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MINI-REVIEW

Wound healing applications of biogenic colloidal silver and gold nanoparticles: recent trends and future prospects

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Abstract
Nanotechnology has emerged as a prominent scientific discipline in the technological revolution of this millennium. The scientific community has focused on the green synthesis of metal nanoparticles as compared to physical and chemical methods due to its eco-friendly nature and high efficacy. Medicinal plants have been proven as the paramount source of various phytochemicals that can be used for the biogenic synthesis of colloidal silver and gold nanoparticles as compared to other living organisms, e.g., microbes and fungi. According to various scientific reports, the biogenic nanoparticles have shown promising potential as wound healing agents. However, not a single broad review article was present that demonstrates the wound healing application of biogenic silver and gold nanoparticles. Foreseeing the overall literature published, we for the first time intended to discuss the current trends in wound healing via biogenic silver and gold nanoparticles. Furthermore, light has been shed on the mechanistic aspects of wound healing along with futuristic discussion on the faith of biogenic silver and gold nanoparticles as potential wound healing agents.

Keywords Wound healing · Phytonanotechnology · Silver nanoparticles · Gold nanoparticles · Green synthesis · Nanomedicine

Introduction

A wound can be defined as a damage of the defensive skin epithelial membrane with or without the injury of connective tissue of muscle, bone, or nerves. It can be caused by surgical operation, heat blow, chemicals, cut, pressure, shear, stress cold, friction, or some disease (Hutchinson 1992; Mukherjee et al. 2017). According to a current market research report, the wound care products are predicted to increase from 18.35 billion US dollars in 2017 to 22.01 billion USD by 2022 (Rohan 2017). Generally, the wound healing industry is bifurcated based on two types of wound care products used to treat chronic and acute wounds.

Chronic wounds Chronic wounds are usually considered to be a silent epidemic that possesses serious threat towards public health and global economy. According to the worldwide advanced wound care market analysis, the patients suffering from chronic wounds are now getting better treatment due to the newly developed wound care products that are safe, effective, and useful in faster healing. Technavio's analysts forecasted the global advanced wound care market that grow at a 4.69% (CAGR) from 2013 to 2018 in the USA, Canada, UK, China,

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India, and the rest of the world (WiseGuyReports 2017). Accordingly in USA, nearly 15% of Medicare beneficiaries (8.2 million) had at least one type of chronic wound in which 4% have surgical infections followed by 3.4% diabetic infections. All the wound types cost 28.1–96.8 billion USD (Nussbaum et al. 2017). Another study reported the incidence of chronic wounds in nine million insured persons in Germany (Heyer et al. 2016). In UK, the economic burden that wounds carry out on the National Health Service was estimated at the cost of £5.3 billion by managing 2.2 million wounds (Guest et al. 2015). In Australia, the estimated direct health care costs of chronic wounds ~ A$3 billion per annum that is equivalent to ~ 2% of Australian national health care expenditure (Graves and Zheng 2014). Accordingly, 241 patients with chronic wounds of more than 2-week duration were studied in the wound healing department in Shanghai with the mean treatment cost of 12,055.4 ± 9206.3 Chinese yuan (Sun et al. 2017).

Acute wounds Acute wounds are found in patients who pass through surgical treatments, traumas, abrasions, or epithelial burns. These wounds are produced due to incisions; as a result, the patients become more prone to bacterial infections. Therefore, for treating such type of wound infections, implementation of new strategies is required. Recently, a study was conducted in North America, Europe, and Asia to determine the rates of surgical site infections (SSIs). In the mentioned regions, an average SSI was found to be 1.9% while 1.0% of the population has *Staphylococcus aureus* SSI rates undergoing spine surgery. Similarly, 49.3% people have *S. aureus* infections towards spinal SSIs whereas 37.9% to the methicillin-resistant *Staphylococcus aureus* (MRSA) (Patel et al. 2017). According to a systematic review conducted in the USA, economic burden was increased on the people treated for SSIs. In the USA, the rate of SSIs is continuously increasing and the patients were found to have complex comorbidities (Berríos-Torres et al. 2017). Currently, a prevalence study was conducted in UK to estimate the people having complex wounds due to ulcers in their lower limbs, pressure ulcers, and wounds after surgical operations. In this study, all the complex wounds were estimated to be 1.47 per 1000 people (Cullum et al. 2016). According to a latest report, an estimated 30 billion AUD loss occurs due to road accidents including > 3.7 billion AUD loss per annum to the financial plan of the Australian government (Bradley 2017).

Conventional methods to treat chronic and acute wounds have become a serious threat to the public health and global economy. Therefore, alternative strategies should be developed for the cost-effective and targeted treatment of wound infections. In this scenario, the emerging field of nanobiotechnology may provide an alternative platform to develop novel therapeutic agents for the treatment of wound infections. Due to the lack of a comprehensive review, we designed this article to highlight the green synthesis of colloidal silver and gold nanoparticles as prospective therapeutic agents for wound healing. The current article explains the mechanism of wound healing foreseeing the latest developments in the field and mechanistically describes the application of biogenic NPs as promising future wound healing agents.

Mechanism of wound healing: process of angiogenesis

Wound healing (WH) represents a complex biological process that contains a stepwise sequence of cellular and molecular interactions directed to repair the injured tissue in order to reinstate its defensive barrier function. The process of WH takes place in four different coinciding phases, which are hemostasis, inflammation, proliferation, and remodeling (Gurtner et al. 2008; Janis and Harrison 2014). In WH, different mediators comprising growth factors, cytokines, and chemokines which act through their specific receptors are involved to stimulate wound closure (Qing 2017). Initially after the skin injury, the exposed sub-endothelium, collagen, and tissue factor stimulate platelet aggregation. It causes degranulation and release chemotactic factors (chemokines) and growth factors (GFs) to form the clot. All the mentioned processes accomplish an effective hemostasis (Martin and Leibovich 2005). Neutrophils are penetrated at the site of wound infection after the release of platelets, and accumulation of fibrin matrix occurs. Subsequently, after 2–3 days of wound injury, the monocytes are released and developed into macrophages used in the WH process (Cohen and Mosser 2013). The next proliferative phase of WH is characterized by accumulation of different cell profusion in connective tissue. It involves tremendous amounts of cells including fibroblast, keratinocytes, and endothelial cells that move towards the injured cite. The extracellular matrix (ECM) including proteoglycans, hyaluronic acid, collagen, and elastin builds up a granulation tissue to substitute the original formation of clot. Many kinds of cytokines and GFs participate in this process including transforming growth factor-b family (TGF-b1–3), interleukin (IL) family, and angiogenesis factors (i.e., vascular epidermal growth factor) (Lian and Li 2016). This phase continues for days and weeks. Afterward, remodeling is the last phase of WH, which necessitates an accurate stability between apoptosis of existing cells and regeneration of new cells. It is characterized by the gradual degradation of profuse ECM followed by type I and type III collagen that are very crucial at this stage, and the process may take few months to several years (Plikus et al. 2017; Tsai et al. 2017).

Limitations of conventional treatment strategy

Currently, several medicines are available in the market that are frequently used for WH, like blood clotting formation, inflammatory responses, platelet function, and cell proliferation. These medicines include glucocorticoid steroids, non-steroidal anti-inflammatory, and chemotherapeutic drugs.

Glucocorticoid steroids

These therapeutic agents are usually known as anti-inflammatory mediators that restrain the wound repair process through comprehensive anti-inflammatory properties and overthrow the cellular wound reactions together with fibroblast proliferation and collagen synthesis. These drugs are recommended to patients for the prevention of nausea and vomiting. However, glucocorticoids are immunosuppressive and are associated with atypical or opportunistic infections in either short-term (high dose) or chronic (long term > 21 days) administration. Documented problems comprise hyperglycemia, psychosis, peptic ulceration, and poor bone healing (Bartlett and Hartle 2013; Dhatariya 2013).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to manage inflammation, rheumatoid arthritis, and pain management. According to the AAPCC-NPDS annual report, 107,047 cases were registered who ingested ibuprofen. Among them, 46,920 documented NSAID ingestions are given to children aged 5 years or younger (Gummin et al. 2017). NSAIDs (ibuprofen, naproxen, diclofenac, ketoprofen, indomethacin, and acetylsalicylic acid) were used as non-selective cyclooxygenase-1 (COX-1) and COX-2 inhibitors. The current NSAIDs (rofecoxib, celecoxib, etoricoxib, and valdecoxib) explicitly inhibit COX-2. Both (COX-1 and 2) produce prostaglandins which are responsible for regulating inflammation (Varga et al. 2017; Weintraub 2017).

Chemotherapeutic drugs

These therapeutic agents are premeditated to inhibit the metabolic pathways that are very crucial in cell division, angiogenesis, and wound repair. These drugs also interfere cell movement into the wound, decline the formation of primary wound matrix, reduce the fabrication of collagen, harm fibroblast production, and constrain shrinkage of wounds. Moreover, these mediators usually deteriorate the immune system of the patients, thus slowing down the wound repair process. Chemotherapy induces neutropenia, anemia, and thrombocytopenia; as a result, the patient become more susceptible to infection, diminishing the oxygen availability to the wound, and the patients are at risk of too much bleeding at the wound site (Franz et al. 2007). Currently, several cellular signaling pathways have been identified which are involved in angiogenesis that can be utilized in producing novel therapeutic agents for targeted therapies. Different types of angiogenesis inhibitors have been reported including bevacizumab, brivanib, cabozantinib, cediranib, everolimus, lenvatinib, linifanib, nintedanib, ramucirumab, refametinib, regorafenib, sorafenib, trebananib, and vatalanib (Berretta et al. 2016).

Interface of nanotechnology, plants, and wound healing

The currently available therapeutic agents for the treatment of wound infections are very costly, unsafe, and toxic for the surrounding healthy tissues. In this regard, nanotechnology has the prospective competence to engross the matter of concerns at the molecular level as it is a vibrant discipline connecting biology, chemistry, and physics. Significant research in nanotechnology has established new prospects for developing potential therapeutic agents (Kanwal et al. 2017; Khan et al. 2018). These NPs carry specific size and shape and with their distinctive optical and thermal characteristics can be applicable for the treatment of wound infections. Therefore, researchers have focused to find out an alternate therapeutic approach by using biocompatible and safer green methods using plants for the fast and economical synthesis of biogenic colloidal silver and gold NPs (Kasithevar et al. 2017; Ovais et al. 2018; Venkatachalam et al. 2015; Wang et al. 2017). Mechanism of plant extract-mediated synthesis and stabilization of AuNPs and AgNPs is shown in Fig. 1, while a detailed scheme of synthesis, optimization, characterization, and prospective use as wound healing agent is shown in Fig. 2. Until now, the nanoparticles were synthesized by different physical and chemical methods. However, the current research is almost focused on the biological synthesis of NPs (Ovais et al. 2016). In this regard, the microorganisms (bacteria and fungi) can also be used for the synthesis of NPs; however, plants will provide a more suitable platform for the safer and green biocompatible synthesis since they lack the use of several costly and toxic chemical compounds for growth in the media (Ovais et al. 2017b). Additionally, the synthesis of plant-based NPs is fast, stable, and economical. Moreover, the NPs can be synthesized with different sizes and shapes as compared to their synthesis via organisms.

Medicinal plant extracts reduce salt solutions leading to formation of corresponding nanoparticles. Such green-synthesized nanoparticles are formed due to the presence of phytochemicals, e.g., phenolics, flavonoids, polysaccharides, vitamins, and amino acids as reducing agents in aqueous plant extracts (Ahmad et al. 2017; Ayaz et al. 2016, 2017; Kasithevar et al. 2017; Khalil et al. 2017b, d; Ovais et al. 2016, 2017b; Zohra et al. 2018). Green-synthesized nanoparticles do not need to be capped by adding chemical agents as they are already capped by the phytochemicals released by extracts (Ali et al. 2017; Ayaz et al. 2017; Barabadi et al. 2017b; Khalil et al. 2017a, c, e; Subbaiya et al. 2017). Nanoparticles are synthesized by the

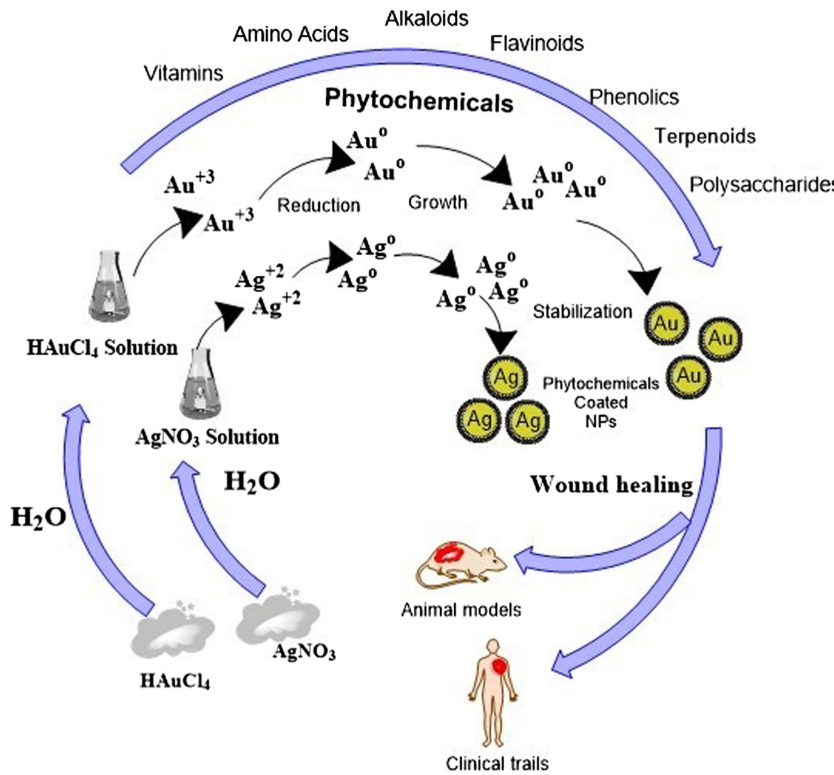

Fig. 1 Mechanism of plant extract-mediated synthesis and stabilization of AuNPs and AgNPs for wound healing application

medicinal plant extracts and do not have hazardous chemicals and, hence, find enormous applications in medicine (Barabadi et al. 2017a; Ovais et al. 2017a).

The combination of nanotechnology and medicinal plants possesses tremendous importance in nanomedicine, particularly for treatment of wound healing (Anwar et al. 2017; Emmanuel et al. 2017). Various green-synthesized metal nanoparticles have been regarded as safe for drug delivery due to their biological activities like antibacterial, antifungal, antiviral, and anti-inflammatory. Most importantly, few nanoparticles like silver and gold have found a place in the healing of wounds (Oyarzun-Ampuero et al. 2015; Pannerselvam et al. 2017).

Significance of silver and gold nanoparticles in wound healing

Nanoscale silver plays remarkable role in healing of wounds because of its cost-effectiveness, safety, lower toxicity, and broad-spectrum resistance against different microorganisms (Yah and Simate 2015). Silver is highly antibacterial metal known for centuries (Konop et al. 2016), but silver nanoparticles are new-age bullets because of their large surface area to volume ratio that causes enhancement of their effectivity (Gunasekaran et al. 2011). Moreover, the presence of a thicker peptidoglycan layer (60 to 80 nm) in Gram-positive bacteria and a thinner peptidoglycan layer (20–40 nm) along with the presence of lipopolysaccharides and teichoic acids in Gram-negative bacteria results in differential healing effects produced by silver nanoparticles. Coated/capped silver nanoparticles (natural process in green synthesis) have their size even much smaller that exposes the reactive and catalytic sites for quick counterattacks during inflammation, proliferation, and remodeling. Silver nanoparticles are loaded on cotton fabrics for wound dressing by a definite procedure and then used as bacterial killers for the fastest healing of wounds (Gunasekaran et al. 2011). It was illustrated that silver nanoparticles block the respiratory pathways of cells keeping them alive so that the reproliferation of skin cells (fibroblasts and keratinocytes) might take place leading to its reconstruction with the passage of time, hence restoring the skin surface (Rigo et al. 2013). An in vivo study suggested that the suppression of the innate immune system is involved in accelerating the process of wound healing and deaccelerating the scarring process (Heydarnejad et al. 2014). The time span for healing of damaged area depends on the size and morphology of silver nanoparticles, and their improvement in cosmetics occurs in a dose-dependent manner revealed by molecular studies (Tian et al. 2007). Gold nanoparticles, along with epigallocatechin gallate and α-lipoic acid, have proved to be highly antioxidant and anti-inflammatory resulting in skin wound healing in vivo (Leu et al. 2012). Collagen and gold nanoparticle composites produced skin wound healing response in a dose-dependent manner (Akturk et al. 2016). It was recently reported that

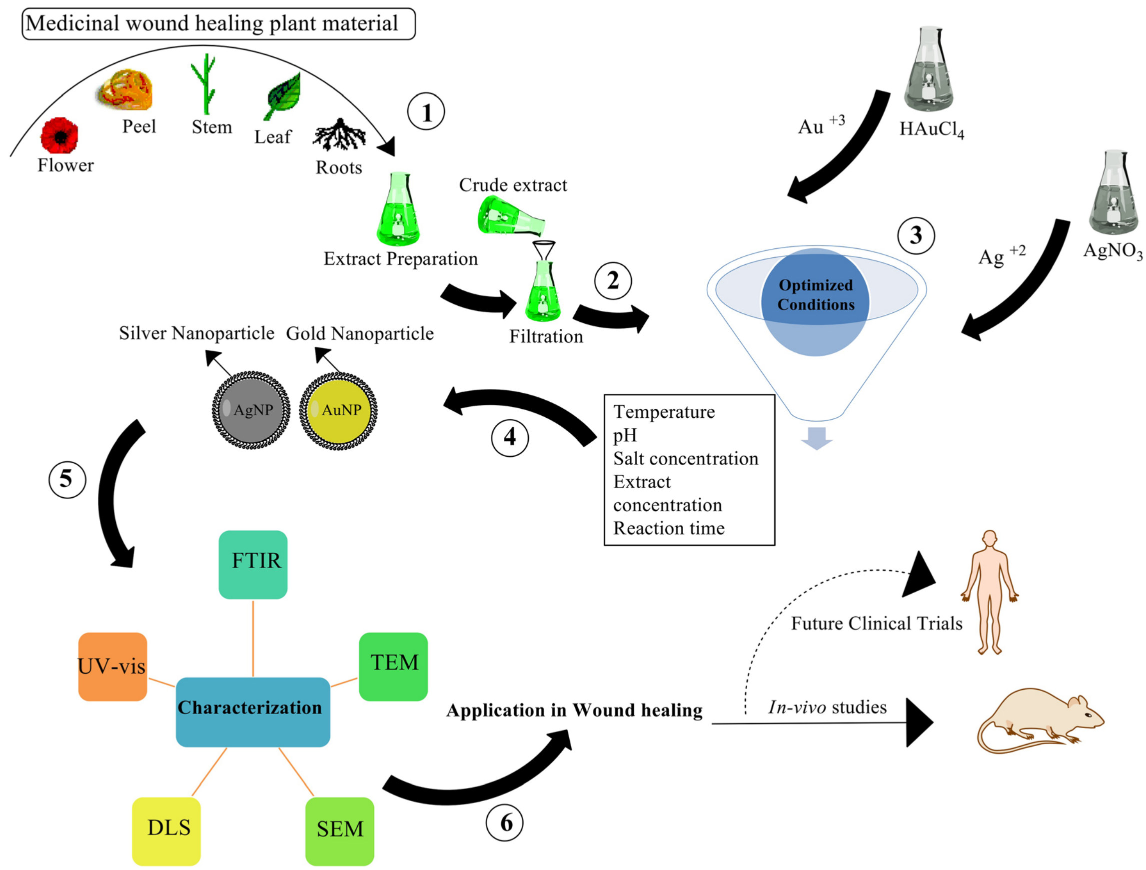

Fig. 2 Detailed scheme of AgNP and AuNP synthesis, optimization, characterization, and prospective use as wound healing agent. In step 1, extract of wet/dry plant material is obtained via standard protocol. Steps 2 and 3 deal with the optimization of AgNP and AuNP synthesis by varying different reaction parameters. In step 4, nanoparticles of both Ag and Au are obtained in the form of pellet by centrifugation of reaction mixture. Step 5 deals with proper characterizations and elucidation of synthesized nanoparticle morphology, size, shape, functional groups attached, etc. In step 6, properly characterized and highly stable nanoparticles are exploited for wound healing application

phytochemically stabilized gold nanoparticles coating on a hydrocolloid membrane have significant effects on the cure of cutaneous wounds (Kim et al. 2015). Gold nanoparticles exert positive influence on healing of wound infections by means of photobiomodulation therapy (Lau et al. 2017). Furthermore, a study was carried out on cryopreserved fibroblast culture along with gold nanoparticles for the treatment of burns in rats. The antimicrobial and antioxidative effects of gold nanoparticles proved very effective in wound healing and regeneration of damaged collagen tissues (Volkova et al. 2016). Gold nanoparticles are involved in secretion of proteins (IL-8, IL-12, VEGF, and TNF-α) which are important candidates for wound healing via their antiangiogenic and anti-inflammatory activity (Pivodová et al. 2015).

Biogenic synthesis of gold and silver nanoparticles implicated in WH

We have reviewed numerous studies which report the synthesis of silver and gold NPs using different plant extracts applicable in wound healing shown in Table 1. Green-synthesized MNPs using *Aloe vera*, *Solanum xanthocarpum* L., *Indigofera aspalathoides*, *Solanum indicum*, *Ziziphus nummularia* and *Citrullus colocynthis*, *Kigelia Africana*, *Coriandrum sativum*, *Arnebia nobilis*, *Cassia auriculata*, *Virola oleifera*, *Viburnum trilobum*, *Tridax procumbens*, *Lansium domesticum*, *Azadirachta indica*, *Dimocarpus longan*, *Cucumis sativus*, *Coleus forskohlii*, and *Orchidantha chinensis* have been found to be remarkably effective in healing of burns and normal wounds, respectively (Fig. 3) (Al-Shmgani et al. 2017; Appapalam and Panchamoorthy 2017; Arunachalam et al. 2013; Augustine et al. 2016; Bhagavathy and Kancharla 2016; Chandran et al. 2006; Dhapte et al. 2014; Elbagory et al. 2017; Garg et al. 2014; Kumarasamyraja and Swamivelmanickam 2014; Mohanta et al. 2017; Naraginti et al. 2016; Pannerselvam et al. 2017; Pothireddy et al. 2016; Raghuwanshi et al. 2017; Shankar et al. 2015; Shinwari et al. 2003, 2006; Venkatachalam et al. 2015; Wang et al. 2017). *Arnebia nobilis* root extract-synthesized silver nanoparticles revealed enhancement of hydrogel-mediated wound healing process (Garg et al. 2014). Biosynthesized silver nanoparticles

Table 1 Studies reporting phytosynthesized silver and gold nanoparticles as potential wound healing agents

Plant	Part used	Nanoparticle synthesized	Size	Shape	Experimental design	References
Arnebia nobilis	Root	AgNPs	40–70 nm	Spherical	Wound healing potential of the biogenic nanoparticles was studied by preparing them in a hydrogel. Excision wound model was used to study the wound healing potential.	Garg et al. (2014)
Cassia auriculata	Whole plant	AgNPs	15–90 nm	Spherical	Application of silver nanoparticles was studied in excision-based models. Tensile strength and wound closure were the wound healing parameters.	Kumarasamyraja et al. (2014)
Bryonia laciniosa	Leaves	AgNPs	15 nm	Spherical	Biogenic silver nanoparticle-based gel was prepared in gellan gum. In vivo studies were used to investigate the wound healing potential accompanied by ELISA based on vitro assays for quantification of cytokines.	Dhapte et al. (2014)
Lansium domesticum	Whole plant	AgNPs	74 nm	Fruit peel	AgNPs at the rate of 0.1% (*w/w*) in pluronic gels were used for wound healing. Tensile strength, collagen content, and wound closure were studied.	Shankar et al. (2015)
Cucumis sativus	Leaves	AgNPs	21–23 nm	Spherical	Biogenic silver nanoparticle-based ointment in paraffin base was studied in excision wound-based model.	Venkatachalam et al. (2015)
Azadirachta indica	Leaf	AgNPs	60–85 nm	Spherical and cubical	Nanoparticles were studied in the form of ointment in diabetes-induced rats for wound healing.	Bhagavathy et al. (2016)
Coleus forskohlii	Root	AgNPs	5–15 nm	Spherical	Nanoparticles were applied as topical treatment, and various parameters like healing rate and collagen quantification were studied.	Naraginti et al. (2016)
Coleus forskohlii	Root	AuNPs	5–18 nm	Nanorods, nanoprisms, and nanotriangles	Same as above.	Naraginti et al. (2016)
Catharanthus roseus	Leaves	AgNPs	20 nm	Spherical	Excision wound model was used to check the wound healing potential.	Al-Shmgani et al. (2017)
Biophytum sensitivum	Whole plant	AgNPs	11.4 nm	Spherical	Phytogenic nanoparticles were immobilized with calcium pectinate to make a wound dressing, while their antibacterial activities were studied.	Augustine et al. (2016)
Cinnamomum verum	Bark	AgNPs	78.8 nm	Spherical	The biogenic nanoparticles were investigated in different wound models like incision wound model, excision wound model, and dead space wound model.	Pothireddy et al. (2016)
Woodfordia fruticosa	Flowers	AuNPs	65 nm	Prisms and rods	Nanoformulation using biogenic gold nanoparticles and carbopol was prepared and studied for various wound healing parameters. Epithelialization, wound closure, collagen quantification, and histopathology were performed.	Raghuwanshi et al. (2017)
Delonix elata	Leaves	AgNPs	36 nm	Spherical	Nanoparticles were coated on muslin cloth and checked for wound healing potential by investigating the size of lesions.	Wang et al. (2017)
Ardisia solanacea	Leaves	AgNPs	27 nm	Spherical	In vitro wound healing assay was performed using normal fibroblast cell lines (BJ-5Ta). Wound healing was confirmed through phase contrast microscopy.	Mohanta et al. (2017)
Galenia africana	Aerial parts	AuNPs	11 nm	Spherical	Antimicrobial potential of biogenic nanoparticles against wound-related bacteria was explored.	Elbagory et al. (2017)
Hypoxis hemerocallidea	Aerial parts	AuNPs	26 nm	Spherical	Same as above	Elbagory et al. (2017)
Cassia roxburghii	Leaves	AgNPs	35 nm	Spherical	Biogenic AgNPs were impregnated with cotton fabrics in different test concentrations.	Pannerselvam et al. (2017)
Aerva lanata	Whole plant	AgNPs	5–50 nm	Spherical	Antimicrobial potential of biogenic nanoparticles against wound-related bacteria.	Appapalam et al. (2017)

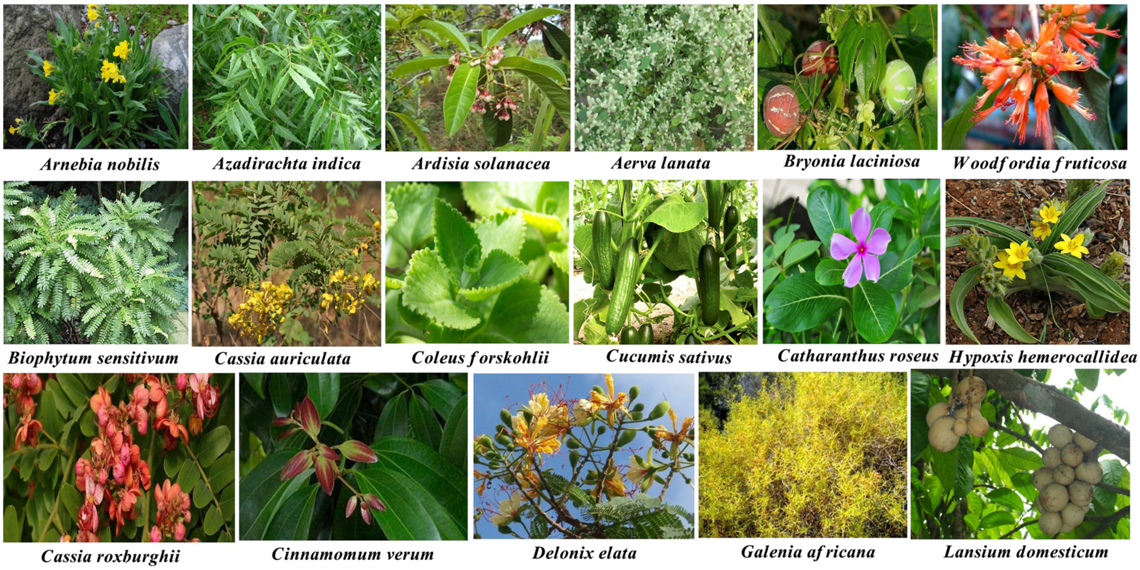

Fig. 3 Various medicinal plants utilized in green synthesis of AgNPs and AuNPs for wound healing application. Adapted with permission from Shinwari et al. (2003) and Shinwari et al. (2006)

modulated by peel extracts of *Lansium domesticum* possess antimicrobial activity that provides relief from all types of wounds. Pluronic F-127 gels used as delivery system for silver nanoparticles have been found highly beneficial for treating inflammation and swelling (Shankar et al. 2015). Silver nanoparticles synthesized using an aqueous extract of *Viburnum trilobum* (cranberry powder) possess greater wound healing ability because of the presence of a higher quantity of antioxidants of cranberry that behave as reducing as well as capping agents (Ashour et al. 2015). Leaf extracts of *Azadirachta indica* resulting in silver nanoparticle formation cause marked alleviation of wounds by angiogenesis of the targeted tissue in vivo (Bhagavathy and Kancharla 2016). A symbiotic relationship of an endophytic fungus and a Chinese medicinal herb, *Orchidantha chinensis*, leading to silver nanoparticle production possesses excellent healing potential against infected wounds (Wen et al. 2016).

Gold nanoparticles synthesized from various medicinal herbs also have demonstrated remarkable wound healing potential (Awan et al. 2017; Milaneze et al. 2014). *Aloe vera* extracts forming gold and silver nanoparticles were found beneficial for reducing wound infections (Chandran et al. 2006). Gold and silver nanoparticles synthesized using root extract of *Coleus forskohlii* showed antibacterial, antioxidant, and anti-inflammatory action in albino Wistar rats (Naraginti et al. 2016).

Mechanism of wound healing via biogenic NPs

Different authors have explained different proposed mechanisms which are manifested by the biogenic nanoparticles to promote wound healing. In the wound healing process, collagen plays an important role. It is observed that an elevated concentration of hydroxyproline around the wound area is considered as an indicator for the high amount of collagen fiber that leads to the enhancement of the tensile strength, which is an indication of wound healing. Recently, gold nanoparticles biosynthesized using *Woodfordia fruticosa* were complexed with carbopol for making an ointment. The results indicated a high level of hydroxyproline and therefore collagen fibers resulting in tensile strength as well as accelerated healing process as indicated in Figs. 4 and 5 (Raghuwanshi et al. 2017). Another important matrix by which the efficiency in wound healing is determined is by the process of rapid epithelization. Dhapte et al. (2014) investigated the wound healing potential of a gel formulation containing silver nanoparticles biosynthesized through *Bryonia laciniosa* and compared the results with already available marketed cream containing silver sulfadiazine as an active component. After the 14 days of wound healing experiment, 92% healing was observed in the biogenic silver nanoparticle-based gel while 78% wound healing was observed in the marketed cream. The authors attributed rapid wound healing of biogenic silver to an effective epithelization process. Furthermore, significant inflammatory response and scar formation were reported for the silver sulfadiazine cream; however, there were negligible scaring and no rubor formation in the case of biogenic silver nanoparticle-based gel. The improved appearance of the wound was attributed to the immunomodulatory potential of biogenic silver altering the cytokine cascade (Dhapte et al. 2014). Furthermore, the quantification of cytokines indicated the initiation of wound healing from a very low level of IL-6 and IL-10 which could be the potential reason of scarless wound healing with low inflammation induced by biogenic

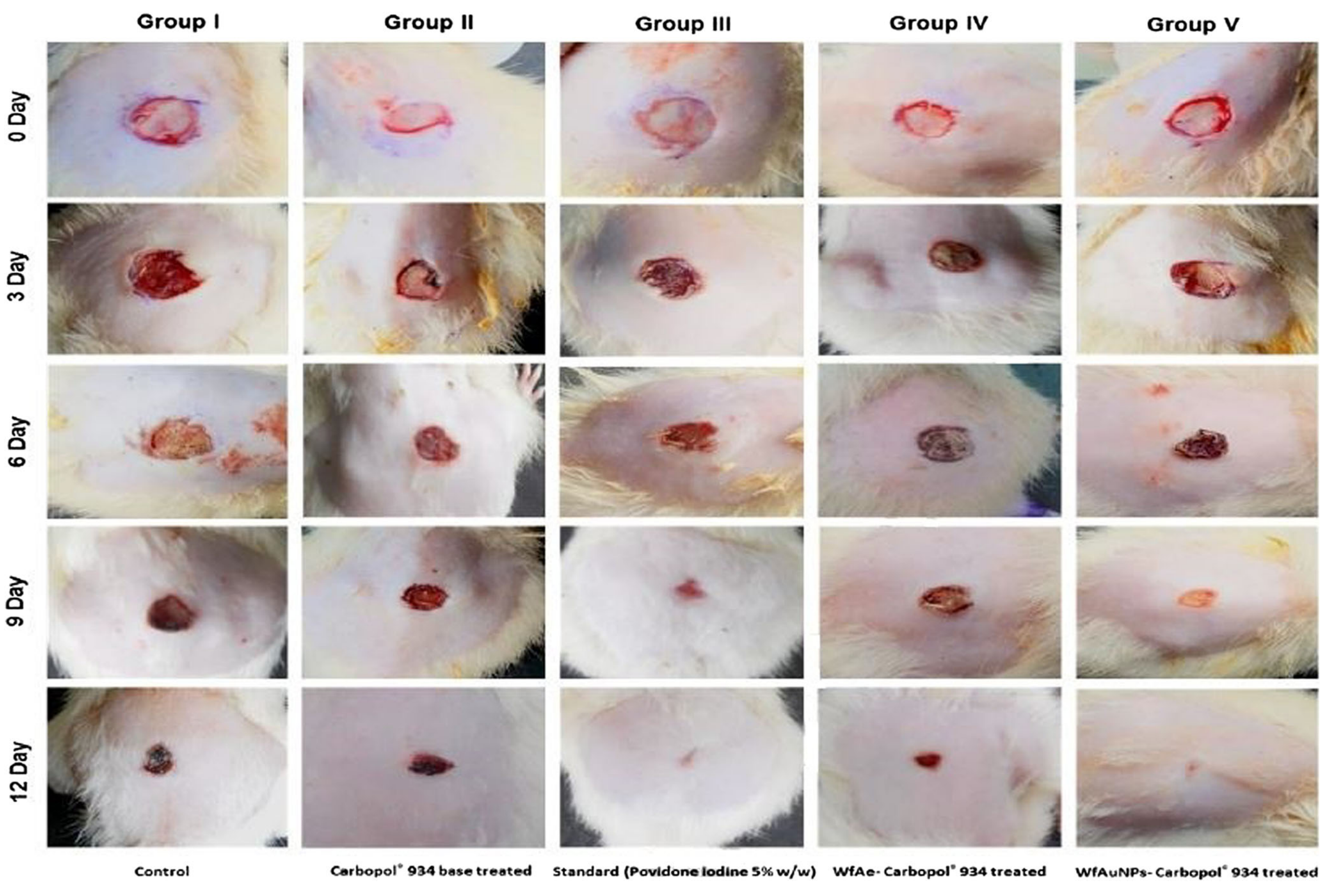

Fig. 4 Wound healing assessment of full thickness excision wounds in Wistar albino rats. Macroscopic appearance of wound closure (group I to group V) at 0, 3, 6, 9, and 12th days after treatment with different formulations. Adapted with permission from Raghuwanshi et al. (2017)

silver nanoparticle-based gel. IL-6 is a pro-inflammatory cytokine that can induce activation of monocytes and proliferation of fibroblasts, which can lead to inflammatory response. Moreover, macrophages and neutrophils are recruited by IL-6 to the wound site for keratinocyte migration, cellular proliferation, and extracellular matrix production which can lead to scar formation. As a response to the inflammation, keratinocytes produce IL-10 to neutralize the inflammation caused by IL-6. Less IL-6 leads to lower IL-10 and hence suggests decrease in the inflammation as well as scar formation. Furthermore, in a study by Venkatachalam and coworkers, the biogenic silver nanoparticle-based ointment in paraffin base was studied in excision wound-based model (Venkatachalam et al. 2015). The study reported tremendous activity of nanobased ointment in comparison to the standard drug Betadine ointment as shown in Fig. 6. Recently, *Catharanthus roseus*-mediated silver nanoparticles indicated substantial recovery of wound after 4 days relative to the positive and negative control groups. The wound closure was reported to be 98% as compared to 85% in the control. The authors suggested that the antimicrobial potential of the biogenic silver nanoparticles may have led to the improved and fast recovery of the wound. No contamination in the wound area led to the efficient restoration of tissue integrity (Al-Shmgani et al. 2017). Other rapid wound repairing properties of silver nanoparticles were attributed to the potential of modulating the differentiation of fibroblasts leading to wound contraction (Gunasekaran et al. 2011). Key advances in proposed mechanisms of wound healing shown by green-synthesized AuNPs and AgNPs are sketched in Fig. 7.

A recent study on the chemically synthesized silver nanoparticles yields interesting results for wound healing in zebra fish (Seo et al. 2017). Silver nanoparticles were applied directly to the wounds as well as used in immersion. The AgNP immersion indicated rapid healing as compared to the direct application of the silver nanoparticles in zebra fish. The fast healing rate of the immersion treatment of AgNPs to the laser-induced wound in zebra fish was attributed to the well-defined differentiation of the epidermal cells to skin cells. The effective wound healing by the treatment of silver nanoparticles was also evidenced by gene expression studies involved in wound repair. In another research study, AuNPs synthesized via laser ablation yielded promising results in wound care (Lau et al. 2017). As synthesized, AuNPs were treated alone and with photobiomodulation for cutaneous wounds, and both revealed beneficial results. The author argued an inflammatory response and effective angiogenesis as the potential cause of effective wound repair. Other studies have found that high

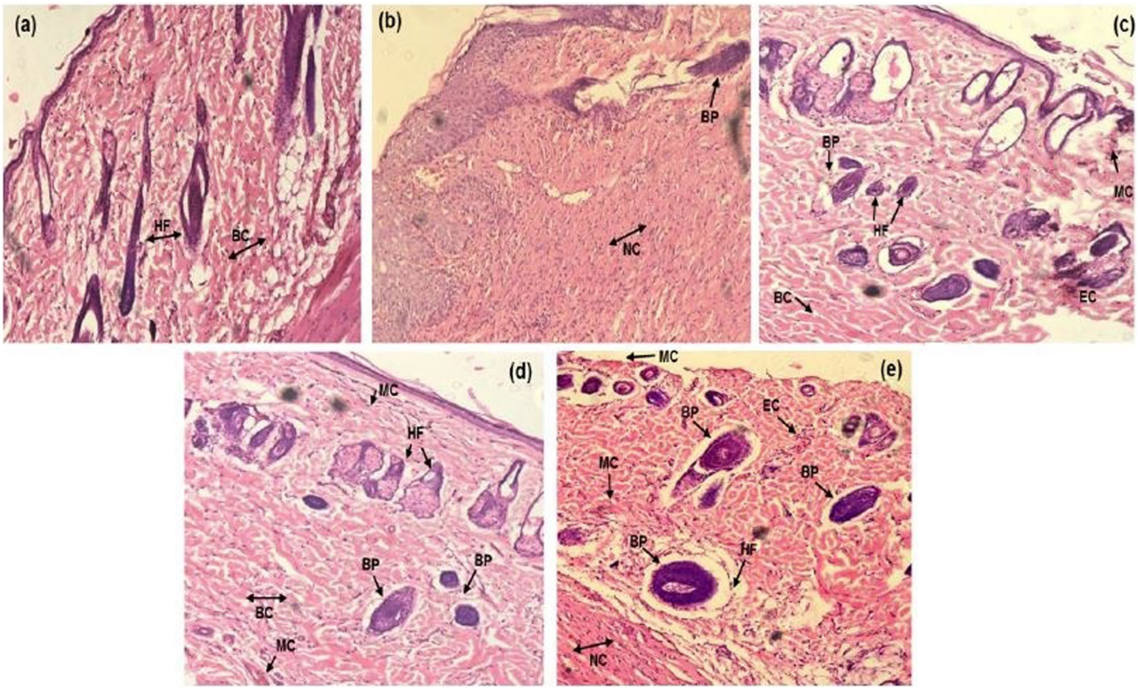

Fig. 5 Micrographs of H&E-stained wounded tissues for **a** control, **b** Carbopol® 934 ointment base treated, **c** standard, povidone iodine 5% (*w*/*w*) ointment treated, **d** WfAe-Carbopol® 934 treated, and **e** WfAuNPs-Carbopol® 934 nanoformulation treated after 15 days of treatment. Re-synthesized blood capillaries (BC), hair follicles (HF), monocytes (MC), blood platelets (BP), and erythrocytes (EC) are indicated by arrows. Adapted with permission from Raghuwanshi et al. (2017)

expression of collagen, angiopoietin 1/2 (Ang-1/2), and vascular endothelial growth factor (VEGF) by the treatment with AuNPs results in accelerated angiogenesis in wound healing process. In another recent study, the wound healing potential of AuNPs was attributed to its antioxidation, anti-inflammation, and non-antiangiogenesis properties which lead to the formation of fibroblasts and decrease in the apoptosis of cells eventually contributing to the wound healing process (Volkova et al. 2016).

In vitro biocompatibility of biogenic AgNPs and AuNPs

Metallic nanoparticles are known for their interaction with cellular components leading to the generation of ROS causing cellular damage (Lee et al. 2017). Usually, the same mechanism is reported for the toxicity of biogenic nanoparticles in cancer cells, parasites, and other microbial entities. Silver and gold nanoparticles are particularly considered toxic due to their biological reactivity. Therefore, before any biomedical applications involving biogenic silver and gold nanoparticles materialize, it is important to establish the safety and compatibility of the phytogenic nanoscaled silver and gold. While following the same feat, many researchers have investigated the toxicity of phytogenic silver and gold nanoparticles against normal cells in vitro. In one of the recent study, *Salacia chinensis*-mediated silver nanoparticles indicated a non-toxic nature towards normal human fibroblasts cells (L929) at different concentrations (2.4–78.62 μg/mL). At all the tested concentrations, the cell viability was greater than 95%. Similarly, at the highest concentration of 78.62 μg/mL, the hemolysis induced as < 3% that falls within the biocompatible range (Jadhav et al. 2018). In a comparative study on the *Olax scandens*-mediated silver nanoparticles and chemically derived silver nanoparticles, the former was found to be biocompatible up to 15 μM against different normal human cell lines like HUVEC, CHO, and H9C2 while chemically synthesized silver nanoparticles manifested cytotoxicity at lower doses. At further higher concentration, i.e., 30 μM, the *Olax scandens*-mediated silver nanoparticles induced mild toxicity (Mukherjee et al. 2014). The hemocompatability of the *Croton bonplandianum*- and *Syzygium cumini*-mediated silver nanoparticles has also been established (Beg et al. 2017; Bhanumathi et al. 2017).

Recently, the compatible nature of the biogenic gold nanoparticles has also been thoroughly investigated. *Clitoria ternatea*-mediated gold nanoparticles indicated excellent hemocompatability. At the highest tested concentration of 120 μg/mL, 3.75% hemolysis was observed (Vanaraj et al. 2017). Biocompatibility of the tea-mediated gold nanoparticles in MCF-7 and PC-1 after 24 h of treatment has been established (Nune et al. 2009). Biogenic gold nanoparticles mediated by soybeans also indicated compatibility in fibroblast cells.

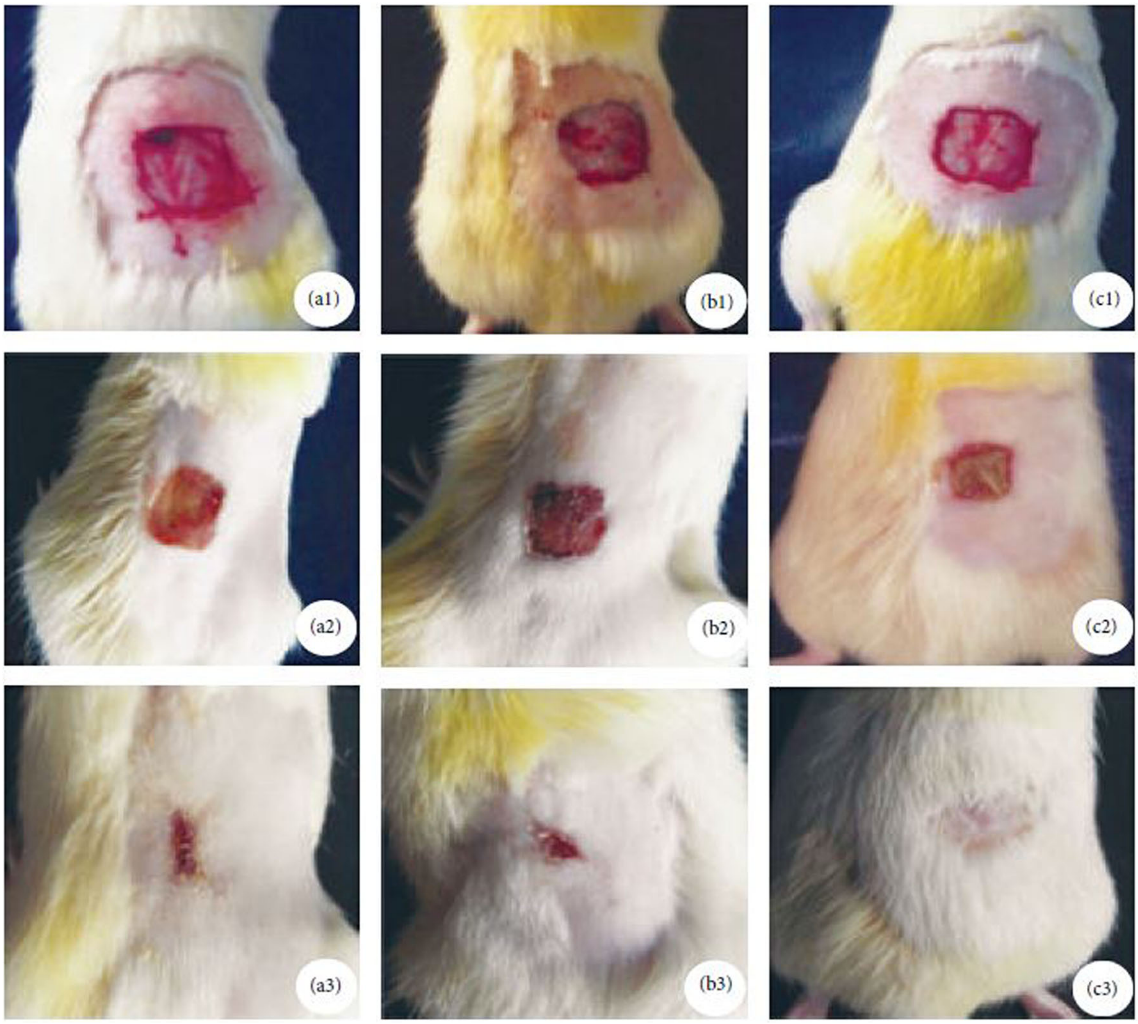

Fig. 6 Progress of cutaneous wound healing in negative-control rats untreated (a1–a3), positive control rats treated with standard drug Betadine ointment (b1–b3), and experimental rats treated with biomolecules loaded LEAgNP-based ointment (c1–c3). Wounds of the dorsal skin before and after treatment without (a1–a3) and with (b1–b3, c1–c3) ointments. Adapted with permission from Venkatachalam et al. (2015)

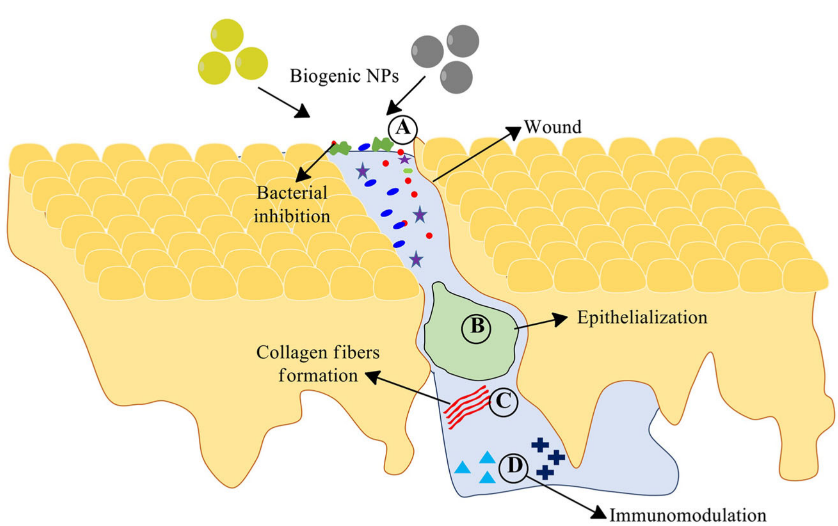

Fig. 7 Key advances in proposed mechanisms of wound healing shown by biogenic AuNPs and AgNPs. A biogenic AgNPs and AuNPs inhibiting various bacterial growth, ultimately enhancing wound healing process, B enhanced epithelization by nanoparticles, C increase in the production of collagen fibers, D immunomodulation

Lantana montevidensis-inspired gold nanoparticles indicated compatibility in CHO cells. The compatibility was assessed in the concentration range of 4 to 30 μM, and the response was dose dependent. At 4 μM, excellent compatibility was reported (Mukherjee et al. 2015). The cytocompatibility of the *Eclipta alba*-stabilized gold nanoparticles has also been demonstrated (Mukherjee et al. 2012). The method of synthesis plays a greater role in imparting the toxic or compatible nature to metallic nanoparticles. Chemically derived silver nanoparticles have recently been reported to manifest cytotoxicity towards cells (Chen et al. 2015), but it appears that phytochemical-stabilized nanoparticles have significantly reduced toxicity. Therefore, from the various clinical studies, it can be concluded that biogenic silver and gold nanoparticles are ideal for wound healing and other biomedical applications; however, further research should be carried out to establish the safety of these metal-based plant-derived nanoparticles.

Authors' conclusion and future prospects

The development of fast, economical, biocompatible, and safer green methods has shown great potential to synthesize biogenic colloidal silver and gold NPs. However, there are many underlying molecular mechanisms that are involved in the synthesis of biogenic nanoparticles that have not been portrayed yet. Investigation of these mechanisms can play a crucial role for the modified synthesis and enhanced yield of these NPs. Additionally, an advanced approach will be put forward to design and use the significant wound healing metabolites for the synthesis of such NPs. The mentioned methodologies will be helpful for the development of these NPs with a controlled shape and size. Such stratagems will upsurge the wound healing potential of biogenic NPs for the better treatment of wound infections.

Currently, very few studies as discussed are available on the wound healing potential of green-synthesized NPs. Therefore, detailed investigation of the molecular mechanisms involving different pathways is required, whereas the involvement of such pathways will be helpful to understand how these nanomedicines will be unique to wound healing. In order to develop more efficacious, cheap, and biocompatible metal NPs, further research is needed to explore different medicinal plants for the green synthesis of these NPs. The chemically synthesized NPs have main consequences of toxicity that can be replaced by the green-synthesized metal NPs which do need further coating with biocompatible surfactants and polymers. However, the protein corona effect in the case of biogenic NPs should be investigated in detail. This cutting-edge technology has a tremendous potential for the development of novel therapeutic agents via the interface of medicinal plants, nanoparticles, and wound healing. The application of biogenic silver and gold nanoparticle in WH relatively presents a new area of research. So far, the initial in vivo results are very promising and exciting. Further research is needed, though, to accomplish the mechanisms involved in WH by using biogenic silver and gold nanoparticles and to bring these NPs in to the clinical phase for the treatment of wound infections.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals or human participants performed by any of the authors.

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