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Review

Use of Metallic Nanoparticles Synthesized from Plant Extracts in Wound Healing—A Review

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Abstract: Wound healing is rarely seen as a problem in healthy individuals; however, under certain pathophysiological conditions, this process can be impaired, leading to the emergence of chronic wounds, which are themselves a serious public health problem. This work aimed to review the most important recent literature on the use of nanoparticles of Ag, Au, and Zn produced from plant extracts and their application as healing agents. To that end, we provide an insight into the pathophysiology of wound healing and the main routes to obtaining metallic nanoparticles. The methodology of synthesis, which is part of the so-called green synthesis, has been the focus of several studies on the use of medicinal plants as a substrate to produce silver, gold, and zinc nanoparticles. Their use as wound healing agents is closely related to their natural antimicrobial, anti-inflammatory, and cicatrizing properties. Finally, we address in vitro and in vivo studies on the efficiency of metallic nanoparticles (MNPs) synthesized from plant extracts and applied to wound healing in different pharmaceutical forms. For instance, the excellent wound contraction rates obtained from silver and gold NPs, respectively, were obtained from *Euphorbia milii* (92%) and *Plectranthus aliciae* (almost 97%) extracts in in vivo and in vitro analyses. Based on the satisfactory results, we find that MNPs are a potential therapeutic alternative compared to traditional synthetic healing agents and foresee the production of new pharmaceutical drugs.

Keywords: green synthesis; metallic nanoparticles; nanotechnology; natural treatment; plant extracts; wound healing

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1. Introduction

The skin is an organ with several functions, the main being the protection against external damages to which we are exposed daily, such as chemical, physical, and microbiological aggressions. When this barrier is damaged, it initiates a coordinated repair mechanism involving different cells and molecules in order to provide efficient healing. This process happens in four stages—hemostasis, inflammation, proliferation, and remodeling—and can be negatively influenced by factors such as genetic alterations, diabetes, kidney failure, obesity, aging, substance abuse, malnutrition, infections, and the use of certain medications. Complications from chronic non-healing wounds are varied; patients are at risk of severe pain, sepsis, hospitalization, and amputations, as well as reduced quality of life, depression, distress, anxiety, and embarrassment [1–3].

These complications lead to high treatment costs, estimated at 1–3% of total health spending in developed countries. Although there are several wound healing therapies, they do not always provide satisfactory results in more severe cases, making chronic wounds a relevant public health problem. Therefore, it is necessary to constantly search for low-cost, effective therapies that lead to less environmental and financial damage [4,5]. For this reason, recent studies have focused on several strategies that try to improve wound healing, with emphasis on the development of nanoscale products.

Reducing material to the nanoscale provides greater surface area, resulting in improved physicochemical properties. Among the most studied nanoparticle (NP) formulations, metallic ones (of silver, gold, and zinc) have shown the best results, such as low in vivo toxicity, bacteriostatic and bactericidal properties, and tissue recovery. Furthermore, nanofibrous materials can be used as a delivery system for drugs, proteins, and growth factors, which are also healing and/or antimicrobial agents [2,6,7].

Medicinal plants have been used throughout history by several societies. These traditional therapies are still in use, which have encouraged research into the biological properties of renowned medicinal plants, such as those used to treat wounds. In this context, studying the synthesis of MNPs from plant extracts becomes an interesting research field and should be associated with wound healing, as they provide bioactive compounds responsible for the chemical reactions involved in producing NPs [8,9]. Considering that carbohydrates, lipids, and proteins are important phytochemicals present in medicinal plants and that their biological activities are well-known to be closely related to the healing process, we have numbered the publications reporting the healing activity of the above three molecules from the last 5 years. The great number of publications on carbohydrates (almost 11,000), lipids (almost 24,000), and proteins (almost 56,000) is bigger than a few studies (almost 6000) reporting the healing activity of MNPs synthesized from plant extracts.

Therefore, associating metals and plant species containing phytochemicals that display the same healing and antimicrobial properties suggests the emergence of promising nanoparticles that effectively treat wounds and prevent complications [10], thus being suggested to be investigated. Additionally, the methodology of nanoparticle production falls within the so-called green synthesis, which makes it an environmentally safe, low-cost innovative route.

Understanding the relevance of the problems that arise from wound complications and costs, we present this review of the most significant recent in vivo and in vitro studies on the use of MNPs synthesized from plant extracts as healing agents. We also discuss the pathophysiology of wound healing and the methodology of the synthesis for NPs.

2. Method

The present study is a qualitative review of scientific articles available in the electronic databases Scientific Electronic Library Online (SciELO), National Library of Medicine (PubMed), and ScienceDirect. At every stage, data search, selection, extraction, and analysis were carried out in pairs and then discussed among the authors when the most relevant publications were chosen for this study. In case of disagreement, an independent reviewer was consulted to help reach a decision.

Regarding data selection, as inclusion criteria, we used articles in the original categories, literature reviews, systematic reviews, and meta-analyses. All selected publications were in English with the following descriptors present in the title and/or abstract: wound healing, nanotechnology, metallic nanoparticles, green synthesis, plant extract, silver nanoparticles, gold nanoparticles, copper nanoparticles, titanium nanoparticles, and cerium nanoparticles.

Any publications not in English or not related to the focus of this study, as well as those published in another format (dissertation, thesis, case report, conference summary, etc.), were immediately excluded. Research articles of the last 10 years presenting wound closure rates from in vivo and in vitro healing activity evaluations were preferred over those from previous periods.

3. Results

3.1. Wound Healing Process

The skin is the largest organ in the human body. It is responsible for important functions, such as protection against mechanical forces and infections, fluid balance, and thermal regulation; thus, maintaining its integrity is essential. However, when damages

occur, a complex cascade of different cell types and signaling molecules is started in order to undo it [11].

The stimuli that lead to the regeneration of lesioned skin can be external or internal, as well as physical, chemical, electrical, or thermal. Shortly after an injury, the sequential stages of tissue repair start, namely hemostasis, inflammation, proliferation, and remodeling. These stages do not necessarily occur in sequence but overlap, as different areas of the wound may reach each stage at a different moment [12,13]. Figure 1 summarizes the wound healing process and the main biochemical and cellular elements involved in tissue repair.

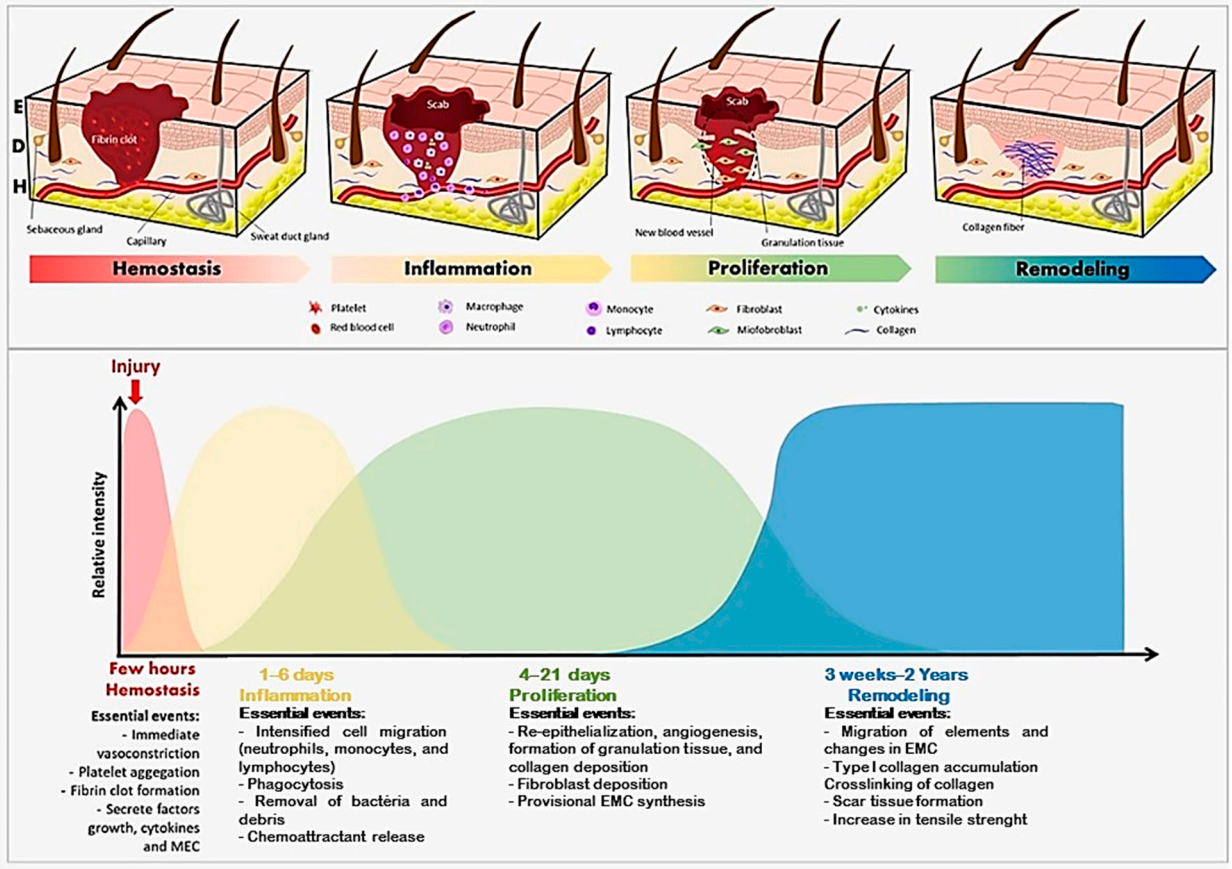

Figure 1. The four steps necessary for wound healing and their main cellular and molecular components. Hemostasis begins just after injury, in which platelet aggregation and the fibrin clot prevent blood loss. Inflammation occurs between 1 and 6 days with the aim to clean the region and prevent infections; neutrophils, monocytes, and lymphocytes participate in the process, and chemoattractants are released. During the proliferation stage, the granulation tissue emerges with the presence of fibroblasts, angiogenesis, and collagen deposition, in addition to the synthesis of extracellular matrix (ECM) components. Finally, the remodeling phase, which can last for up to 2 years, is responsible for depositing more matrix and remodeling by fibroblasts, thus causing contraction and wound closure.

In the first stage, hemostasis, the exposed subendothelium, collagen, and tissue factor will activate platelet aggregation, which results in degranulation and the release of chemotactic and growth factors (chemokines and GFs, respectively) to form the fibrin clot, thereby preventing blood loss. Next, the inflammatory phase begins, in which mast cells release histamine, inducing the influx of neutrophils at the injury site; they clean debris and microorganisms, creating a favorable environment for healing. Monocytes also arrive at the site, differentiating into macrophages, facilitating phagocytosis and the cleaning up of cell debris. The hemostatic and inflammatory stages usually last up to 72 h [14,15].

The following stage is proliferation, leading to an accumulation of various cells and a profuse connective tissue. Here, keratinocytes migrate to close the wound space while

new blood vessels are formed (angiogenesis) and granulation tissue formation (fibroplasia) starts with fibroblast proliferation. Fibroblasts are responsible for producing extracellular matrix (ECM) and forming deposits of collagen, an important protein that has more than 20 different types and plays an essential role in scar formation, with type III collagen being predominant in this stage. The fibroblasts migrate to the wound edge and form an intact basement membrane between the epidermis and the dermis, which is necessary to restore integrity and function to the injured skin. Actin-rich fibroblasts, known as myofibroblasts, then accumulate at the edges of the wound, constricting them toward the center [16,17].

Macrophages and regulatory T cells (Tregs) are also important at this stage. Tregs are responsible for controlling the local immune response, thus preventing further damage, and directly contributing to cell differentiation within injured tissues through the growth factor amphiregulin, similar to the epidermal growth factor (EGF). Ending local inflammation is, therefore, a key function of Tregs in wound healing. Several cytokines and GFs also participate in this stage—the Transforming Growth Factor-β (TGF-β) family, including TGF-β1, TGF-β2, and TGF-β3, the interleukin (IL) family (IL-4, IL-10, IL-13), and angiogenesis factors (vascular epidermal growth factor, VEGF). This phase lasts for days or weeks.

Finally, in the remodeling stage, fibroblasts complete the deposited matrix remodel, the blood vessels regress, and myofibroblasts cause general wound contraction. The gradual degradation of profuse ECM and immature type III collagen, in addition to the formation of mature type I collagen, also occurs. This spans from a few months to a few years [14,15,18,19].

Any interruption in the natural healing cascade can affect subsequent stages and potentially result in abnormal healing and chronic wounds. Also, any damage that extends into the deeper reticular layer of the skin causes scarring, which represents an aesthetic discomfort and clinical and financial burden, especially when hypertrophic and keloid scars develop [20,21].

Some wounds can evolve from acute to chronic conditions, with difficult healing and a noticeable delay in physiological repair. Chronic wounds are defined as recurrent wounds or those that last more than six weeks, the most common among them being non-healing pressure ulcers, venous ulcers, and diabetic foot ulcers. Some host factors favor the appearance of this condition, such as compromised vasculature, diabetes, systemic arterial hypertension, neuropathies, prolonged immobility, interfering medications, immunocompromise, neoplasms, and critical states such as terminal illnesses and organ failure. Complications like low self-esteem, difficulties at work and sleeping, and pain and infections can also be observed in patients, significantly reducing the quality of life. In addition, the increasing prevalence of chronic noncommunicable diseases is a significant issue that financially burdens the health system [22,23].

Several treatments for acute to chronic wounds have been studied; unfortunately, there are few effective therapies that accelerate healing and reduce scarring burden, thus developing new dressings that constitute a great challenge in this field. An ideal dressing should preserve a moist environment to avoid heat generation, allow for normal debridement and gas and fluid exchange, protect against bacterial infection, absorb wound odor, show low to no adherence to the wound, and be easily removed. It is also expected to be nontoxic and hypoallergenic while remaining biocompatible, biodegradable, and overall sustainable, especially when prepared using modern biotechnology [24].

Aiming at developing more effective treatments that can decrease aesthetic discomfort and clinical and financial burden, several studies have encouraged the use of natural products for treating acute and chronic wounds, especially those based on the vast popular knowledge and ancient use of medicinal plants as healing agents.

3.2. Biotechnological Application of Natural Products

Natural products have been used for 60,000 years, with a wide variety of plants employed in traditional medicines, such as Chinese and Indian. Ethnopharmacology can be defined as the interdisciplinary scientific exploration of biologically active agents tradi-

tionally employed or observed by man; it is where all medicines originate, compiling a vast knowledge of plant-derived drugs. With the advances in research and the consequent greater understanding of medicinal plants and their molecular makeup, it has been possible to reach great therapeutic benefits from natural products, posting them as potential preventive and curative drugs for various pathologies [25,26].

Phytotherapy—in this case, the knowledge presented by different ethnic groups about vegetation—has been growing in visibility among health professionals as a consequence of the growing number of reports on the efficiency of its treatments. The most popular application methodologies of this knowledge include infusions (teas) of plant parts or single herbs standardized for extraction, while the pharmaceutical industry produces drugs from isolated compounds through industrial separation and extraction of components with proven therapeutic properties [27].

From the standpoint of plant physiology, most bioactive compounds are secondary metabolites; that is, they do not participate in basic metabolism (energy production, protein synthesis, etc.). Thus, their role is generally linked to interactions with the external environment, either by acting as protective agents against ultraviolet radiation (flavonols), defense against herbivory (glucosinolates and some polyphenols), or pollinator attractants (anthocyanins) [28].

Considering Brazil's abundant biodiversity, with over 15% of all living species on the planet, it is possible to affirm that a significant number of plants with therapeutic potential can be found in its territory. Due to the exploitation of different bioactive compounds in the rich Brazilian flora, the chemistry of natural products is one of the main areas of research in the country. Together, these serve as a basis for the development of new pharmaceutical research, with several studies focusing on fractionation, isolation, and structural understanding of secondary plant metabolites, in addition to the assessment of their biological properties [29,30].

3.3. Extracts from Medicinal Plants

As a rule, medicinal plants are either processed for direct consumption as a form of phytotherapy or directed for experimental purposes, in which case there are several steps involved, including proper harvesting, identification, and authentication by a specialist, drying, and grinding, followed by the extraction, fractionation, and isolation of bioactive components [31].

Extraction is the separation of medicinally active portions of the plant using selective and standardized methodologies. The main extraction techniques are maceration, infusion, percolation, digestion, decoction, Soxhlet extraction, ultrasound-assisted extraction, turboextraction, countercurrent extraction, microwave-assisted extraction, ultrasound extraction, supercritical fluid, extraction in solid phase, and column chromatography [32,33].

Extraction techniques using solvents are the most common and comprise the following phenomena: (1) the solvent penetrates the solid matrix; (2) the solute dissolves in the solvent; (3) the solute is diffused out of the solid matrix; and (4) the extracted solutes are collected. The most appropriate solvent for each step should be analyzed in terms of the plant part that will be used, the chemical nature of the target compound, and solvent availability. Polar solvents, such as water, methanol, and ethanol, are used to extract polar components; nonpolar solvents, such as hexane and dichloromethane, extract nonpolar components. In addition, efficient extraction is influenced by the size of the plant particles, with <0.5 mm being a suitable dimension for the efficient contact between solvent and target particles [31,33,34].

After applying the more suitable technique, the plant extract is obtained; it will be ready for use in the form of dry powder or fluid extract, and either later incorporated into pharmaceutical forms, such as tablets or capsules, or have their isolated chemical components evaluated [32].

3.4. Nanotechnology and Nanoparticles

The term nanotechnology was coined by Professor Norio Taniguchi in 1974, but its primordial basis was established in 1959 by the American physicist Richard Feynman in the lecture "There is a lot of space in the background"; it is now related to the resizing of materials to the nanometric scale—particle sizes varying between 1 and 100 nm—and their manufacture and manipulation. With the development of new technologies and techniques over the years, the manipulation of systems on a nanometric scale resulted in nanomaterials. This made it possible to reach minuscule dimensions with a high surface-to-volume ratio, that is, a large contact surface, which is essential to generate significant changes in the physical and chemical properties of nanomaterials [35].

Nanotechnology is considered one of the most promising fields of the 21st century, and it is possible to list its contributions to almost every scientific branch, including physics, computer sciences, engineering, materials sciences, chemistry, and biology [36]. The obtainment of NPs is possible through various routes by using chemical reagents or physical processes, starting from small-scale products or large-scale materials, which are then divided into nanometric fragments. These methodologies could vary according to the substrate and application of interest, presenting advantages and risks inherent to the chosen route.

Two main methodologies are used in nanoparticle production, the first, top-down, involves the consecutive cutting or slicing of a bulk (macroscopic) material, which generates particles on a nanometric scale. The most popular, however, is bottom-up, where small precursor particles are assembled [37,38]. Considering that NPs are used in the health sciences, there are several physical, chemical, and biological methods for their synthesis, and the choice will be made according to the expected physical and chemical characteristics of the final product, such as size, dispersion, chemical miscibility, and optical properties [39,40]. More specifically, MNPs have gained prominence in recent years because of their promising results in scientific research, which directed them for medical purposes, for example, new perspectives in the treatment of wounds. In the topics below, we describe the main methodologies for obtaining NPs, specifically those considered environmentally friendly, that is, which encourage and improve eco-friendly techniques.

3.4.1. Physicochemical Methods of Production of MNPs

Physical NP synthesis refers to the use of bulk materials, physical forces, or either mechanical or steam-based processes (Figure 2). Mechanical, electrical, luminous, and thermal energies are used to reduce particle size and agglomeration in the absence of leveling or stabilizing agents. The advantages of physical synthesis are allowing reasonable particle size control, satisfactory NP structure control, and low pollution manufacture. Nevertheless, its disadvantages are related to mandatory particle deposition on a substrate, i.e., particles cannot be easily transferred to a solution, thus hindering particle protection and promoting low yield, high energy consumption, and the need for more sophisticated equipment [39,41–43].

Physical Synthesis

The most common physical methods for the preparation of AgNPs include evaporation–condensation, laser ablation, electrical energy, light energy, and microwave plasma. These methods are used to decompose synthetic media to produce reducing substances (O^{2-}, ethanol, and ethylene glycol) that react with silver ions. They offer advantages such as speed, the absence of the need for toxic reagents, and the use of radiation as a reducing agent. However, the main disadvantages are associated with high energy consumption, long duration for process completion, low yield, and non-uniform distribution [44–46].

Physical methods for obtaining AuNPs, such as pyrolysis, nanolithography, thermolysis, and radiation-induced methods comprise controlled techniques for cutting, milling, and shaping the substrate in the shape of interest. However, as a relevant disadvantage, some imperfections could be observed on the NP's surface. Another limitation is the high

cost of synthesis, which requires a large amount of energy to guarantee high values of pressure and temperature [47].

Considering zinc nanoparticles, the literature reports the use of physical techniques involving thermal evaporation, physical vapor deposition, ultrasonic irradiation, thermal/laser ablation, arc plasma, spraying, explosion processes, and mechanical/ball milling. Compared to the other mentioned NPs, some disadvantages are related to parameter controls, the use of robust equipment, demand for high energy input, amorphous aspects than crystallinity, high costs, and discharge instability [48,49].

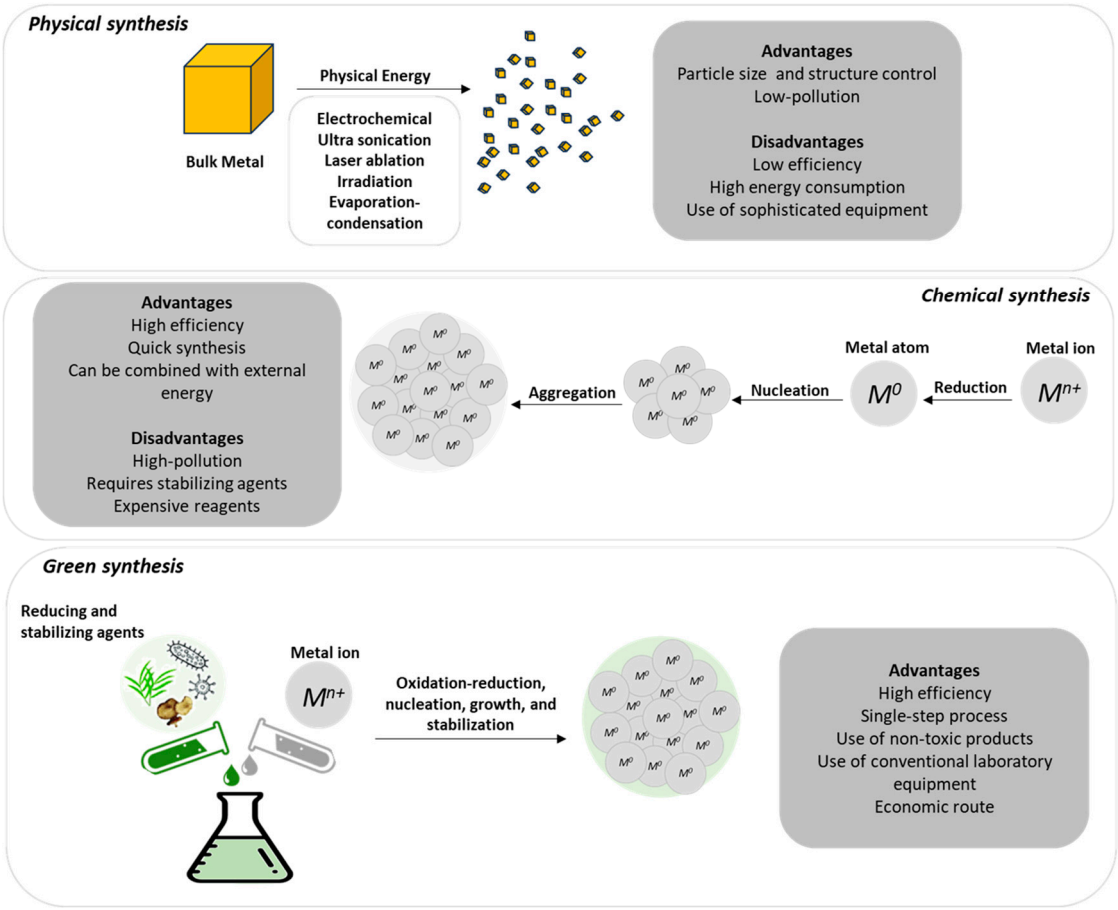

Figure 2. Different methods of MNP synthesis.

Chemical Synthesis

Chemical synthesis is the most common method of producing NPs. In summary, this happens by reducing metallic cations to a neutral state using appropriate reducing agents—sodium borohydride, citric acid, sodium citrate, polyols, and sulfites—in a two-step process: (1) nucleation and (2) subsequent growth [43]. The use of stabilizing agents is recommended because they generate electric charges and repulsive forces around the NPs, controlling their growth and preventing aggregation. The most widely used stabilizing agents are sulfur and phosphorus binders, polymers, surfactants, and anionic species such as citrate, halides, carboxylates, and polyoxoanions. Steric stabilization is also possible by inducing MPs to interact with bulky groups such as organic polymers and alkylammonium cations, responsible for preventing aggregation via steric repulsion [47,50]. Additionally, chemical synthesis can be combined with external energy sources such as photochemical, electrochemical, microwave-assisted, and sonochemical processes; however, despite being reliable, high yielding and time saving, it generates great environmental pollution due to the chemical agents involved [43].

Among chemical synthesis methods, chemical reduction is one of the main techniques, requiring a reducing agent to transform Ag^+ into AgNPs. In general, the process begins with the reaction of a neutral silver atom, obtained from a silver salt, typically silver nitrate ($AgNO_3$). Sodium borohydride is considered a good reducing agent, producing AgNPs ranging from 5 to 20 nm, while trisodium citrate is more effective in synthesizing nanoparticles between 60 and 100 nm. There are some limitations in producing AgNPs with defined sizes; in this case, an additional step is required to prevent particle aggregation using, for example, polyvinylpyrrolidone, a size-controlling and protective agent [44–46].

The main advantage of the above-mentioned approach is that a considerable number of NPs can be easily synthesized by coupling low operational costs. However, some limitations could also be reported; for example, the number of chemical agents involved, such as metal precursors, reducers, and stabilizing/protective agents. These compounds are necessary to ensure the formation of stable colloids but may cause potential toxicity risks to humans and the environment. Another technique reported for the chemical synthesis of AgNPs is ultrasonic spray pyrolysis, which produces nanoparticles with controlled and uniform particle size by generating aerosol from diluted aqueous solutions of metal salts. In oxygen-free conditions, Ag^+ is reduced by heating the material to temperatures of 600–1000 °C to synthesize AgNPs, considered a direct production route with the particle size dependent on aerosol droplets [45,46,51].

Gold nanoparticles (AuNPs), when produced through self-assembly techniques of individual species (atoms, molecules, or clusters) via chemical synthesis, are obtained through a more cost-effective route that allows for better control in product development, particularly in terms of size, shape, and more homogeneous chemical composition. In this context, bottom-up methods are generally wet chemical synthesis processes, including chemistry, electrochemistry, and sonochemistry. However, these methodologies have limitations concerning the separation of NPs within the reaction medium, which may contain toxic chemicals, organic solvents, and other reagents [47].

Some techniques for the chemical synthesis of AuNPs are described in the literature, such as the Turkevich synthesis, which involves trisodium citrate as a reducing agent, later modified by the addition of sodium borohydride ($NaBH_4$). The Brust–Schiffrin method is one of the most well-known procedures for synthesizing spherical AuNPs soluble in organic solvents by using reagents such as tetraoctylammonium bromide, cetyltrimethylammonium chloride, and cetyltrimethylammonium bromide (CTAB). In the seeded growth synthesis of AuNPs, the use of $NaBH_4$, cetyltrimethylammonium bromide, acetone, cyclohexane, 2-bis(10,12-tricosadiynoyl)-sn-glycero-3-phosphocholine, and trisodium citrate is also reported. Finally, the synthesis of AuNPs with ascorbic acid, a well-known antioxidant, biodegradable, and biocompatible molecule, resulted in lower levels of toxicity, as observed in [47].

Various chemical synthesis mechanisms are found in the literature for zinc nanoparticles. Chemical precipitation is a methodology that converts soluble substances into a solid or insoluble form, thus being the most adopted method for the synthesis of ZnONPs. Reagents such as tetramethylammonium hydroxide, dimethyl sulfoxide, sodium hydroxide, and tartaric acid are reported for this synthesis. The sol–gel method is also frequently used for the production of metal oxide NPs, employing reagents such as 2-methoxyethanol, monoethanolamine, and polyethylene glycol. Microemulsions are also utilized for the synthesis of inorganic NPs via the thermodynamically stable dispersion of two immiscible liquids in the presence of surfactant and co-surfactant as stabilizers. Some reagents involved in this process include N,N,N-cetyltrimethylammonium bromide, cyclohexane, butanol, ammonia, Triton X-100, Span, Tween, and n-hexanol [48,49].

Moreover, other techniques are described in various studies, for example, microwave-assisted synthesis, sonochemical synthesis, chemical vapor deposition, electrochemical deposition, atomic/molecular condensation, solvothermal method, spray pyrolysis, laser pyrolysis, and aerosol pyrolysis. However, the extensive use of surfactants, high cost of

precursors, toxicity, low yield, low deposition rate, low penetration, low solubility, and mechanical instability are important disadvantageous aspects reported by them [48,49].

Searching for processes with less negative impact, several studies have focused on developing more sustainable and economically viable alternatives for current metallic NP syntheses. Thus, the biological route, also known as green synthesis, emerges as a new production path, showing promising responses from bacteria, fungi, algae, and plant extracts.

3.4.2. Green Synthesis

In recent decades, researchers have been encouraging the use of so-called green chemistry, projecting a significant reduction or total elimination of environmentally hazardous waste through two main steps: implementing sustainable processes and preventing pollution at atomic and molecular levels. With that in mind, the use of non-toxic chemicals, environmentally benign solvents, and renewable materials is expected. Regarding metallic NP synthesis, potentially favorable green chemistry strategies are, for example, using water as a solvent and employing non-toxic reducing agents, naturally sourced stabilizers, and conventional laboratory equipment [52–54].

Consequently, the biological route, with the use of plants and microorganisms, emerges as a potentially sustainable option over conventional synthesis processes. Green synthesis is a methodology performed in a single step without consuming nor producing toxic or polluting chemicals and is considered an economical, high-yielding, and environmentally friendly route. In recent years, plants have been extensively studied for NP biosynthesis, with different applications in the health sciences.

Green Synthesis from Plant Extracts

Plant extracts are filled with bioactive molecules—vitamins, alkaloids, carotenoids, phenolics, fats, carbohydrates, and proteins—and enzymes can be found in leaves, roots, flowers, fruits, and rhizomes, which are responsible for different biological properties retained by the extracts. When acting as reducing and stabilizing agents, these molecules can facilitate NP oxidation–reduction, nucleation, growth, and stabilization [55–57].

The presence of metals at toxic levels for the plant can induce excessive production of reactive oxygen species (ROS), damaging cellular macromolecules and causing morphological, metabolic, and physiological irregularities, but as mentioned, plants produce chelating molecules, which neutralize metal toxicity, such as phenolic compounds, which act as antioxidants against ROS even at high concentrations of metallic ions. As a consequence of this metallic ion detoxification, plant extracts are reported as one of the main sources of the biological route in NP production. Among the most important phenolics with the ability to perform green NP synthesis are flavonoids, a family of natural polyphenolics that include flavone, flavonol, flavanone, flavanonol, and isoflavone derivatives [58].

Several studies have focused on improving NP synthesis from plant extracts using metals (silver and gold) and metallic (iron, zinc, and zirconium) oxides to produce NPs with different applications in biomedical sciences [59]. Their results indicate that biologically produced nanoparticles are more efficient and beneficial than those synthesized through physical and chemical processes, retaining antibacterial, antifungal, antioxidant, antibiofilm, and cytotoxic properties [60].

Variations in the concentration of the plant extract cause changes in the absorption intensity, size, shape, dispersion, and agglomeration of MNPs. A decrease in the concentration of the plant extract results in a larger size, while higher concentrations can lead to the production of smaller, spherical, and isotropic MNPs with good dispersion and no agglomeration [61–63]. The study by Lin et al. (2019) effectively illustrates this information, wherein the AuNPs synthesized with a higher concentration of M. lucida leaf extract exhibit a size below 15 nm and a spherical shape, in contrast to a size exceeding 100 nm and a hexagonal shape for AuNPs synthesized with a lower concentration of plant extract. A plausible explanation for this is that the decrease in the concentration of the plant

extract also reduced the availability of phytochemicals for encapsulation, resulting in an agglomeration and consequently larger AuNPs [63].

3.5. Characterization of MNPs

The physicochemical characteristics of NPs influence their behavior, biodistribution, release, stability, safety, and efficacy. Therefore, different characterization methods are of paramount importance to analyze the functional properties of the produced particles, such as shape, size, morphology, and surface area. Combining a variety of techniques allows obtaining more information about the reaction product, enabling the determination of the quality of the synthesized nanoparticles [64].

A variety of techniques are primarily employed, including ultraviolet-visible spectroscopy (UV-Vis), X-ray diffraction (XRD), energy-dispersive X-ray analysis (EDAX), particle size distribution (PSD), Zeta potential (ZP), photoluminescence (PL), dynamic light scattering (DLS), Raman spectroscopy (R), infrared spectroscopy (IR), cyclic voltammetry (CV), nanoparticle tracking analysis (NTA), Fourier-transform infrared spectroscopy (FTIR), thermogravimetric analysis (TGA), selected area electron diffraction (SAED), atomic force microscopy (AFM), scanning electron microscopy (SEM), field-emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM), and high-resolution transmission electron microscopy (HRTEM) [65,66].

It is worth noting that the characterization of a specific biomaterial depends on the complexity of the matrix, analyte concentration, and physicochemical composition. Among the techniques employed, some are more extensively executed by researchers in the field and reported in the literature (Figure 3). Dynamic Light Scattering (DLS) is an approach focused on measuring the size, size distribution, and degree of aggregation of NPs. The Zeta potential analyzer is used to determine the surface charge of NPs, considering a surface value above +30 mV and below −30 mV as the target for minimizing NP aggregation and ensuring their stability. Fourier-transform infrared spectroscopy (FTIR) determines the structure and content of NPs, with absorption bands in the mid-infrared region (4000–400 cm^{-1}) verifying the presence of functional groups and secondary metabolites in samples, often responsible for reduction and stabilization processes. Additionally, UV-visible spectroscopy is essential, analyzing the wavelength that characterizes the presence of NPs in the range of 300 to 800 nm, with the expected wavelength for AgNPs between 400 and 460 nm, also assessing their stability over time [64,65,67,68].

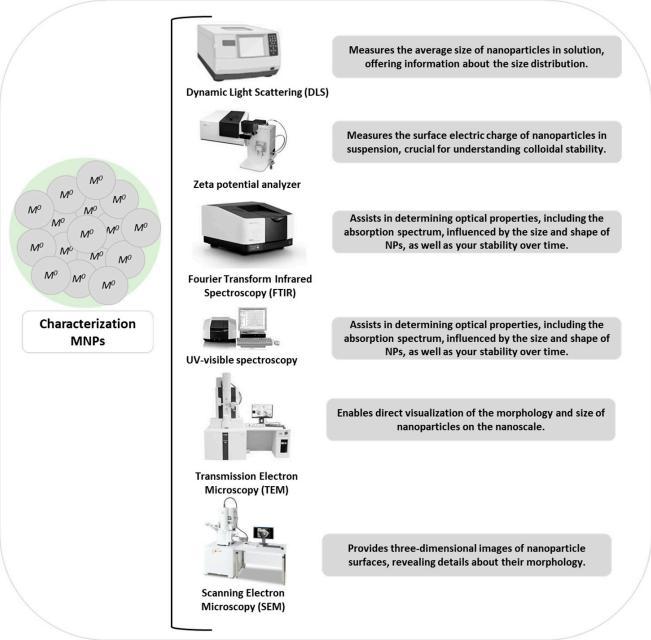

Figure 3. Summary of the main techniques used in the characterization of NPs.

Furthermore, the analysis of the shape of NPs is of great importance in the characterization stage, and this can be evaluated using microscopy techniques such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (Figure 4). The latter, for instance, is a common technique for analyzing the size, size distribution, and shape of NPs. Other microscopy techniques, such as AFM, can also be used to analyze the size, 3D shape, and elemental composition of NPs [64,68].

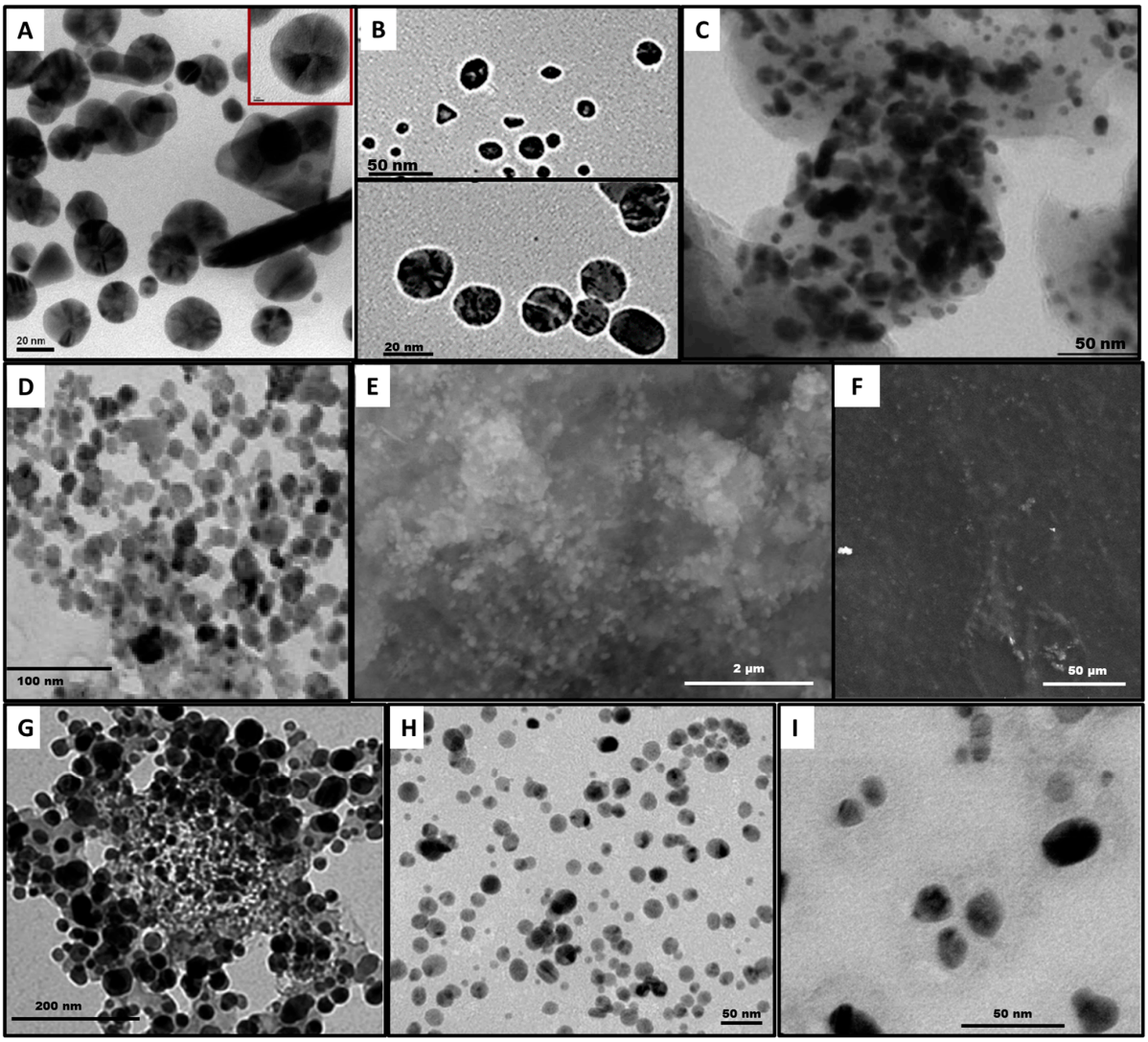

Figure 4. Representatives' imagens of metallic nanoparticles: Morphologies of the three AuNPs in HR-TEM images obtained by green synthesis with vegetal extracts of *Acalypha indica* ((**A**) [69]); *Plectranthus aliciae* ((**B**) [70]); and *Chamaecostus cuspidatus* ((**C**) [71]). HR-TEM imagem of ZnO-NPs obtained from *Acacia nilotica* ((**D**) [72]); SEM imagem of ZnO-NPs obtained from *Calendula officinalis* ((**E**) [73]); and SEM imagem of filmogenic formulation composed of 1.75 g gelatin, 0.5 g bentonite and 0.1 g ZnO-NPs obtained by green synthesis with *Nettle* extract ((**F**) [74]). Morphologies of the three AgNPs in HR-TEM images obtained from *Azadirachta indica* ((**G**) [75]); *Lindera strychnifolia* ((**H**) [76]); and *Curcuma longa* ((**I**) [77]). High Resolution Transmission Electron Microscopy (HR-TEM); Transmission Electron Microscopy (TEM); Scanning electron microscopy (SEM). Adapted from Boomi et al. (2020) [69], Lambrechts et al. (2022) [70], Ponnanikajamideen et al. (2019) [71], Rasha et al. (2020) [72], Acar et al. (2023) [73], Nozari et al. (2021) [74], Chinnasamy et al. (2021) [75], Ahn et al. (2019) [76], and Maghimaa et al. (2020) [77].

3.6. MNPs and the Wound Healing

Nanotechnology is a promising field of innovative research on wound treatment that makes possible the synthesis of biocompatible nanomaterials (NMs) such as liposomes, solid lipid nanoparticles, polymeric micro- and nanospheres, carbon nanotubes, nanoscaffold, and metallic nanoparticles. Due to their high effectiveness in a minimal dose, nanoparticles emerge as new therapeutic alternatives for healing: their reduced dimensions and improved physicochemical properties provide intracellular drug delivery with the possibility of topical administration and increased half-life, decreasing the number of applications and, thus, treatment costs. Additionally, the encapsulation of drugs within NMs allows for multiple drug release profiles, aiding wound healing [22,66].

NMs also provide soft, flexible, biocompatible wound dressings that can display important healing properties that include antimicrobial activity, exudate absorbance, protection against trauma, and heat build-up of the injured region. Overall, there are two main NM groups used in wound healing: (1) those that display beneficial intrinsic properties for wound healing, and (2) those employed as delivery vehicles [24].

Among the main studied NMs, MNPs have been gaining great visibility for improving wound healing. Several studies have shown satisfactory effects when NPs are synthesized from plants through green synthesis, which is another relevant aspect for choosing the green route. Table 1 shows important recent findings in the literature that demonstrate the potential of NPs synthesized from plant extracts with gold, zinc, and silver salts.

Table 1. Effects on the healing process of wounds treated with different metal nanoparticles synthesized from plant extracts.

Metal	Plant	Experimental Model	Phytochemicals	Methodology	Results	References
Gold	*Acalypha indica*	In vivo assay with BALB/c mice	Sildenafil citrate, Geniposidic acid, 3,5-dimethylphenol, Palmitic acid, Borneol, 2-Hexyl-1-octanol, and α-Terpinyl acetate.	A 20 mm incision was made on each animal's back; focus group treated with AuNPs and excised for histological evaluation.	AuNPs accelerated the inflammatory stage, speeding initial blood vessel formation and collagen matrix remodeling; skin regeneration, and wound contraction faster than control.	[69]
Gold	*Plectranthus aliciae*	Cell Culture in Human Keratinocyte Cell Line HaCaT	-	Scratch assay	AuNPs induced 96.7 ± 1.0% wound closure.	[70]
Gold	*Chamaecostus cuspidatus*	In vivo assay with male Wistar rats	-	Type 2 diabetes rats by STZ model; focus group treated with AuNPs via oral administration; macroscopic evaluation of wound and biochemical analysis of blood.	Diabetic rats treated with AuNPs and plant extract showed better healing than control after 4 weeks. The treatment restored their blood glucose, glycogen, and insulin levels.	[71]
Zinc	*Acacia modesta*	In vivo assay with *Sprague dawley* rats	-	Wounds were inflicted on surgical sutures and treated with zinc oxide nanoparticles (ZnO-NPs).	Treated rats with faster epithelialization and contraction, mild inflammation, absence of infection; increased collagen fiber, fibroblastic cells, lower inflammatory cells, and faster angiogenesis than standard treated.	[78]
Zinc	*Acacia nilotica*	In vivo assay with rats	-	A 20 mm skin excision was performed on each animal's back. KPC infection induced using 20 µL of KPC bacterial suspension (CFU 10^8) on surgery day (day 0). On day 3, treatment with asynthesized ZnO-NP ointment started.	On day 14, infected and uninfected control animals showed wound contraction at 63% and 64%, resp.; infected animals treated with imipenem ointment showed 54%; infected animals treated with ZnO-NPs showed contraction at 98%.	[72]
Zinc	*Calendula officinalis*	Cell culture in murine Fibroblast cell line L929	-	Scratch assay	ZiNPs induced 69.1% wound closure, but did not differ from the control group.	[73]

Table 1. *Cont.*

Metal	Plant	Experimental Model	Phytochemicals	Methodology	Results	References
Zinc	*Nettle* sp.	In vivo assay with adult female rats	-	A burn wound measuring 1.5 × 1.5 cm^2 was performed on each animal's back. The Focus group was treated with filmogenic formulation (bentonite 0.50 g/60 mL of chitosan 1% (*w*/*v*), 1.75 g gelatin, and 0.1 g ZnO-NPs. Rats were examined daily for 7 days	The group treated with the formulation showed complete wound healing with no signs of burned skin.	[74]
Silver	*Azadirachta indica*	In vivo assay with adult male albino mice	Flavonoids, phenolics, terpenoids, and terpenes	Wounds treated with AI-AgNPs (0.3, 1, and 3 mg) immobilized in PF127 hydrogel.	Almost complete wound closure by day 10 in mice treated with 1.0 mg AI-AgNPs-PF127 hydrogel.	[75]
Silver	*Aloe barbadensis Miller* and *Curcuma longa*	In vitro healing and cytotoxicity assays using human embryonic kidney cell lines (HEK-293)	-	Inoculation of AgNPs in cell culture. Cellular modifications observed with an optical microscope; cell-covered area measured with Image-J software (version 1.54h).	AgNPs with turmeric extract produced a non-toxic pattern in addition to faster and more sustained cell growth compared to other AgNPs.	[79]
Silver	*Delonix elata*	In vivo treatment of anorectal wounded area in patients weighing 64 kg	Alkaloids, saponins, theroids, tannins, carotene, phenolics, anthocyanins, glycosides, flavonoids, and others.	Daily application of AgNP-coated cloths; wound closure assessed daily.	AgNPs synthesized by leaf aqueous extract showed healing properties on anorectal surgical wounds in humans.	[80]
Silver	*Lindera strychnifolia*	Cell culture in Fibroblast cell line NIH3T3	-	Cell scraping of NIH3T3 cells.	AgNPs induced 64% wound closure.	[76]
Silver	*Madhuca longifolia*	In vivo wound healing bioassay in Swiss albino mice	3-hydroxy flavones, 3,6 dihydroxyflavone, dihydroquercetin, quercetin, myricetin 3-O-arabinoside, myricetin 3-O-galactoside, and dihydroxyl quercetin	A 100 mm^2 excision was made; treated using paraffin-based ointment with 70 mg/g AgNPs. Wound closure assessed by measuring the affected area.	Wound closure was 80.33% for the animals treated with AgNP ointment.	[81]
Silver	*Catharanthus roseus*	In vivo assay with male albino mice using an excision wound model	-	A 20 × 20 mm^2 excision was made on each animal's back; treated with 2 mL of synthesized AgNP (2 mM) once a day for 12 days.	Animals in the focus group (AgNP) showed better healing (closure at 98%) compared to those in the control group (85%).	[82]

Table 1. *Cont.*

Metal	Plant	Experimental Model	Phytochemicals	Methodology	Results	References
Silver	*Prosopis juliflora*	Excision wound model performed in mice	-	A 10 mm skin excision was made, treated with AgNP ointment and Carbopol; regular treatment. Wound reduction measured and photographed on days 1, 6, 10, and 15.	Wound closure in animals treated with AgNPs and Carbopol was significantly higher than in the other two groups (treated with Carbopol alone or povidone-iodine).	[83]
Silver	*Rhizophora apiculata*	Cell culture in murine Fibroblast cell line L929	Glycosides, saponins, terpenoids, flavonoids, and phenols	Scratch wound migration assay.	AgNPs increased more potent cell migration and wound closure than plant extract.	[84]
Silver	*Curcuma longa* L.	Cell culture in murine Fibroblast cell line L929	-	Scratch wound migration assay.	AgNPs increased cell migration indicating active fibroblastic cell proliferation and growth.	[77]
Silver	*Ardisia solanacea*	Cell culture in human fibroblasts BJ-5Ta	Alkaloids, tannins, phenolic compounds, and flavonoids	Scratch wound migration assay.	Positive effect on wound healing for synthesized AgNPs.	[85]
Silver	*Parrotiopsis jacquemontiana*	Skin excision in male rats	Flavonoids, tannins, coumarins, phlobatannins, steroids, phenols, alkaloids, saponins, sterols, betacyanin, vitamin C, proteins, oils, and resins.	Wound area was measured (mm) every 5 days; contraction assessed using those measurements	Wound closure increased over time for all groups; AgNP values were higher than the positive control, which were higher than the negative control. No scar formation on the former by the end of day 15.	[86]
Silver	*Euphorbia milii*	Skin excision in albino male rats	-	A 50 mm^2 dorsal excision was made; treated with ointment of synthesized AgNPs at 10%. Wound area analyzed on a 3-day interval from day 0 until full epithelialization.	Wound contraction of control was 77.08%; group I (nitrofurazone) was 82.56%; group II (AgNPs) was 91.45%.	[87]
Silver	*Scutellaria barbata*	Cell culture in L929 fibroblasts cell line	-	Scratch wound migration assay.	AgNPs induced wound healing via proliferation, differentiation, and migration of L929 fibroblast cells.	[9]
Silver	*Syzygium aromaticum*	In vivo assay with male and female albino rats	-	A dorsal excision was made; Formulation AgNP cream (3% AgNP or 5% AgNP) was applied once every day for 10 days until complete healing.	5% AgNP cream showed relatively superior tensile strength compared to that of the control group; and a significant increase in collagen deposition and epithelialization.	[88]

Table 1. *Cont.*

Metal	Plant	Experimental Model	Phytochemicals	Methodology	Results	References
Silver	*Tridax procumbens*	In vivo assay with mice	-	A 4.5 cm^2 skin excision was made on each animal's back; AgNP-loaded chitosan-based gel applied once a day until full healing.	AgNP group showed significant progressive healing in comparison to those receiving negative (placebo) and standard (1% silver sulfadiazine) treatments.	[89]
Silver	*Catharanthus roseus* and *Azadirachta indica*	In vivo assay with female BALB/c mice	-	A 5 mm excision was made on each animal's back; treated with a formulation containing AgNPs from either *C. roseus* or *A. indica*. Commercially available povidone-iodine ointment used as positive control.	Wound closure for AgNP treatments was significantly higher (94% ± 1 *C. roseus*; 87% ± 1 *A. indica*) than control groups (76% ± 1 for negative; 79% ± 1 for positive). AgNP group did not show microbial growth, bleeding, or pus during experiment; the negative control showed notable irritation.	[90]
Silver	*Pisonia alba*	Cell culture of human dermal fibroblasts (HDF)	-	Scratch wound migration assay and analysis of cell migration in cells treated with AgNPs. Measurements performed at 0, 24, and 48 h of incubation.	AgNPs stimulated collagen production and deposition on the wound site. Wound closure was 23.32% ± 2.29 and 17.21% ± 1 for 25 µg/mL at hours 24 and 48, resp.	[91]
Silver	*Cotyledon orbiculata*	Cell culture of HaCaT, KMST-6, and CHO	Polyphenols, flavanols, tannins, and flavonols	Scratch wound migration assay using a *C. orbiculata* aqueous extract or AgNPs.	Extract induced faster closure compared to negative control (untreated cells) in all lines. In HaCaT and CHO cells, AgNPs (2.5 µg/mL) more efficient than extract and positive control (allantoin)	[92]
Silver	*Periploca hydaspidis*	In vivo assay with Sprague Dawley rats	Tannins, flavonoids, phenols, coumarins, alkaloids, anthocyanins, saponins, glycosides, and vitamin C	A cut was made on each animal's back and treated with plant extract or AgNPs.	Plant extract (20, 35, and 75%) and AgNPs (30, 60, and 100%) produced greater wound closure than negative control (25, 45, and 85%) on days 5, 10, and 15, resp.	[93]

- Not included.

3.6.1. Silver Nanoparticles (AgNPs)

In recent years, plants have been extensively studied for AgNP biosynthesis with different applications in the health sciences. Biomolecules present in the plant extract can perform oxidation–reduction of Ag^+ ions from the silver salt to Ag^0, as well as nucleation, growth, stabilization, and, finally, formation of AgNPs [55,57].

AgNPs are the most studied nanoparticles in wound healing due to their antimicrobial, anti-inflammatory, and healing properties, and have been successfully produced through different technologies and tested as healing agents [22,94,95]. For example, AgNPs have exhibited excellent anti-inflammatory properties in both animal models and clinical trials, reducing the expression and release of pro-inflammatory cytokines and mast cell infiltration, leading to wound healing with minimal scarring. Additionally, they stimulate keratinocyte proliferation and migration and help in fibroblast differentiation into myofibroblasts, providing wound contraction and faster healing, including in diabetic ulcers [96].

Another relevant point is that bacterial resistance was not observed, an important aspect, since controlling bacterial infection is a crucial part of managing chronic wounds. It is reported that, due to their nanometric size and larger contact surface, AgNPs destroy the bacterial membrane and permeate the microorganism, causing intracellular damage. The stimulation of oxidative stress, the release of metallic ions (Ag^+)—which can inactivate vital biological systems (DNA, peptides, and cofactors)—and non-oxidative mechanisms help explain how they act as healing agents [22,95].

3.6.2. Gold Nanoparticles (AuNPs)

Gold has an inert nature and low toxicity. Gold nanoparticles possess bactericidal, bacteriostatic, antioxidant, and anti-inflammatory properties, making them interesting for the treatment of wound healing [97,98]. In particular, spherical AuNPs (gold nanoparticles) have a large surface area, making them highly prone to receiving electrons and interacting with reactive oxygen species (ROS) to remove or deactivate them, aiding in tissue repair [99,100].

In BALB/c mice with infected diabetic wounds, gold nanoparticles produced from the aqueous extract of *Acalypha indica* (spherical and rod-like nanostructures with 20 nm of size) displayed extraordinary wound healing capability as well as antibacterial, antioxidant, and anti-inflammatory activity [69]. The main advances in elucidating the healing mechanisms of biogenic AuNPs are related to inhibiting microbial growth and improving epithelialization. It is reported that green-synthesized AuNPs increase the hydroxyproline content around the wound area, which is an indicator of a high amount of collagen fiber and increased tensile strength. Additionally, immunomodulation mechanisms are also involved [101].

3.6.3. Zinc Oxid and Other MNPs

Other nanoparticles with promising characteristics for healing are those of zinc oxide (ZnONPs). They induce perforations in the bacterial cell membrane, making them a reliable antibacterial agent [102]. Nozari et al. (2021) synthesized ZnONPs via green synthesis from *Nettle* leaf extract, with a mean size of 30 nm, and incorporated them into flexible films of chitosan/alginate and chitosan/bentonite and observed that the films improved the healing process. However, considering the flexibility, water absorption, and wound healing of bentonite-containing composites, the composite film of chitosan/bentonite (containing 0.50 g of bentonite) incorporation with gelatin and ZnONPs was more promising [74]. On the other hand, Acar et al. (2023) produced ZnONPs with *Calendula officinalis* flower extracts and although they exhibited antioxidant activity, the nanoparticles did not show potential in accelerating cellular migration to L929 cells compared with the control [73].

Other metallic nanoparticles that have evidence in the literature of being produced by plant-mediated green synthesis and have actions on wound healing are cerium and titanium NPs. Incisions on the skin of male albino rats were performed and treated with chitosan

hydrogel membrane loaded with 1% and 5% cerium nanoparticles. Animals treated with cerium nanoparticles showed maximum wound contraction, inducing collagen deposition, and increased skin tensile strength compared to the group treated only with chitosan membrane, which exhibited a visibly larger wound at the end of the analyses. Furthermore, the nanoparticles demonstrated higher antioxidant activities and bactericidal effects against both Gram-positive and Gram-negative strains [103].

Ahmad et al. (2022) conducted an in vivo trial with diabetic male Wistar albino rats, using nanoparticles produced with titanium dioxide (TiO_2) and *Ocimum sanctum* leaf extract as a reducing agent. A dorsal excision was performed on the animals and treated with chitosan gel containing TiO_2 nanoparticles, with an analysis of wound area contraction, epithelization time, and wound closure time. Animals treated with the gel containing TiO_2 nanoparticles showed faster epithelization ($p < 0.05$) compared to those treated with chitosan gel [104]. Previous studies with titanium dioxide nanoparticles synthesized with aqueous extract from *Origanum vulgare* leaves also exhibited significant wound healing activity in albino rats. The TiO_2NPs-treated wound showed no pus, bleeding, or microbial infections, unlike untreated rats that had persistent inflammation. The TiO_2NPs-treated wound revealed significant wound contraction from the 4th day, reaching 94% closure by the 12th day, while control animals had 86% closure [105].

4. Conclusions

Several biomedical applications of MNPs have been extensively studied. Among them, the development of formulations able to accelerate wound healing stands out as very promising. An important pathway to synthesizing NPs is via the use of plant extracts, which makes the process more financially friendly and sustainable, considering its low environmental impact. Therefore, numerous studies have investigated the potential role of these NMs in the healing process using different experimental models and methodologies and have reached satisfactory results. This is mostly linked to their physicochemical properties, the antibacterial and healing effects of the metals involved, and their joint effect with the bioactive compounds in the medicinal plant extracts studied.

We visualize future review works based on the perspective of large-scale production of drugs containing greenly synthesized NPs. Those formulations could depict NPs as promising compounds for the industry, thus allowing their production in an available form to the general population and, consequently, suggesting the prevention of complications from poor healing and/or infections, significantly improving the quality of life of patients by reducing aesthetic discomfort and the clinical and financial burden, among others.

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Conflicts of Interest: The authors declare no conflicts of interest.

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