



# Phytonanotherapeutic Applications of Plant Extract-Synthesized Silver Nanoparticles in Wound Healing—a Prospective Overview

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## Abstract

Chronic wounds continue to pose severe threats to public health and the global economy. This is because the healing process is hindered by several factors, such as bacterial infections, comorbid conditions, age, and lifestyle. Medical wound therapy is currently based on long-term antibiotic use, and its activity has been limited by various factors, including treatment efficacy, toxicity, and increased risk of opportunistic infections. The advent of novel techniques such as nanotechnology can provide sustainable platforms for developing reliable, cost-effective, and innovative wound healing interventions. In this context, plant extract-synthesized silver nanoparticles (AgNPs) have become attractive to the clinical community because of their wide range of biological properties, such as antibacterial, anti-inflammatory, and wound healing effects. These AgNPs could be used in the development of better dressings for wounds. This review aims to provide readers with recent advances in the application of plant extract-synthesized AgNPs in wound care and management. The article provides a general overview of wounds healing process, the global prevalence of wounds, and the economic impact of chronic wounds. In addition, the limitations of conventional wound treatment strategies and the need for alternative approaches are discussed. Finally, clinical studies that have used plant extract-synthesized AgNPs in wound healing and antimicrobial activities, are highlighted.

**Keywords** Wound healing · Chronic wounds · Silver nanoparticles · Green synthesis · Medicinal plants · Anti-inflammatory · Antimicrobial

## Abbreviations

AgNPs	Silver nanoparticles
NPs	Nanoparticles
MDR	Multidrug-resistant
DF	Diabetic foot
NSAIDs	Nonsteroidal anti-inflammatory drugs
Ag	Silver
AgNO <sub>3</sub>	Silver nitrate

IL-1	Interleukin-1
TNF	Tumor necrosis factor
TGF	Transforming growth factor
ROS	Reactive oxygen species
Cl	Chloride

## 1 Introduction

The global prevalence of wounds has increased over the years, and this has put a strain on the global health economy. Wounds are exacerbated by several clinical and metabolic disorders, such as microbial infections, hypoxia, tumors, diabetes mellitus, poor nutrition, alcoholism, smoking, the presence of necrotic tissue, and poor blood circulation. Most of these factors, if not all, have been reported to alter and slow down the healing process [1–3] by causing prolonged inflammation and sepsis [3, 4]. The wound healing process follows sequential intracellular and extracellular pathways, such as inflammation, proliferation, and remodeling to restore the integrity and

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anatomical functions of the affected epithelial tissues [5]. In cases where the wound does not heal naturally, various therapeutic agents, including glucocorticoids, non-steroidal anti-inflammatories, and vasoconstrictors, are conventionally used to aid this process. However, recent studies have reported the limitations of these products and have raised the need to embrace alternative strategies in wound healing management and treatment [2, 6, 7]. Interestingly, medicinal plant extracts have been used by different populations of the world as traditional remedies to treat wounds. This approach has continued to receive more attention due to the availability, efficacy, and limited side effects of plant-based medicine [8]. Furthermore, recent advances in nanotechnology have provided the benefit of using plant extracts to reduce and stabilize metallic ions to form NPs, which in turn may provide a form of a sustained delivery system that is necessary for the wound healing process [9].

The field of green chemistry and the framework of the principles of this approach have played an important role in the development of green nanotechnology [10]. Green nanotechnology offers a combined economic, social, health, and environmental benefit in the fabrication of metallic NPs (MNPs) and their subsequent use for pharmaceutical or biomedical purposes [6, 10]. The physical, chemical, and biological properties of MNPs are more unique than those of bulk materials due to their high surface-to-volume ratios and small sizes [11]. These, in turn, can strongly influence their interactions with biological components while exerting therapeutic performance.

MNPs such as AgNPs are used in biomedical applications due to their antiviral, antibacterial, antifungal, anticancer, anti-diabetic, anti-inflammatory, and wound healing properties [12]. As a result, various chemical and physical methods have been developed for the preparation of these NPs [13]. However, the use of biological entities, such as microbes or plants, in green nanotechnology is far superior, and this has continued to gain more attention. Various studies have also reported that biological methods for AgNPs synthesis eliminate the use of expensive and toxic chemicals while providing an increased energy efficiency, and more ecologically friendly products compared to NPs obtained by chemical or physical methods [14–16]. AgNPs synthesized with plant extracts have also been shown to have great prospects in wound management and the treatment of wound-associated multidrug-resistant (MDR) pathogens [17, 18]. This review provides recent advancements in the application of AgNPs synthesized from plant extracts (nanotechnology) and phytomedicine in the wound healing process to alleviate the burden and economic impact of non-healing wounds.

## 2 The Classification of Wounds

The skin is the largest and most exposed organ in the human body, serving as a natural barrier against various insults [19–21]. It can be easily burned or injured by physical trauma resulting in a wound, a breakage, or an opening in the anatomical structure of the skin. These breaks commonly affect the body structures such as the subcutaneous tissue, tendons, nerves, blood vessels, muscles, and bones, among others [21, 22]. Wounds can occur due to surgery, injury, and other underlying conditions such as pressure, limited mobility, vascular diseases, diabetes, and repeated trauma [4, 5, 23]. Regardless of the cause, untreated wounds can cause inflammation, pain, infection, and sometimes organ failure [24].

Wounds are classified as either acute or chronic according to the pathogenesis and the duration of the healing period [5, 23]. An acute wound is an injury to the skin in which healing occurs through an ordered and expected sequence of physiological events [25]. These events lead to a sustained restoration of the anatomical and functional integrity of the affected skin parts within a short period [26]. An acute wound can occur anywhere in the body and ranges from scratches to deep wounds that affect nerves, blood vessels, and muscles. The most common forms of acute wounds occur due to accidents, trauma, animal bites, burns, gunshots, and surgical incisions [5]. In most cases, they are characterized by no microbial contamination; however, if the immune system does not clear microbial loads, it can develop into a biofilm, thereby resisting treatment attempts or taking a long time to heal [23, 27]. Wounds that take a longer time and nonorderly set of stages to heal are considered chronic wounds [25]. Chronic wounds can proceed through the sequence of a reparative process without restoring the anatomical and functional integrity of the affected skin parts [5, 25]. This process is worsened by local factors such as temperature, infection, and oxygenation, as well as systemic factors (stress, age, sex hormones, medications, proteins and minerals dietary deficiencies, obesity, immunocompromised conditions, smoking, and alcohol) [3, 28, 29]. Common examples of chronic wounds include pressure ulcers, venous leg ulcers, ischemia or arterial insufficiency ulcers, and diabetic foot (DF) ulcers [5, 22, 23, 25, 30]. Due to their uncoordinated ways of healing, these wounds are prone to pathological processes, such as increased inflammation, persistent microbial infections, necrosis, and decreased oxygenation of the subepithelial tissue [23, 31]. These conditions have made the treatment of chronic wounds more difficult and have had considerable impacts on patients, their caregivers, and healthcare facilities [22].

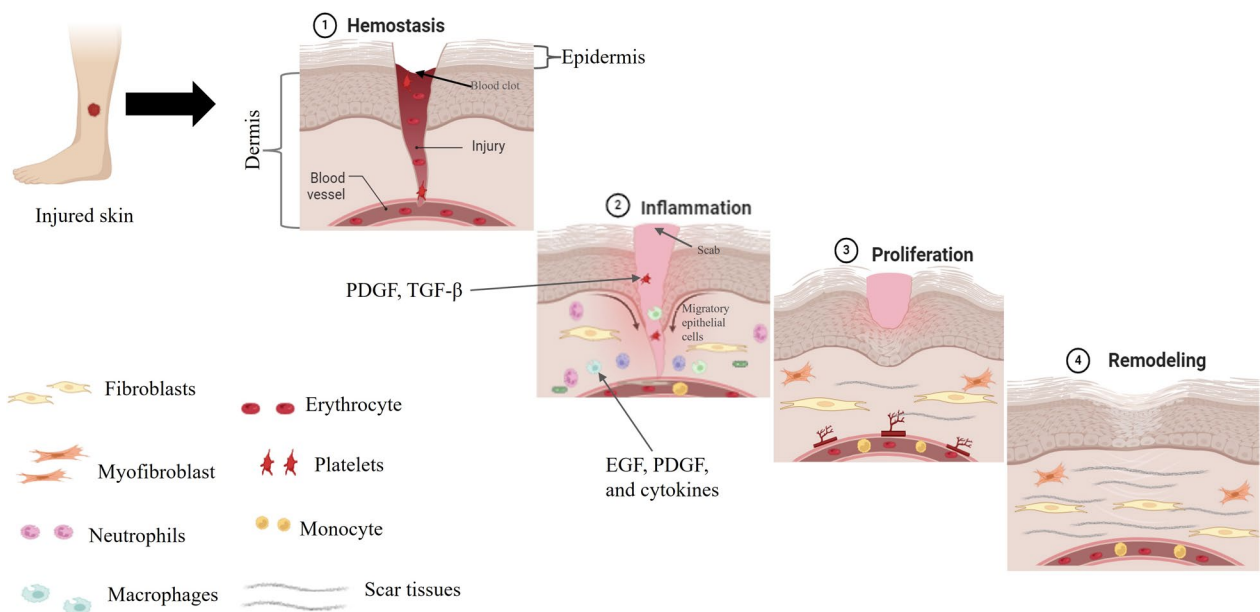
### 3 Normal Wound Healing Process

Wound healing is a natural process that begins immediately after an injury. The wound healing process is a highly integrated and overlapping process that follows four stages viz: hemostasis, inflammation, proliferation, and tissue remodeling (Fig. 1). These four stages must occur in sequence to bring about successful wound healing [5, 30, 32]. Hemostasis begins immediately after an injury occurs, and the goal is to stop bleeding after vascular damage [33]. This process is initiated by the constriction of blood vessels to reduce blood flow, causing platelet activation, adhesion, and aggregation at the wound site. Exposure to collagen in the endothelial matrix triggers platelet activation, and key glycoproteins such as fibronectin, fibrin, vitronectin, von Willebrand factor, and thrombospondin, cause the formation of a plug in the wound. At the same time, platelet aggregation results in the deposition of clotting factors in the wound area which coagulate with fibrin to form a bulk of blood clotting. Platelets within the plug release two important cellular mediators; platelet-derived growth factor (PDGF) and transforming growth factor  $\beta$  (TGF- $\beta$ ) which are required to initiate an inflammatory response [33–36].

Inflammation, as the second phase, prevents wound infections. This phase often occurs within the first 24 h after injury and can take up to 5 days in acute wounds and significantly longer in chronic wounds [37]. Immediately, after the bleeding stops, inflammatory cells migrate to the wound, and this is marked by the successive infiltration of neutrophils,

macrophages, and lymphocytes [29, 38]. Highly motile neutrophils are recruited to the wound site by the PDGF and TGF- $\beta$  within an hour after the injury to serve as first responders. These cells infiltrate the wound site to destroy and remove bacteria, damaged tissue, and other foreign particles through a process called phagocytosis [29, 34]. Due to the low pH properties of the wound site at 48–72 h, macrophages are activated to release growth factors such as vascular endothelial growth factor (EGF), PDGF, and cytokines that are important in stimulating angiogenesis, inflammatory response, activation of granulation tissue, and fibroblast cells [29, 32–34]. Lymphocytes are the last cells to arrive at the wound site, signaling the end of the inflammatory process. They are recruited to ensure tissue repair by the action of chemoattractants such as, interleukin-1 (IL-1), complement components, and immunoglobulin G (IgG) breakdown products [34, 39]. Finally, if it is necessary, the inflammatory phase of wound healing will continue, ensuring that all excess bacteria and debris from the wound are removed.

The proliferative phase of the wound healing cascade occurs once the ongoing injury has stopped, hemostasis has been achieved, the inflammatory response has been regulated, and the wound is free of debris [28, 39]. This phase of tissue repair begins the third day after the injury and can last for about two weeks. It is characterized by neovascularization, and replacement of the provisional matrix formed during hemostasis with granulation tissue at the wound site [5, 38, 39]. Granulation tissue is a vascular complex of fibroblasts, granulocytes, macrophages, blood vessels, and



**Fig. 1** Schematic illustration of the four natural and overlapping phases of the wound healing process and the key proteins involved. The image was drawn using the BioRender software

collagen bundles, which help the wounded skin partially regain its structure and function. Fibroblasts migrate to the wound sites from the surrounding dermis, or fibrocytes (for a long-lasting wound) in response to cytokines and cellular mediators such as PDGF, TGF- $\beta$ , and basic fibroblast growth factor (bFGF) previously introduced into the wound by platelets and macrophages [40]. While at the wound site, the fibroblast degrades the provisional wound matrix by producing proteinases, such as matrix metalloproteinases (MMPs), and replacing collagen and other components of extracellular matrix (ECM) (e.g., fibronectin, hyaluronic acid, proteoglycans, and glycosaminoglycans) that fill the wound gap and provide a scaffold for cell adhesion, growth, and differentiation during which is necessary for wound repair [28, 40, 41]. Rebuilding the vascular network is crucial because wound healing requires nutrients and oxygen. Therefore, growth factors, such as, VEGF, PDGF, bFGF, and the serine protease thrombin in the wounds recruit the endothelial cells from existing vessels to start the formation of new blood vessels through a process called angiogenesis [40, 41]. Macrophages also play a key role in promoting vascular networking by guiding the sprouting of new blood vessels, removing superfluous vessels through phagocytosis, and activating MMPs for ECM remodeling [42].

The final phase of the wound healing process, tissue remodeling starts around the third week of injury and can last for years [1, 29, 39]. During this period, there is a regression of many newly produced capillaries, and the vascular density of the wound is restored to normal. This phase is characterized by changes in collagen cell type, quantity, and organization to enhance tensile strength. For example, type III collagen synthesized in the ECM is replaced by type I collagen fibers. This collagen remodeling requires MMPs and alters collagen synthesis to produce a scar. The levels of angiogenic activities are also reduced to restore tissues to their pre-wound state while increasing the tensile strength of the wound to approximately 80% of the original state [33, 34]. The result of tissue remodeling is the formation of a normal epithelium and fully mature scar tissue [29].

#### 4 Microbial Infections of Wounds

Acute and chronic wounds are usually colonized by microorganisms acquired from endogenous sources (such as mucous membranes), exogenous sources (such as the environment), and skin microflora [43, 44]. The presence of these microbes does not always imply that infections have occurred, as specific bacteria at physiological levels can help facilitate the wound healing process [44, 45]. The wound-microbial interactions have been widely studied and categorized based on the host immune responses. Skin commensals such as *Staphylococcus epidermidis* and *Corynebacterium* species

have been shown to influence the rate of wound healing. Under normal conditions, both microbial wound colonization and contamination do not inhibit the wound healing process. However, when wound colonization intensifies, this could result in a state referred to as critical colonization in the wound infection continuum. At this stage, the host's immune system cannot regulate colonizing microbes, resulting in wound infection. Wound infections are caused by the presence of replicating microorganisms in the wound at a level that invokes a local or systemic immune response of the host, thus impeding the healing process [20, 44–47]. Wound infections are commonly polymicrobial, infected by communities of aerobic and anaerobic pathogens [45] of bacteria and fungi origin. A retrospective study identified *Staphylococcus aureus* (79.4%) and *Pseudomonas aeruginosa* (40.2%) as the predominant species in about 240 patients diagnosed with wound infections. To a lesser extent, the presence of *Escherichia coli*, *Proteus mirabilis*, and *Acinetobacter baumannii* was also reported [48]. Similarly, *S. aureus*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, and *Klebsiella pneumoniae* were the most common bacterial isolates in an investigation of the distribution and antimicrobial resistance pattern of bacteria among 815 patients with various types of chronic wounds in a hospital [49]. Other studies have also found that *S. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *Streptococcus* spp., *Enterococcus* spp., *P. mirabilis*, and *Corynebacterium* spp. are the bacterial populations most encountered in chronic wound infections [46, 50–52]. Some genera of endogenous fungi, including *Candida*, *Curvularia*, and *Malassezia*, have also been identified from chronic wound infections [45]. The microbiome of various chronic wounds has also been reported, including venous, pressure, and DF ulcers [53]. Consequently, the presence of these microflorae in wounds, especially the biofilm of resistance strains, results in poor treatment results while decreasing the efficiency of the wound healing process [30, 54].

#### 5 Prevalence, Complications, and Economic Impact of Chronic Wounds

Chronic wounds impose a significant burden on the affected individual and society, causing persistent pain, financial burden, hospitalization, amputation, and premature death of patients [5, 45]. The silent epidemic of chronic wounds affects different parts of the world [4, 5, 55], and studies have shown that 1 to 2% of the population in developed countries will experience chronic wounds during their lifetime [25, 56]. For example, in the USA, chronic wounds affect more than 6.5 million individuals annually [25, 57]. A previous retrospective Medicare study in 2014 showed that 8.2 million patients experience a minimum of one category of wound [58]. A recent follow-up study conducted by the

authors also found that the number of Medicare patients with at least one type of wound increased from 8.2 million to 10.5 million for 5 years [59]. In the UK and Australia, 2.2 million and 420,000 patients, respectively, are affected by chronic wounds. The annual prevalence of chronic wounds in Finland is between 1.3 and 3.6% [60], 6% of the Welsh population, and an estimated 1.5 to 2 million individuals in European populations [4, 61]. A retrospective study investigating the prevalence of chronic wounds in a hospital inpatient setting in Northern China revealed a significant increase in wounds from 16.8 to 26.4 per 1000 inpatients within the first 4 years of the study [62]. Although there is limited information on the prevalence of chronic wounds in Africa, recent research in Uganda and Nigeria has established that an average of 35 and 48 patients, respectively, are diagnosed with chronic wounds monthly [63, 64]. Despite the underreported cases of chronic wounds in various parts of Africa, it annually accounts for approximately 30–42% of hospital attendance and 9% of deaths [65, 66].

Chronic wounds are associated with significantly high rates of mortality and morbidity. For example, up to 70% and 50% of deaths occur within 5 years of first amputation, and 5 years of obtaining a DF ulcer, respectively [67, 68]. A previous study by Jupiter et al. reported that the mortality rate in patients with foot ulceration was 40% in 5 years [69]. A study on 338 consecutive patients from the Multidisciplinary DF Team also found that foot ulceration was reduced to 60% at 5 years [70]. A prospective observational study conducted on 80 patients affected by sepsis in an intensive care unit has reported a mortality rate of 67.5% [71]. Similarly, when compared to the population of the same patient without surgical site infections (SSI), SSI can result in long-term disability after surgery and a 2- to 11-fold increase in the risk of death [72].

Chronic wounds present a significant economic burden on the healthcare systems and society, costing billions of dollars annually in various parts of the world. The global market for advanced wound care products, which was predicted to be US\$12 billion in 2020, is expected to grow to \$18.7 billion by 2027. The UK National Health Services estimated the annual cost of wound management at £2870 per patient [73]. The cost of wound management for Medicare patients ranged from \$28.1 to \$96.8 billion for wound care [58, 74]. The estimated annual cost of treating chronic wounds in the USA, the UK, and Wales is \$25 billion, £5.1 billion, and £328.8 million, respectively [4, 61, 75].

The effects of chronicity on the cost and management of various categories of wounds have also been studied. For instance, the cost of treating pressure ulcers can range from £4300 to £6400 per patient in the UK [76]. An estimate of the cost of managing pressure ulcers in the US health care system stands at \$11 billion per year, and costs of managing venous ulcers were estimated at 3.5 billion [4]. A similar

study conducted in Australia revealed a cost of US\$1.64 billion for pressure injuries, \$249.69 million for diabetic ulcers, and \$802.5 million for venous ulcers [67, 73]. Therefore, solving the problem of chronic wounds could save millions of dollars and reduce wound care expenses.

## 6 Conventional Wound Healing Treatments

Skin tissue repair and healing are among the most complicated biological processes that occur in humans [2]. Several drugs are currently available in the market to maintain healthy skin and accelerate wound healing processes, such as blood clot formation, inflammatory responses, platelet function, and cell migration. These therapeutic agents include glucocorticoid steroids, non-steroidal anti-inflammatory drugs, chemotherapeutic drugs, and silver. Glucocorticoid steroids are characterized by anti-inflammatory effects and suppression of cellular wound responses, such as fibroblast growth and collagen production [1, 77]. Non-steroidal anti-inflammatory drugs (NSAIDs) are generally used for the treatment of pain, inflammation, and rheumatoid arthritis to aid recovery by decreasing the duration of the inflammatory phase of healing [1, 77, 78]. Reduced inflammation and pain allow for the initiation of active rehabilitation, which accelerates wound recovery in patients [78]. Chemotherapeutic drugs are designed to restrict the cellular metabolic processes involved in proliferation, angiogenesis, and other pathways that are essential for wound repair. Silver has potent antimicrobial properties and is commonly used in wound care products to prevent infections. Although, the metallic form of silver ( $\text{Ag}^0$ ) is not associated with any therapeutic properties, silver ion ( $\text{Ag}^+$ ) has a broad antimicrobial spectrum due to their cytotoxic effects on microorganisms [79]. The cytotoxic effects of  $\text{Ag}^+$  are mainly attributed to their ability to interact with various cellular components of microorganisms, disrupting essential cellular processes such as respiration, DNA replication, and cell division. This disruption ultimately leads to cell death via various mechanisms as described elsewhere [80]. The complexity of these mechanisms explains why bacteria rarely develop resistance to  $\text{Ag}^+$ , unlike most common antibiotics [81]. There are a growing number of silver dressings, which are already available and are presented as creams (e.g., silver sulfadiazine), foams (e.g., Aquacel Ag, Contreet Ag, and Biatain Ag), hydrogels (Silvasorb and Silverseal), hydro-fibers (AQUACEL Ag), hydrocolloids (DuoDERM Hydroactive Gel), film (Acticoat), and alginates (Askina Calgitrol Ag), among others [82, 83]. Furthermore,  $\text{Ag}^+$  has been found to exhibit low toxicity to human cells at concentrations effective against microorganisms, making it attractive for use in wound dressings and other applications where broad-spectrum antimicrobial activity is required.

## 7 Limitations of Conventional Wound Healing Treatments

Conventional drugs can cause various undesirable effects, such as low efficacy, allergic responses, high risk of infection, rapid drying of wound area, and other side effects [84]. For instance, the use of glucocorticoid steroids in wound healing has been associated with incomplete granulation of tissue and reduced wound contraction. Furthermore, high dosage over a short period or long-term administration of glucocorticoids (such as chronic wounds) can result in immunosuppressive effects that tend to increase the risk of opportunistic infections [1, 7, 85]. Previous animal model studies found that NSAID drugs, such as ibuprofen, have anti-proliferative effects on wound healing resulting from reduced fibroblast numbers, delayed epithelialization, reduced wound contraction, and weakened angiogenesis [1, 86]. The use of chemotherapeutic drugs in wound treatment can result in decreased fibroplasia and neovascularization of wounds. In addition, these agents produce immunosuppressive effects on the host, thereby disrupting the inflammatory phase of wound healing and predisposing the wound to infections [61, 77]. Chemotherapeutic agents can also induce anemia, neutropenia, and thrombocytopenia, making wounds more susceptible to infection, and increasing the risk of excessive bleeding at the wound site [1, 85]. Despite the widespread use of silver in the fight against MDR pathogens, indiscriminate use can lead to the development of resistance with significant adverse effects on human health and the environment [87]. Furthermore, studies have reported conditions in which excessive silver deposition or accumulation in the body results in argyria. Argyria occurs when  $\text{Ag}^+$  products are ingested or applied to the skin over a prolonged period. This condition is not toxic to the body but is characterized by an irreversible blue-grey discoloration of the eyes' skin, nails, mucous membranes, or other light-exposed areas in the body [23, 79, 81]. Furthermore, studies have shown that wound dressing with  $\text{Ag}^+$  at high concentrations can be cytotoxic to fibroblasts and keratinocytes, resulting in delayed epithelialization [79, 88]. Therefore, the judicious use of silver-containing products is key to maximizing their effectiveness. Overall, because of these limitations, ongoing research is exploring alternative, and more efficient approaches to identify more effective and targeted treatments while optimizing the use of existing agents to promote wound healing outcomes.

## 8 Phytomedicines as Alternative Medicines for Wound Healing

Traditional healers have used medicinal plants for millennia in the treatment of trauma, infection, and wounds [89]. Studies have shown that 80% of developing and underdeveloped populations still depend on medicinal plants

as their main source of health care [90, 91]. A previous study that examined African plants also documented that more than 160 species from 70 plant families distributed in Ethiopia, Cameroon, Mali, Egypt, Ghana, and Nigeria are used for wound healing; with 26 and 35 plant families in South Africa and Zimbabwe, respectively [92]. The growing relevance of medicinal plants in wound management is due to their easy accessibility, low side effects, and various mechanisms of action [15, 93, 94]. Medicinal plants promote wound healing by facilitating blood clotting, fighting inflammation, perfusion, increasing collagen deposition, formation of organized re-epithelialization, granulation tissue, and wound closure [95]. Recent research on medicinal plants with wound healing properties is presented in Table 1. The medicinal values of these plants have been attributed to the synergistic effects of various bioactive compounds such as flavonoids, essential oils, alkaloids, tannins, terpenoids, saponins, and phenolic compounds [96]. Therapeutic applications of medicinal plants are limited by several issues, including short half-life, poor solubility, structural instability in the biological environment, fast metabolism, rapid clearance, and elimination. However, novel delivery strategies that allow the incorporation of plant extracts or secondary metabolites into suitable nanomaterials can improve their solubility, stability, bioavailability, and therapeutic efficacy [9, 97]. Conjugating secondary metabolites on the surface of inorganic nanomaterials presents a powerful innovative approach in nanotechnology. This technique takes advantage of the unique properties of both secondary metabolites and inorganic nanomaterials to enhance the stability, bioactivity, safety profile, and targeted action of the inorganic nanomaterial [52, 98]. However, it is essential to thoroughly study and understand the interactions between the secondary metabolites and nanomaterials to maximize their potential while minimizing side effects.

## 9 Nanobiotechnology Applications in Wound Healing

Nanotechnology is a branch of applied science and technology that deals with the manufacture and manipulation of atoms at the nanoscale size, ranging from 1 to 100 nm in diameter [114]. The field of nanotechnology has gained increasing attention in biomedicine due to its ability to resolve various biological problems, both in the treatment and diagnostic of various diseases, such as diabetes, cancer, cardiovascular diseases, and wound healing [85]. Nanotechnology-based treatment options have been explored as an efficient approach for targeting the complexity of the normal wound healing process as well as the pathophysiology of chronic wounds. Nanomaterials can be used as wound

**Table 1** Medicinal plants with wound healing properties

Plant	Plant parts	Assay/Type of wounds	Observed mechanisms	Reference
<i>Aloe muth-muth</i>	Gel and whole leaves	In vitro (scratch assay on HaCaT cell line)	Cell migration	[99]
<i>Aloe vera</i>	Leaves	In vitro (cell proliferation and scratch assays)	Proliferation and migration of fibroblasts and keratinocytes	[100]
<i>Aristolochia saccata</i>	Leaves	In vitro (scratch assay on L929 cell line)	Expression of collagen 1	[101]
<i>Artemisia judaica</i>	Aerial parts	In vivo (skin burn induction model)	Anti-inflammatory effect	[102]
<i>Boerhavia diffusa</i>	Leaves	In vivo (excisional wound assays)	Stimulation of keratinocytes	[103]
<i>Calendula officinalis</i>	Flowers	In vivo (incisional wound model)	Proliferation and migration of fibroblasts	[24]
<i>Citrus tamurana</i>	Peels	In vitro (TIG-119 cell lines)	Cell migration and proliferation responses	[24]
<i>Cynodon dactylon</i>	–	In vivo (incisional and excisional wound model)	Anti-inflammatory properties	[24]
<i>Ehretia laevis</i>	Leaves	Burn injury	Granulation, collagenization & re-epithelization	[104]
<i>Globularia arabica</i>	Leaf	In vivo (excisional wound model)	Acceleration of collagen and hydroxyproline synthesis	[105]
<i>Iris florentina</i>	Different plant parts	In vivo (excisional wound model)	Fibroblast proliferation, the formation of collagen, and increased vascular density	[24]
<i>Mentha pulegium</i> and <i>Lavandula stoechas</i>	Aerial parts	In vivo (excisional wound model)	Induction of cell migration	[106]
<i>Phyllanthus muellerianus</i>	Aerial parts	In vivo (excisional and incisional wound model)	Keratinocytes proliferations	[107]
<i>Pistacia vera</i>	Resins	In vivo (excisional wound model)	Granulation and epithelialization of wounds	[108]
<i>Plumbago zeylanica</i> , <i>Datura stramonium</i> , and <i>Argemone mexicana</i> (polyherbal drugs)	Stem, leaf, and aerial parts	In vivo (incisional and excisional wound model)	Proliferation and mobilization of fibroblast and keratinocytes, and angiogenesis	[109]
<i>Pyrostegia venusta</i>	Flowers	In vivo (incisional and excisional wound model)	Epithelialization, fibroplasia, and neovascularization	[110]
<i>Scrophularia striata</i>	Aerial parts	In vivo (excisional wound model)	Anti-inflammatory properties	[111]
<i>Teucrium polium</i>	Aerial parts	In vivo (excisional wound model)	Acceleration of re-epithelization	[112]
<i>Vernonia auriculifera</i>	Leaves	In vivo (incisional, excisional, and burn wound models)	Macrophage cell proliferation, collagen synthesis, and angiogenesis	[113]

healing agents or exploited as vehicles to deliver therapeutic agents that can intrinsically aid in the wound healing process [85, 115]. This can be done by using NPs as carriers for cell therapies, antioxidants, antibiotics, growth factors, nucleic acids, small molecules (e.g., nitric oxide and thrombin), and other agents that can stimulate wound healing [85]. The main goal of this approach is to protect therapeutic agents from hydrolytic enzymes and to ensure the slow release of therapeutic agents, thus increasing the therapeutic window of such therapeutic agents [116]. Furthermore, MNPs such as silver, gold, lead, zinc, and platinum have long been integrated into wound dressings to prevent microbial infections and accelerate tissue repair, due to their physicochemical and optoelectronic properties [32, 85, 117, 118]. These

dressings provide a moist environment that is conducive to wound healing while delivering the antimicrobial benefits of the NPs. Of these NPs, silver has gained substantial attention due to its unique distinctive optical, catalytic, electrical, broad-spectrum antimicrobial properties and the ease of reducing its salts ( $\text{Ag}^+$ ) to form stable zero-valent silver ( $\text{Ag}^0$ ) [119–121].

## 9.1 Synthesis of AgNPs

AgNPs have shown a wide range of biological activities, including antiviral, antibacterial, antifungal, antinematodal, anticancer, and anti-inflammatory

properties [12, 23, 122]. As a result of these excellent properties, various synthesis protocols have been exploited to conserve the physicochemical properties and meet the need for AgNPs. For instance, several chemical and physical methods such as gamma irradiation, thermal decomposition, chemical reduction, laser ablation, electron irradiation, photochemical, and microwave-assisted processes, among others have been used to synthesize AgNPs. All these synthesis methods have been extensively reviewed by others [13, 14]. Conventional chemical and physical techniques make use of protocols that can be costly with high radiation and concentrated reductants, which can be toxic to humans and the environment, thus limit their use in medical fields [123–125].

Consequently, the quest for rapid, cost-effective, and environmentally friendly synthesis procedures led to the fabrication of nanomaterials using biological agents, providing an alternative to traditional physical and chemical methods [13, 125–127]. This biological approach, sometimes called “green synthesis,” uses entities such as microorganisms or plants to produce MNPs [13, 14, 128]. Commonly used microorganisms in the synthesis of NPs are bacteria, yeast, fungi, and algae. In this process, metal ions are trapped on the surface (extracellular) or inside (intracellular) of the microbial cells and then reduced to NPs in the presence of various biomolecules, such as amino acids, proteins, enzymes, organic materials, sugar molecules, and many other metabolites that act as capping and stabilizing agents [123, 129]. This method of synthesis is associated with several drawbacks, including complicated protocols for microbial culture, strict aseptic culturing conditions, and storage. Additionally, considering the slow rate of NPs production and the low yield, these methods seem impractical for use on an industrial scale. Furthermore, the complexity of recovering the NPs from the microorganisms can further complicate the use of these methods at an industrial scale [130].

Several studies have reported on the synthesis of AgNPs from various plant species and parts [6, 119] by mixing plant extracts with silver nitrate ( $\text{AgNO}_3$ ) in one step. Plant extracts or their phytoconstituents (such as alkaloids, vitamins, tannins, phenolics, and saponins, among others) are believed to act as reducing and capping agents [14, 119, 120]. Plant extracts are preferable candidates for the green synthesis of NPs, as they do not require toxic stabilizers, high temperatures, or expensive media for microbial growth, and can be performed without fear of contamination [119, 129, 131]. In addition, plants are readily accessible, and the extracts can be obtained from various parts, including the stem, root, latex, fruits, seeds, peels, and bark.

### 9.1.1 Antimicrobial Application of Green Synthesized AgNPs

The use of silver to fight infections has a long history, and its nanoforms are more effective and biocompatible antimicrobial agents. Given this, extensive research has been conducted on the application of AgNPs to overcome the threat of antimicrobial resistance [128, 132]. Studies have shown that microorganisms cannot easily become resistant to AgNPs due to their multi-target actions on pathogens [5, 133]. This explains the potency and broad-spectrum antimicrobial activities of AgNPs against a wide range of microbes. Various studies have reported the use of extracts obtained from different parts of plants in the formulation of AgNPs as antimicrobial agents against a wide range of pathogens. Examples of these studies are described in Table 2. It has also been shown that the antimicrobial activities of AgNPs are dependent on their physicochemical characteristics, such as size, shape, aggregation state, and surface charge [134, 135].

The size and surface area of AgNPs have an impact on cellular absorption, cutaneous penetration, and cell toxicity. Smaller NPs with larger surface areas are generally more effective because of better penetration, enhanced release of  $\text{Ag}^+$  ions, and more effective contact with microbial cells. These properties allow AgNPs to disrupt cellular processes, induce oxidative stress, and prevent the formation of biofilms, thereby, providing an effective antimicrobial activity [157]. Beyond the size, shape, and morphology of AgNPs, their interactions with biological membranes and cells can also affect their interactions. For example, rod-shaped NPs may penetrate microbial cells more effectively than spherical ones, leading to higher activity. Holubnycha et al. [158] compared two types of AgNPs with different physicochemical properties and found that NPs characterized by a cubic shape and a higher surface-to-volume-ratio exhibited a higher antimicrobial performance than spherical NPs. Hanan et al. [159] reported that NPs synthesized with plant extracts are predominantly spherical or quasi-spherical, demonstrating a greater potency than hexagonal, rod, and triangular NPs. Other studies have reported that aggregation states can affect AgNPs surface area, reactivity, and bioavailability, resulting in lower cellular uptake by microbial cells and decreased antimicrobial compared to dispersed particles [160]. Therefore, understanding and controlling the aggregation state of AgNPs is critical for their optimum application as antimicrobial agents.

Gram-negative bacteria are more susceptible to AgNPs compared to Gram-positive [143, 154, 161]. The susceptibility of Gram-negative bacteria could be based on the presence of the negatively charged lipopolysaccharide structure that is absent in Gram-positive bacteria [121]. These negatively

charged molecules bind to the positive ions that are released from the AgNPs, leading to the uptake of Ag<sup>+</sup> ions and increased intracellular damage. AgNPs can cause inhibition or death of bacteria by adherence to the cell, causing degradation of the membrane and cell wall, the generation of reactive oxygen species (ROS) resulting in cell damage, and intracellular destruction of DNA and proteins through interactions with sulfur and phosphorus groups which are part of these biomolecules. All these mechanisms have been extensively reviewed elsewhere [130, 162–164]. Overall, these broad mechanisms of action make AgNPs an option in the development of novel biomedical applications [165].

### 9.1.2 Wound Healing Applications of Green-Synthesized AgNPs

The use of plant extracts to synthesize NPs for use in wound healing has gained significant attention in the last decade, as demonstrated by the search for articles using the keywords “green AgNPs and wound healing” in the Scopus database, which generated 338 articles published between 2010 and February 2024. Nanomaterials are believed to promote wound healing rates and address the limitations of medicinal plants, including the solubility and stability of phytochemicals at wound sites [9, 166, 167]. This is because plant extract-mediated NPs are hydrophilic, thereby increasing the attractiveness of medicinal plants and their phytochemicals in biomedical applications [168]. This approach has been used to aid in the biodistribution and bioavailability of natural products targeting specific tissues or organs [97, 166]. Badhwar et al. [167] formulated the quercetin NP-hydrogel to enhance the low aqueous solubility and poor skin penetration of the phytochemical. A further in vivo study using quercetin-loaded AgNPs in hydrogel matrices for diabetic wound healing revealed that the topical application of the NPs accelerated healing compared to the marketed gel that was used as a control. The authors also established that the co-delivery of quercetin and AgNPs had a synergistic impact on the treatment of diabetic wounds. Another recently published animal study also found that curcumin-decorated AgNPs increased the efficacy of a conventional antidiabetic drug (metformin) by suppressing drug-induced hepatotoxicity [169]. Table 3 lists examples of recent studies on the use of green synthesized AgNPs in wound healing and repair.

### 9.1.3 Green-Synthesized AgNPs as Antimicrobial Agents in Wound Healing

The biggest impediment to wound healing is the microbial consortium encased in a self-produced extracellular polysaccharide matrix that allows it to grow and become resistant to antimicrobial agents [5]. AgNPs can result in faster and better quality wound healing by increasing relative

humidity, the absorption capacity of blood secretions, removal of excess exudates, and continuous exchange of oxygen at the wound site, thus preventing microbial colonization [180]. As a result, various studies have focused on designing plant extract-based AgNPs to respond to the microenvironment of wound sites [18, 181–183]. Plant extract-synthesized AgNPs formulated from *Juniperus excelsa*, *Synechocystis* sp., *Hibiscus sabdariffa*, and *Salvia officinalis*, among others, have also been combined with conventional antibiotics such as cefoxitin, erythromycin, cefaclor, fosfomycin, colistin, and chloramphenicol to demonstrate synergistic activities [52, 184–187]. Some of these studies further established that AgNPs are promising and effective antibacterial agents against MDR microbes that are commonly associated with wounds [186, 187]. Finally, in addition to their therapeutic benefits in wound healing, AgNPs are less toxic to humans and the environment [149].

### 9.1.4 Green-Synthesized AgNPs as Anti-Inflammatory Agents in Wound Healing

Inflammation is an essential natural defense mechanism that the immune system uses to combat infections [15, 188]. Chronic inflammation or disruptions in the normal healing process can lead to complications, as is the case in chronic wounds. Hence, understanding the intricate interaction between inflammation and wound healing is crucial for developing therapeutic strategies to enhance healing and minimize scarring [189]. The wound healing promotional effects of nanomaterials have been linked with their ability to suppress inflammation [190]. The important roles of plant extract-synthesized AgNPs as anti-inflammatory agents have been demonstrated. For example, AgNPs produced using an aqueous extract of *Cotyledon orbiculata* showed anti-inflammatory effects by inhibiting macrophage secretion of pro-inflammatory cytokines [15]. The cream formulation using AgNPs derived from the leaves of *Ehretia cymosa* had better anti-inflammatory activities and more promising wound healing effects compared to both diclofenac and the extract [17]. Green synthesized AgNPs using aqueous bark extract of *Mangifera indica* showed anti-inflammatory effects, and could be considered in the development of effective therapeutic strategies against inflammation-related diseases [191]. Similarly, the green synthesis of AgNPs using European black elderberry (*Sambucus nigra*) fruit extracts was reported to possess in vitro and in vivo anti-inflammatory effects by decreasing the level of cytokine production [192]. Various studies have also established the potential anti-inflammatory activity of AgNPs derived from aqueous extracts of *Solanum khasianum* leaf [193], *Parthenium hysterophorus* leaf [194], *Selaginella myosurus* [195] *Calophyllum tomentosum* [140], petroleum ether, and ethyl acetate fractions of soft coral (*Nephthea* sp.) [196].

Table 2 Antimicrobial activities of selected green synthesized AgNPs

Plants	Plant parts	Synthesis condition	Morphology of the AgNPs	Average size (nm)	Pathogens	Methods	Reference
<i>Allium sativum</i>	Garlic extracts	Exposure to bright sunlight for 15 min	Spherical and poly-dispersed	7.3	<i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i>	Agar well diffusion	[136]
<i>Artemisia nilagirica</i>	Leaf extract	Room temperature	Square	70–90	<i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> , <i>Proteus subtilis</i>	Agar well diffusion	[137]
<i>Artemisia vulgaris</i>	Leaf extracts	15 min agitation followed by incubation at room temperature for 2 h	Round and polydisperse	25	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> , and <i>Hemophilus influenza</i>	Disc diffusion	[138]
<i>Azadirachta indica</i>	Leaf extracts	Incubation in the dark at room temperature	Spherical and irregular	34	<i>Staphylococcus aureus</i> and <i>Escherichia coli</i>	Disc diffusion	[139]
<i>Calophyllum tomentosum</i>	Leaf extracts	Room temperature for 1 h	Spherical and uniform	24	<i>Staphylococcus aureus</i> , <i>Klebsiella aerogenes</i> , <i>Escherichia coli</i> and <i>Pseudomonas aeruginosa</i>	Disc diffusion	[140]
<i>Ceropegia thwaitesii</i>	Leaf extract	30 °C in a shaker for 72 h	Spherical	100	<i>Vibrio cholerae</i> , <i>Pseudomonas aeruginosa</i> , <i>Corynebacterium</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Mycobacterium</i> spp., <i>Salmonella typhi</i> , <i>Shigella flexneri</i> , <i>Proteus mirabilis</i> , <i>Klebsiella pneumoniae</i> , <i>Bacillus subtilis</i> , and <i>Micrococcus luteus</i>	Disc diffusion	[141]
<i>Cleome viscosa</i>	Fruits extract	Room temperature in the dark for 24 h	Spherical	5–30	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Bacillus subtilis</i> , and <i>Klebsiella pneumoniae</i>	Agar well diffusion	[142]
<i>Cucumis prophetarum</i>	Leaf extracts	80 °C for 3 h with constant stirring	Spherical, ellipsoidal, and irregular	90	<i>Salmonella typhi</i> and <i>Staphylococcus aureus</i>	Disc diffusion	[143]
<i>Dioscorea bulbifera</i>	Tuber extracts	4–50 °C with reflux	Nanorods and triangles	8–20	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Salmonella typhi</i> , and <i>Bacillus subtilis</i>	Disc diffusion	[14, 144]

Table 2 (continued)

Plants	Plant parts	Synthesis condition	Morphology of the AgNPs	Average size (nm)	Pathogens	Methods	Reference
<i>Echinochloa stagnina</i>	Shoots extract	pH 7 kept in the dark at room temperature overnight	Monodispersed and spherical	18–39	MDR <i>Klebsiella oxytoca</i> and <i>Pseudomonas aeruginosa</i>	Disc diffusion method and micro broth dilution assay	[145]
<i>Eclipta alba</i>	Leaf extracts	Stirring at 37 °C for 30 min	Cubic	310–400	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , and <i>Pseudomonas aeruginosa</i>	Agar well diffusion	[14, 146]
<i>Ferula pseudodalliacea</i>	Root extracts	80 °C for 15 min	–	–	<i>Acinetobacter baumannii</i> , <i>Bacillus cereus</i> , <i>Enterococcus faecalis</i> , <i>Enterococcus faecium</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> , and <i>Candida albicans</i>	Disc diffusion	[147]
<i>Ficus benghalensis</i>	Spruce bark extracts	pH 4 and 9 for 3 h at 60 °C	Spherical	35	<i>Bacillus cereus</i> and <i>Escherichia coli</i>	Disc diffusion	[148]
<i>Gnaphalium polycaulon</i>	Leaf extracts	Stirred for 1 h at room temperature	Spherical and triangle	< 50	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , and <i>Candida albicans</i>	Agar well, micro broth dilution method	[149]
<i>Heritiera fomes</i> (Hf) and <i>Sonneratia apetala</i> (Sa)	Leaf extracts	Stirring at ambient temperature and direct exposure to sunlight for 12 h	–	50 (Hf), 20–30 and 70–100 (Sa)	<i>Staphylococcus aureus</i> , <i>Shigella flexneri</i> , <i>Vibrio cholera</i> , <i>Staphylococcus epidermidis</i> , <i>Bacillus subtilis</i> , and <i>Escherichia coli</i>	Disc diffusion	[138]
<i>Ixora brachypoda</i>	Leaf extracts	pH 8.5 and incubation in a dark for 48 h	Spherical and polydispersed	18–50	Bacterial strains: <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Pseudomonas aeruginosa</i> , and <i>Escherichia coli</i> Fungal strains: <i>Alternaria alternata</i> , <i>Candida albicans</i> , <i>Magnaporthe grisea</i> , and <i>Fusarium oxysporum</i>	Agar well diffusion	[150]

Table 2 (continued)

Plants	Plant parts	Synthesis condition	Morphology of the AgNPs	Average size (nm)	Pathogens	Methods	Reference
<i>Morinda citrifolia</i>	Leaf extracts	90 °C in a shaker for 1 h	Spherical	27	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter aerogenes</i> , <i>Bacillus cereus</i> , and <i>Enterococci</i> sp.	Disc diffusion	[151]
<i>Musa paradisiaca</i>	Peel extracts	pH 4 followed by incubation in the dark at 40–100 °C for 72 h	Spherical	23.7	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , and <i>Candida albicans</i>	Disc diffusion	[14, 152]
<i>Plantago lanceolata</i>	Leaf extracts	Stirred at room temperature for 4 h	Spherical	55	<i>Staphylococcus aureus</i> , <i>Proteus vulgaris</i> , <i>Agrobacterium tumefaciens</i> , and <i>Escherichia coli</i>	Agar well diffusion	[153]
<i>Plantago major</i>	Leaf extracts	pH 10 stirred under 70 °C for 1 h	Spherical	10–20	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> and <i>Escherichia coli</i>	Disc diffusion	[154]
<i>Terminalia chebula</i>	Fruits extract	Room temperature for 15–20 min	Pentagons, spherical, triangular	< 100	<i>Staphylococcus aureus</i> and <i>Escherichia coli</i>	Agar well diffusion	[14, 155]
<i>Zataria multiflora</i>	Extract from aerial parts	pH 9 and incubation for 48 h at 28 °C	Spherical	25.5	<i>Staphylococcus aureus</i>	Agar well diffusion, broth microdilution	[156]

**Table 3** Green-synthesized AgNPs in wound healing and repair

Plant extract	Origin	The solvent used for extractions	Type of experiment	Observed activity	References
<i>Arnebia nobilis</i>	Roots	Aqueous	In vivo (excision wounds)	Wound contraction	[170]
<i>Catharanthus roseus</i> and <i>Azadirachta indica</i>	Leaves	Aqueous	In vivo (excision wounds)	Wound contraction	[171, 172]
<i>Coleus forskohlii</i> and <i>Arnebia nobilis</i>	Roots	Aqueous	In vivo (excision wounds)	Re-epithelialization	[173]
<i>Coriolus versicolor</i> and <i>Boletus edulis</i>	Whole plant	Aqueous	In vitro (scratch assay)	Enhances cell migration	[174]
<i>Cotyledon orbiculata</i>	Leaves	Aqueous	In vitro (scratch assay)	Cell migration and proliferation of fibroblasts, keratinocytes, and epithelial cells	[15]
<i>Gnaphalium polycaulon</i>	Leaves	Methanol	In vivo (excision wounds)	Wound contraction	[149]
<i>Ocimum sanctum</i>	Leaves	Aqueous	In vitro (scratch assay)	Fibroblast cell migration	[175]
<i>Persicaria odorata</i>	Leaves	Aqueous	In vitro (scratch assay)	Cell migration	[176]
<i>Punica granatum</i>	Peel	Ethanol	In vivo (diabetic induction)	Re-epithelization	[177]
<i>Salsola vermiculata</i>	Leaves	Aqueous	In vivo (excision wounds)	Inflammatory cell infiltrations, Collagen fiber formation, Re-epithelization	
<i>Tectona grandis</i>	Wood flour	Aqueous	In vivo (excision wounds)	Granulation tissue formation, collagen deposition, and re-epithelization	[178]
<i>Tragia involucrate</i>	Roots	Methanol	In vivo (excision wounds)	Collagen synthesis	[179]

### 9.1.5 Antioxidant Properties of AgNPs and Its Application in Wound Healing

Oxygen-dependent redox-sensitive signaling mechanisms are essential for effective wound healing [197]. Therefore, ROS levels must be appropriately balanced to preserve the redox state. However, when this balance is distorted and the levels of ROS increase significantly, the result is oxidative stress, which disrupts the normal wound healing cascade resulting in a chronic wound. Therefore, treating wounds with antioxidant agents may be effective in reversing chronicity [197–199]. Various studies have attributed the wound healing effects of medicinal plant extracts to their ability to scavenge free radicals [200, 201]. Other studies suggested that green synthesized AgNPs have enhanced the scavenging activity compared to the plant extracts used to synthesize the AgNPs. For instance, Guntur et al. [202] used various assays to confirm that the antioxidant activity of the biosynthesized AgNPs was significantly higher than the extract of the plant, *Desmostachya bipinnata* from which the NPs were synthesized. A similar study involving biosynthesized AgNPs using *Melia azedarach* also supported that the NPs have higher scavenging activity compared to the plant extract [203]. In addition, the combination of enzymatic and non-enzymatic scavenging methods by Keshari et al. [198] showed that AgNPs synthesized from *Cestrum nocturnum* have more

antioxidant activity compared to vitamin C [198]. Khanh et al. [204] used gelatin to stabilize AgNPs and encapsulate curcumin to form a therapeutic composite and found that the formulations can be used as an antioxidant agent to enhance wound healing.

## 10 Ag-based Wound Healing Products in Clinical Trials

Ag-based products have been utilized in several clinical trials to treat wounds, particularly burns and other kinds of wounds, including DF ulcers. Some of these products are now available as commercially marketed wound dressing products [27, 205]. Acticoat is a wound dressing material containing AgNPs with an average size of 15 nm [205]. The validated properties of acticoats as observed in most human trials include wound healing, reduced infection at the wound site, and reduction in pain. Acticoat, when combined with silver sulfadiazine and chlorhexidine digluconate cream, can also be effective in preventing infections in burns [27]. Other case reports on the use of Acticoat in wound healing have been extensively reviewed elsewhere [205].

The U.S. Food and Drug Administration has approved Ag-based biocomposite products from different companies for wound healing applications. These products are available under different brand names such as, Aquacel™

(ConvaTec), Bactigras™ (Smith and Nephew Limited), Tegaderm™ (3 M), and PolyMem Silver™ (Aspen), among others. Preclinical studies have also shown that the incorporation of AgNPs into naturally derived biomaterials like modified cotton fabrics, bacterial cellulose, chitosan, and sodium alginate can significantly improve wound healing management and treatment [5, 206]. Selected wound-related studies that have established a completed clinical trial on the use of Ag-based products according to ClinicalTrials.gov since 2008 are presented in Table 4.

## 11 Conclusion and Future Perspectives

The various challenges associated with the treatment of chronic wounds have resulted in a pressing need to source alternative therapeutic agents for wound healing. Nanoscience is a growing and significant field with a variety of biomedical applications that offer cutting-edge care for various types of wounds. The current review has discussed the potential of plant extract-synthesized AgNPs in the development of novel wound healing agents with multifunctional properties, such as antimicrobial, anti-inflammatory, antioxidant, and accelerated wound closure.

In comparison to conventional topical treatments, plant extract-synthesized AgNPs are soluble, cost-effective, and less toxic to humans. In addition, they can efficiently offer broad-spectrum antimicrobial activities against polymicrobial infections, biofilms, and antibiotic-resistant pathogens, thus reducing pathological inflammation and stimulating tissue repair. Nanomaterials also provide efficient penetration and distribution of bioactive compounds at wound sites. Consequently, the integration of AgNPs into wound dressings can provide a sustained and controlled release of therapeutic agents into wound sites. Despite these benefits, their AgNPs are not without risks. Adverse outcomes such as cytotoxicity to healthy cells, oxidative stress, delayed wound healing, and the potential development of antimicrobial resistance underscore the need for cautious and well-regulated use. Furthermore, the systemic absorption and possible environmental impact of AgNPs necessitate thorough investigations. Therefore, there is a need for further investigations on the exact mechanisms of action, optimization of synthesis protocols, toxicological studies, and robust clinical or regulatory pathways. By addressing these areas, plant extract-based AgNPs can serve as a cornerstone of advanced wound care, providing effective, safe, and sustainable treatments for a wide range of patients.

**Table 4** AgNPs-based products in clinical trials for antimicrobial and wound healing agents

Clinical trial ID	Aim of the study	Duration	Participants	Location
NCT01950546	To evaluate the effectiveness of nanosilver fluoride for controlling the growth of <i>S. mutans</i> present in dental plaque of children	September–December 2014	30	Brazil
NCT04834245	To evaluate the effects of Hydrogel/Nano Ag-based Dressing and traditional dressing on DF wound	January–December 2019	30	Cairo, Egypt
NCT04431440	To investigate the bactericidal effects of AgNPs on Methicillin and Vancomycin-Resistant <i>Staphylococcus aureus</i> from critically ill patients	June–October 2020	150	Assiut, Egypt,
NCT03752424	To evaluate the antimicrobial activity of topical AgNPs	November 2019–January 2021	30	Buraydah, Saudi Arabia
NCT05231330	To evaluate the effects of AgNPs in comparison to silver diamine fluoride in the management of deep carious lesions	March 2020–March 2021	36	Suez, Egypt
NCT00659204	To compare the antimicrobial efficacy of AgNPs gel to a commercialized alcohol-based hand gel	April–August 2008	40	Washington, United States
NCT02761525	To determine whether oral topic AgNPs are effective in reducing potential pathogen microbial loads in mechanical ventilation patients	October 2014–July 2015	50	Not provided
NCT05221749	To assess the antibacterial effects of nano-silver fluoride (NSF) with caries activity in dentin caries lesions of primary teeth in comparison to nano-silver diamine fluoride	March–June 2022	50	Alexandria, Egypt
NCT04775238	To investigate the antibacterial, antibiofilm, and synergistic effect of AgNPs in combination with antibiotics on nosocomial bacteria	February–July 2021	100	Sohag, Egypt

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## Declarations

**Ethics Approval** Not applicable.

**Competing Interests** The authors declare no competing interests.

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## References

- Guo, S., & DiPietro, L. A. (2010). Factors affecting wound healing. *Journal of dental research*, 89(3), 219–229.
- Maheswary, T., Nurul, A. A., & Fauzi, M. B. (2021). The insights of microbes' roles in wound healing: A comprehensive review. *Pharmaceutics*, 13(7), 981.
- Odimegwu, D. C., Ibezim, E. C., Esimone, C. O., Nworu, C. S., & Okoye, F. B. C. (2008). Wound healing and antibacterial activities of the extract of *Dissotis theifolia* (Melastomataceae) stem formulated in a simple ointment base. *Journal of Medicinal Plants Research*, 2(1), 11–16.
- Lindholm, C., & Searle, R. (2016). Wound management for the 21st century: combining effectiveness and efficiency. *International Wound Journal*, 13, 5–15.
- Paladini, F., & Pollini, M. (2019). Antimicrobial silver nanoparticles for wound healing application: Progress and future trends. *Materials*, 12(16), 2540.
- Aboyewa, J. A., Sibuyi, N. R., Meyer, M., & Oguntibeju, O. O. (2021). Green synthesis of metallic nanoparticles using some selected medicinal plants from southern africa and their biological applications. *Plants*, 10(9), 1929.
- Ovais, M., Ahmad, I., Khalil, A. T., Mukherjee, S., Javed, R., Ayaz, M., et al. (2018). Wound healing applications of biogenic colloidal silver and gold nanoparticles: Recent trends and future prospects. *Applied Microbiology and Biotechnology*, 102(10), 4305–4318.
- Negahdari, S., Galehdari, H., Kesmati, M., Rezaie, A., & Shariati, G. (2017). Wound healing activity of extracts and formulations of aloe vera, henna, adiantum capillus-veneris, and myrrh on mouse dermal fibroblast cells. *International Journal of Preventive Medicine*, 8(1), 18.
- Hajialyani, M., Tewari, D., Sobarzo-Sánchez, E., Nabavi, S. M., Farzaei, M. H., & Abdollahi, M. (2018). Natural product-based nanomedicines for wound healing purposes: Therapeutic targets and drug delivery systems. *International Journal of Nanomedicine*, 13, 5023.
- Nath, D., & Banerjee, P. (2013). Green nanotechnology—A new hope for medical biology. *Environmental Toxicology and Pharmacology*, 36(3), 997–1014.
- Mat Yusuf, S. N. A., Che Mood, C. N. A., Ahmad, N. H., Sandai, D., Lee, C. K., & Lim, V. (2020). Optimization of biogenic synthesis of silver nanoparticles from flavonoid-rich *Clinacanthus nutans* leaf and stem aqueous extracts. *Royal Society Open Science*, 7(7), 200065.
- Chawla, V., & Sathaye, S. (2017). Biosynthesis of silver nanoparticles using methanolic extracts of *Acorus calamus*, and assessment of its antioxidant and antimicrobial activity. *Journal of Medicinal Plants Studies*, 5(3), 358–363.
- Dhand, C., Dwivedi, N., Loh, X. J., Ying, A. N. J., Verma, N. K., Beuerman, R. W., et al. (2015). Methods and strategies for the synthesis of diverse nanoparticles and their applications: A comprehensive overview. *Rsc Advances*, 5(127), 105003–105037.
- Huq, M. A., Ashrafudoulla, M., Rahman, M. M., Balusamy, S. R., & Akter, S. (2022). Green synthesis and potential antibacterial applications of bioactive silver nanoparticles: A review. *Polymers*, 14(4), 742.
- Tyavambiza, C., Elbagory, A. M., Madiehe, A. M., Meyer, M., & Meyer, S. (2021). The antimicrobial and anti-inflammatory effects of silver nanoparticles synthesised from *Cotyledon orbiculata* aqueous extract. *Nanomaterials*, 11(5), 1343.
- Vallepu, N., Gaddam, S. A., Kotakadi, V. S., Goli, P. P., SG, D. V. R., & Gudivada, S. (2021). Biogenic silver nanoparticles can be an effective and efficient water purification agents of future. *Inorganic and Nano-Metal Chemistry*, 51(9), 1195–206.
- Adeleye O, Badru A, Oyinloye O, Fagbohun A, Bakre L, Bamiro O, et al. Green synthesized silver nanoparticles for cream formulation: Its anti-inflammatory and healing activities. IOP Conference Series: Materials Science and Engineering: IOP Publishing; 2020. 012016.
- Appapalam, S. T., & Panchamoorthy, R. (2017). Aerva lanata mediated phytofabrication of silver nanoparticles and evaluation of their antibacterial activity against wound associated bacteria. *Journal of the Taiwan Institute of Chemical Engineers*, 78, 539–51.
- Kalantari, K., Mostafavi, E., Afifi, A. M., Izadiyan, Z., Jahangirian, H., Rafiee-Moghaddam, R., et al. (2020). Wound dressings functionalized with silver nanoparticles: Promises and pitfalls. *Nanoscale*, 12(4), 2268–2291.
- Negut, I., Grumezescu, V., & Grumezescu, A. M. (2018). Treatment strategies for infected wounds. *Molecules*, 23(9), 2392.
- Okur, M. E., Karantas, I. D., Şenyiğit, Z., Okur, N. Ü., & Siafaka, P. I. (2020). Recent trends on wound management: New therapeutic choices based on polymeric carriers. *Asian Journal of Pharmaceutical Sciences*, 15(6), 661–684.
- Agyare, C., Boakye, Y. D., Bekoe, E. O., Hensel, A., Dapaah, S. O., & Appiah, T. (2016). African medicinal plants with wound healing properties. *Journal of ethnopharmacology*, 177, 85–100.
- Nqakala, Z. B., Sibuyi, N. R., Fadaka, A. O., Meyer, M., Onani, M. O., & Madiehe, A. M. (2021). Advances in nanotechnology towards development of silver nanoparticle-based wound-healing agents. *International Journal of Molecular Sciences*, 22(20), 11272.

24. Firdous, S. M., & Sautya, D. (2018). Medicinal plants with wound healing potential. *Bangladesh Journal of Pharmacology*, *13*(1), 41–52.
25. Järbrink, K., Ni, G., Sönnergren, H., Schmidtchen, A., Pang, C., Bajpai, R., et al. (2016). Prevalence and incidence of chronic wounds and related complications: A protocol for a systematic review. *Systematic Reviews*, *5*(1), 1–6.
26. Wallace, H. A., Basehore, B. M., & Zito, P. M. (2023). *Wound healing phases*. StatPearls Publishing.
27. Mihai, M. M., Dima, M. B., Dima, B., & Holban, A. M. (2019). Nanomaterials for wound healing and infection control. *Materials*, *12*(13), 2176.
28. El-Ashram, S., El-Samad, L. M., Basha, A. A., & El Wakil, A. (2021). Naturally-derived targeted therapy for wound healing: Beyond classical strategies. *Pharmacological Research*, *170*, 105749.
29. Singh, S., Young, A., & McNaught, C.-E. (2017). The physiology of wound healing. *Surgery (Oxford)*, *35*(9), 473–477.
30. Rahim, K., Saleha, S., Zhu, X., Huo, L., Basit, A., & Franco, O. L. (2017). Bacterial contribution in chronicity of wounds. *Microbial Ecology*, *73*(3), 710–721.
31. Raziyeva, K., Kim, Y., Zharkinbekov, Z., Kassymbek, K., Jimi, S., & Saparov, A. (2021). Immunology of acute and chronic wound healing. *Biomolecules*, *11*(5), 700.
32. Barroso, A., Mestre, H., Ascenso, A., Simões, S., & Reis, C. (2020). Nanomaterials in wound healing: From material sciences to wound healing applications. *Nano Select*, *1*(5), 443–460.
33. Criollo-Mendoza, M. S., Contreras-Angulo, L. A., Leyva-López, N., Gutiérrez-Grijalva, E. P., Jiménez-Ortega, L. A., & Heredia, J. B. (2023). Wound healing properties of natural products: Mechanisms of action. *Molecules*, *28*(2), 598.
34. Diller, R. B., & Tabor, A. J. (2022). The role of the extracellular matrix (ECM) in wound healing: A review. *Biomimetics*, *7*(3), 87.
35. Rodrigues, M., Kosaric, N., Bonham, C. A., & Gurtner, G. C. (2019). Wound healing: A cellular perspective. *Physiological Reviews*, *99*(1), 665–706.
36. Schultz, G. S., Chin, G. A., Moldawer, L., & Diegelmann, R. F. (2011). Principles of wound healing. In Fitridge, R., & Thompson, M. (Eds.), *Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists* (p. 423). University of Adelaide Press.
37. Aitcheson, S. M., Frentiu, F. D., Hurn, S. E., Edwards, K., & Murray, R. Z. (2021). Skin wound healing: Normal macrophage function and macrophage dysfunction in diabetic wounds. *Molecules*, *26*(16), 4917.
38. Schultz, G. S., Chin, G. A., Moldawer, L., & Diegelmann, R. F. (2011). Principles of wound healing. In R. Fitridge, & M. Thompson (Eds.), *Mechanisms of vascular disease: A reference book for vascular specialists* [Internet] (p. 23). University of Adelaide Press.
39. Velnar, T., Bailey, T., & Smrkolj, V. (2009). The wound healing process: An overview of the cellular and molecular mechanisms. *Journal of International Medical Research*, *37*(5), 1528–1542.
40. Landén, N. X., Li, D., & Ståhle, M. (2016). Transition from inflammation to proliferation: a critical step during wound healing. *Cellular and Molecular Life Sciences*, *73*, 3861–85.
41. Wilkinson, H. N., & Hardman, M. J. (2020). Wound healing: Cellular mechanisms and pathological outcomes. *Open biology*, *10*(9), 200223.
42. Hong, H., & Tian, X. Y. (2020). The role of macrophages in vascular repair and regeneration after ischemic injury. *International Journal of Molecular Sciences*, *21*(17), 6328.
43. Bowler, P., Duerden, B., & Armstrong, D. G. (2001). Wound microbiology and associated approaches to wound management. *Clinical Microbiology Reviews*, *14*(2), 244–269.
44. Swanson, T., Angel, D., Sussman, G., Cooper, R., Haesler, E., Ousey, K., ... & Call, E. (2016). *Wound infection in clinical practice: principles of best practice*. University of Huddersfield.
45. Kadam, S., Nadkarni, S., Lele, J., Sakhalkar, S., Mokashi, P., & Kaushik, K. S. (2019). Bioengineered platforms for chronic wound infection studies: How can we make them more human-relevant? *Frontiers in Bioengineering and Biotechnology*, *7*, 418.
46. Bessa, L. J., Fazii, P., Di Giulio, M., & Cellini, L. (2015). Bacterial isolates from infected wounds and their antibiotic susceptibility pattern: Some remarks about wound infection. *International Wound Journal*, *12*(1), 47–52.
47. Schultz, G. S., Sibbald, R. G., Falanga, V., Ayello, E. A., Dowsett, C., Harding, K., et al. (2003). Wound bed preparation: a systematic approach to wound management. *Wound repair and regeneration*, *11*, S1–S28.
48. Puca, V., Marulli, R. Z., Grande, R., Vitale, I., Niro, A., Molinaro, G., et al. (2021). Microbial species isolated from infected wounds and antimicrobial resistance analysis: Data emerging from a three-years retrospective study. *Antibiotics*, *10*(10), 1162.
49. Guan, H., Dong, W., Lu, Y., Jiang, M., Zhang, D., Aobuliaximu, Y., et al. (2021). Distribution and antibiotic resistance patterns of pathogenic bacteria in patients with chronic cutaneous wounds in China. *Frontiers in Medicine*, *8*, 609584.
50. Rahim, K., Saleha, S., Zhu, X., Huo, L., Basit, A., & Franco, O. L. (2017). Bacterial contribution in chronicity of wounds. *Microbial Ecology*, *73*, 710–21.
51. Tom, I. M., Ibrahim, M. M., Umoru, A. M., Umar, J. B., Bukar, M. A., Haruna, A. B., et al. (2019). Infection of wounds by potential bacterial pathogens and their resistogram. *Open Access Library Journal*, *6*(7), 1–13.
52. Patel, J., Kumar, G. S., Roy, H., Maddiboyina, B., Leporatti, S., & Bohara, R. A. (2024). From nature to nanomedicine: Bioengineered metallic nanoparticles bridge the gap for medical applications. *Discover Nano*, *19*(1), 1–24.
53. Xu, Z., & Hsia, H. C. (2018). The impact of microbial communities on wound healing: A review. *Annals of Plastic Surgery*, *81*(1), 113–123.
54. Tzaneva, V., Mladenova, I., Todorova, G., & Petkov, D. (2016). Antibiotic treatment and resistance in chronic wounds of vascular origin. *Clujul Medical*, *89*(3), 365.
55. Järbrink, K., Ni, G., Sönnergren, H., Schmidtchen, A., Pang, C., Bajpai, R., et al. (2016). Prevalence and incidence of chronic wounds and related complications: A protocol for a systematic review. *Systematic Reviews*, *5*(2016), 1–6.
56. Sen, C. K. (2021). Human wound and its burden: updated 2020 compendium of estimates. *Advances in Wound Care*, *10*(5), 281–92.
57. Guimarães, I., Baptista-Silva, S., Pintado, M. L., & Oliveira, A. (2021). Polyphenols: A promising avenue in therapeutic solutions for wound care. *Applied Sciences*, *11*(3), 1230.
58. Nussbaum, S. R., Carter, M. J., Fife, C. E., DaVanzo, J., Haught, R., Nusgart, M., et al. (2018). An economic evaluation of the impact, cost, and medicare policy implications of chronic non-healing wounds. *Value in Health*, *21*(1), 27–32.
59. Carter, M. J., DaVanzo, J., Haught, R., Nusgart, M., Cartwright, D., & Fife, C. E. (2023). Chronic wound prevalence and the associated cost of treatment in Medicare beneficiaries: Changes between 2014 and 2019. *Journal of Medical Economics*, *26*(1), 894–901.
60. Gupta, S., Sagar, S., Maheshwari, G., Kisaka, T., & Tripathi, S. (2021). Chronic wounds: Magnitude, socioeconomic burden and consequences. *Wounds Asia*, *4*, 8–14.

61. Lo, Z. J., Lim, X., Eng, D., Car, J., Hong, Q., Yong, E., et al. (2020). Clinical and economic burden of wound care in the tropics: A 5-year institutional population health review. *International Wound Journal*, *17*(3), 790–803.
62. Yao, Z., Niu, J., & Cheng, B. (2020). Prevalence of chronic skin wounds and their risk factors in an inpatient hospital setting in northern China. *Advances in Skin & Wound Care*, *33*(9), 1–10.
63. Khalim, W., Mwesigye, J., Tungotoy, M., & Twinomujuni, S. S. (2021). Resistance pattern of infected chronic wound isolates and factors associated with bacterial resistance to third generation cephalosporins at Mbarara Regional Referral Hospital. *Uganda. Plos one*, *16*(12), e0261264.
64. Iyun, A. O., Ademola, S. A., Olawoye, O. A., Michael, A. I., & Oluwatosin, O. M. (2016). Point prevalence of chronic wounds at a tertiary hospital in nigeria. *Wounds: A Compendium of Clinical Research and Practice*, *28*(2), 57–62.
65. Abeje, B. A., Bekele, T., Getahun, K. A., & Asrie, A. B. (2022). Evaluation of wound healing activity of 80% hydromethanolic crude extract and solvent fractions of the leaves of *urtica simensis* in mice. *Journal of Experimental Pharmacology*, *14*, 221–241.
66. Builders PF, Builders MI (2016) Wound care: traditional African medicine approach. Worldwide wound healing—Innovation in natural and conventional methods Intech 1–28.
67. Graves, N., & Zheng, H. (2014). Modelling the direct health care costs of chronic wounds in Australia. *Wound Practice & Research: Journal of the Australian Wound Management Association*, *22*(1), 20–24.
68. Sen, C. K. (2019). Human wounds and its burden: An updated compendium of estimates. *Advances in Wound Care*, *8*(2), 39–48.
69. Jupiter, D. C., Thorud, J. C., Buckley, C. J., & Shibuya, N. (2016). The impact of foot ulceration and amputation on mortality in diabetic patients. I: From ulceration to death, a systematic review. *International Wound Journal*, *13*(5), 892–903.
70. Rubio, J. A., Jiménez, S., & Lázaro-Martínez, J. L. (2020). Mortality in patients with diabetic foot ulcers: Causes, risk factors, and their association with evolution and severity of ulcer. *Journal of Clinical Medicine*, *9*(9), 3009.
71. Mohamed, A. K. S., Mehta, A. A., & James, P. (2017). Predictors of mortality of severe sepsis among adult patients in the medical Intensive Care Unit. *Lung India: Official Organ of Indian Chest Society*, *34*(4), 330.
72. Waltz, P. K., & Zuckerbraun, B. S. (2017). Surgical site infections and associated operative characteristics. *Surgical Infections*, *18*(4), 447–450.
73. Graves, N., Phillips, C. J., & Harding, K. (2022). A narrative review of the epidemiology and economics of chronic wounds. *British Journal of Dermatology*, *187*(2), 141–148.
74. Bowers, S., & Franco, E. (2020). Chronic wounds: Evaluation and management. *American Family Physician*, *101*(3), 159–166.
75. Phillips, C. J., Humphreys, I., Fletcher, J., Harding, K., Chamberlain, G., & Macey, S. (2016). Estimating the costs associated with the management of patients with chronic wounds using linked routine data. *International Wound Journal*, *13*(6), 1193–1197.
76. Paschou, S. A., Stamou, M., Vuagnat, H., Tentolouris, N., & Jude, E. (2018). Pain management of chronic wounds: Diabetic ulcers and beyond. *Maturitas*, *117*, 17–21.
77. Ovais, M., Ahmad, I., Khalil, A. T., Mukherjee, S., Javed, R., Ayaz, M., et al. (2018). Wound healing applications of biogenic colloidal silver and gold nanoparticles: recent trends and future prospects. *Applied Microbiology And Biotechnology*, *102*, 4305–18.
78. Chen, M. R., & Dragoo, J. L. (2013). The effect of nonsteroidal anti-inflammatory drugs on tissue healing. *Knee Surgery, Sports Traumatology, Arthroscopy*, *21*, 540–9.
79. Khansa, I., Schoenbrunner, A. R., Kraft, C. T., & Janis, J. E. (2019). Silver in wound care—friend or foe?: A comprehensive review. *Plastic and Reconstructive Surgery-Global Open*, *7*(8), e2390.
80. Rybka, M., Mazurek, Ł., & Konop, M. (2022). Beneficial effect of wound dressings containing silver and silver nanoparticles in wound healing—from experimental studies to clinical practice. *Life*, *13*(1), 69.
81. Medici, S., Peana, M., Nurchi, V. M., & Zoroddu, M. A. (2019). Medical uses of silver: History, myths, and scientific evidence. *Journal of Medicinal Chemistry*, *62*(13), 5923–5943.
82. Munteanu, A., Florescu, I., & Nitescu, C. (2016). A modern method of treatment: The role of silver dressings in promoting healing and preventing pathological scarring in patients with burn wounds. *Journal of Medicine And Life*, *9*(3), 306.
83. Laurano, R., Boffito, M., Ciardelli, G., & Chiono, V. (2022). Wound dressing products: A translational investigation from the bench to the market. *Engineered Regeneration*, *3*(2), 182–200.
84. Monika, P., Chandraprabha, M. N., Rangarajan, A., Waiker, P. V., & Chidambaramurthy, K. N. (2022). Challenges in healing wound: role of complementary and alternative medicine. *Frontiers in Nutrition*, *8*, 791899.
85. Nethi, S. K., Das, S., Patra, C. R., & Mukherjee, S. (2019). Recent advances in inorganic nanomaterials for wound-healing applications. *Biomaterials Science*, *7*(7), 2652–2674.
86. Upadhyay, A., Amanullah, A., Joshi, V., Dhiman, R., Prajapati, V. K., Poluri, K. M., et al. (2021). Ibuprofen-based advanced therapeutics: Breaking the inflammatory link in cancer, neurodegeneration, and diseases. *Drug Metabolism Reviews*, *53*(1), 100–121.
87. Safain, K. S., Islam, M. S., Amatullah, J., Al Mahmud-Un-Nabi, M., Bhuyan, G. S., Rahman, J., et al. (2023). Prevalence of silver resistance determinants and extended-spectrum  $\beta$ -lactamases in bacterial species causing wound infection: First report from Bangladesh. *New Microbes and New Infections*, *52*, 101104.
88. Nešporová, K., Pavlík, V., Šafránková, B., Vágnerová, H., Odráška, P., Židek, O., et al. (2020). Effects of wound dressings containing silver on skin and immune cells. *Scientific reports*, *10*(1), 15216.
89. Balekar, N., Katkam, N. G., Nakpheng, T., Jehtae, K., & Srichana, T. (2012). Evaluation of the wound healing potential of *Wedelia trilobata* (L.) leaves. *Journal of Ethnopharmacology*, *141*(3), 817–24.
90. Fokunang, C. N., Ndikum, V., Tabi, O. Y., Jiofack, R. B., Ngameni, B., Guedje, N. M., & Lohoue, J. (2011). Traditional medicine: past, present and future research and development prospects and integration in the National HealthSystem of Cameroon. *African Journal of Traditional, Complementary and Alternative Medicines*, *8*(3), 284–295.
91. Tyavambiza, C., Dube, P., Goboza, M., Meyer, S., Madiehe, A. M., & Meyer, M. (2021). Wound healing activities and potential of selected african medicinal plants and their synthesized biogenic nanoparticles. *Plants*, *10*(12), 2635.
92. Builders, P. F., & Builders, M. I. (2016). Wound care: traditional African medicine approach. *Worldwide Wound Healing*, *3*, 1–24.
93. Farahpour, M. R. (2019). Medicinal plants in wound healing. *Wound Healing Current Perspectives*, *2019*, 33–47.
94. Yazarlu, O., Iranshahi, M., Kashani, H. R. K., Reshadat, S., Habtemariam, S., Iranshahi, M., et al. (2021). Perspective on the application of medicinal plants and natural products in wound healing: A mechanistic review. *Pharmacological Research*, *174*, 105841.
95. Shedoeva, A., Leavesley, D., Upton, Z., & Fan, C. (2019). Wound healing and the use of medicinal plants. *Evidence-Based Complementary and Alternative Medicine*, *2019*(1), 2684108.

96. Gorain, B., Pandey, M., Leng, N. H., Yan, C. W., Nie, K. W., Kaur, S. J., ... & Choudhury, H. (2022). Advanced drug delivery systems containing herbal components for wound healing. *International Journal of Pharmaceutics*, 617, 121617.
97. Dewi, M. K., Chaerunisaa, A. Y., Muhaimin, M., & Joni, I. M. (2022). Improved activity of herbal medicines through nanotechnology. *Nanomaterials*, 12(22), 4073.
98. Saravanan, M., Barabadi, H., & Vahidi, H. (2021). Green nanotechnology: Isolation of bioactive molecules and modified approach of biosynthesis. Biogenic nanoparticles for cancer theranostics. *Elsevier*, 2021, 101–122.
99. Fouché, M., Willers, C., Hamman, S., Malherbe, C., & Steenekamp, J. (2020). Wound healing effects of Aloe muthuth: In vitro investigations using immortalized human keratinocytes (HaCaT). *Biology*, 9(11), 350.
100. Teplicki, E., Ma, Q., Castillo, D. E., Zarei, M., Hustad, A. P., Chen, J., et al. (2018). The effects of aloe vera on wound healing in cell proliferation, migration, and viability. *Wounds: a Compendium of Clinical Research and Practice*, 30(9), 263–8.
101. Bolla, S. R., Al-Subaie, A. M., Al-Jindan, R. Y., Balakrishna, J. P., Ravi, P. K., Veeraraghavan, V. P., et al. (2019). In vitro wound healing potency of methanolic leaf extract of *Aristolochia saccata* is possibly mediated by its stimulatory effect on collagen-1 expression. *Heliyon*, 5(5), e01648.
102. Mohammed, H. A., Qureshi, K. A., Ali, H. M., Al-Omar, M. S., Khan, O., & Mohammed, S. A. (2022). Bio-evaluation of the wound healing activity of *Artemisia judaica* L. as part of the plant's use in traditional medicine; Phytochemical, antioxidant, anti-inflammatory, and antibiofilm properties of the plant's essential oils. *Antioxidants*, 11(2), 332.
103. Juneja, K., Mishra, R., Chauhan, S., Gupta, S., Roy, P., & Sircar, D. (2020). Metabolite profiling and wound-healing activity of *Boerhavia diffusa* leaf extracts using in vitro and in vivo models. *Journal of Traditional and Complementary Medicine*, 10(1), 52–59.
104. Thakre, R., Bhake, A., Tekade, P., Harne, K., & Borkar, P. S. (2021). Evaluation of *Ehretia laevis* Roxb.(Khandu Chakka/ Ajan Vruksha) in the wound healing adjudged by histological examination of the tissue. *Indian Journal of Forensic Medicine & Toxicology*, 15(2), 713–21.
105. Alsarayreh, A. Z. A., Attalah Oran, S., & Shakhanbeh, J. M. (2022). In vitro and in vivo wound healing activities of *Globularia arabica* leaf methanolic extract in diabetic rats. *Journal of Cosmetic Dermatology*, 21(10), 4888–900.
106. Baali, F., Boumerfeg, S., Boudjelal, A., Denaro, M., Ginestra, G., Baghiani, A., et al. (2022). Wound-healing activity of Algerian *Lavandula stoechas* and *Mentha pulegium* extracts: From traditional use to scientific validation. *Plant Biosystems-An International Journal Dealing with all Aspects of Plant Biology*, 156(2), 427–439.
107. Boakye, Y. D., Agyare, C., Ayande, G. P., Titiloye, N., Asiamah, E. A., & Danquah, K. O. (2018). Assessment of wound-healing properties of medicinal plants: The case of *Phyllanthus muellerianus*. *Frontiers in Pharmacology*, 9, 945.
108. Boudjelal, A., Napoli, E., Benkhaled, A., Benazi, L., Bey, R., Gentile, D., et al. (2022). In vivo wound healing effect of Italian and Algerian *Pistacia vera* L. resins. *Fitoterapia*, 159, 105197.
109. Dev, S. K., Choudhury, P., Srivastava, R., & Sharma, M. (2019). Antimicrobial, anti-inflammatory and wound healing activity of polyherbal formulation. *Biomedicine & Pharmacotherapy*, 111, 555–67.
110. Neto, J. A. R., Tarôco, B. R. P., Dos Santos, H. B., Thomé, R. G., Wolfram, E., & de A Ribeiro, R. I. M. (2020). Using the plants of Brazilian Cerrado for wound healing: From traditional use to scientific approach. *Journal of Ethnopharmacology*, 260, 112547.
111. Ghashghaii, A., Hashemnia, M., Nikousefat, Z., Zangeneh, M. M., & Zangeneh, A. (2017). Wound healing potential of methanolic extract of *Scrophularia striata* in rats. *Pharmaceutical Sciences*, 23(4), 256–263.
112. Meguellati, H., Ouafi, S., Saad, S., & Djemouai, N. (2019). Evaluation of acute, subacute oral toxicity and wound healing activity of mother plant and callus of *Teucrium polium* L. subsp. *geyrii* Maire from Algeria. *South African Journal of Botany*, 127, 25–34.
113. Lambebo, M. K., Kifle, Z. D., Gurji, T. B., & Yesuf, J. S. (2021). Evaluation of wound healing activity of methanolic crude extract and solvent fractions of the leaves of *Vernonia auriculifera* Hiern (Asteraceae) in mice. *Journal of Experimental Pharmacology*, 13, 677–692.
114. Badrunnisa, S., & Menghani, S. S. (2023). Review on health sciences applications of nanotechnology. *Journal of Coastal Life Medicine*, 11, 94–100.
115. Hamdan, S., Pastar, I., Drakulich, S., Dikici, E., Tomic-Canic, M., Deo, S., et al. (2017). Nanotechnology-driven therapeutic interventions in wound healing: Potential uses and applications. *ACS Central Science*, 3(3), 163–175.
116. Naskar, A., & Kim, K.-s. (2020). Recent advances in nanomaterial-based wound-healing therapeutics. *Pharmaceutics*, 12(6), 499.
117. Bag, J., Mukherjee, S., Tripathy, M., Mohanty, R., Shendha, P. K., Hota, G., et al. (2023). Platinum as a novel nanoparticle for wound healing model in *Drosophila melanogaster*. *Journal of Cluster Science*, 34(2), 1087–1098.
118. Zhang, C., Liu, J., Ahmeda, A., Liu, Y., Feng, J., Guan, H., et al. (2022). Biosynthesis of zinc nanoparticles using *Allium saralicum* RM Fritsch leaf extract; Chemical characterization and analysis of their cytotoxicity, antioxidant, antibacterial, antifungal, and cutaneous wound healing properties. *Applied Organometallic Chemistry*, 36(12), e5564.
119. Anjum, S., Abbasi, B. H., & Shinwari, Z. K. (2016). Plant-mediated green synthesis of silver nanoparticles for biomedical applications: Challenges and opportunities. *Pakistan Journal of Botany*, 48(4), 1731–1760.
120. Jain, N., Jain, P., Rajput, D., & Patil, U. K. (2021). Green synthesized plant-based silver nanoparticles: Therapeutic prospective for anticancer and antiviral activity. *Micro and Nano Systems Letters*, 9(1), 1–24.
121. Willian, N., Syukri, S., Zulhadjri, Z., & Arief, S. (2021). Marine plant mediated green synthesis of silver nanoparticles using mangrove *Rhizophora stylosa*: Effect of variable process and their antibacterial activity. *F1000Research*, 10, 768.
122. Masum, M. M. I., Siddiq, M. M., Ali, K. A., Zhang, Y., Abdallah, Y., Ibrahim, E., et al. (2019). Biogenic synthesis of silver nanoparticles using *Phyllanthus emblica* fruit extract and its inhibitory action against the pathogen *Acidovorax oryzae* strain RS-2 of rice bacterial brown stripe. *Frontiers in Microbiology*, 10, 820.
123. Yasmin, K., Qasim, N. M., Muhammad, N., & Ikram, U. (2018). Biomimetic synthesis of silver nanoparticles for breast cancer therapeutics and its mechanism. *Int J Nanotechnol Nanomedicine*, 3, 1–9.
124. Patra, J. K., & Baek, K. H. (2014). Green nanobiotechnology: factors affecting synthesis and characterization techniques. *Journal of Nanomaterials*, 2014(1), 417305.
125. Barabadi H, Ashouri F, Soltani M, Vaziri NA, Rabbani D, Saravanan M, et al. (2023) Bioengineered silver nanoparticles for antimicrobial therapeutics. *Bioengineered Nanomaterials for Wound Healing and Infection Control*. Elsevier; 2023. 443-73
126. Alsaiani, N. S., Alzahrani, F. M., Amari, A., Osman, H., Harharah, H. N., Elboughdiri, N., et al. (2023). Plant and Microbial Approaches as Green Methods for the Synthesis of

- Nanomaterials: Synthesis, Applications, and Future Perspectives. *Molecules*, 28(1), 463.
127. Patra JK, Baek K-H (2015) Green nanobiotechnology: Factors affecting synthesis and characterization techniques. *Journal of Nanomaterials* 2014:219–.
  128. Iqbal J, Ahmad J, Rehman MMU, Barabadi H, Ovais M (2023) Phytonanotechnology: A greener approach for bioengineering of nanomaterials and their wound healing, antimicrobial, and biofilm inhibitory activities. *Bioengineered Nanomaterials for Wound Healing and Infection Control*. Elsevier; 2023. 407–41
  129. Ullah, M. N., Umer, A., Aadil, M. A., Rehman, F., & Ramzan, N. (2017). Plant-based synthesis of silver nanoparticles and their characteristic properties. *Bioinspired, Biomimetic and Nanobiomaterials*, 6(1), 20–36.
  130. Behzad, F., Naghib, S. M., Tabatabaei, S. N., Zare, Y., & Rhee, K. Y. (2021). An overview of the plant-mediated green synthesis of noble metal nanoparticles for antibacterial applications. *Journal of Industrial And Engineering Chemistry*, 94, 92–104.
  131. Patel P, Agarwal P, Kanawaria S, Kachhwaha S, Kothari S (2015) Plant-based synthesis of silver nanoparticles and their characterization. *Nanotechnology and plant sciences*. Springer; 2015. 271–88
  132. Sofi, M. A., Sunitha, S., Sofi, M. A., Pasha, S. K., & Choi, D. (2022). An overview of antimicrobial and anticancer potential of silver nanoparticles. *Journal of King Saud University-Science*, 34(2), 101791.
  133. Lee, N.-Y., Ko, W.-C., & Hsueh, P.-R. (2019). Nanoparticles in the treatment of infections caused by multidrug-resistant organisms. *Frontiers in Pharmacology*, 10, 1153.
  134. Osonga, F. J., Akgul, A., Yazgan, I., Akgul, A., Eshun, G. B., Sakhaee, L., et al. (2020). Size and shape-dependent antimicrobial activities of silver and gold nanoparticles: A model study as potential fungicides. *Molecules*, 25(11), 2682.
  135. Abbasi, R., Shineh, G., Mobaraki, M., Doughty, S., & Tayebi, L. (2023). Structural parameters of nanoparticles affecting their toxicity for biomedical applications: A review. *Journal of Nanoparticle Research*, 25(3), 43.
  136. Rastogi, L., & Arunachalam, J. (2011). Sunlight based irradiation strategy for rapid green synthesis of highly stable silver nanoparticles using aqueous garlic (*Allium sativum*) extract and their antibacterial potential. *Materials Chemistry and Physics*, 129(1–2), 558–563.
  137. Vijayakumar, M., Priya, K., Nancy, F., Noorlidah, A., & Ahmed, A. (2013). Biosynthesis, characterisation and anti-bacterial effect of plant-mediated silver nanoparticles using *Artemisia nilagirica*. *Industrial Crops and Products*, 41, 235–40.
  138. Rasheed, T., Bilal, M., Iqbal, H. M., & Li, C. (2017). Green biosynthesis of silver nanoparticles using leaves extract of *Artemisia vulgaris* and their potential biomedical applications. *Colloids and Surfaces B: Biointerfaces*, 158, 408–15.
  139. Ahmed, S., Saifullah, A. M., Swami, B. L., & Ikram, S. (2016). Green synthesis of silver nanoparticles using *Azadirachta indica* aqueous leaf extract. *Journal of Radiation Research and Applied Sciences*, 9(1), 1–7.
  140. Govindappa, M., Hemashekhar, B., Arthikala, M.-K., Rai, V. R., & Ramachandra, Y. (2018). Characterization, antibacterial, antioxidant, antidiabetic, anti-inflammatory and antityrosinase activity of green synthesized silver nanoparticles using *Calophyllum tomentosum* leaves extract. *Results in Physics*, 9, 400–8.
  141. Muthukrishnan, S., Bhakya, S., Kumar, T. S., & Rao, M. (2015). Biosynthesis, characterization and antibacterial effect of plant-mediated silver nanoparticles using *Ceropegia thwaitesii*—An endemic species. *Industrial Crops and Products*, 63, 119–24.
  142. Lakshmanan, G., Sathiyaseelan, A., Kalaichelvan, P., & Murugesan, K. (2018). Plant-mediated synthesis of silver nanoparticles using fruit extract of *Cleome viscosa* L.: assessment of their antibacterial and anticancer activity. *Karbala International Journal of Modern Science*, 4(1), 61–8.
  143. Hemlata, M. P. R., Singh, A. P., & Tejavath, K. K. (2020). Bio-synthesis of silver nanoparticles using *Cucumis prophetarum* aqueous leaf extract and their antibacterial and antiproliferative activity against cancer cell lines. *ACS Omega*, 5(10), 5520–5528.
  144. Ghosh, S., Patil, S., Ahire, M., Kitture, R., Kale, S., Pardesi, K., et al. (2012). Synthesis of silver nanoparticles using *Dioscorea bulbifera* tuber extract and evaluation of its synergistic potential in combination with antimicrobial agents. *International Journal of Nanomedicine*, 7, 483.
  145. Shehabeldine, A. M., Elbahnasawy, M. A., & Hasaballah, A. I. (2021). Green phytosynthesis of silver nanoparticles using *echinochloa stagnina* extract with reference to their antibacterial, cytotoxic, and larvicidal activities. *BioNanoScience*, 11(2), 526–538.
  146. Premasudha, P., Venkataramana, M., Abirami, M., Vanathi, P., Krishna, K., & Rajendran, R. (2015). Biological synthesis and characterization of silver nanoparticles using *Eclipta alba* leaf extract and evaluation of its cytotoxic and antimicrobial potential. *Bulletin of Materials Science*, 38(4), 965–973.
  147. Kocak, Y., Oto, G., Meydan, I., Seckin, H., Gur, T., Aygun, A., et al. (2022). Assessment of therapeutic potential of silver nanoparticles synthesized by *Ferula Pseudalliacea* rech. *F. plant. Inorganic Chemistry Communications*, 140, 109417.
  148. Lu, H., Liu, S., & Zhang, Y. (2022). Development of novel green synthesized silver nanoparticles with superior antibacterial and wound healing properties in nursing care after rectal surgery. *Journal of Inorganic and Organometallic Polymers and Materials*, 32(3), 773–780.
  149. Shanmugapriya, K., Palanisamy, S., Boomi, P., Subaskumar, R., Ravikumar, S., & Thayumanavan, T. (2021). An eco-friendly *Gnaphalium polycaulon* mediated silver nanoparticles: Synthesis, characterization, antimicrobial, wound healing and drug release studies. *Journal of Drug Delivery Science and Technology*, 61, 102202.
  150. Bhat, M., Chakraborty, B., Kumar, R. S., Almansour, A. I., Arumugam, N., Kotresha, D., et al. (2021). Biogenic synthesis, characterization and antimicrobial activity of *Ixora brachypoda* (DC) leaf extract mediated silver nanoparticles. *Journal of King Saud University-Science*, 33(2), 101296.
  151. Sathishkumar, G., Gobinath, C., Karpagam, K., Hemamalini, V., Premkumar, K., & Sivaramakrishnan, S. (2012). Phytosynthesis of silver nanoscale particles using *Morinda citrifolia* L. and its inhibitory activity against human pathogens. *Colloids and Surfaces B: Biointerfaces*, 95, 235–40.
  152. Ibrahim, H. M. (2015). Green synthesis and characterization of silver nanoparticles using banana peel extract and their antimicrobial activity against representative microorganisms. *Journal of Radiation Research and Applied Sciences*, 8(3), 265–275.
  153. Shah, M. Z., Guan, Z.-H., Din, A. U., Ali, A., Rehman, A. U., Jan, K., et al. (2021). Synthesis of silver nanoparticles using *Plantago lanceolata* extract and assessing their antibacterial and antioxidant activities. *Scientific Reports*, 11(1), 1–14.
  154. Sukweenadhi, J., Setiawan, K. I., Avanti, C., Kartini, K., Rupa, E. J., & Yang, D.-C. (2021). Scale-up of green synthesis and characterization of silver nanoparticles using ethanol extract of *Plantago major* L. leaf and its antibacterial potential. *South African Journal of Chemical Engineering*, 38(1), 1–8.
  155. Kumar, K. M., Sinha, M., Mandal, B. K., Ghosh, A. R., Kumar, K. S., & Reddy, P. S. (2012). Green synthesis of silver nanoparticles using *Terminalia chebula* extract at room temperature and their antimicrobial studies. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 91, 228–33.

156. Barabadi, H., Mojab, F., Vahidi, H., Marashi, B., Talank, N., Hosseini, O., et al. (2021). Green synthesis, characterization, antibacterial and biofilm inhibitory activity of silver nanoparticles compared to commercial silver nanoparticles. *Inorganic Chemistry Communications*, *129*, 108647.
157. Dong, Y., Zhu, H., Shen, Y., Zhang, W., & Zhang, L. (2019). Antibacterial activity of silver nanoparticles of different particle size against *Vibrio Natriegens*. *PLoS ONE*, *14*(9), e0222322.
158. Holubnycha, V., Husak, Y., Korniienko, V., Bolshanina, S., Tveresovska, O., Myronov, P., et al. (2024). Antimicrobial activity of two different types of silver nanoparticles against wide range of pathogenic bacteria. *Nanomaterials*, *14*(2), 137.
159. Hanan, N. A., Chiu, H. I., Ramachandran, M. R., Tung, W. H., Mohamad Zain, N. N., Yahaya, N., et al. (2018). Cytotoxicity of plant-mediated synthesis of metallic nanoparticles: A systematic review. *International Journal of Molecular Sciences*, *19*(6), 1725.
160. Bruna, T., Maldonado-Bravo, F., Jara, P., & Caro, N. (2021). Silver nanoparticles and their antibacterial applications. *International Journal of Molecular Sciences*, *22*(13), 7202.
161. Dong, Y., & Sun, X. (2019). Antibacterial Mechanism of Nanosilvers. *Current Pharmacology Reports*, *5*(6), 401–409.
162. Mythili, R., Srinivasan, P., Praburaman, L., Al-Ansari, M. M., Al-Humaid, L., Vijayalakshmi, S., & Selvankumar, T. (2021). Biogenic production of silver nanoparticles from milk of *Capra aegagrus hircus* and mechanism of antibacterial activity on different bacteria. *Applied Nanoscience*, *13*, 1611–1618.
163. Wahab, S., Khan, T., Adil, M., & Khan, A. (2021). Mechanistic aspects of plant-based silver nanoparticles against multi-drug resistant bacteria. *Heliyon*, *7*(7), e07448.
164. Xu, L., Wang, Y.-Y., Huang, J., Chen, C.-Y., Wang, Z.-X., & Xie, H. (2020). Silver nanoparticles: Synthesis, medical applications and biosafety. *Theranostics*, *10*(20), 8996.
165. Xu, L., Yi-Yi, W., Huang, J., Chun-Yuan, C., Zhen-Xing, W., & Xie, H. (2020). Silver nanoparticles: Synthesis, medical applications and biosafety. *Theranostics*, *10*(20), 8996.
166. Bonifacio, B. V., da Silva, P. B., dos Santos Ramos, M. A., Negri, K. M. S., Bauab, T. M., & Chorilli, M. (2014). Nanotechnology-based drug delivery systems and herbal medicines: A review. *International Journal of Nanomedicine*, *9*, 1.
167. Badhwar, R., Mangla, B., Neupane, Y. R., Khanna, K., & Popli, H. (2021). Quercetin loaded silver nanoparticles in hydrogel matrices for diabetic wound healing. *Nanotechnology*, *32*(50), 505102.
168. Ibrahim, N. H., Taha, G. M., Hagaggi, N. S. A., & Moghazy, M. A. (2024). Green synthesis of silver nanoparticles and its environmental sensor ability to some heavy metals. *BMC Chemistry*, *18*(1), 7.
169. Hassan, I., Al-Tamimi, J., Ebaid, H., Habila, M. A., Alhazza, I. M., & Rady, A. M. (2023). Silver nanoparticles decorated with curcumin enhance the efficacy of metformin in diabetic rats via suppression of hepatotoxicity. *Toxics*, *11*(10), 867.
170. Garg, S., Chandra, A., Mazumder, A., & Mazumder, R. (2014). Green synthesis of silver nanoparticles using *Arnebia nobilis* root extract and wound healing potential of its hydrogel. *Asian Journal of Pharmaceutics (AJP)*, *8*(2), 95.
171. Chinnasamy, G., Chandrasekharan, S., Koh, T. W., & Bhatnagar, S. (2021). Synthesis, characterization, antibacterial and wound healing efficacy of silver nanoparticles from *Azadirachta indica*. *Frontiers in Microbiology*, *12*, 611560.
172. Lakkim, V., Reddy, M. C., Pallavali, R. R., Reddy, K. R., Reddy, C. V., Bilgrami, A. L., et al. (2020). Green synthesis of silver nanoparticles and evaluation of their antibacterial activity against multidrug-resistant bacteria and wound healing efficacy using a murine model. *Antibiotics*, *9*(12), 902.
173. Patil, S., & Chandrasekaran, R. (2020). Biogenic nanoparticles: A comprehensive perspective in synthesis, characterization, application and its challenges. *Journal of Genetic Engineering and Biotechnology*, *18*, 1–23.
174. Kaplan, Ö., Tosun, N. G., Özgür, A., Tayhan, S. E., Bilgin, S., Türkekel, İ, et al. (2021). Microwave-assisted green synthesis of silver nanoparticles using crude extracts of *Boletus edulis* and *Coriolus versicolor*: Characterization, anticancer, antimicrobial and wound healing activities. *Journal of Drug Delivery Science and Technology*, *64*, 102641.
175. Gupta, I., Kumar, A., Bhatt, A. N., Sapra, S., & Gandhi, S. (2022). Green synthesis-mediated silver nanoparticles based biocomposite films for wound healing application. *Journal of Inorganic and Organometallic Polymers and Materials*, *32*(8), 2994–3011.
176. Lubis, F. A., Malek, N. A. N. N., Sani, N. S., & Jemon, K. (2022). Biogenic synthesis of silver nanoparticles using *Persicaria odorata* leaf extract: Antibacterial, cytocompatibility, and in vitro wound healing evaluation. *Particuology*, *70*, 10–19.
177. Scappaticci, R. A. F., Berretta, A. A., Torres, E. C., Buszinski, A. F. M., Fernandes, G. L., Dos Reis, T. F., et al. (2021). Green and chemical silver nanoparticles and pomegranate formulations to heal infected wounds in diabetic rats. *Antibiotics*, *10*(11), 1343.
178. Dangi, P., Choudhary, S., Singh, D., & Jangir, O. (2019). Wound healing efficacy of green synthesized silver nanoparticles from *tectona grandis* wood flour extract in Wistar rats. *Journal of Advanced Scientific Research*, *10*(04 Suppl 2), 296–303.
179. Samy, R. P., Gopalakrishnakone, P., Sarumathi, M., & Ignacimuthu, S. (2006). Wound healing potential of *Tragia involucrata* extract in rats. *Fitoterapia*, *77*(4), 300–302.
180. Ruffo, M., Parisi, O. I., Dattilo, M., Patitucci, F., Malivindi, R., Pezzi, V., et al. (2022). Synthesis and evaluation of wound healing properties of hydro-diab hydrogel loaded with green-synthesized AGNPS: In vitro and in ex vivo studies. *Drug Delivery and Translational Research*, *12*(8), 1881–1894.
181. Bold, B. E., Urnukhsaikhan, E., & Mishig-Ochir, T. (2022). Biosynthesis of silver nanoparticles with antibacterial, antioxidant, anti-inflammatory properties and their burn wound healing efficacy. *Frontiers in Chemistry*, *10*, 972534.
182. Sibanda, S., Shoko, R., Chishaya, K., Chimwanda, P., Nyoni, S., & Ndlovu, J. (2022). Antimicrobial effect of *Brachystegia boehmii* extracts and their green synthesised silver zero-valent derivatives on burn wound infectious bacteria. *All Life*, *15*(1), 1117–1125.
183. Mehwish, H. M., Liu, G., Rajoka, M. S. R., Cai, H., Zhong, J., Song, X., et al. (2021). Therapeutic potential of *Moringa oleifera* seed polysaccharide embedded silver nanoparticles in wound healing. *International Journal of Biological Macromolecules*, *184*, 144–58.
184. Gad El-Rab, S. M., Halawani, E. M., & Alzahrani, S. S. (2021). Biosynthesis of silver nano-drug using *Juniperus excelsa* and its synergistic antibacterial activity against multidrug-resistant bacteria for wound dressing applications. *3 Biotech*, *11*, 1–16.
185. Younis, N. S., Mohamed, M. E., & El Semary, N. A. (2022). Green synthesis of silver nanoparticles by the Cyanobacteria *synechocystis* sp.: Characterization, antimicrobial and diabetic wound-healing actions. *Marine Drugs*, *20*(1), 56.
186. Aljeldah, M. M., Yassin, M. T., Mostafa, A. A.-F., & Aboul-Soud, M. A. (2023). Synergistic antibacterial potential of green synthesized silver nanoparticles with fosfomycin against some nosocomial bacterial pathogens. *Infection and Drug Resistance*, *16*, 125–142.
187. Yassin, M. T., Mostafa, A. A.-F., Al-Askar, A. A., & Al-Otibi, F. O. (2022). Synergistic antibacterial activity of green synthesized silver nanomaterials with colistin antibiotic against multidrug-resistant bacterial pathogens. *Crystals*, *12*(8), 1057.

188. Zhao, R., Liang, H., Clarke, E., Jackson, C., & Xue, M. (2016). Inflammation in chronic wounds. *International Journal of Molecular Sciences*, *17*(12), 2085.
189. Karppinen, S. M., Heljasvaara, R., Gullberg, D., Tasanen, K., & Pihlajaniemi, T. (2019). Toward understanding scarless skin wound healing and pathological scarring. *F1000Research*, *8*, 787.
190. Zhang, K., Lui, V. C., Chen, Y., Lok, C. N., & Wong, K. K. (2020). Delayed application of silver nanoparticles reveals the role of early inflammation in burn wound healing. *Scientific Reports*, *10*(1), 1–12.
191. Philippe Belle Ebanda Kedi1 BNE, Vandi Deli, Awawou PaboudamGbambie, Agnes Antoinette Ntomba, Ülkü Kökçam-Demir et al (2020) In vitro and in vivo anti-inflammatory activity of green synthesized silver nanoparticles from the aqueous bark extract of *Mangifera indica* Linn. (Anacardiaceae). *International Journal of Green and Herbal Chemistry* *9*(3), 345-60
192. David, L., Moldovan, B., Vulcu, A., Olenic, L., Perde-Schrepler, M., Fischer-Fodor, E., et al. (2014). Green synthesis, characterization and anti-inflammatory activity of silver nanoparticles using European black elderberry fruits extract. *Colloids and Surfaces B: Biointerfaces*, *122*, 767–77.
193. Chirumamilla, P., Vankudoth, S., Dharavath, S. B., Dasari, R., & Taduri, S. (2022). In vitro anti-inflammatory activity of green synthesized silver nanoparticles and leaf methanolic extract of *Solanum khasianum* Clarke. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences*, *92*(2), 301–307.
194. Ahsan, A., Farooq, M. A., Ahsan Bajwa, A., & Parveen, A. (2020). Green synthesis of silver nanoparticles using *Parthenium hysterophorus*: Optimization, characterization and in vitro therapeutic evaluation. *Molecules*, *25*(15), 3324.
195. Patil, S., & Chandrasekaran, R. (2020). Biogenic nanoparticles: A comprehensive perspective in synthesis, characterization, application and its challenges. *Journal of Genetic Engineering and Biotechnology*, *18*(1), 1–23.
196. Abdelhafez, O. H., Ali, T. F. S., Fahim, J. R., Desoukey, S. Y., Ahmed, S., Behery, F. A., et al. (2020). Anti-inflammatory potential of green synthesized silver nanoparticles of the soft coral *Nephthea* sp. supported by metabolomics analysis and docking studies. *International Journal of Nanomedicine*, *15*, 5345.
197. Zhang, W., Chen, L., Xiong, Y., Panayi, A. C., Abududilibaier, A., Hu, Y., et al. (2021). Antioxidant therapy and antioxidant-related bionanomaterials in diabetic wound healing. *Frontiers in Bioengineering and Biotechnology*, *9*, 707479.
198. Keshari, A. K., Srivastava, R., Singh, P., Yadav, V. B., & Nath, G. (2020). Antioxidant and antibacterial activity of silver nanoparticles synthesized by *Cestrum nocturnum*. *Journal of Ayurveda and Integrative Medicine*, *11*(1), 37–44.
199. Martins-Green M, Saeed S (2020) Role of oxidants and antioxidants in diabetic wound healing. *Wound Healing, Tissue Repair, and Regeneration in Diabetes*. Elsevier; 2020. 13-38
200. Ashenafi, E., Abula, T., Abay, S. M., Arayaselassie, M., & Sori, M. (2023). Evaluation of the antioxidant and wound healing properties of 80% methanol extract and solvent fractions of the leaves of *Vernonia auriculifera* Hiern. (Asteraceae). *Clinical, Cosmetic and Investigational Dermatology*, *16*, 279–99.
201. Ghuman, S., Ncube, B., Finnie, J., McGaw, L., Njoya, E. M., Coopoosamy, R., et al. (2019). Antioxidant, anti-inflammatory and wound healing properties of medicinal plant extracts used to treat wounds and dermatological disorders. *South African Journal of Botany*, *126*, 232–240.
202. Guntur, S. R., Kumar, N. S., Hegde, M. M., & Dirisala, V. R. (2018). In vitro studies of the antimicrobial and free-radical scavenging potentials of silver nanoparticles biosynthesized from the extract of *Desmostachya bipinnata*. *Analytical Chemistry Insights*, *13*, 1177390118782877.
203. Chinnasamy, G., Chandrasekharan, S., & Bhatnagar, S. (2019). Biosynthesis of silver nanoparticles from *Melia azedarach*: Enhancement of antibacterial, wound healing, antidiabetic and antioxidant activities. *International Journal of Nanomedicine*, *14*, 9823–9836.
204. Loan Khanh, L., Thanh Truc, N., Tan Dat, N., Thi Phuong Nghi, N., van Toi, V., Thi Thu Hoai, N., et al. (2019). Gelatin-stabilized composites of silver nanoparticles and curcumin: Characterization, antibacterial and antioxidant study. *Science and Technology of Advanced Materials*, *20*(1), 276–290.
205. Boroumand, Z., Golmakani, N., & Boroumand, S. (2018). Clinical trials on silver nanoparticles for wound healing. *Nanomedicine Journal*, *5*(4), 186–191.
206. Burduşel, A.-C., Gherasim, O., Grumezescu, A. M., Mogoantă, L., Fica, A., & Andronescu, E. (2018). Biomedical applications of silver nanoparticles: An up-to-date overview. *Nanomaterials*, *8*(9), 681.

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