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Wound Healing: Traditional plant based and Modern wound dressing-An update

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Abstract

Wound healing is a long expensive process and represent a major burden to patients, healthcare providers and healthcare systems. There are many risk factors, such as age, malnutrition, infections, smoking, medications or radiation, associated with improper wound healing. Wound dressings are divided into traditional plant based or conventional dressings (such as cotton gauze, bandages, lint, plasters) and modern multifunctional dressings (such as foams, films, bio-plymers based, hydrocolloids, hydrogels, nanocomposites). Conventional dressings are known as passive wound dressings and are useful to cover and stabilize modern wound dressings. 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. Traditional healers are significant for public health in Indian rural communities, and many individuals have confidence in the healing attributes of herbal medicine. The wound healing remedies from *Ayurveda* are safe and gentle on the body. The *Ayurvedic* treatment of wound healing suggested the use of herbal formulations. Therefore, plant constituent based wound dressings are very effective treatment in the management of wound healing process. Plants contain many natural bioactive compounds that help to fasten the process of wound healing and regenerate tissue at the wound site. Hydrogels are considered as ideal wound dressings because they mimic the skin structure, promoting the growth factor synthesis and autolysis process. It was stated that biofilms impact chronic wound healing by delaying the inflammatory and maturation phases. NFC-based hydrogels can be used in advanced wound care applications. Nanoparticles have been widely used as promising candidates for wound treatment. Nanotechnology offers excellent opportunities to address the problems of non- or slow-healing wounds, as wound healing solutions can be designed to be multifactorial and cell-type specific.

Keywords: Antimicrobial dressings; Antiseptic; Bacterial nanocellulose (BC); Biofilm; Chronic wounds; Nanoparticles; Nanocoatings; Plant cellulose (PC); Wound dressing

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1. Introduction

Wound healing represents an important medical problem. Wounds are injuries which occur when sudden, rash, and mostly unexpected accidents affect the integrity of skin [1-20]. The injury may result from different causes such as cuts, crushes, thermal/radiation burns, or surgical events, and could be extended from superficial damages, which affect only the skin's layers, to deep tissues (muscles, nerves, and blood vessels) destruction [1-20]. The human skin consists of two tissue layers: an upper and a lower layer, called the epidermis and dermis, respectively [1-20, 32]. The epidermis consists mainly of keratinocyte cells and affords the skin its barrier properties [1-20]. The core components of the dermis include cells such as fibroblasts, macrophages and adipocytes, together with matrix components such as collagen and elastin, which give the skin its strength and elasticity [1-20, 32]. Together, these skin layers form a vital protective barrier against the environment. The main concern in wounds management is the high risk for chronicity [1-20]. Among the patients hospitalized for acute conditions, 25–50% present or develop wounds during hospitalization, with high risk of infection and chronicity [1-32]. Wounds of an acute or chronic etiology affect millions of people worldwide, with increasing prevalence every year [1-20]. The rate of infection of surgical incisions is 3–4% and causes an 5% additional increase in mortality [1-20-40]. Currently, a wide range of pharmaceutical products such as creams, gels, ointments, powders, pastes, and patches, with healing, antimicrobial, and/or moisturizing effects are available for wound management [1-20]. The medical approach of wound care must be correlated with patients' individual reactivity and preferences in order to maximize the treatment compliance. Fibrosis and tissue regeneration are opposite processes related with wound repair [1-20-35].

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 [46-53]. The wound repair process has several phases: (1) homeostasis/coagulation, (2) inflammatory cell recruitment, (3) proliferative phase and (4) maturation phase [1-20]. These cellular and molecular events are highly coordinated and controlled [1-50]. The phases are not separated but rather they overlap and influence each other. The healing phases are strictly followed by acute wounds, which progress through each stage towards successful epithelialization and wound closure [1-40]. There are many risks factors, such as age, malnutrition, infections, smoking, medications or radiation, associated with improper wound healing [1-30]. Healing is a complex process that involves an orderly and timely sequence of events, divided into three differential phases: the coagulation and inflammatory phase, the proliferation and tissue formation phase, and the maturation and remodeling phase [1-30].

Many factors in the wound healing process are still not well understood, but the role of the Mesenchymal stem/stromal cells (MSCs) in the process seems to be useful [1-20]. Several risk factors, chronic inflammation, and some diseases lead to a deficient wound closure, producing a scar that can finish with a pathological fibrosis [1-20]. Guillamat-Prats [11] reported that mesenchymal stem/stromal cells (MSCs) are widely used for their regenerative capacity and their possible therapeutically potential [11]. There are many pathologies that can affect the wound healing and scarring processes, such as diabetes, obesity, hypertension and vascular diseases [1-20-50]. Many wounds need intensive treatment, such as necrotic wounds, ulcers, diabetic wounds, extremity wounds with edema and chronic wounds [1-60]. Chronic wounds are often infected with biofilm bacteria and characterized by high oxidative stress [4,5, 7, 16, 52]. Chronic wounds are wounds that fail to progress through the normal consecutive phases of wound healing in an orderly and timely manner [1-60]. They represent a major burden to patients, healthcare providers and healthcare systems [1-55]. While wounds may be colonized with a variety of microorganisms, tissue invasion or damage does not happen necessarily [1-50].

The laboratory and clinical evidence now establish that the bacterial biofilm is a major potentiator of wound intractability and delayed healing [4,5, 7, 16, 52]. Furthermore, Luze et al., (2022) [5] reported that biofilm is responsible for faulty wound healing and wound chronicity [4,5, 7, 16, 52]. Luze et al., (2022) [5] also mentioned that pathogenic biofilms are an important factor for impaired wound healing, subsequently leading to chronic wounds [5]. Nonsurgical treatment of chronic wound infections is limited to the use of conventional systemic antibiotics and antiseptics [1-25]. Wound dressings based on bacterial nanocellulose (BNC) are considered a promising approach as an effective carrier for antiseptics [4-7, 14-17, 52, 53, 89]. Based on Luze et al., (2022) [5] results, antiseptic-loaded BNC represents a promising and effective approach for the treatment of biofilms [5]. Additionally, the prolonged exposure to the antiseptics does not affect the healing outcome [4,5, 7, 16, 52]. Prevention and treatment of chronic wound infections may be feasible with this novel approach and may even be superior to existing modalities [4,5, 7, 16, 52]. Microbial infections are one of the main causes that impair the wound healing process, and *Staphylococcus aureus*, a commensal member of the skin microbiota, is one of the main causative agents of wound infections [4,5, 7, 16, 52]. A high proportion of these infections are caused by *Staphylococcus aureus*, which, in addition to β-lactams, has acquired resistance to almost all the antibacterial agents used to treat it, limiting therapeutic options [4,5, 7, 16, 52, 89]. In the following section, the types of wound dressings, traditional plant based dressings and modern wound dressing methods have been discussed and updated.

2. Types of Wound Dressings

Wound dressings are divided into traditional plant based or conventional dressings (such as cotton gauze, bandages, lint, plasters) and modern multifunctional dressings (such as foams, films, hydrocolloids, hydrogels, nanocomposites) [1-30, 50-100]. Conventional dressings are known as passive wound dressings and are useful to cover and stabilize modern dressings [1-30, 50-100]. The latter dressings are defined as interactive products which modulate the entire healing cascade by controlling the damaged tissue microenvironment (moisture, temperature, pH), stimulating the granulation and re-epithelization processes, and inhibiting microbial growth [1-30, 50-175].

3. Traditional Wound Dressing

Wound dressing materials designed to aid wound healing date as far back as 2000 BC, when they were made of clay, plants and herbs [1-30, 50-175]. Since then, the development of wound dressings has continuously evolved with the advances made by humankind, and today more than 5,000 wound care products exist on the market. Wound dressings are medical devices that aid the healing of wounds by protecting the wound and providing an environment for improved healing [1-30-177]. Apart from these basic properties, modern wound dressings can have a number of healing-enhancing properties. Historically, wound dressings were made of leaves and herbal plants [1-30, 50-175]. It was later found that many of these herbs have antibacterial properties, affording these early dressings some of the desirable properties of a wound dressing. Traditional dressings include cotton wool, bandages and gauzes [1-30, 50-175]. These simple dressings are more commonly used as secondary dressings, i.e., as the layer providing outer protection for a topical pharmaceutical formulation or a bioactive primary dressing [1-30, 50-175]. Studies on the antimicrobial and healing activities of extracts, essential oils, or metabolites obtained from native plants have been reported in many countries that have a diverse flora and traditions with the use of medicinal plants for the treatment of wound infections [1-30, 50-175].

4. Plant based Wound Dressing

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 [13, 20-50-175]. Traditional healers are significant for public health in Indian rural communities, and many individuals have confidence in the healing attributes of herbal medicine [13, 20- 50-175].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 [13, 20-50-175]. 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 [13, 20-50-175]. *Ayurveda* is a holistic approach to health and wellness that emphasizes balance between body, mind, and spirit [13, 20-50-175]. It is one of the oldest and the most respected Indian medicinal traditions in the world [13, 20-50-175]. *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 [13, 20-50-175]. The wound healing remedies from *Ayurveda* are safe and gentle on the body [13, 20-50-175]. The *Ayurvedic* treatment of wound healing suggested the use of herbal formulations [13, 20-50-175]. These herbs have been sourced from nature and have been used for thousands of years [13, 20-50-175]. Therefore, plant constituent based wound dressings are very effective treatment in the management of wound healing process [13, 20-50-175]. The Complementary and Alternative Herbal Medicines (CAM) [70, 132, 134 -175] is a promising approach to improvising clinical and medical challenges faced by non-healing chronic wounds [13, 20-50-175]. The plant derived essential oils are used as active secondary compounds in polysaccharide-based wound dressings [13, 20-50-175].

Herbal medicines in wound treatment or care include disinfection, debridement, and providing a moist atmosphere which facilitates development of appropriate natural healing climate [13, 20-50-175]. Folklore cultures employ a significant number of plants to treat cuts, wounds, and burns [13, 20-50-175].

Various herbal formulations have helped to accelerate the wound healing process and are useful in wound treatment [13, 20-50-175]. Bioactive secondary metabolites of plants could be used for wound healing, including alkaloids, essential oils, flavonoids, tannins, terpenoids, saponin, fatty acids, and phenols [13, 20-50-175]. These active compounds could improve the wound-healing process by influencing one of the healing stages through antibacterial, antifungal, antioxidant, and anti-inflammatory effects [13, 20-50-175]. Plants contain many natural bioactive compounds that help to fasten the process of wound healing and regenerate tissue at the wound site [13, 20-50-175]. Some examples of medicinal plants and their wound healing effects are listed below [13, 20-50-175]. Herbal remedies and drugs have played a significant role in curing diseases throughout the history of mankind [13, 20-50-175]. Herbal medicines have the potential to treat and cure illnesses like ulcers, healing of wounds, skin infections inflammation, scabies, leprosy and venereal disease [13, 20-50-175].

Plants play a significant role in conventional wound treatments [13, 20-50-175]. 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 [13, 20-50-175]. Phytochemical substances are found in plants that are utilized to treat skin problems [13, 20-50-175]. The plant-derived active agents ensure desirable properties of the biomaterial, supporting wound re-epithelialization and its angiogenesis [13, 20-50-175]. 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 [13, 20-50-175]. 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 [13, 20-50-175].

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 [13, 20-50-175]. Alternative medical systems such as naturopathy and *Ayurveda* utilize herbal medications as an important part of wound therapy [13, 20-50-175]. 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. Conventional wound dressing materials seem to be insufficient to facilitate and support wound healing mechanism [13, 20-50-175]. 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 [13, 20-50-175]. Thus, they are considered as promising materials for wound dressing applications [13, 20-50-175].

Wound healing, a vital physiological process of tissue repair or remodelling, which still remains a challenge in the Indian healthcare system [1-13, 20-50-175]. Different wound dressings containing antibiotics and antibacterial agents, nanoparticle based wound dressings prevent bacterial infection and bio film formation in the wound bed [1-13, 20-50-175]. 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 [1- 20-50-175]. 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 [13, 20-50-175]. There are a variety of herbal plants that have wound healing properties [13, 20-50-175]. Plant-based constituents have been extensively used for the treatment and management of different types of wounds [13, 20-50-175]. 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 [13, 20-50-175]. 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 [13, 20-50-175].

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) [13, 20-50-175]. The herbal extracts and fractions effectively arrested bleeding from fresh wounds, inhibited microbial growth and accelerated wound healing [13, 20-50-175]. 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 [13, 20-50-175]. With the advent of nanotechnology and availability of novel materials, wound management is becoming more effective and patient-centric [13, 20-50-175]. Newer technologies like 3D printing are also providing advantageous options for developing different drug delivery systems for managing wounds [1-20-50-175].

Widely used medical plants are rich in bioactive natural compounds with immunomodulatory properties [13, 20-50-175]. 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 [13, 20-50-175]. Hence, zinc and vitamin C levels of the herbal extracts can be determined [13, 20-50-175]. Zinc content of the plant extracts used for wound healing purposes might have a great contribution in the healing process [13, 20-50-175].

As a consequence, naturally derived active agents may control the inflammatory response and promote re-epithelialization and wound contraction [13, 20-50-175]. Currently, there are many reports in the literature on dressing materials loaded with curcumin [13, 20-50-175]. Furthermore, it was revealed that tested biomaterials loaded with curcumin enhanced collagen accumulation [13, 20-50-175]. 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 [13, 20-50-175]. The plant antimicrobial compounds accelerate and promote skin regeneration by influencing cell migration and the extracellular matrix (ECM) deposition [13, 20-50-175]. 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 [13, 20-50-175]. 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 [13, 20-50-175]. Topically administered drugs are effective in faster wound contraction due to the larger availability at the wound site [13, 20-50-175]. 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 [13, 20-50-175]. 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 process [13, 20-50-175]. Following is the list of medicinal plants used in the treatment of wound healing and dressing [13, 20-50-175].

1) Turmeric (*Curcuma longa*) (*Zingiberaceae*) Rhizomes part is used, 2)*Cannabis sativa* (*Cannabaceae*), 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*) (*Ginkgoacea*e) 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* (*Fabacea*e), 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, 93) Liquorice or Mulethi (*Glycyrrhiza glabra*) (*Fabaceae*) roots [13, 20-50-175].

Some of the most important plant secondary metabolites influencing wound healing process include cannabidol (CBD), 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 [13, 20-50-175].

Essential oils of plants are secondary metabolites characterized by the antibacterial, antifungal, anti-inflammatory, antioxidant, and antiviral properties [13, 20-50-175]. Plant based essential oils are comprised of a complex mixtures of volatile phytochemicals from diverse classes including monoterpenes, sesquiterpenes, and phenylpropanoids [13, 20-50-175]. Thus, essential oils of plants possessed features that are useful in the chronic wound management [13, 20-50-175]. Thyme oil (*Thymus vulgaris*) belongs to the mint family *Lamiaceae* is also a best medicine for wound healing. Another essential oil widely used in wound healing is Tea tree oil (TTO), which is extracted from the leaves of *M. alternifolia* [13, 20-50-175]. Tea tree oil (*Melaleuca alternifolia*), the volatile essential oil derived mainly from the Australian native plant *Melaleuca alternifolia* belong to the family *Myrtaceae.* 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 [13, 20-50-175]. Rather than being rich in camphor, Ravintsara oil also contains higher concentration of 1, 8-cineole (45-55%) [13, 20-50-175]. 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 [13, 20-50-175]. Garlic oil (*Allium sativum)* belong to the family *Amaryllidaceae* is one of the common medicine for wound healing in India [13, 20-50-175]. The essential oil of *Laurus nobilis* belongs to the family *Lauraceae* also used for the wound healing [13, 20-50-175]. 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 [13, 20-50-175]. 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 Cannabis oil, 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*) [13, 20-50-175]. Camphor tree (*Cinnamomum camphora*) leaf extract and oil has been used for the wound healing [13, 20-50-175]. Another study demonstrated the antimicrobial activity of cinnamon, lemongrass, and peppermint essential oils encapsulated in cellulose-based fiber dressings [13, 20-50-175]. *Cannabis sativa* oil is also used for the topical applications [1-20-50-175].

Cannabis sativa has been used for thousands of years for recreational, medicinal, or religious purposes [20-51, 178-220]. *Cannabis sativa*, (Hemp)-based materials are regarded as important components of wound dressings [20-51, 178-220]. Hemp is considered a botanical class of "*Cannabis sativa*", and it has been used in various applications, including paper, textiles, biodegradable plastic, and animal feed, as well as for medicinal use [20-51, 178-220]. CBD oil also contains a wide variety of fatty acids, proteins, amino acids, vitamins A, C, and E, β-carotene, and minerals, specifically phosphorus, potassium, magnesium, sulfur, and calcium [20-51, 178-220]. Owing to these, CBD oil can be used as a remedy for skin lesions. Moreover, unsaturated fatty acids accelerate wound healing processes and reduce inflammation. Cannabis oil is also readily available, which is an additional advantage [20-51, 178-220].

5. Modern Wound Dressing

On the basis of literature survey, modern wound dressings, on the other hand, consist of more recently developed alternatives that have been designed to maintain a moist wound bed, and incorporate many of the desirable properties of a wound healing dressing [1-20-50-175]. Such dressings are usually in the form of gels, thin films or foam sheets; examples being hydrocolloid dressings, alginate dressings and hydrogels [1-20-50-175]. Wound management represents a well-known continuous challenge and concern of the global healthcare systems worldwide [1-20-50-175]. The challenge is on the one hand related to the accurate diagnosis, and on the other hand to establishing an effective treatment plan and choosing appropriate wound care products in order to maximize the healing outcome and minimize the financial cost [1-20-50-175]. The market of wound dressings is a dynamic field which grows and evolves continuously as a result of extensive research on developing versatile formulations with innovative properties [1-20-50-175]. Hydrogels are one of the most attractive wound care products which, in many aspects, are considered ideal for wound treatment and are widely exploited for extension of their advantages in healing process [1-20-50-175]. Smart hydrogels (SHs) offer the opportunities of the modulation physico-chemical properties of hydrogels in response to external stimuli (light, pressure, pH variations, magnetic/electric field, etc.) in order to achieve innovative behavior of their three-dimensional matrix (gel–sol transitions, self-healing and self-adapting abilities, controlled release of drugs) [1-20-50-175]. The SHs response to different triggers depends on their composition, cross-linking method, and manufacturing process approach [1-20-50-175]. Both native or functionalized natural and synthetic polymers may be used to develop stimuli-responsive matrices, while the mandatory characteristics of hydrogels (biocompatibility, water permeability, bioadhesion) are preserved [1-20-50-175].

6. Hydrogel

Hydrogels were documented for the first time in 1960, when Wicherke and Lim prepared a gel based on hydroxymethylacrylate for medical application [1-20-50-175].

Now a days, hydrogels still fascinate biomedical researchers, having applications in tissue engineering (bone, cartilage, and muscles), cell growth, wound healing, controlled drug release, biosensors, and medical devices [1-20-50-175]. Hydrogels are defined as three-dimensional (3D) hydrophilic polymer networks capable of encapsulating large amounts of water or biological fluids [1-20-50-175]. As a result of their hydrophilic character, oxygen permeability, ability of diffusion, cell and molecules adhesion, and ease of use, hydrogels demonstrated important beneficial effects for wound care. In many aspects, hydrogels are considered ideal wound dressings because they mimic the skin structure, promoting the growth factor synthesis and autolysis process [1-20-50-175]. Moreover, their ability to incorporate and release a wide variety of active pharmaceutical ingredients (APIs) makes hydrogels suitable for the management of draining painful wounds, radiation wounds, minor burns, or dry wound [1-20-50-175].

On the basis of literature survey, hydrogels have several advantages, such as the :3D structure, similar to the extracellular matrix, which plays a key role in cell proliferation, debridement, and exchange of vital substances for epidermal cells; hydrophilicity, associated with hydrophilic groups of the polymer matrix: NH_2, -COOH, -OH, -$CONH_2$, -CONH-, and -SO_3H; water absorption capacity, due the porosity degree; high degree of flexibility similar to human tissue, due the water content; biodegradability and biocompatibility [1-20-50-175]. Along with the positive aspects, some drawbacks reduce the applicability of hydrogels in medical practice [1-20-50-175]. These include poor mechanical stability, high risk for microbial contamination (except chitosan-based hydrogels), toxicity potential, degradation, and variable release [1-20-50-175].

Hydrogels based on natural/semi-synthetic/synthetic polymers (CS, methylcellulose, gelan gum, poloxamers, polyethylenglycol (PEG), poly (N-isopropylacrylamide) (PNIPA), poly (vinyl alcohol) (PVA), poly (N-vinylcaprolactam) and their derivatives) respond to temperature variations with sol–gel transitions due to thermal disturbance of the pre-existing equilibrium between the hydrophilic and hydrophobic units in the 3D networks [1-20-50-175]. These hydrogels, which mimic the extracellular matrix, can be easily functionalized with bioactive molecules, and may exhibit a controlled degradation rate [1-20-50-175].

Tatarusanu et al., (2023) [3] reported that hydrogels have passed the test of time, being used for more than 120 years in wound healing [1-20-50-175]. Because of their undeniable benefits in the healing process, hydrogels constantly have attracted the interest of researchers in the medical and pharmaceutical area and sustained efforts are made to improve and to innovate the performances of hydrogels and to widen their biomedical applications [1-20-50-175]. SHs is a large category of versatile 3D matrices which has made it possible to design intelligent products with the target of overcoming the limitation of traditional hydrogels and properly responding to the increasing prevalence of wounds with impaired healing [1-20-50-175].

Hydrogels are water-swollen materials made of synthetic or natural polymeric networks [3]. Natural polysaccharides such as cellulose, chitosan, hyaluronic acid and alginate have been widely used to prepare hydrogels [3]. The gels are held together by chemical bonding, molecular entanglement, and/or secondary forces including ionic, hydrogen-bonding or hydrophobic forces [3]. Their ability to absorb large amounts of water (many times their dry weight) is due to the hydrophilic functional groups attached to the polymer backbone [1-20-50-175]. Hydrogels can be designed with molecular-scale precision, thus allowing control over properties such as mechanical strength, swelling, biodegradability, and chemical and biological response to stimuli [1-20-50-175]. Within the biomedical field, hydrogels are of special interest in tissue engineering and regenerative medicine, drug delivery, as well as wound healing [1-20-50-175]. The aqueous environment of hydrogels gives them the ability to protect and release fragile drugs (such as growth factors), which makes them interesting for drug delivery applications, while their high water content affords them many of the desirable properties of a wound healing dressing (e.g. promoting a moist environment and debridement, good gaseous exchange, low tissue adhesion and providing patient comfort through cooling and soft texture) [1-20-50-175]. Commercial hydrogels used for wound healing applications are made of a variety of polymers, such as cellulose derivatives, alginate and hyaluronic acid [1-20-50-175].

According to Naomi et al., (2020) [6], apart from BC and PC, other products such as hydrogels, poly lactic-co-glycolic acid (PLGA), and 3D living constructs are being studied for their effectiveness in wound healing [6]. In current era, 3D bioprinting gaining much attention as other available biomaterial due to its ability to design cell components in microarchitecture. Interestingly, since the cell origin is from patient itself, there is a low possibility for immune rejection [1-20-50-175]. However, the challenge here is the bio-ink [1-20-50-175]. Fortunately, researchers have concluded that hydrogels prepared from hyaluronic acid is a convenient and safe source due to its cell friendly nature [6]. According to Naomi et al., (2020) [6], moreover, within a short period of time, hydrogels can be tailored with methacrylic anhydride and 3, 3 '-dithiobis (propionylhydrazide) with the presence of UV [1-20-50-175]. This ensures a proper microenvironment for the wound, which in turn accelerates the normal healing mechanism [6]. Other than this, excellent biocompatibility, absorption capacity, rapid degradation rate, and high swelling ratio are some of advantages integrating hydrogel as a choice for wound healing [1-20-50-175].

7. Nanofibrillated cellulose (NFC) -based Hydrogels

Wood-based nanofibrillated cellulose (NFC) was chemically functionalized and crosslinked using calcium to obtain a self-standing hydrogel [1-20-50-175]. The NFC hydrogel was evaluated in terms of its physicochemical properties, biocompatibility, blood interactions, bacterial interactions, *in vivo* wound healing ability and, finally, as a protein carrier [1-20-50-175]. Parallel with the assessment of the NFC hydrogel, modified versions of the material were tested to investigate the tunability of the above-mentioned characteristics, wound healing ability of the calcium cross linked NFC hydrogel, represents an important milestone in the research on NFC towards advanced wound care applications [1-20-50-175]. It is expected that the easily modifiable nature of the material can be exploited to further develop the NFC hydrogel to suit the treatment needs for a broad range of wound types [1-20-50-175]. NFC-based hydrogels can be used in advanced wound care applications [1-20-50-175]. Therefore, future research on NFC-based hydrogels be focused on developing next generation treatments for the societal problematic chronic wounds through the modification and optimization of the NFC hydrogel platform described [1-20-50-175].

Pranantyo et al., (2024) [7] reported that conventional wound dressings are not designed to promote the closure of hard-to-heal chronic wounds [7]. A common characteristic of chronic wounds is prolonged inflammation [7]. The study reported by Pranantyo et al., (2024) introduces a crosslinked hydrogel with two covalently bound, ultralow-leachable bioactive components: the highly potent antibacterial cationic PIM and the antioxidative NAC [7]. The composite hydrogel exhibits efficient and broad-spectrum biofilm removal capabilities, while also accelerate the healing process in infected diabetic wounds [7]. It is intrinsically antibacterial and antioxidative and does not required other processes such as photothermal irradiation so that this standalone dressing is easy and safe to use [7]. Unlike previous dual functionality dressings, the crosslinked hydrogel is completely devoid of leachable antibiotics, metal compounds, carbon nanotubes or nanoparticles [7]. This ultra-low leaching feature distinguishes it from many other drug-releasing wound dressings, promoting a safer and more biocompatible alternative [7]. It has good structural integrity and is easy to be removed cleanly from the wounds [7]. Furthermore, different formats such as films and fibers can be made to conform to wounds [7]. These advantages greatly enhance patient comfort and support an uncomplicated healing process [1-20-50-175].

8. Cellulose biopolymer

According to Naomi et al., (2020) [6], cellulose is a naturally existing element in the plants cell wall and in several bacteria [6]. Cellulose is a polysaccharide that has the most readily available biopolymer in nature for over a thousand years [1-20-50-175]. It is the most essential molecule of a plant that has been identified as the major component of a cell wall. Cellulose is glucose in a linear form, which is also known as nhydroglucose, and this is linked together by β-1,4, in means of the glucose residues [1, 6,14,15, 17, 52, 53, 89]. The linear structure of cellulose is well-maintained in the form of a cellulose chain, due to the presence of a hydrogen bond that holds the oxygen atom and hydroxyl together

[1, 6,14,15, 17, 52, 53, 89]. Cellulose can be classified as α, *β*, and *Υ* based on its ability to dissolve in a sodium hydroxide (NaOH) solution, with an optimum concentration [1, 6,14,15, 17, 52, 53, 89]. Generally, plants serve as the main source of cellulose. The cellulose that is extracted from plants exhibits an exceptional property, which makes it suitable to be widely used in the pharmaceutical industry. Cotton and woods are main sources of production of cellulose. Plant-derived cellulose is naturally stable and non-toxic [1, 6,14,15, 17, 52, 53, 89]. Bacterial cellulose (BC) can also be derived through the fermentation process [2], specifically, if the bacteria are aerobic bacteria [1, 6,14,15, 17, 52, 53, 89]. According to Naomi et al., (2020) [6], the unique characteristics of bacterial cellulose (BC), such as non-toxicity, biodegradability, hydrophilicity, and biocompatibility, together with the modifiable form of nanocellulose, or the integration with nanoparticles, such as nanosilver (AgNP), all for antibacterial effects, contributes to the extensive usage of BC in wound healing applications [1, 6,14,15, 17, 52, 53, 89, 115, 117, 118, 119]. Nevertheless, with a minimum amount of modification, plant-derived cellulose and bacterial cellulose (BC) have been proven scientifically to be used for skin healing, wound dressings, template for bone tissue, 3D nerve cell proliferation and differentiation, artificial blood vessels, cartilage, urinary tracts, vertebrae disks, larynx tissues, ligaments, cartilage, tendons, muscles, etc [1, 6,14,15, 17, 52, 53, 89]. Therefore, cellulose has been proven to have very high surface area per unit mass which maximize the outcome upon application [1, 6,14,15, 17, 52, 53, 89]. According to Naomi et al., (2020) [6], cellulose serves as an attractive candidate for wound healing application [1, 6,14,15, 17, 52, 53, 89]. Bacterial cellulose (BC) is turally pure, with an absence of lignin, hemicellulose, and other contaminants when compared to the extracellular matrix [1, 6,14,15, 17, 52, 53, 89]. These special characteristics are the main reasons for the extensive use of BC in biomedical and clinical settings than those of plant-derived cellulose (PC) [1, 6,14,15, 17, 52, 53, 89]. Cellulose is widely accepted to be incorporated into the biomedical field, due to its biocompatibility to human cells [1, 6,14,15, 17, 52, 53, 89]. Both plant-derived cellulose (PC) and BC differ in their means of macromolecular characteristics [1, 6,14,15, 17, 52, 53, 89]. PC contains impurities, such as hemicellulose and lignin, with a moderate water holding capacity (60%), and it possesses a moderate level of tensile strength and crystallinity [1, 5, 6,14,15, 17, 52, 53, 89]. Meanwhile, BC is chemically pure. It has a hydrophilic and high-water holding capacity (100%), with high crystallinity, and it possesses a high tensile strength [1, 5, 6,14,15, 17, 52, 53, 89]. A wide range of studies has been performed on bacterial cellulose (BC) and plant cellulose (PC), in order for it to be potentially used in wound healing and in therapeutics filed [1,5, 6,14,15, 17, 52, 53, 89]. Furthermore, bacterial cellulose (BC and PC may act as a scaffolding layer for the recovery of a vast range of cells and tissues, demonstrating that it may ultimately emerge in the future to become an exceptional platform for medicinal technology [1, 5, 6,14,15, 17, 52, 53, 89]. If bacterial cellulose (BC) can be mass processed efficiently, it can eventually become a crucial biomaterial that can be used as a substitute for currently available wound dressings [1, 5, 6,14,15, 17, 52, 53, 89].

Luze et al., (2022) [5] reported that the use of bacterial nanocellulose (BNC) as carriers for various “active” substances might be a clinically feasible approach to address this problem [1, 5, 6,14,15, 17, 52, 53, 89]. This biomaterial meets several desirable characteristics of an “ideal” wound dressing such as being non-adhesive, reducing the number of dressing changes, allowing pH modulation of the wound bed or providing a moisture balance and cooling effect [1, 5, 6,14,15, 17, 52, 53, 89]. In this context, BNC-based wound dressings are considered a suitable carrier for different commercially available antiseptics to directly inhibit bacterial growth [1, 5, 6,14,15, 17, 52, 53, 89]. Luze et al., (2022) [5] also confirmed that the continuous and therapeutic release of active ingredients observed in BNC-based dressings is considered beneficial for wound treatment applications due to the homeostasis of steady concentrations over the entire treatment period [5].

Luze et al., (2022) [5] reported that available evidence suggests that the majority of chronic wounds are colonized by pathogenic biofilms hindering wound healing, resulting in ineffective treatment, burdening both the patient and the healthcare providers [5]. BNC-based wound dressings loaded with commercially available antiseptics demonstrated a potent efficacy against biofilms formed by a variety of microbes found to be prevalent within chronic wounds, including *S aureus*, *P. aeruginosa*, and *C. albicans* [5]. Additionally, no negative influence was observed in the wound healing parameters analyzed, showing that even a 7-day treatment using the BNC loaded with antiseptics would not disturb the normal healing process [5]. Results are comparable to available silver-based wound dressings, whereby further advantages of BNC such as the possibility for pH-monitoring of the wound bed are to be highlighted. Luze et al., (2022) [5] reported that antiseptic-loaded BNC-based wound dressings might therefore, be an effective modality in the prevention and treatment of colonized, chronic wounds [5]. Future studies are essential to investigate and compare the *in vivo* efficacy of this approach in clinical care [5].

It was stated that biofilms impact chronic wound healing by delaying the inflammatory and maturation phases [1, 4,5, 7, 16, 52]. Moreover, polymicrobial biofilms impair wound healing more significantly than monomicrobial biofilms, potentially due to synergistic interactions among bacteria expressing different virulence phenotypes [1, 4,5, 7, 16, 18, 52]. Very recently Kart et al., (2024) [18] reported that biofilms are a severe problem for public health because of the contributing recurrence of infections [1, 4,5, 7, 16, 52]. Therefore, combating biofilms is a critical issue. Kart et al., (2024)

[18] demonstrated that loaded zinc oxide (ZnO), zinc oxide borax (ZnOBorax), zinc copper oxide ($ZnCuO_2$) nanoparticles and borax into bacterial cellulose (BC) to impart anti-biofilm and wound healing activity [18]. The prepared BC loaded with nanoparticles (BC–NPs) was analyzed via scanning electron microscopy [18]. The nanoparticles' geometric structure and placement in BC fibres were observed. Kart et al., (2024) [18] evaluated the biofilm inhibition and biofilm degradation activities of the BC–NPs against some pathogens via a crystal violet (CV) assay and XTT (2,3-bis (2-methoxy- 4-nitro-5-sulfophenyl)-2 H-tetrazolium-5-carboxanilide) reduction assay [18]. The effects of BC–NPs on cell proliferation and wound-healing ability were analysed in L929 cell line. BC–NPs exhibited better biofilm degradation activity than biofilm inhibition activity [18]. According to the results of the CV assay, BC–ZnONPs, BC–Borax and BC–ZnOBoraxNPs inhibited 65.53%, 71.74% and 66.60% of biofilm formation of *Staphylococcus aureus*, respectively [18]. BC–ZnCuO2NPs showed the most degradation activity on *Pseudomonas aeruginosa* and *Listeria innocua* biofilms [18]. The XTT reduction assay results indicated a considerable reduction in the metabolic activity of the biofilms [18]. Moreover, compared to the control group, BC loaded with borax and ZnO nanoparticle promoted cell migration without cytotoxicity [18].

Currently, collagen-based wound dressings are the most investigated solutions to obtain efficient coatings and to facilitate healing for both acute and chronic wounds [1, 5, 6,14,15, 17, 52, 53, 89]. They can be in various forms, from hydrogels to solid dressings, and are applied directly on most wounds [1, 5, 6,14,15, 17, 52, 53, 89]. The main advantages of such dressings rely on the fact that they facilitate wound repair by maintaining a suitable local environment [1, 5, 6,14,15, 17, 52, 53, 89].

9. Nanotechnology

Nanotechnology offers unprecedented opportunities and cutting-edge solutions to designing efficient biomedical approaches [1, 18, 62, 83, 85, 112, 115, 141, 142]. Numerous nanomaterials have been developed for application in wound care and healing [1-18, 62, 83, 85, 112, 115, 141, 142]. Nanostructures are revolutionary compounds that aim to enhance the therapeutic delivery of growth factors, antimicrobial agents, gene therapy vectors, and others to the wound [1, 13, 18, 62, 83, 85, 112, 115, 141, 142]. The most explored approaches for the management of wounds refer to the development of nano-devices for (i) inflammation control, (ii) cellular proliferation and re-epithelization, and (iii) tissue remodeling [1-18- 62, 83, 85, 112, 115, 141, 142].

Nanotechnology shows promising openings, either by the intrinsic antimicrobial properties of nanoparticles or their function as drug carriers [1-18- 62, 83, 85, 112, 115, 141, 142]. Nanoparticles and nanostructured coatings can be active at low concentrations toward a large variety of infectious agents; thus, they are unlikely to elicit emergence of resistance [1-18- 62, 83, 85, 112, 115, 141, 142]. Nanoparticles might contribute to the modulation of microbial colonization and biofilm formation in wounds [1-18- 62, 83, 85, 112, 115, 141, 142]. Wound healing involves a complex interaction between immunity and other natural host processes, and to succeed it requires a well-defined cascade of events [1-18- 62, 83, 85, 112, 115, 141, 142]. Chronic wound infections can be mono- or polymicrobial but their major characteristic is their ability to develop a biofilm. A biofilm reduces the effectiveness of treatment and increases resistance [1-18- 62, 83, 85, 112, 115, 141, 142]. A biofilm is an ecosystem on its own, enabling the bacteria and the host to establish different social interactions, such as competition or cooperation. With an increasing incidence of chronic wounds and, implicitly, of chronic biofilm infections, there is a need for alternative therapeutic agents [1-18- 62, 83, 85, 112, 115, 141, 142].

Nanoparticles have been widely used as promising candidates for wound treatment [1-18- 62, 83, 85, 112, 115, 141, 142]. Silver nanoparticles (AgNPs) have been known for decades to have strong bactericidal effects, broad-spectrum antimicrobial activity, and, importantly, they are currently utilized for the therapy of both acute and chronic wounds in various preparations [1-18- 62, 83, 85, 112, 115, 141, 142]. Inorganic metallic and oxide nanoparticles have numerous applications in the biomedical and pharmaceutical industries [1-18- 62, 83, 85, 112, 115, 141, 142]. Certain types, such as silver (Ag), copper (Cu), titanium, (Ti), iron (Fe), and zinc oxide (ZnO), have shown significant antimicrobial activity [1-18- 62, 83, 85, 112, 115, 141, 142]. In addition, such nanoparticles have a wide antimicrobial spectrum and do not interfere with the selection of resistant mutants, being efficient also against biofilms and antibiotic-resistant isolates [1-18- 62, 83, 85, 112, 115, 141, 142]. Silver-based formulations are utilized for avoiding microbial contamination and for the treatment of chronic wounds, such as ulcers and burns [1-18- 62, 83, 85, 112, 115, 141, 142]. Currently, numerous wound coatings, which contain AgNPs, are available on the market for the treatment of wounds [1-18- 62, 83, 85, 112, 115, 141, 142]. AgNPs represent an antimicrobial alternative for the future since they have numerous mechanisms of action against microbial cells. They are able to induce membrane pores and can also activate the production of reactive oxygen species (ROS) response within the cells, which leads to the death of the microorganisms [1-18- 62, 83, 85, 112, 115, 141, 142]. AgNPs can release active ions at the wound site, which can penetrate the tissues but also the preformed biofilms, and can induce toxic effects in biofilm-embedded cells, thus destabilizing mature biofilms [1-18- 62, 83, 85, 112, 115, 141, 142]. Along with their antimicrobial impact, AgNPs can promote wound healing via immune regulation.

Innovative hybrid scaffolds made of metallic nanosilver particles–collagen/chitosan are able to regulate fibroblast migration and macrophage activation in a rat model [1-18- 62, 83, 85, 112, 115, 141, 142]. Zinc oxide (ZnO) nanoparticles have also been proven to enhance antimicrobial properties, being efficient in vitro, and to treat wound infections in vivo. Moreover, recent studies have proven that ZnO nanoparticles may inhibit biofilm formation of relevant pathogenic and opportunistic bacteria, such as P. aeruginosa [1-18- 62, 83, 85, 112, 115, 141, 142]. ZnO nanoparticles were proven to be efficient in preventing wound infection in mice and they are currently being intensively investigated for antimicrobial wound dressings [1-18- 62, 83, 85, 112, 115, 141, 142]. Current trends in wound management are to develop biocompatible polymeric coatings and dressings containing ZnO nanoparticles, with no cytotoxic effects, that promote healing and inhibit microbial colonization at the wound site [1-18- 62, 83, 85, 112, 115, 141, 142]. Although Ag and ZnO nanoparticles are the most investigated for advanced wound dressings and coatings, recent trends are considering other nanoparticles in the design of polymeric matrices for promoting wound healing of particular types of wounds [1-18- 62, 83, 85, 112, 115, 141, 142]. Magnetite, silica, and copper anoparticles are being intensively investigated for their great biomedical potential and antimicrobial properties. Copper nanoparticles have attracted attention for wound healing applications due to their ability to promote angiogenesis. Magnesium oxide (MgO) NPs demonstrated antimicrobial behavior against Gram-negative and Gram-positive bacteria, spores, and viruses [1-18- 62, 83, 85, 112, 115, 141, 142]. Nitric oxide (NO) NPs are directly involved in several antimicrobial mechanisms. Their antibacterial properties are directly related to their shape and size. Organic NPs have several antimicrobial properties including releasing antibiotic and antimicrobial agents or penetrating cell membranes using cationic groups [1-18- 62, 83, 85, 112, 115, 141, 142]. Polymeric antibacterial agents in the nanometer range are known for their long-lasting antimicrobial activity [1-18- 62, 83, 85, 112, 115, 141, 142]. Some of their advantages include chemical stability, non-volatility, and non-toxicity to biological membranes, e.g., skin. Among several organic NPs, chitosan NPs have exhibited antimicrobial, antiviral, and antifungal action [1-18- 62, 83, 85, 112, 115, 141, 142]. The advantages of using chitosan include its biocompatibility, antimicrobial features, and low immunogenicity. The antimicrobial activity of chitosan NPs depends on various factors such as pH and solvent [1-18- 62, 83, 85, 112, 115, 141, 142]. It has been reported that it inhibits the activity of metallic NPs. Therefore, it is used mainly with antibiotics. The antimicrobial activity of chitosan NPs is not yet fully understood [1-18- 62, 83, 85, 112, 115, 141, 142].

Based on current knowledge, the ideal therapeutic agent should achieve multiple objectives, including antimicrobial, immunomodulatory, and regenerative effects [1-18- 62, 83, 85, 112, 115, 141, 142]. Nanotechnology reveals promising openings, either by the intrinsic antimicrobial properties of nanoparticles or by their function as drug carriers [1-18- 62, 83, 85, 112, 115, 141, 142]. However, nanotechnology is also important for the development of nanostructured bioactive dressings and coatings [1-18- 62, 83, 85, 112, 115, 141, 142]. Nanoparticles are active at low concentrations toward a large variety of infectious agents. Importantly, they are unlikely to provoke the emergence of resistance and have the ability to modulate microbial colonization and biofilm formation [1-18- 62, 83, 85, 112, 115, 141, 142].

The main principle of nanotechnology is the engineering of materials on the nanoscale, furnishing them with characteristics such as high surface area, functional surfaces and novel structural designs [1-18- 62, 83, 85, 112, 115, 141, 142]. In this way, materials can be designed with unique properties not seen in their bulk counterparts, such as higher reactivity to the environment, interesting mechanical, electronic, photonic or optical properties, and bioactivity [1-18- 62, 83, 85, 112, 115, 141, 142]. Nanotechnology offers excellent opportunities to address the problems of non- or slow-healing wounds, as wound healing solutions can be designed to be multifactorial and cell-type specific [1-18- 62, 83, 85, 112, 115, 141, 142].

Topical and stimuli-responsive delivery devices are also possible, and this degree of specificity provides the unique opportunity to target specific dysfunctional processes in wound healing without systemically affecting the host [1-18- 62, 83, 85, 112, 115, 141, 142]. The benefits of this include more efficient treatment, lower risk of systemic side-effects and reduced toxicity due to efficacy at a lower dosage [1-18- 62, 83, 85, 112, 115, 141, 142]. For these reasons, extensive efforts are today being devoted to research on nanotechnological wound healing solutions [1-18- 62, 83, 85, 112, 115, 141, 142]. Nanotechnological wound healing solutions can be roughly divided into two categories: intrinsic nanodevices and nanocarriers [1-18- 62, 83, 85, 112, 115, 141, 142]. Intrinsic nanodevices comprise material structures with built-in wound healing properties, while nanocarriers are devices that are employed as delivery vehicles for therapeutic agents [1-18- 62, 83, 85, 112, 115, 141, 142]. In the study reported by Kart et al., (2024) [18] BC was successfully modified with ZnONPs, borax, ZnOBoraxNPs and ZnCuO2NPs, and they were confirmed by SEM analysis. The BC-ZnCuO2NPs showed good antibiofilm activity against *C. albicans* ATCC 64548, *E. coli* ATCC 10536, *S. aureus* ATCC 29213 and *L. innocua* [18]. Moreover, the biofilm degradation efficacy of BC–ZnONPs, BC–Borax, and BC–$ZnCuO_2$NPs towards preformed biofilms of *P. aeruginosa* and *L. innocua* were significant [18]. Also, BC–Borax and BC–ZnONPs have showed wound healing activity [18]. All of these results suggest that BC-NPs can be considered for use in wound-healing dressings and other biomedical applications by restricting and inhibiting biofilm formation towards different bacteria in wounds [18].

Next generation wound dressings include nanocoatings that contain nanoparticles with intrinsic antimicrobial properties, active at low concentrations toward a large variety of infectious agents, and that are unlikely to provoke the emergence of resistance [1-18- 62, 83, 85, 112, 115, 141, 142]. Moreover, nanoparticles can act as drug carriers for other antimicrobial agents (such as plant-derived compounds, bacteriophages, antimicrobial peptides), microbiome regulators (probiotics, prebiotics), or agents that could accelerate wound healing (i.e., growth factors, stem cells etc.) [1-18- 62, 83, 85, 112, 115, 141, 142].

10. Conclusion

Wound healing is a dynamic process and many cellular players and structures are involved in the process. The wound healing process is associated with cell migration and proliferation, extracellular matrix remodeling, angiogenesis and re-epithelialization. In normal conditions, a wound will lead to healing, resulting in reparation of the tissue. The biological process of successful wound healing is achieved through four precisely programmed, consecutive phases: hemostasis, inflammation, proliferation, and remodeling. Wound dressings are divided into traditional plant based or conventional dressings (such as cotton gauze, bandages, lint, plasters) and modern multifunctional dressings (such as foams, films, bioplymers based, hydrocolloids, hydrogels, nanocomposites). Conventional dressings are known as passive wound dressings and are useful to cover and stabilize modern dressings. 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. Cellulose serves as an attractive candidate for wound healing application. Bacterial cellulose (BC) is naturally pure, with an absence of lignin, hemicellulose, and other contaminants when compared to the extracellular matrix. This ceelulose biomaterial meets several desirable characteristics of an "ideal" wound dressing such as being non-adhesive, reducing the number of dressing changes, allowing pH modulation of the wound bed or providing a moisture balance and cooling effect. Hydrogels are one of the most attractive wound care products which, in many aspects, are considered ideal for wound treatment and are widely exploited for extension of their advantages in healing process. NFC-based hydrogels can be used in advanced wound care applications. Composite hydrogel exhibits efficient and broad-spectrum biofilm removal capabilities, while also accelerate the healing process in infected diabetic wounds. Nanotechnology offers excellent opportunities to address the problems of non- or slow-healing wounds, as wound healing solutions can be designed to be multifactorial and cell-type specific. Current trends in wound management are to develop biocompatible polymeric coatings and dressings containing ZnO nanoparticles, with no cytotoxic effects, that promote healing and inhibit microbial colonization at the wound site. Nanoparticles might contribute to the modulation of microbial colonization and biofilm formation in wounds. Silver nanoparticles (AgNPs) have been known for decades to have strong bactericidal effects, broad-spectrum antimicrobial activity, and, importantly, they are currently utilized for the therapy of both acute and chronic wounds in various preparations.

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