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Systematic Review

Green Synthesis of Silver Nanoparticles as a Wound Healing Agent: a Systematic Review of the Biological Activities

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ABSTRACT

Background: The implication of nanotechnology includes silver nanoparticles to medical sciences, and has a revolutionary impact on therapeutic and diagnostics management. Many studies reported that silver nanoparticles (AgNPs) application can accelerate the wound healing process. This study aimed to systematically review the biological activities of the silver nanoparticles as a wound healing agent.
Subjects and Method: This article was a systematic review study conducted by searching for articles from online databases such as EBSCO, PubMed, Science Direct, and World Scientific. Populations: laboratory animals; Intervention: green synthesis of silver nanoparticles; Comparison: a standard ointment for wounds such as povidone-iodine, etc; Outcome: wound healing. The independent variable is the green synthesis of silver nanoparticles, the dependent variable is wound healing. The inclusion criteria for this study were full articles using an experimental study, with the publication year until 2022. The data extraction was focused on the biological activities of silver nanoparticles and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for systematic reviews.
Results: A total of 8 articles reviewed in this study were from countries: Egypt, India, Saudi Arabia, Singapore, and China. The green synthesis of AgNPs was accomplished using a natural aqueous extract from leaves such as Azadirachta indica, Tridax procumbens, the combinations of *Catharanthus roseus* and *Azadirachta indica, Scutellaria barbata*, the fungus *Fusarium verticillioides*, or cyanobacterial platforms (ex: *Phormidium sp., Synechocystis sp, and arthrospira sp polysaccharides*). All studies were animal-based experimental with wounds infected with bacteria and inflicted in regards to the experiment. All trials resulted in favor of the AgNPs ointment treated group compared to the untreated group or the standard ointment group.
Conclusion: Our review suggested that all studies about the efficacy of AgNPs as wound-healing therapy showed positive results.

Keywords: biological activities, silver nanoparticles, wound healing.

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BACKGROUND

The skin is an organ covering the entire body, capable of maintaining internal balance and preventing microbial invasion from the outside. Our bodies can repair damaged tissue on their own, but it takes time. However, a variety of factors can result in serious skin injuries, which can lead to wound infection, uncontrolled bleeding, and serious complications (Khorasani et al., 2018; Qian et al., 2021; Wang et al., 2021). Thus, it is critical to develop novel wound dressings with multifunctional properties such as hemostasis, low hemolysis, long-term antibacterial activity, and wound healing (Jayakumar et al., 2011; Thi et al., 2020; Zandi et al., 2021).

As an important aspect of nanotechnology, nanoparticles (NPs, less than 100 nm in one dimension) have been developed for a variety of applications, especially in the area of nanomedicine (Thorley and Tetley, 2013). Nanomaterials have been widely used in pharmaceutical applications for site-specific, temporal, and controlled drug release (Fatima et al., 2021).

Green synthesis is described as the eco-friendly method of synthesising nanoparticles using plant, plant compounds, or microbial resources rather than harmful chemicals as a reducing agent (Park, 2014). Because of their strong biocidal effect, AgNPs are universally used as a strong antimicrobial agent in the biomedical field. Aside from antimicrobial activity, AgNPs have shown to be effective antifungal, anti-inflammatory, antiviral, antiangiogene-sis, and antiplatelet agent. AgNPs are now used in the textile, food, and pharmaceutical industries due to their potential activities. Some biomedical applications of AgNPs have already been approved by the US Food and Drug Administration (Atiyeh et al., 2007; Kalimuthu Kalishwaralal et al., 2009; Kim et al., 2009; Lara et al., 2010; Nadworny et al., 2010; Oei et al., 2012; S. Shrivastava et al., 2009).

AgNPs' low cytotoxicity and small size allow them to damage microbial cell membranes and cause loss of activity of enzymes, RNA, and DNA, resulting in bacterial death (Rai et al., 2009). Further-more, AgNPs are non-toxic and have high mechanical qualities. They are designed to produce a moist environment surrounding the wound and are capable of promoting continuous oxygen during the wound healing process, and the AgNPs present in the material help to prevent microorganism growth and infection around the wound site (Pryshchepa et al., 2020).

The current study systematically reviews the wound healing efficacy of AgNP derived from such plants, as measured by various microscopic methods.

SUBJECTS AND METHOD

1. Study Design

This study uses a systematic review study design. The Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) standards were followed for conducting this systematic review (Hutton et al., 2015). Only English language-based literature was used in an electronic search of EBSCO, PubMed, Science Direct, and World Scientific from their establishment to July 31, 2022. The search term used was (nanotechnology) AND (wound healing). Additionally, to find any pertinent studies, we manually examined the referenced articles of earlier review papers.

2. Inclusion Criteria

All studies were included if they met the following eligibility criteria: articles discussing about green synthesis of silver nanoparticles as a wound healing agent; independent variables influencing green synthesis of silver nanoparticles using every kinds of extract; dependent variables discussing about the every kinds of wound healing; and experimental studies published in English only.

3. Exclusion Criteria

Case series, case reports, human-based randomized controlled trials, literature reviews, editorials, and studies not meeting the inclusion criteria were excluded.

4. Study Variables

The independent variables is green synthesis of silver nanoparticles, the dependent variable is wound healing.

5. Operational Definition of Variables

The strategy for research was PICO: 1) Populations: laboratory animals; 2) Intervention: green synthesis of silver nanoparticles; 3) Comparison: a standar ointment for wound such as povidone–iodine or etc; 4) Outcome: wound healing.

Green synthesis of silver nanoparticles: defines as the use of plant or plant parts for the bioreduction of metal ions into their elemental form in the size range 1–100 nm (Pal et al., 2019).

Wound healing: defines as a complex biological process that consists of hemostasis, inflammation, proliferation, and remodeling (Guo and Dipietro, 2010).

6. Study Instruments

The effectiveness of the experimental studies was evaluated using the Risk of Bias (RoB) tool for animal intervention studies (SYRCLE's RoB tool) established by The Cochrane Collaboration.

RESULTS

A total 1559 articles were found after a preliminary search of the four electronic databases. All the articles were imported into Mendeley, and the results from the databases were merged, obtaining 919 articles. Using a duplicate removal tool (Mendeley), 640 duplicates were removed. Screening of the abstracts, remaining articles identified 884 unrelated articles. Of the remaining 35 articles, 8 studies met the inclusion criteria, and 26 studies were excluded. The findings of our literature search are summarized in Figure 1.

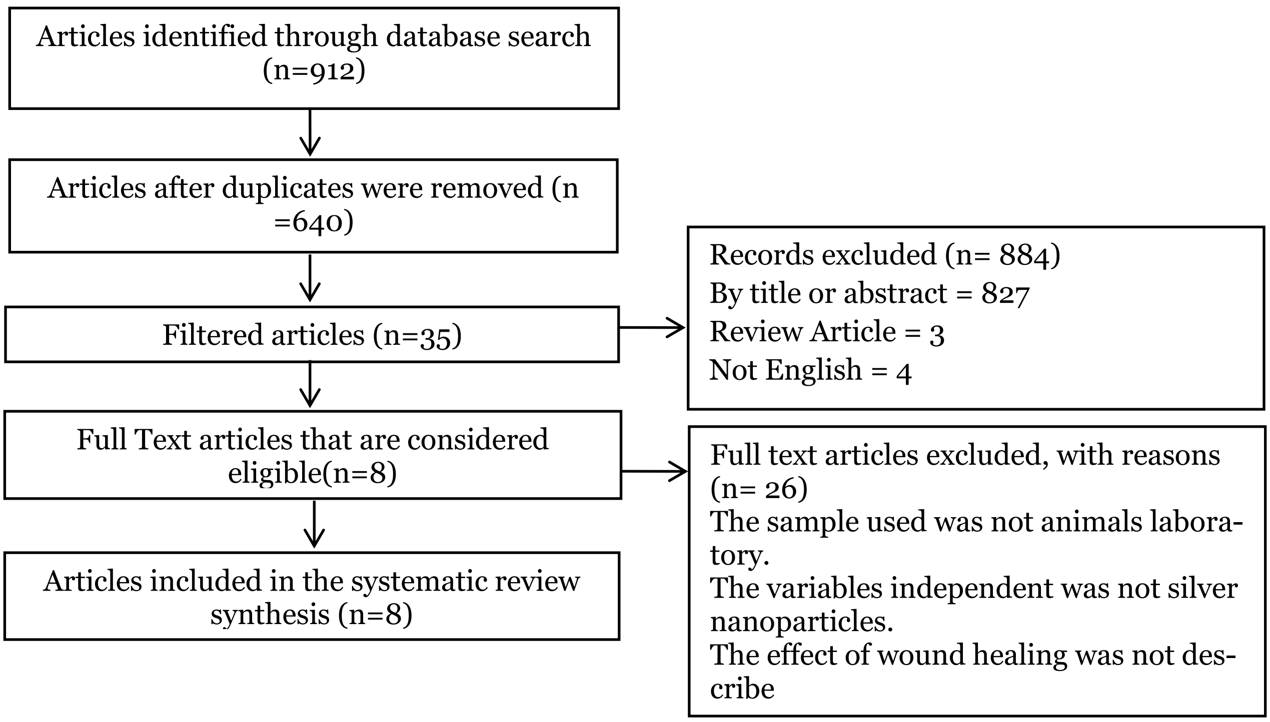

Figure 1. PRISMA flowchart

Table 1. Article Search Results

Author (Year)	Tittle	Journal	Method	Results	Conclusion
Chinnasamy et al.,(2021)	Biosynthesis of silver nanoparticles from Melia azedarach: Enhancement of antibacterial, wound healing, antidiabetic and antioxidant activities	International Journal of Nanomedicine	Laboratory experiment	Characterized of silver nanoparticles are UV-Vis spectroscopy, energy-dispersive X-ray spectroscopy, SEM, and TEM. AI-AgNPs-PF127 Hydrogel is a low-toxic, eco-friendly delivery vehicle with potential in wound healing.	This sustainable, green synthesis of AgNPs is a competitive alternative to conventional methods and will play a significant role in biomedical applications of Melia azedarach.
El-Deeb et al., (2020)	Biogenically Synthesized Polysaccharides-Capped Silver Nanoparticles: Immunomodulatory and Antibacterial Potentialities Against Resistant *Pseudomonas aeruginosa*	Frontiers in Bioengineering and Biotechnology	Experimental study	Characterized of silver nanoparticles are XRD and TEM. The recovered biogenic AgNPs proved to be non-cytotoxic on PBMc cells, and their antibacterial effects were proved in vitro against *Staphylococcus aureus*, *Streptococcus mutans*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Escherischia coli*, and *Proteus sp*. (antibiotic resistant bacterial strains).	AgNPs has a unique property in controlling bacterial wound infections and improving the healing process of damaged tissues.
Fatima et al., (2021)	Green Synthesized Silver Nanoparticles Using Tridax Procumbens for Topical Application: Excision Wound Model and Histopathological Studies	Pharmaceutics	Laboratory experiment	Characterized of silver nanoparticles are Aqueous extract of Tridax Procumbens. Green synthesized silver nanoparticles (AgNPs) were prepared by reacting silver nitrate (0.3 M) with leaf extract and characterized by particle analysis, FTIR, XRD, SEM, BET, and TGA. The results revealed formed AgNPs were nano-sized (Mean= 138; SD=2.1 nm), monodispersed (PDI: Mean= 0.46; SD= 0.3), inter-particle repulsion (zeta: Mean= −20.4; SD=5.20 mV), stabilized, crystalline and, spherical with size ranging from 80–100 nm as per SEM micro photos. The BET analysis of AgNPs presents the surface area (12.861 m2/g), pore volume (0.037 cc/g), and pore radius (24.50 nm).TGA	A histopathological study further confirmed the almost normal skin structure of treated animal tissue compared to standard and negative control. Thus, green synthesized AgNPs loaded chitosan-based topical gel can potentially be used for wound healing application.

				results show a loss of 13.39% up to 300 ◦C.	
Lakkim et al., (2020)	Green synthesis of silver nanoparticles and evaluation of their antibacterial activity against multidrug-resistant bacteria and wound healing efficacy using a murine model	Antibiotics Journal	Laboratory experiment	Characterized of silver nanoparticles are *Catharanthus roseus* and *Azadirachta indica* extracts. Group I: mice treated with C. roseus Ag NPs and A. indica Ag NPs Group II: Povidone-iodine ointment that is available on the market was used as a positive control for treated mice.	Phytoderivatives such as leaf constituents and proteins of plants act as masking agents on nanoparticles. Green-synthesized Ag NPs exhibited in-vivo wound healing efficacy and antibacterial activity against MDR *E. coli*, *K. Pneumoniae*, *S. aureus*, and *P. aeruginosa* strains.
Mekkawy et al., (2017)	In vitro and in vivo evaluation of biologically synthesized silver nanoparticles for topical applications: Effect of surface coating and loading into hydrogels	International Journal of Nanomedicine	Laboratory experiment	Characterized of silver nanoparticles are extract of the fungus Fusarium verticillioides. UV-Vis spectroscopy, dynamic light scattering, X-ray diffraction, SEM, and TEM. The antibacterial activities of different AgNPs dispersions were investigated against Gram-positive bacteria (methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*) by determination of the minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs)	Superior antibacterial activity and wound-healing capability, with normal skin appearance and hair growth, were demonstrated for the hydrogel formulations, as compared to the silver sulfadiazine cream. Histological examination of the treated skin was performed using light microscopy, whereas the location of AgNPs in the skin epidermal layers was visualized using transmission electron microscopy
Wen et al., (2016)	Symbiosis theory-directed green synthesis of silver nanoparticles and their application in infected wound healing	International Journal of Nanomedicine	Laboratory experiment	Characterized of silver nanoparticles are scutellaria barbata extract. The outcome are UV–Vis spectroscopic analysis, TEM, AFM, FTIR and XRD. The AgNPs were analyzed by various characterization techniques to reveal their morphology, chemical composition, and stability. Also, the relationship between Chinese medicinal	A simple one-pot green synthesis of stable AgNPs using the versatile strain *P. spinulosum* OC-11 at room temperature was reported in this study. It was confirmed that the proteins produced by the endophytic fungus capped on the AgNPs

				herbs, endophytic fungi, and the property of AgNPs was investigated for the first time.	and secured the nanoparticles with low aggregation, improved the inhibitory effect, and raised the identification to *S. aureus*, *P. aeruginosa*, and *E. coli* of the AgNPs
Younis et al., (2021)	Silver nanoparticles green synthesis via *Cyanobacterium phormidium sp.*: Characterization,wound healing, antioxidant, antibacterial, and anti-inflammatory activities	European Review for Medical and Pharmacological Sciences	Laboratory experiment.	Characterized of silver nanoparticles are phormidium sp. UV and FTIR spectrometric methods. The antimicrobial activity of AgNPs was scrutinized against MRSA either alone or in combination 0.5% chloramphenicol.	Biogenic AgNPs produced by *Phormidium sp.* showed significant antimicrobial together with wound healing abilities.
Younis et al., (2022)	Green Synthesis of Silver Nanoparticles by the *Cyanobacteria Synechocystis sp.*: Characterization, Antimicrobial and Diabetic Wound-Healing Actions	Marine Drugs Journal	Laboratory experiment.	*Characterized of silver nanoparticles was* Synechocystis sp. *The outcome* UV and FTIR spectrometric methods. The cyanobacterium biosynthesized spherical AgNPs with a diameter range of 10 to 35 nm. The produced AgNPs exhibited wound-healing properties verified with increased contraction percentage, tensile strength and hydroxyproline level in incision diabetic wounded animals. AgNPs treatment decreased epithelialization period, amplified the wound closure percentage, and elevated collagen, hydroxyproline and hexosamine contents, which improved angiogenesis factors' contents (HIF-1α, TGF-β1 and VEGF) in excision wound models	Biosynthesized AgNPs via *Synechocystis sp.* exhibited antimicrobial, anti-oxidative, anti-inflammatory, and angiogenesis promoting effects in diabetic wounded animals.

DISCUSSION

In this review we discussed the effectiveness of AgNPs as wound healing therapy agent. Wound healing consists of 4 stages: hemostasis, inflammation, proliferation, and remodeling, with the goal of restoring the structural, functional, and physiological integrities of injured tissues. immune function, and collagen formation. Any interruption, deviation, or prolonga-tion in the healing process would prolong tissue damage and thus the repair process, contributing to chronic wound healing (Judith et al., 2010; Kurahashi and Fujii, 2015; MacKay and Miller, 2003; Velnar et al., 2009).

Silver was one of the frequently used antibacterial agents before the introduction of antibiotics (Alexander, 2009). Silver compounds, silver ions, and silver nanoparticles (AgNPs) have been validated extensively for their antibacterial, antifungal, and antiviral activities (Brandt et al., 2012; Jaiswal et al., 2010; Khatami et al., 2015; Li et al., 2011; Rai et al., 2009). Among several tested metallic nanoparticles, AgNPs were found to be the most effective antimicrobial agent against bacteria, viruses, and other eukaryotic microorganisms (Gong et al., 2007).

AgNPs can be used as an effective broad spectrum antibacterial agent against Gram negative and Gram-positive bacteria including antibiotic-resistant bacteria (Percival et al., 2007). The broad-spectrum antibacterial effectiveness of AgNPs is due to their small size that enhances the accumulation in the microbial membrane and thus results in disruption and loss of integrity of the microbial membrane (Ayala-Núñez et al., 2009; Kvítek et al., 2008; Pérez-Díaz et al., 2016; Rahisuddin et al., 2015).

AgNPs are fabricated by different methods including chemical, physical, and green methods (Abid et al., 2002; Andrade et al., 2014; Birla et al., 2009; Gurunathan et al., 2014). Green chemistry method is preferred because the synthesized products are obtained from natural extracts. Green chemistry involves different biological methods for the synthesis of AgNPs which employ plants extract or microorganisms, such as fungi and bacteria (Birla et al., 2009; Jadhav et al., 2016; K Kalishwaralal et al., 2008; Rahisuddin et al., 2015).

Medicinal plants are being studied extensively for their use in wound healing, and the ancient knowledge of medicinally important plants, as well as their increased popularity and utility, has increased interest in discovering new natural products useful in the healing process. Several studies have confirmed the anti-inflammatory, pro-collagen synthesis, antioxidant, and antibacterial activities of natural products derived from plants and microbes, which could be beneficial for healing. Natural products' biocompatibility and the presence of various bioactive phytochemicals promote the healing process and make them economically suitable for designing and fabricating dressings (Thakur et al., 2011).

The Neem tree, Azadirachta indica A. Juss., is known for its large spectrum of compounds with biological and pharmacological interest. These include, among others, activities that are anticancer, antibacterial, antiviral, and anti-inflammatory (Braga et al., 2021).

Arthrospira Platensis has significant antioxidant activity, prevents viruses from entry into target cells and inhibits the colonisation of wounds by multi-resistant bacteria (Wollina et al., 2018).

Tridax procumbens procumbens had potent inhibitory effects on antioxidant and antibacterial activities. These biological activities may be attributed to the presence of fatty acids, flavonoids, and sterols in this plant (Andriana et al., 2019).

Catharanthus roseus is a medicinal plant, which can produce monoterpene indole alkaloid (MIA) metabolites with biological activity and is rich in vinblastine and vincristine. The use of C. roseus in the topical management of wound healing is supported by increased wound contraction and tensile strength, increased hydroxy-proline content, and antimicrobial activity (Nayak & Pinto Pereira, 2006; She et al., 2019).

Scutellaria barbata is a perennial herb which was vastly prescribed in Chinese medicine to treat inflammations, infections and it is also used a detoxifying agent (Priya V et al., 2021). Fusarium verticillioides (teleomorph Gibberella moniliformis) is the main fungal agent of ear and kernel rot of maize (Zea mays L.) worldwide (Covarelli et al., 2012).

Cyanobacteria have been widely explored for their potential applications in wound healing, as they are the rich source of bioactive compounds with antibacterial, antitumor, antiviral, antioxidant, and antifungal activities (Parwani, 2021). Cyanobacteria are oxygenic photosynthetic bacteria that are found in a variety of forms such as unicellular and filamentous, marine and freshwater, free-living symbiotic, edible, and poisonous. This group of organisms has the ability to produce a large number of primary and secondary metabolites and is thus known to have powerful biological activities. Secondary metabolites are low molecular weight natural organic compounds that are required for normal growth and development of these organisms. These metabolites have numerous applications in medicine, industries, and biotechnology. These metabolites are a rich source of bioactive compounds, with cyanobacteria being the most promising producers. Cyanobacteria have received a lot of attention in recent decades for their medicinal and wound healing properties. They are the organisms of choice due to their ease of availability, rapid regeneration, and vast diversity, which has piqued the interest of researchers in their potential as medicine and functional foods. As a result, their potential as a source of new therapeutic lead compounds has been recognized over the last two decades. Secondary metabolites from cyanobacteria have a variety of medicinally important activities, including antitumor, antibacterial, antifungal, antiviral, anti-inflammatory, immunomodulatory, and protease inhibition. These biological activities aid in wound healing in a variety of ways. Despite their powerful biological activities, very few cyanobacterial forms are known to aid in wound healing. Thus, this chapter provides an overview of cyanobacterial bioactive compounds that are responsible for their various biological activities that promote wound healing (Barrow, C., and Shahidi, 2007; Dorador et al., 2008; Singh et al., 2017; Taton et al., 2006).

Based on the results and discussion above, it can be concluded that all the research conducted on AgNPs for the wound-healing activities exhibited positive results. The novel biogenic AgNPs nanofilm's simultaneous antioxidant and antimicrobial activity demonstrated its potential for use as wound therapy. However, due to the limitation of studies conducted over the years, the biological activities of AgNPs require further research in the in vitro, in vivo, and clinical fields to confirm their efficacy.

AUTHORS CONTRIBUTION

Galih participated in data collection, reviewed the data, and drafted the manuscript. Widiastuti Samekto contributed to the interpretation of the results and revised the manuscript. Galih also conceived the idea. Agus Subagio, Hardhono Susanto, and Luky Dwiantoro. participated in reviewing the manuscript, and provided valuable comments. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST
There is no conflict of interest in this study.

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