbon nanotubes (CNTs), have been widely explored in wound healing and other applications because of their superior physicochemical and potential biomedical properties to the nanoscale level (1-21, 26, 31, 34, 83, 84). **Carbon nanotubes** (CNTs) -based hydrogels are widely used for wound-healing and antibacterial applications (1-21, 26, 31, 34, 83, 84). **Carbon nanotubes** (CNTs)-based materials exhibited improved antimicrobial, antibacterial, adhesive, antioxidants, and mechanical properties, which are beneficial for the wound-healing process (1-21, 26, 31, 34, 83, 84). **Carbon nanotubes** (CNTs)-based composite hydrogels demonstrated superior antibacterial potential to corresponding pure polymer hydrogels (1-21, 26, 31, 34, 83, 84). The accelerated wound healing was observed with **carbon nanotubes** (CNTs)-based hydrogels (1-21, 26, 31, 34, 83, 84).

Wound dressing

Wound healing is a therapeutic challenge due to the complexity of the wound (1-21, 26, 34, 38-40, 83, 84). Various wounds could cause severe physiological trauma and bring social and economic burdens to the patient (1-21, 26, 34, 38-40, 83, 84). Conventional wound dressings were originally made from cotton gauze or non-woven blends of similar materials (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). Different types of wound dressing have been developed in different physical forms such as sponges, hydrocolloids, films, membranes, and hydrogels (1-21, 26, 34, 38-40, 83, 84, 139).

Wound dressings are generally classified as traditional wound dressings (Gauze, lint, bandage), modern wound dressings (Film, foam, hydrocolloid, hydrogel, alginate, nanoparticle based), and bioactive wound dressings (drug-loaded dressings, antibacterial dressings). Each of these formulations possesses distinct characteristics making them appropriate for the treatment of a specific wound (1-21, 26, 34, 38-40, 83, 84). Alginate, chitosan, collagen, and cellulose are the most used biomaterials for wound-dressing products (1-21, 26, 34, 38-40, 47, 83, 84). **Alginate** is the most commonly used biomaterial among other bio-products with wound healing properties (1-21, 26, 34, 38-40, 47, 83, 84, 139).

In contrast to the conventional approaches using gauze and **cotton bandages** in order to cover the wound, there is a broad range of polymer-based materials in the world market (e.g., gels, foams, and films) that can ensure a faster and more effective wound healing process by facilitating the function of the wound (1-21, 26, 34, 38-40, 42, 47, 83, 84). A high range of medicinal substances, such as antibiotics, vitamins, growth factors, anti-inflammatory agents, anesthetics, etc., are used in the fabrication of wound dressings in order to alleviate the inflammatory response and support the healing process (1-21, 26, 34, 38-40, 42, 47, 83, 84, 139).

One of the key parameters in **wound dressing** materials, specifically in burn wounds, is water content and the water holding capacity, which keeps the wound hydrated and adsorbs exudates (1-21, 26, 34, 38-40, 42, 47, 83, 84). An ideal wound dressing should: (**1**) absorb excessive exudates; (**2**) control the moisture in the wound bed; (**3**) possess good mechanical stability; (**4**) have great gases transmission; (**5**) protect from microorganism colonization and infections; (**6**) be non-toxic, biocompatible, and biodegradable; (**7**) ensure easy and non-painful removal after completed skin regeneration; and (**8**) be available at an acceptable cost (1-21, 26, 34, 38-40, 42, 47, 83, 84). Since a moist environment is crucial for accelerated wound healing, modern **hydrogel** dressings containing 70–90% water have recently attracted a lot of attention (1-21, 26, 34, 38-40, 42, 47, 83, 84). This type of wound dressing provides an easy application and removal without any tissue damage and can be used for burns, chronic and necrotic wounds, and pressure ulcers (1-21, 26, 34, 38-40, 42, 47, 83, 84). However, an underlying disease, poor nutrition, infection, and inappropriate wound management lead to delayed wound healing, which may progress to a chronic wound and organ loss (36).

In a recent study, the use of β-1,3-glucan (curdlan) as a base for the production of bioactive dressing materials (curdlan/agarose and curdlan/chitosan) that were additionally enriched with vitamin C and/or hydrocortisone to improve healing of chronic and burn wounds (1-21, 26, 34, 38-40, 42, 47, 83, 84, 99).

Wound healing is a complex process that depends on internal and external conditions (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). Therefore, the acceleration of wound treatment must involve promoting the healing process (35). **Wound dressings**, including films and foam dressings, are made from various materials or biologics that can facilitate cell migration (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). Wound dressings have been fabricated out of different types of materials and various formats, for example fiber mats and hydrogels, and may contain additivities like silver for anti-bacterial properties (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). Conventional wound dressings served to create a sealed wound environment to keep out infection, while also creating a moist environment to promote the wound healing process (35). There is a vast number of treatments available in the market for the management of wounds and burns, representing a multi-billion dollar industry worldwide (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84).

Many **wound dressings** are developed to provide a competitive advantage during wound healing such as providing protection against infection, keeping the wound moist, elimination of

exudates, wound healing acceleration, mechanical protection, easy removal, biocompatibility, biodegradation, and non-toxicity (36).

A suitable covering, which protects wound infection and provides an appropriate wound environment, is one of the important factors for the reduction of delayed wound healing (36). For wound dressing development, finding a technique that is clean, safe, and cost-effective to create a new dressing while maintaining the basic dressing properties is still challenging (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84).

A novel cost-effective wound dressing material based on low-methoxy pectin and NaA-zeolite particles with controlled albumin release properties has been reported (96). In vitro wound healing assay indicated that albumin-loaded hydrogels showed no toxic effects on the fibroblast cells (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84, 96). Therefore, albumin molecules possibly behaved as additional cross-linker agents for **pectin–zeolite hydrogel films** (96). Poly(vinyl alcohol) (PVA) is a polymer that is commonly used in the fabrication of hydrogels and used in wound healing applications (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84, 96). Poly(vinyl alcohol) (PVA) **hydrogels** for wound healing often include other materials to stimulate the wound healing response such as curcumin or zinc oxide nanoparticles for antibacterial properties (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84, 96). Further phlorotannins, derived from brown algae, which have been shown to promote fibroblast migration (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84, 96).

Other polysaccharides, including **chitosan, alginate, and cellulose**, have also been used to fabricate hydrogels and have shown promise as wound healing therapeutics (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84, 96). A polymer similar to **Poly(vinyl alcohol**) (PVA), poly(ethylene glycol) (PEG), is also commonly used for the fabrication of hydrogels, where Polymyxin B conjugated to PEG has been shown to be antibacterial, and when combined as a hybrid with alginate can promote wound regeneration (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84, 96).

All new tissue formation processes begin between two and ten days after skin injury. A well-known component present in skin is **hyaluronan**, also known as hyaluronic acid (35). **Hyaluronan** is a polysaccharide and is commonly used in hydrogels for wound healing (35). The basal layer of the epidermis, where proliferating keratinocytes are located, has high levels of **hyaluronic acid** (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). Furthermore, hydrogels that have incorporated hyaluronan have been shown to promote **blood clotting** and possess antibacterial properties (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84).

Wound dressing: Vitamins

Vitamins are widely used in various cosmetic products and creams due to their leading significance in wound healing and skincare (1-21, 26, 34, 38-40, 42, 47, 83, 84). Among many vitamins, tocopherol (vitamin E), **L-ascorbic acid** (vitamin C), and retinol (vitamin A), which possess anti-inflammatory and anti-oxidant effect in wound dressing fabrication (1-21, 26, 34, 38-40, 42, 47, 83, 84). Deficiencies in L-ascorbic acid resulted in decreased collagen synthesis, impaired angiogenesis, and reduced fibroblast proliferation (1-21, 26, 34, 38-40, 42, 47, 83, 84). Its deficiency is also associated with increased susceptibility to the wound infections (40). It was proven that vitamin A significantly improved the wound healing process (40). Retinoic acid formed by the metabolism of retinol increases fibroblast proliferation. However, simultaneous reduction in collagen synthesis was observed (1-21, 26, 34, 38-40, 42, 47, 83, 84, 139). Vitamin E facilitates wound protection against numerous infection and supports wound healing due to its antioxidant properties, stabilization of granulation tissue, and stimulation of re-epithelialization (1-21, 26, 34, 38-40, 42, 47, 83, 84).

It is well known fact that **vitamin C** is crucial for the wound healing process. Further, it was confirmed that the addition of vitamin C to a chitosan/agarose foam-like dressing supported fibroblast viability and proliferation (1-21, 26, 34, 38-40, 42, 47, 83, 84). The wound size was reduced by 92.27% in case of vitamin B12-enriched biomaterial and by only 64.62% when scaffold without vitamin B12 was applied (1-21, 26, 34, 38-40, 42, 47, 83, 84). It was also shown that a combination of vitamin E and **Aloe vera** gel had a positive impact on cell–matrix interaction and cellular viability (40). Among all the bioactive compounds, vitamin-loaded wound dressings were characterized by the widest variety of improved properties and the lowest limitations (1-21, 26, 34, 38-40, 42, 47, 83, 84). This indicated the possibility to significantly increased the biomedical potential of wound dressings by incorporation of **vitamins A, C, and E** into the structure of biomaterials during the production of wound care products (1-21, 26, 34, 38-40, 42, 47, 83, 84, 139).

Natural plant polymer wound dressing

Current wound dressings are comprised of a wide range of material types including natural plant extracts (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). The natural polymers (biopolymer) are generally selected for wound treatment over synthetic counterparts due to their non-toxicity to the human body and being economical (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). **Cellulose** can be found in a wide range of living species, which is mainly harvested from cotton and trees (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84).

Electrospun Fiber mat wound dressing

Another wound dressings includes electrospun mats that create a coverage for the wound (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). **Fiber mats** prepared from polymers, including polycaprolactone, often include incorporation of a biological material like collagen to mimic the dermis (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). Fiber mats produced from natural materials, including dermal proteins, can be made to create wound dressings that mimic the **extracellular matrix (ECM**) of the skin (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). Fibronectin is one such protein found within the dermis and has been used to make scaffolds for potential wound healing therapies (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84).

Bacterial cellulose (BC) wound dressing

Bacterial cellulose (BC) is a **natural polymer** that is synthesized from bacterial sources (38). It reveals suitable biological biocompatibility and biodegradability and also possess unique physical and chemical properties of **Bacterial cellulose (BC**) such as ultrafine nanofiber network, high crystallinity, high water retention capacity, and high tensile strength which make it suitable as a biomaterial for wound healing (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). The bacterial infection is the most common clinical complication related to skin conditions, and it plays a key role in delaying the healing process (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). In recent years, the (BC)-based biomaterials have attracted attention for various applications such as wound dressing, dental implants applications due to their porous structure, non-toxicity, histocompatibility, and biocompatibility (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). In addition, the Bacterial cellulose (BC)-based dressings showed better dermal burn treatment than silver sulfadiazine cream (38). The Bacterial cellulose (BC)-based wound dressings are more cost-effective in long term clinical studies compared to conventional fiber dressings (surgical pads, tulle grass, and saline-soaked gas) as well as synthetic foams and alginate dressings (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). The transparency of Bacterial cellulose (BC)-wound dressing provides heat absorption and pain reduction making

it suitable as a bandage for the patient with a burn wound (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). The pain can be usually diminished by the proper control of moisture at the wound site (38). In other words, the capability to retain the humidity prevents the dehydration of wound dressing and in turn, its attachment to the wound (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). Naturally, **Bacterial cellulose** (BC) is non degradable in the human body due to the lack of cellulose enzymes (38). The conventional wound healing treatments are bandage and gauze which possess several restrictions such as susceptibility to infection, non biodegradability, and secondary tissue damage (38). The reproduction of the **3D extracellular matrix** (ECM) of skin and efficient oxygen permeability is among the important characteristics of an ideal wound dressing (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84).

Alginates wound dressings

Alginates (ALG), are linear water soluble high swelling natural anionic polysaccharides obtained from brown algae cell walls and from some bacteria strains such as *Pseudomonas* or *Azotobacter* (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). They are biopolymers consisting of 1,4 -linked β -D-mannuronic acid (M) and 1,4 α-L-guluronic acid (G) monomers (47). One of the most promising alginate forms being used in helping wound healing is the **hydrogel** because it keeps the moisture, absorbs the excessive exudates, and reduces local pain because it has a cooling effect, it does not adhere to the wound bed and it can hold active compounds such as various drugs, signalling molecules, or stem cells (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 83, 84). Other advantages of alginate wound dressings include their easy removal, hemostatic properties, flexibility, permeability to water vapour, carbon dioxide, oxygen, and protection against bacterial infections (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 83, 84). However, **alginates** are non-adhesive, and they may provoke allergic reactions in individuals allergic to seaweed-derived products or when the exudates amount is not enough for forming the removable gel (46, 47).

Semi-permeable film wound dressings

Semi-permeable film wound dressings are made of adhesive, thin, porous, transparent polyurethane that allows oxygen, carbon dioxide, and aqueous vapour transmission from the wound through the wound dressing (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84). These semi-permeable film wound dressings presented a good texture, biocompatibility, and cost-effective (46, 47). However, the main drawbacks of these wound dressings are represented by their potential traumatic removal and the excessive pooling of exudates when used on heavily exuding wounds (46).

Hydrocolloid wound dressings

Hydrocolloid wound dressings are moisture-retentive dressings composed of two layers, one is suspension of hydrophilic colloidal particles and a polyurethane layer that is impermeable to bacteria (46). **Hydrocolloid** dressings contain gel-forming agents (e.g., gelatin, sodium carboxymethylcellulose, and pectin) and other materials, such as elastomers and adhesive coatings (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84). Other important advantages of hydrocolloids wound dressings include pain-free removal, barrier properties against water, oxygen, or bacteria, and the promotion of angiogenesis and granulation (46).

Hydroactive wound dressings

Hydroactive wound dressings are multilayered polymer dressings that are based on a moist principle (46). This phenomenon is highly useful in preventing wound drying, promoting wound healing, and reducing the risk of maceration (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84). Moreover, **hydroactive** wound dressings do not stick to the wound bed, thus lowering patient trauma on wound dressing removal, soothing painful wounds, and ensuring patient comfort and tolerability (46). **Hydroactive wound dressings** have shown promising results in the clinic, particularly effective in managing chronic wounds (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 96).

Marine polysaccharide wound dressings

Wound dressings have become a crucial treatment for wound healing due to their convenience, low cost, and prolonged wound management (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 100). As cutting-edge biomaterials, **marine** polysaccharides derived from the most marine organisms possesses various bioactivities, which allowing them to be processed into various forms of wound dressings (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 100). The application of **marine polysaccharides** in wound dressings is particularly important for the studies of wound therapy(1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 100). The diverse bioactivities of marine polysaccharides including antibacterial, anti-inflammatory, haemostatic properties, etc., providing excellent wound management and accelerate wound healing (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 100). Meanwhile, these biomaterials have higher biocompatibility and biodegradability compared to synthetic ones (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 100). On the other hand, **marine polysaccharides** can be combined with copolymers and active substances to prepare various forms of dressings (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 100). Among them, emerging types of dressings such as nanofibers, smart **hydrogels** and injectable hydrogels are at the research frontier of their development (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 100). Therefore, **marine polysaccharides** are essential materials in wound dressings fabrication and have a promising future (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 100).

Nanofiber membrane wound dressings

A new generation of wound dressings with the ability to quickly accelerate the wound healing process is **nanofiber** membranes with active materials (1-21, 26, 34, 38-40, 42, 47, 83, 84). The production of **nanofiber membrane** can be performed using any kind of electrospun solution (36, 38, 40, 83). One of the most practical **electrospinning** methods in tissue engineering is skin regeneration (1-21, 26, 34, 38-40, 42, 47, 83, 84)**.** In general, a biologically active factor play an active role in the recovery of skin process (1-21, 26, 34, 38-40, 42, 47, 83, 84). Bioactive agents include antibacterial particles, growth factors, stem cells, vitamins, and other factors that are effective in wound healing in combination with nanofiber membranes (1-21, 26, 34, 38-40, 42, 47, 83, 84). **Nanofibrous** membranes are a potential candidate for delivering bioactive agents to the wound site and among the skin substitutes, bioactive **wound dressings** are one of the most efficient and most attractive groups (1-21, 26, 34, 38-40, 42, 47, 83, 84).

Textile wound dressings were also used as protectors against pathogens and external injuries (46). In case of designing smart textiles, **electrospun nanofibers** are becoming popular especially due to the possibility of loading bioactive molecules within the **nanofiber** (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84, 96). Moreover, nanofibers can mimic the extracellular matrix (ECM), forming a highly porous structural support for growing cells accelerating skin healing (46). Another approach to designing advanced textile dressings involves the addition of micro and **nanoparticles** (1-21, 26, 34, 35, 36, 38-40, 42, 46, 47, 48, 83, 84).

Wound dressing: Scaffold

A **scaffold** is comprised of the polymeric central components, which are used to deliver cells, drugs, and genes into the body (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). Scaffold structure is a novel carrier for cell and drug delivery that enhances wound healing through differentiation of endothelial and epithelial cells and production of angiogenic growth factors in cutaneous wounds (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). **Collagen** is the most used biopolymer for wound healing, as numerous scaffolds available on the market are based on this material (46). In a recent study, the scaffolds were prepared from **agarose** and **sericin** using the freeze-drying method (D) or freeze-thawing together with the **freeze-drying method** (TD) (36). Moreover, plasticizers were added into the scaffold to improve their properties (36). Freeze-drying and freeze-thawing are physical crosslinking techniques that are used in biomaterial preparations (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). Adding **plasticizers**, especially glycerin, into the scaffolds significantly increased elongation properties, leading to an increase in elasticity of the scaffold (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). The wound healing property of sericin has been reported in many medical research studies (36). **Sericin** increased the attachment of human skin fibroblasts, activated cell migration and proliferation, and activated collagen synthesis, resulting in wound healing acceleration without **cytotoxicity** (36). Both the freeze-drying method (D) or freeze-thawing together with the freeze-drying method (TD) methods could be used as the production of natural scaffolds (36). All **scaffolds** were non-cytotoxic and could activate cell migration, referring to wound healing properties as a controlled drug release scaffold (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). Furthermore, adding a wound healing accelerating agent into the wound dressing could improve the performance of the wound dressing (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). Sericin, collagen, and epidermal growth factor are natural activating wound healing agents (36).

Recently, pH-sensitive polymeric **scaffolds** started to gain interest in wound healing (36 38). The efficacy of scaffolds resides in the fact that the normal human skin pH is between 4 and 6, while, in the case of an injury, it raises the physiological value (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). Therefore, a pH-sensitive scaffold made of **polyacrylamid**e (PAM)-grafted flax seed mucilage graft co-polymeric hydrogel (36, 38). The scaffold showed maximum swelling at 7.4 pH, tissue compatibility, satisfactory fibroblast growth, and sufficient collagen deposition, being considered promising materials for wound management (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84). **Chitosan** is another highly researched material, especially for scaffolds able to perform drug delivery beyond their physical support role (1-21, 26, 34, 35, 36, 38-40, 42, 47, 83, 84).

The **3D scaffold** have been fabricated in the form of films, membranes, and fibrous structures (138). The s**caffold** then populated with antibacterial drugs or nanoparticles for the protection of wounds against external germs such as bacterial (138). **Electrospun 3D scaffolds** typically have a high interconnected porous structure and an excellent surface area (138). This high porosity provides the ability to transfer nutrients and oxygen as well as metabolic waste removal and facilitates intercellular communication and increases cell viability and proliferation (138).

Wound dressing: Hydrogels

Hydrogels are good candidates for wound dressings as they are able to form a barrier from pathogens, as well as create a hydrated environment to help promote the body's own wound healing response (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84). **Hydrogels** are natural or synthetic cross-linked polymers with a water content of over 90%. 3D polymeric gels have a porous structure that can retain large amounts of water in their network and can absorb wound exudates (138). Hydrogels are complex three-dimensional structures composed of hydrophilic water insoluble polymers that can absorb high water volumes (46). Thus, **hydrogels** present an excellent moisturizing ability and play a significant role in cleansing necrotic tissue (46). Moreover, hydrogels are generally transparent, offering the possibility for easy wound monitoring (46). Hence, hydrogel dressings can be employed in the treatment of various wounds, including burns, surgical wounds, pressure ulcers, and radiation dermatitis (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84).

Hydrogels are classified in terms of various factors such as origin (natural or synthetic), water content (low swelling, medium swelling, high swelling, and superabsorbent), porosity (nanoporous, microporous, macroporous, and superporous), and biodegradability (biodegradable and non- or slowly degradable) (138).

Hydrogels are also classified into two categories based on the type of crosslinking: physical or chemical (138). In physical hydrogels, polymer chains are joined together by hydrophobic forces, hydrogen bonds (H-bonding), electrostatic interactions, and molecular entanglements (138). Hydrogels with physical cross-links are often preferred for medical and pharmaceutical applications as the utilization of toxic chemical cross linkers could be avoided (138).

In chemical hydrogels, however, the polymer chains are joined together by chemical bonding like covalent bonds (138). In fact, physical or covalent cross-links help to maintain the stability of the hydrogel structure (138). **Hydrogels** can be ideal wound dressings due to their non adhesive properties, elasticity, and similarity to the living tissue (138). Hydrogels with the ability to transfer nutrients and oxygen can be suitable candidates for large wounds and burns treatment (138, 139). The combination of nanoparticles with a specific matrix allows synergistic actions (1-21,34, 83, 84). Polymeric hydrogels are widespread in wound healing process (1-21, 34, 83). Their porous structure can absorb large amounts of exudates, maintain moisture in the wound site, and permit oxygen permeation (1-21, 34, 83, 84 Moreover, hydrogels showed physical properties similar to those of living tissue (1-21, 34, 83). Hydrogels have attracted a great deal of attention for biomedical applications, due to their 3D and ECM-like structure (138).

Hydrogels may be used in the form of swollen cross-linked networks, films/membranes, or in the form of porous structures for the preparation of wound dressings (138). Methods for fabricating a porous hydrogel structure often include freeze-drying (lyophilization), electrospinning, gas foaming, phase separation, and 3D-printing (138). The **3D-printed** drug delivery systems have the potential to provide customized innovative solutions. It is possible to rapidly prototype or customize using 3D printing to fabricate designs with a digitally controlled layer-by-layer deposition technique using **computer-aided design** (CAD) (138).

Drugs used in wound dressing

The most common drugs used in wound dressings are as follows.

1. Gentamicin (Gtm):

Gentamicin (Gtm) is antibiotic, commonly used to treat bacterial infection. Its mode action is inhibition of bacterial protein synthesis by binding to 30S ribosomes (138). It is also widely used drugs in wound treatment (138). **Gentamicin** (Gtm) is a strong and effective antibiotic against different types of bacteria (gram-positive and gram-negative) (138). Therefore, Gentamicin (Gtm) is widely used topically in the treatment of superficial skin infections. **Hydrogel** wound dressings containing Gentamicin (Gtm) have significant acceleration in wound healing compared to non-drug wound dressings (138).

2. Vancomycin (Van)

Vancomycin (Van) is the first water-soluble glycopeptide antibiotic (138). One of the reasons for using vancomycin (Van) is its low cost in a powder form (138). The main use of vancomycin (Van) is for severe infections caused by **gram-positive bacteria** (138). The mode of action of **vancomycin** (Van) as antibiotic is to kill bacteria by disrupting its cells' wall biosynthesis (138). **Vancomycin** (Van) powder is commonly used for combat bacterial colonization in spinal and orthopedic surgeries (138). One of the problems with Van is fast clearance due to its solubility in water, for this reason, it is usually used as an ointment or gel (138).

3. Erythromycin (Ert)

Erythromycin (Ert) is a medium-spectrum macrolide family antibiotic produced by *Streptomyces erythreus* (138). **Erythromycin** (Ert) is known as an antibacterial agent and is often used for gram positive bacterial infections (138). Preparation of wound dressings from composition of natural polymers with Erythromycin (Ert) is common in various methods such as **electrospinning**, which protects against bacterial infection by controlled Erythromycin (Ert) delivery to the wound site (138).

4. Ciprofloxacin (Cip)

Ciprofloxacin (Cip) (1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid) is a member of antibiotics family and derivatives of fluoroquinolones, which is known as the fifth largest generic antibiotic in the world (138). **Ciprofloxacin** (Cip) is used to treat wound infections caused by gram-positive and gram-negative bacteria due to its low minimal inhibitory concentration and lower microbial resistance (138).

5. Tetracycline (Tec)

Tetracycline (Tec) is known as a cationic antibiotic and is widely used for various infection treatments such as acne, periodontal, and urinary (138). **Tetracycline** (Tec) controls bacterial growth by inhibiting enzymatic reactions, synthesizing proteins and ribosomes, and altering cytoplasmic membrane synthesis (138).

6. Polyhexanide *(*Polyhexamethylene biguanide (PHMB*)*

Polyhexanide (Polyhexamethylene biguanide*)* (PHMB) has been used for various therapeutic applications due to its antibacterial properties (138). **Polyhexanide (Polyhexamethylene biguanide)** (PHMB) is recommended in the topical treatment of wounds in situations where a long time of contact with drugs is required. PHMB is active against gram negative and gram-positive bacteria, fungi, and yeasts (138).

7. Dialkylcarbamoyl chloride (DACC*)*

Dialkylcarbamoyl chloride (DACC) is a highly hydrophobic fatty acid derivative (138). Since the cell wall of the microorganisms responsible for surgical site infection or chronic wound colonization is hydrophobic, they adhere irreversibly to the **Dialkylcarbamoyl chloride** (DACC)-designed wound dressing (138). The mechanism of Dialkylcarbamoyl chloride (DACC) antibacterial effect is physical binding and deletion, and therefore, there is no risk of bacterial resistance (138).

8. Antiseptic Reagents

Antiseptic reagents are a suitable alternative to antibiotics due to their wider range of action (138). For example, one of the antiseptic reagents is **polyvinyl pyrrolidone-bound iodine** (PVP) (138). It is composed of iodine binding to polyvinyl pyrrolidone and is soluble in water (138). PVP is an active antiseptic reagent against gram negative and gram-positive bacteria, fungi, protozoa, and several viruses such as the H1N1 flu virus (138).

Another common antiseptic reagent is **cadexomer iodine** (CIOD), which is composed of biodegradable spherical hydrophilic beads of cadexomer starch and 0.9% w/w iodine (138). Due to its physical and antimicrobial properties, cadexomer iodine (CIOD) removes many of the barriers to healing (such as excessive exudates, slough, and bioburden) that are found especially in chronic wounds (138).

Wound healing: Herbal medicine treatment

Wound healing from ancient times remains a challenging clinical issue for effective wound treatment (1-21, 26, 30-83, 103-137). Hence, wound healing has gained major attention in the healthcare (1-26-35, 83, 84). The biology of wound healing is complicated and highly programmed, through phases of hemostasis, inflammation, proliferation and re-modeling (3-21, 26, 30-47, 83, 84). **Skin disorders** are a worldwide health problem that normally affect human life (3-21, 26, 79-84). Emergence of novel wound healing strategies using medicinal plants in conjunction with nanotechnology has the potential to develop efficacious wound healing therapeutics with enhanced wound repair mechanisms (3-21, 26, 40-84). **Wound healing** involves multiple populations of cells, the extracellular matrix (ECM) and the action of soluble mediators like growth factors and cytokines (3-21, 26, 30-47, 79, 83, 84).

Much research has been centered on wound care, with emphasis on new therapeutic methods and the advancement of acute and chronic wound treatment techniques in ***Ayurveda* (herbal)** (3-26, 30-84, 103-137). The herbal extracts and fractions effectively arrested bleeding from fresh wounds, inhibited microbial growth and accelerated wound healing (3, 21, 26, 82, 83, 84, 103-137). The influence of **natural plant** antimicrobials on the wound-healing process could be explained by their effects on growth factors (epithelial cells, fibroblasts, vascular endothelial cells) as stimulators of wound cells and cellular mechanisms (1-26, 34, 40-84). With the advent of nanotechnology and availability of novel materials, wound management is becoming more effective and patient-centric (3- 21, 26, 83, 84). Newer technologies like **3D printing** are also providing advantageous options for developing different drug delivery systems for managing wounds (1-21, 26, 30-84).

Natural plant derived products and naturally plant derived substances have long been used in wound healing because they possess anti-inflammatory, antioxidant, angiogenic, and cell synthesis-modulating properties (21, 26, 48-84, 103-137). Alternative medical systems such as naturopathy and ***Ayurveda*** utilize herbal medications as an important part of wound therapy (3-21, 26, 48-79, 83, 84, 103-137). Therefore, production of biomaterial through the combination of natural plant or synthetic polymers with the medical plant compounds appears to be a promising strategy to create wound dressings with improved pro-healing properties (3-21, 26, 48-84, 103-137).

The **plant-derived** active agents ensure desirable properties of the biomaterial, supporting wound re-epithelialization and its angiogenesis (3-21, 26, 40-41, 48-84, 103-137). The enhanced wound healing potency of various herbal extracts may be attributed to free radical-scavenging action and the antimicrobial property of the phytoconstituents present in the extract, and the quicker process of wound healing could be function of either the individual or the synergistic effects of bioactive molecules (103-137). These active constituents promote the process of wound healing by increasing the viability of collagen fibrils, by increasing the strength of collagen fibers either by increasing the circulation or by preventing the cell damage or by promoting the DNA synthesis (3- 21, 26, 83, 84, 103-137).

Plants play a significant role in conventional wound treatments (3-21, 26, 30-79, 103-137). Bioactive dressings are usually produced using natural or synthetic polymers. Recently, special attention has been paid to β-glucans that act as immunomodulators and have pro-healing properties (1-21, 26, 34, 35, 38-40, 42, 47, 83, 84, 103-137). Phytochemical substances are found in plants that are utilized to treat skin problems (3-21, 26, 103-

137). Widely used medical plants are rich in bioactive natural compounds with immunomodulatory properties (3-21, 26, 48-83, 103-137). Essential trace elements especially zinc and vitamin C, vitamin E also influences the process of wound repair (83). Vitamin C also acts as cofactors or coenzymes in a number of metabolic functions involved in wound healing. Hence, **zinc** and **vitamin C** levels of the herbal extracts can be determined (83, 103-137). Zinc content of the plant extracts used for wound healing purposes might have a great contribution in the healing process (83, 103-137). As a consequence, naturally derived active agents may control the inflammatory response and promote re-epithelialization and wound contraction (3-21, 26, 30-83, 103-137). Currently, there are many reports in the literature on dressing materials loaded with curcumin (3-21, 26, 40-83, 103-137). Furthermore, it was revealed that tested biomaterials loaded with curcumin enhanced collagen accumulation (3-21, 26, 40, 79-83, 103-137). Thus, it may be assumed that **curcumin**-loaded biomaterials may be potentially promising wound dressings for the management of the wound after skin cancer excision (3-21, 26 30-40, 47,79, 83, 103-137). The plant antimicrobial compounds accelerate and promote skin regeneration by influencing cell migration and the extracellular matrix (ECM) deposition (3-21, 26, 34, 79-83, 103-137). Secondary metabolites like other antibiotic chemical compounds, e.g., such as aminoglycosides, beta-lactams, glycopeptides, quinolones, sulphonamides, and tetracyclines can be used to control wound infections (3-21, 26, 34, 83, 103-137). Active **metabolites** can also act as antioxidant agents and accelerate the wound-healing process by decreasing intracellular Reactive Oxygen Species (ROS) production and controlling the rate of nitric oxide synthase (3-21, 26, 34, 40-47, 79, 83).

Topically administered drugs are effective in faster wound contraction due to the larger availability at the wound site (83). An ointment with water-soluble base is of first choice due to their ease of preparation and eases of cleaning after application (83). The medicaments are dispersed in the base, and later they get divided after the drug penetration into the living cells of skin (83). The results of various studies performed so far are significant for different parameters in wound healing activity when compared with the control group and showed that the usage of **herbal extracts** significantly accelerated wound healing (83, 103-137).

In a traditional **Indian *Ayurvedic*** system of medicine, plants and plant-based constituents have been extensively used for the treatment and management of different types of wounds (3-21, 26, 48-83, 103-137). Traditional healers are significant for public health in Indian rural communities, and many individuals have confidence in the healing attributes of herbal medicine (103-137). The folk healer is one of the important sources for determining the use of herbal medicine for treating people in the local area, and it will be the initiation process for searching for the prominent plants (3-21, 26, 79, 103-137). In the current times, different types of biopolymers are being researched for developing economical, sustainable, stable, and effective delivery system for the treatment of wounds (3-21, 26).

Ayurveda is a holistic approach to health and wellness that emphasizes balance between body, mind, and spirit. It's one of the oldest and the most respected Indian medicinal traditions in the world (3-21, 26, 48-83, 103-137). ***Ayurveda*** focuses on preventing disease, so its approach to treating wounds encompasses a whole range of healthy choices, rather than focusing solely on antimicrobial activity and immediate relief (3-21, 26, 30-83, 103-137). The wound healing remedies from ***Ayurveda*** are safe and gentle on the body (3-37, 83, 103-137). The ***Ayurvedic*** treatment of wound healing suggested the use of herbal formulations (3-21, 26, 48-78, 103-137). These herbs have been sourced from nature and have been used for thousands of years (3-21, 26, 48-79, 83, 103-137). Therefore, **plant** constituent-based wound dressings are very effective treatment in the management of wound healing process (3-21, 26, 48-83, 103-137).

Use of **Complementary and Alternative herbal Medicines** (CAMs) is the only available option that was used universally to treat many diseases including wounds (3-21, 26, 48-78, 103-137). Using **plants with medicinal** properties to treat wounds have been found useful in fighting against infection and accelerate wound healing. This suggests that traditional herbal medicines has a potential future in chronic wound management (3-21, 26, 34, 40-79, 103-137). The use of phytochemicals and naturally plant derived substances is an exciting and clever innovation for chronic wound healing (21, 26, 79, 103-137). The **Complementary and Alternative Herbal Medicines** (CAM) is a promising approach to improvising clinical and medical challenges faced by non-healing chronic wounds (3-21, 103-137). The plant derived essential oils are used as active secondary compounds in polysaccharide-based **wound dressings** (3-21, 26, 34, 40-47, 48-79, 103-137).

Herbal remedies and drugs have played a significant role in curing diseases throughout the history of mankind (3-21, 26, 48-79, 103-137). Herbal medicines have the potential to treat and cure illnesses like ulcers, healing of wounds, skin infections inflammation, scabies, leprosy and venereal disease (1-21, 26, 48-83, 103-137). **Herbal** medicines in wound treatment or care include disinfection, debridement, and providing a moist atmosphere which facilitates development of appropriate natural healing climate (3-21, 26, 48-78). Folklore cultures employ a significant number of plants to treat cuts, wounds, and burns (3-21, 48-77, 103-137). Various **herbal** formulations have helped to accelerate the wound healing process and are useful in wound treatment (3-21, 26, 48-78, 103-137).

Bioactive **secondary metabolites** of plants could be used for wound healing, including alkaloids, essential oils, flavonoids, tannins, terpenoids, saponin, fatty acids, and phenols (3-21, 26, 34, 40-47, 48-79, 103-137). These active compounds could improve the wound-healing process by influencing one of the healing stages through antibacterial, antifungal, antioxidant, and anti-inflammatory effects (3-21, 26, 34, 79-83, 103-137). **Plants** contain many natural bioactive compounds that help to fasten the process of wound healing and regenerate tissue at the wound site (3-21, 26, 34, 40-83, 103-137). Some examples of medicinal plants and their wound healing effects are listed below (3-21, 26, 34-79, 103-137).

Plants with wound healing properties

Following are some of the plant extracts used in the **wound healing** process (3-21, 26, 79, 81, 82, 83, 103-137).

1) Turmeric (*Curcuma longa*) (*Zingiberaceae*) Rhizomes. **2**) Liquorice or Mulethi (*Glycyrrhiza glabra*) (*Fabaceae*) Roots. **3**) Neem (*Azadirachta indica*) (M*eliacaee*) All the parts of plant were used. **4**) **Centella** (*Centella asiatica*) (*Apiaceae*) Leaves. **5**) Carbonal (Mimosa tenuiflora) (Fabaceae) Leaf and stem parts used in wound healing. **6**) Clitoria ternatea (Leguminosae) All the parts of plant were used in wound healing. **7**) Costus speciosus (Zingiberaceae) Rhizome used. **8)** Theaceae (Camellia pubipetala) Leaves used in wound dressing. **9) Forest Champa** (Spermadictyon suaveolens (Rubiaceae): Roots used in wound healing. **10)** Chlorophytum borivillianum (Liliaceae): Rhizome parts. **11)** Sesame (Sesamum indicum L) (Pedaliaceae) seeds were used. **12)** Calendula officinalis (Asteraceae): Flowers and leaves used. **13)** Trumpet tree (Cecropia peltata): Leaves. **14)** Punica granatum (Lythraceae) All parts were used. **15)** Kencur (Kaempferia galanga) (Zingiberaceae) Rhizomes. **16) Jhand tree** Druce (Prosopis cineraria) (Fabaceae) Leaves. **17)** Maidenhair (Ginkgo biloba) (Ginkgoaceae**)** Leaves and seeds. **18)** Indian mulberry (Morinda citrifolia) (Rubiaceae) Leaves and fruits. **19)** Gymnema sylvestre (Asclepiadaceae) Leaf and stem. **20)** Madagascar periwinkle (Vinca rosea or **Catharanthus roseus**) (Apocynaceae) Leaves and flowers. **21)** Asthma Weed (Euphorbia hirta) (Euphorbiaceae) Leaves. **22)** Red sandalwood (Pterocarpus santalinus) (Fabaceae) Bark wood. **23) Lawsonia alba** (Lawsonia

inermis) (Lythraceae) Leaves and roots. **24)** Jandi or Ghaf (Prosopis cineraria) (Fabaceae) Leaves and pods. **25)** Aloe (Aloe vera) (Liliaceae) Leaves. **26)** Bay (Sphagneticola trilobata) (Asteraceae) Leaves. **27)** Adusa (Adhatoda vasica) (Acanthaceae) Leaves. **28)** Humble plant (Mimosa pudica) (Leguminosae) Whole plant is used for wound healing. **29)** Papaya (Carica papaya) (Caricaceae) Latex, fruit. **30)** Jungle flame (Ixora coccinea) (Rubiaceae) Roots and leaves. **31)** Betle Piper (Piper betle L) (Piperaceae) Leaves. **32)** Common wireweed (Sida acuta) (Malvaceae) whole plant. **33**) Drumstick tree (Moringa oleifera) (Moringiaceae) Leaves. **34**) Indian olive (Olea europaea) (Oliaceae) Leaves and oil. **35) Burdock** (Arctium lappa) (Asteraceae) Root extract used treatment of sore throats and skin pathologies boils, rashes, and acne in North America, Europe, and Asia. **36)** Ginseng (Panax ginseng) (Araliaceae) Root or Rhizome part is used wound healing in China, Japan, Korea, and Eastern Siberia. **37)** German chamomile (Chamomilla recutita) (Asteraceae) Apigenin is the rarest flavonoid in chamomile flora and has a remarkable effect on the wound healing process. **38**) Pinus pinaster (Leaf and stem part). **39**) *Lavandula angstiforia* (Lamiaceae) **40**) *Argania spinosa* (Sapotaceae) **41**) *Bursera morelensis* (Burseraceae) **42**) *Hypericum patulum* and *H. perforatum* (Hypericaceae) **43**) *Copaifera paupera* (Fabaceae) **44**) *Avicennia schaueriana* (Verbenaceae) **45)** *Cucurbita pepo* (Cucurbitaceae) **46**) *Ximenia americana* (Olacaceae) **47**) *Fumaria vaillantii* (Papaveraceae) **48**) *Astragali radix* (Fabaceae) **49**) *Sauromatum guttatum* (Araceae) **50**) *Sapindus mukorossi* (Sapindaceae) **51**) *Euphorbia hirta* (Euphorbiaceae) **52**) *Vaccaria segetalis* (Caryophyllaceae**) 53**) *Berula angustifolia* (Apiaceae) **54**) *Pupalia lappacea* (Amaranthaceae) **55)** *Cydonia oblonga* (Rosaceae) **56)** *Chrozophora tinctoria* (Euphorbiaceae) **57**) *Nigella sativa* (Ranunculaceae) **58**) *Elaeis guineensi* (Arecaceae) **59**) *Ficus racemose* (Moraceae) **60)** *Annona muricata* (Annonaceae **) 61)** *Artocarpus communis* (Moraceae) **62**) *Aegle marmelos* (Rutaceae) **63**) *Bacopa monniera* (Plantagiaceae) **64)** *Cinnamomum verum* (Lauraceae) **65**) *Anacardium occidentale* (Anacardiaceae) **66**) *Ephedra alata* (Ephedraceae) **67**) ***Ficus racemose*** (Moraceae) **68)** *Calotropis procera* (Apocynaceae) **69)** Origanum vulgare L. O. vulgare (Lamiaceae) **70**) Ageratina pichinchensis (Asteraceae) **71**) Rehmanniae radix (Scrophulariaceae**) 72**) Radix astragali (Fabaceae) **73**) Angelica sinensis (Apiaceae) **74**) Salvia miltiorrhiza (Lamiaceae)**75**) Alchemilla vulgaris (Rose family) **76)** Phyllanthus muellerianus (Euphorbiaceae). **77) *Camellia sinensis*** (Theaceae) **78)** *Arctium lappa* (Asteraceae) **79**) *Astragalus propinquus* (Fabaceae) and *Rehmannia glutinosa* (Scrophulariaceae**) 80**) *Ampelopsis japonica* (Vitaceae) **81)** *Andrographis paniculata* (Acantheaceae) **82**) *Angelica sinensis* (Apiaceae) in wound healing (21, 26, 78, 80, 81). **83**) *Blumea balsamifera* (Asteraceae) Endemic throughout the tropics and subtropics of Asia, *Blumea balsamifera* (also known as ngai camphor) is used widely as a traditional medicine. In the Philippines, *Blumea balsamifera* is known as sambong and is used as a diuretic. In Ayurveda, *Blumea balsamifera* is known as kakoranda and is used to treat wound healing, fevers, coughs, aches, and rheumatism. **84**) *Boswellia sacra* (*Bursaraceae*) Frankincense, a resinous extract from *Boswellia sacra*, is valued in Africa, India, and the Middle East for the treatment of trauma and inflammatory diseases such as rheumatoid arthritis, and wound healing. **85)** *Caesalpinia sappan* (Fabaceae) is used in wound healing. **86**) ***Carthamus tinctorius*** (Asteraceae). **87**) *Celosia argentea (*Amaranthaceae*). Celosia argentea*, also known as silver cock's comb, is used in traditional medicine to treat skin sores, eruptions, ulcers, mouth ulcers, and other skin diseases. **88**) *Cinnamomum cassia* (Lauraceae). **89**) *Commiphora myrrha* (Burseraceae) **90**) ***Terminalia chebula*** (Combretaceae) **91)** *Terminalia arjuna* (Combretaceae) **92**) Kutaja (*Holarrhena antidysenterica*) (Apocynaceae) Bark and leaf.

Aloe vera is one of the natural polymers of plant origin that contains many antibacterial compounds such as acemannan, pyrocatechol, cinnamic acid, and p-coumaric acid (138). Among the wide range of natural polymers, some of them, such as chitosan, keratin, honey, and pectin, can show relatively good antibacterial activity and therefore, used in wound dressings (138). In many of the previous studies, chitosan, keratin, honey, pectin, and **Aloe vera** have been used in wound healing applications (138).

Phyllanthus muellerianus (PLE) and geraniin possess significant wound-healing activity (80). *Phyllanthus muellerianus* (PLE) and **geraniin** increased hydroxyproline production, collagen production, tensile strength of wound tissues, and TGF-b1 levels in wound bed and also exhibited good cytoprotective activity (80). The aqueous leaf extract of P. muellerianus and its major isolate, geraniin stimulate cellular activity, differentiation, and collagen synthesis of human skin keratinocytes and dermal fibroblasts (80).

Plant Secondary metabolites in wound healing process

Chemical constituents present in above-mentioned plants contains glycosides, curcumin, proteins, glycyrrhizin, **glycyrrhetinic**, asiatic acid, asiaticoside madecassoside, madecassic acid, alkaloids, mimosine (an alkaloid), sitosterol, amino acids, linoleic acid, tannins, polyphenols, oleic acid, 5-Hydroxyimidacloprid, 4,5-dihydroxyimidacloprid, desnitroimidacloprid, 6-chloronicotinic acid, olefin, **triterpenes**, sesquiterpenes, **azadirachtin**, azadirone, nimbin, nimbidin, nimbinin, metronidazole, vitamins A, C, E, sesamolinol, sesamol, sesaminol, sesamolin, patulitrin, diketones, spicigerin, β-sitosterol, stigmasterol, hentriacontane, octasanol, and prosogerin A, B, C, and D, santalin A, B, savinin, calocedrin, pterolinus K, L, pterostilbenes, **coumarins**, naphthoquinone, flavonoids, sterols, triterpene, xanthones, **anthaquinone**, papain, biophenolics, oleuropein secoiridoid, luteolin, vicenin-2, beta-carotene, phenolics, steroids, carbohydrates, terpenoids, carotenoids, flavonoids, cardenolides, **tocopherols**, essential oils, resins, fatty acids, triterpenes, geranyl acetate, ursolicacid, saponin, and various phenolic compounds are responsible for wound healing (21, 26, 103-137). Maximum **plants** and their chemical constituents showed its effects by the mechanism by angiogenesis are NF-κB, TGF-β, VEGF, tumor necrosis factor (TNF), and inducible nitric oxide synthase (iNOS) effect on cytokines ; apart from this different mechanism especially IL-4, IL-5, IL-13, and TGF-β1, reduction in wound size by re-epithelialization is also involved in wound healing (21, 26, 80, 81, 103-137).

Some of the most important **plant secondary metabolites** influencing wound healing process include oleanolic acid, polysaccharides, gentiopicroside, sweroside, swertiamarin, shikonin derivatives (deoxyshikonin, acetyl shikonin, 3-hydroxy-isovaleryl shikonin, and 5,8-Odimethyl acetyl shikonin), asiaticoside, asiatic acid, madecassic, quercetin, isorhamnetin, kaempferol, curcumin, sesamol (3,4 methylenedioxyphenol), coluteol, colutequinone B, hyperforin, catechins, and isoflavonoids that could potentially be new therapeutic agents to treat wounds. These agents usually influence one or more phases of the healing process (3, 21, 26, 80, 81, 83, 103-137).

Wound healing: Plant Essential oils

Essential oils of plants are secondary metabolites characterised by the antibacterial, antifungal, anti-inflammatory, antioxidant, and antiviral properties (34, 43-45). Plant based essential oils are comprised of a complex mixtures of volatile phytochemicals from diverse classes including monoterpenes, sesquiterpenes, and phenylpropanoids (34, 43-45, 48-77, 103-137). As a delivery system for the pharmacological application of essential oils, nano-emulsions are gaining special attention because they are inexpensive and

scalable (34). **Essential oils** of medicinal plants have an extensive applications in medicinal chemistry, pharmaceuticals, aromatherapy particularly in perfume and soap industries (43). Essential oils are odorous, volatile compounds found in plants and are stored in special fragile secretary structures, such as glands, secretary hairs, secretary ducts, secretary cavities or resin ducts (43-45). Essential oils of plants are hydrophobic, soluble in alcohol, non-polar or weakly polar solvents but only slightly soluble in water (43). **Essential oils** have the ability to hamper the growth of a diverse range of pathogens because of the presence of natural compounds produced by the organs of plants (43-45). Essential oils are composed of saturated and unsaturated hydrocarbons, alcohol, aldehydes, esters, ethers, ketones, oxides, phenols and terpenes which may produce characteristic odours (34, 43-45). The nano-formulation strategy is a solution to preserve the therapeutic efficacy of essential oils while minimizing their physicochemical limitations (34). For this purpose, mainly large molecules (e.g., cyclodextrin) and polymers have been used as carriers (34). In fact, the nano-emulsion method is a simple synthetic technique and is applied for a simple composition (34). **Nanoemulsions** are isotropic dispersed systems of two immiscible liquids formed by mixing oil and water and adding surfactant/co-surfactant to obtain a droplet size in the nanometer range (34). **Nanoemulsions** can be classified as water-in-oil (W/O) and oil-in-water (O/W) emulsions (34). O/W nanoemulsions are mainly used in the pharmaceutical field because they are easily washed out and are often used in drug delivery systems (34, 43-45).

The plant essential oils demonstrated the capacity to be used as both a solvent and active material, which improves the synthesis process's sustainability and safety (34, 43). Thus, essential oils of plants possessed features that are useful in the chronic wound management (40). **Thyme oil** (*Thymus vulgaris*) belongs to the mint family *Lamiaceae* is also a best medicine for wound healing (34). The incorporation of **thymol oil** isolated from *Thymus vulgaris* into bacterial cellulose hydrogel in order to improve biological properties of the biomaterial (34, 40, 41, 103-137). The introduced modification not only increased the antibacterial activity against E. coli, *S. aureus, P. aeruginosa,* and *K. pneumoniae*, but also promoted faster wound closure in the in vivo rat animal model (34, 40, 41). Many studies have shown that carvacrol and thymol have anti-inflammatory, antioxidant, skin fibroblast-stimulating, and antibiotic effects in the wound-healing process (34). Even if the use of essential oil nanoemulsion as a food **biopreserver** is more prevalent, their wound-healing potential is noteworthy (34). However, some of the essential oils of plants are toxic and not recommended for the oral consumption. The development of all kinds of wound dressing influenced the design of essential oil nanoemulsions (34, 103-137). The essential oil **nanoemulsions** are combined with biopolymers, such as chitosan presented another kind of wound dressings, such as hydrogel or both situations, as chitosan/alginate films (34, 103-137).

Another essential oil widely used in wound healing is **Tea tree oil** (TTO), which is extracted from the leaves of *M. alternifolia* (34). Tea tree oil (*Melaleuca alternifolia*), the volatile essential oil derived mainly from the Australian native plant ***Melaleuca alternifolia*** belong to the family *Myrtaceae* (34). The presence of terpene hydrocarbons and tertiary alcohols in tea tree oil (TTO) has antimicrobial and anti-inflammatory activity and helps in the regeneration of collagen (34). Cinnamaldehyde (CAL) or (2E)-3-Phenylprop-2-enal is found in cinnamon essential oil (55–76%) isolated from Cinnamon trees, Camphor, and Cassia (34). **Cinnamaldehyde** (CAL) is used in wound healing for antibacterial, antifungal activity and as an anti-inflammatory agent (34). In India **Camphor tree** (*Cinnamomum camphora*) leaf extract and oil has been used for the wound healing (34, 43, 45). Another study demonstrated the antimicrobial activity of cinnamon, lemongrass, and peppermint essential oils encapsulated in cellulose-based fiber dressings (34). On the other hand, another study reported the different types of dressings (ointment, hydrogel, and nanofiber) with 5% turmeric, 1% oregano, and 1% chitosan nanoparticles and compared their antibacterial, antioxidant, and cytotoxicity properties with those of commercial alginate silver dressing (34). Oregano (*Origanum vulgare*) is a plant from the mint family native to Western and Southwestern Eurasia and the Mediterranean region (34). **Turmeric** (*Curcuma longa*) is in the ginger family and a native plant to the Indian subcontinent and southeast Asia. The **essential oils** of these plants have potential applications in wound healing because of their antimicrobial and antioxidant ability (34). Essential oils obtained from eucalyptus (*Eucalyptus globulus*) belongs to family *Myrtaceae* are traditionally used to treat wound healing and various respiratory ailments including pharyngitis, bronchitis, and sinusitis (43). An **eucalyptus oil** nanoemulsion for topical application has been investigated due to the antibacterial and wound-healing potential against *Staphylococcus aureus,* and Wistar rats, respectively (34). *Lawsonia inermis* Linn is extracted from the henna tree and can be used in the healing of chronic and burn wounds due to its antioxidant, analgesic, anti-inflammatory, antibacterial, and antifungal activities (34). These results showed that *Lawsonia inermis* could promote the wound-healing process (34). **Lavender essential oil** (LEO) is extracted from the flowers of *Lavandula angustifolia* and is known as an anti-anxiety, analgesic, antioxidant, and anticancer agent used in wound dressing and the data suggested that the designed dressings affected the vitality of bacteria (34). **Clove oil** extracted from *Syzygium aromaticum* exhibits antioxidant and anticancer activity due to its secondary metabolite eugenol (34). A clove oil **nanoemulsion** was obtained by spontaneous emulsification using triacetin as oil phase, Tween-80 as surfactant, Labrasol as co-surfactant, and distilled water as aqueous phase (34). These experimental results confirmed that clove oil **nanoemulsion** was safe and nontoxic (34, 103-137).

Ravintsara oil is extracted and distilled from the leaves of *Cinnamomum camphora* belongs to the family *Lauraceae* in Madagascar is also used in the wound healing for the topical applications (43). Rather than being rich in camphor, Ravintsara oil also contains higher concentration of 1,8-cineole (45-55%) (43). **Lemon balm oil** (*Melissa officinalis* L.,) belongs to a family *Lamiaceae*, is a perennial plant also used in wound healing and found very effective (43). **Lemon balm oil** has been used externally to treat herpes, sores, gout, insect bites and other skin diseases (43). Garlic oil (*Allium sativum)* belong to the family *Amaryllidaceae* is one of the common medicine for wound healing in India (43). The essential oil of ***Laurus nobilis*** belongs to the family *Lauraceae* also used for the wound healing (43). Rosemary oil (***Rosmarinus officinalis* L.)** belongs to the family *Lamiaceae* is used as quick remedy for the wound healing. Bergamot Oil (Synonym Citrus x bergamia Risso & Poit.) is used for the topical applications in wound healing (43). However, **bergamot oil** is very **toxic** and hence very low concentration of the oil is used for the wound healing topical applications. The other plant essential oils used in wound healing are **Cinnamon Oil** (*Cinnamomum zeylancium* or *Cinnamomum vervun Lauraceae*), *Piper nigrum* (*Piperaceae*), Fennel Oil (*Foeniculum vulgare)* (*Apiaceae*), *Salvia lavandulifolia* (*Lamiaceae*), *Piper nigrum* (*Piperaceae*), *Artemisia frigida* (*Asteraceae*), Clove oil (*Eugenia caryophyllata*) (also known as *Syzygium aromaticum*, *Eugenia aromatica*, *E. carophyllus*) (*Myrtaceae*), Oregano Oil (*Origanum vulgare*) (*Lamiaceae*) and *Achillea clavennae* (*Asteraceae*) (43, 103-137).

CONCLUSION

Wound healing is a complicated multiphase and multifactorial physiological process which needs accelerated healing. The number of patients with **chronic wounds** increases every year. Therefore, proper wound treatment, focused both on increasing the healing rate and quality of healing. Currently, a variety of **wound dressings** have been developed and applied in the clinic for treating all sorts of wounds. The benefits of using a wound dressing as a covering for damaged skin include maintaining a moist environment, absorbing excessive extracellular fluid, creating a barrier against infection, maintaining appropriate temperature, ameliorating cutting health care costs. However, the **wound healing** and wound management is very expensive health care, which poor people cannot afford to bear expenditure.

Herbal medicines in wound treatment or care include disinfection, debridement, and providing a moist atmosphere which facilitates development of appropriate natural healing climate. It is well-known that **natural plant** derived molecules possess anti-inflammatory, antioxidant, angiogenic, and cell synthesis modulating components that are crucial biological functions necessary for wound healing. In addition to this, the use of natural products and naturally derived substances are considered **safe** compared to synthetic molecules and can be much cheaper than conventional therapies. Due to the escalating cost of health care especially in chronic wound management, the use of **Complementary and Alternative herbal Medicines** (CAMs) to treat these wounds would be economical.

The traditional healer is one of the most essential sources for determining the usage of herbal medicine for treating individuals in the community. However, Complementary and Alternative herbal Medicines (CAMs) are subject to the risk of contamination, side effects, and non-specificity in treatment due to the complex structure of phytochemicals and naturally derived substances in the extract (1-26, 103-137). But these limitations do not deter the fact that **Complementary and Alternative herbal Medicines** (CAMs) are promising in challenging non healing wounds (103-137). The application of secondary natural products in active wound dressings as antimicrobial and antioxidant additives is promising, providing fully biodegradable and sustainable biomaterials (103-137). However, there is a deep gap **between laboratory scale research**, clinical scale and even commercialization. Most of the experiments were conducted on animal model. However, some of the **animal model experiments** results showed failure in human clinical trials in case of wound healing. This would be the biggest barrier for the commercialization of **wound healing** dressing materials.

Other therapies range from polymer **hydrogels** to epidermal/ dermal substitutes that incorporate both keratinocytes and dermal fibroblasts. Due to the heterogeneous nature of wounds, there is no “one fits all” therapy. There are continual advancement in technologies used to develop these therapies, from **3D printing** of dressings directly onto a wound, to **stem cell** technologies including induced pluripotent **stem cells**, will result in new wound healing therapies in the future.

Although bacterial cellulose (BC)-based hydrogel possesses attractive characteristics such as biocompatibility, high moisture, and water retention capacity. However, the main drawback of pure Bacterial cellulose (BC) -based **hydrogel** is the lack of antibacterial properties. The mechanical behaviour of Bacterial cellulose (BC)-based wound dressing should be taken into consideration which represents opportunities to design bacterial cellulose (BC)--based **hydrogel.**

Different wound dressings containing antibiotics and antibacterial agents prevent bacterial infection and **biofilm** formation in the wound bed. However, the use of antibiotics and antibacterial nanoparticles in wound healing has some limitations since most of these antibacterial agents have side effects such as **cytotoxicity**. Variety of **allopathic medicines** are available to quickly heal this condition. But, as we all know, there are some major side effects, thus individuals from all over the world are turning to herbal therapy for wound healing. There are a variety of **herbal plants** that have wound healing properties. Therefore, the clinical application of such **antibacterial agents** has always been associated with challenging. Hence preclinical and clinical researches are needed to provide safe methods of wound infection treatment as well as materials and products used for wound care.

The loading of **stem cells** has been suggested as a potential therapeutic. choice. However, it requires large-scale clinical trials. Nowadays, the state-of-the-**art 3D and 4D** printing biomaterials which mimic the extracellular matrix can offer a promising solution to wound treatment in the upcoming future. New formulas, dressings, and medicinal **plant composition** are being explored by researchers for developing cost effective, efficient, stable, and sustainable delivery system for the management/treatment of wounds.

Phytotoxicity is another major problem with applications of **plant based extracts** in wound healing. Therefore, detailed phytochemical study should be conducted before the application of plant based remedies in wound healing.

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