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A REVIEW ARTICLE ON GREEN SYNTHESIS OF NEEM-MEDIATED SILVER NANOPARTICLES AND THEIR APPLICATION IN ANTIBACTERIAL WOUND HEALING PATCHES

[1]Kothare Shilpa N, [2]Nalawade Rutuja G, [3]Sathe Mahesh P, [4]Jathar Vaishali D, [5]Bangar Vilas B.

[1]D Pharmacy, [2]D Pharmacy, [3]M Pharmacy, [4]M Pharmacy, [5]B. Pharmacy

[1]Parikrama Diploma in Pharmaceutical Sciences, Kashti, Maharashtra, India

[2]Parikrama Diploma in Pharmaceutical Sciences, Kashti, Maharashtra, India

[3]Bharati Vidyapeeth Deemed to University, Poona College of Pharmacy Pune, Maharashtra India

[4]Alard School of Pharmacy, Alard University, Pune, Maharashtra, India

[5]Parikrama Diploma in Pharmaceutical Sciences, Kashti, Maharashtra, India

Abstract:

Silver nanoparticles (AgNPs) have emerged as one of the most promising nanomaterials for biomedical applications owing to their remarkable antimicrobial, anti-inflammatory, antioxidant, and wound-healing properties. However, conventional chemical and physical methods employed for AgNP synthesis often involve hazardous reagents, high energy consumption, and environmental concerns. In recent years, green synthesis has gained considerable attention as a sustainable alternative by utilizing plant-derived phytochemicals as natural reducing and stabilizing agents. *Azadirachta indica* (Neem), a medicinal plant extensively used in traditional medicine, possesses a rich phytochemical profile comprising flavonoids, phenolic compounds, terpenoids, alkaloids, tannins, proteins, and polysaccharides that facilitate the eco-friendly synthesis of stable silver nanoparticles. The synergistic interaction between neem phytoconstituents and silver nanoparticles enhances their antibacterial efficacy against a broad spectrum of Gram-positive and Gram-negative microorganisms while simultaneously promoting tissue regeneration and accelerating wound healing. Recent advances have demonstrated the successful incorporation of neem-mediated AgNPs into biopolymeric wound dressings, including chitosan-, polyvinyl alcohol-, alginate-, gelatin-, cellulose-, and hydrogel-based matrices, resulting in improved mechanical strength, moisture retention, controlled silver release, biocompatibility, and prolonged antimicrobial activity. This review comprehensively discusses the phytochemical basis of neem-mediated green synthesis, reaction mechanisms involved in nanoparticle formation, factors influencing synthesis

efficiency, physicochemical characterization techniques, antibacterial and wound-healing mechanisms, fabrication of antibacterial wound patches, and their physico-mechanical and biological evaluation. Furthermore, recent developments, current challenges, regulatory considerations, toxicity concerns, and future prospects for translating neem-mediated silver nanoparticle-based wound dressings into clinical applications are critically examined. The evidence summarized in this review indicates that neem-mediated AgNP-incorporated wound patches represent an environmentally sustainable, cost-effective, and highly promising strategy for the development of next-generation antimicrobial wound care systems.

Keywords: Azadirachta indica, green synthesis, silver nanoparticles, Antibacterial wound patch, Wound healing, Nanotechnology, Phytochemicals, Chitosan, Biopolymeric dressing, antimicrobial activity.

I. INTRODUCTION:

The skin is the largest organ of the human body and serves as the primary protective barrier against microbial invasion, environmental pollutants, ultraviolet radiation, and mechanical injury. Disruption of skin integrity due to trauma, burns, surgical procedures, diabetic ulcers, pressure ulcers, venous leg ulcers, or accidental injuries initiates a complex wound healing process involving haemostasis, inflammation, proliferation, and tissue remodelling.[1] Under normal physiological conditions, these overlapping stages restore the structural and functional integrity of damaged tissue. However, microbial contamination, persistent inflammation, underlying metabolic disorders, and impaired immune responses frequently delay wound healing, resulting in chronic wounds that represent a significant global healthcare challenge. Chronic wounds not only reduce the quality of life of affected individuals but also increase hospitalization rates, healthcare expenditure, and mortality, particularly among elderly and diabetic populations [2].

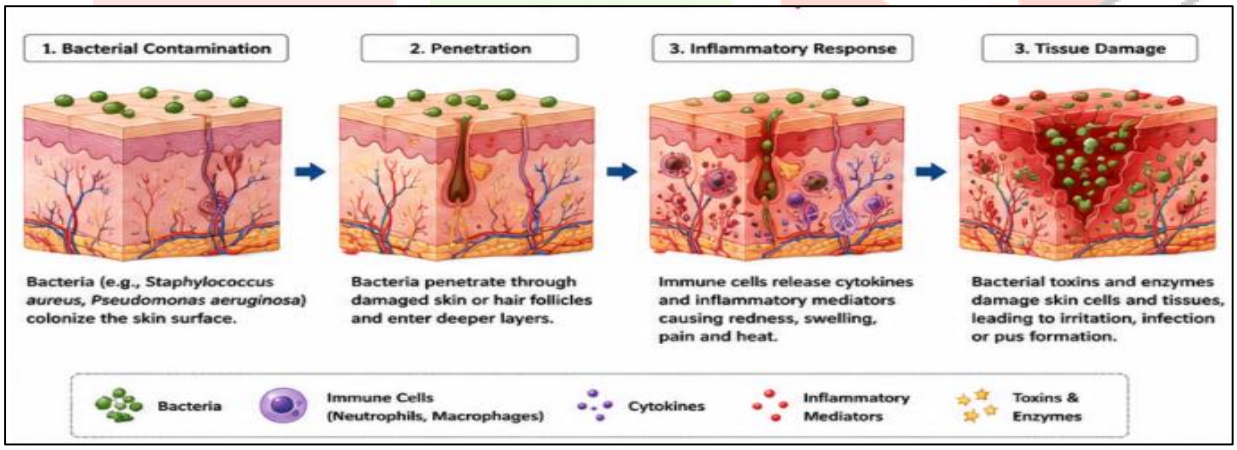

Figure 1: How to bacteria penetrate skin and cause infection.

According to the World Health Organization (WHO), wound infections remain one of the leading causes of morbidity worldwide, particularly in low- and middle-income countries where access to advanced wound care is limited. The increasing prevalence of diabetes mellitus, obesity, vascular disorders, and aging populations has substantially contributed to the rising incidence of chronic non-healing wounds. It has been estimated that approximately 1–2% of the population in developed countries will experience a chronic wound during their lifetime, while diabetic foot ulcers affect nearly 15–25% of diabetic patients. Furthermore, wound infections are frequently associated with opportunistic bacterial pathogens such as *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecalis*. These microorganisms possess the ability to form resilient biofilms that protect bacterial colonies from host immune defences and conventional antimicrobial therapies, thereby complicating treatment and prolonging wound healing. [1,2]

Conventional wound management strategies include sterile gauze dressings, cotton bandages, hydrocolloids, foams, alginates, films, hydrogels, topical antiseptics, and systemic antibiotic therapy. Although these approaches provide physical protection and moisture control, several limitations remain unresolved. Traditional dressings often require frequent replacement, adhere to newly formed tissue causing secondary trauma, exhibit limited antimicrobial activity, and fail to maintain an optimal wound microenvironment. Moreover, the widespread and often inappropriate use of antibiotics has accelerated the emergence of multidrug-resistant (MDR) microorganisms, significantly reducing the clinical effectiveness of existing antimicrobial agents. Antimicrobial resistance has therefore become one of the most serious public health threats of the twenty-first century, creating an urgent need for innovative, biocompatible, and sustainable wound management strategies capable of simultaneously preventing infection and promoting tissue regeneration [3].

Table 1: Global Burden of Chronic Wounds and Their Clinical Impact [3]

Wound Type	Primary Cause	Estimated Prevalence	Common Infecting Microorganisms	Major Clinical Challenges
Diabetic Foot Ulcer	Diabetes mellitus	15–25% of diabetic patients	*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*	Delayed healing, amputation risk
Pressure Ulcer	Prolonged pressure	Common in elderly and immobilized patients	*S. aureus*, *Enterococcus faecalis*	Secondary infection, prolonged hospitalization
Venous Leg Ulcer	Venous insufficiency	1–2% of adults	*P. aeruginosa*, *S. aureus*	Frequent recurrence
Burn Wound	Thermal injury	Millions of cases annually	*P. aeruginosa*, *Acinetobacter baumannii*	Severe infection, sepsis
Surgical Site Infection	Post-operative contamination	2–20% depending on surgery	MRSA, *E. coli*, *Klebsiella pneumoniae*	Increased healthcare cost

Recent advances in nanotechnology have opened new avenues for the development of multifunctional wound dressings with enhanced therapeutic performance. Nanotechnology involves the manipulation of materials with dimensions ranging from 1 to 100 nm, where unique physicochemical properties arise because of increased surface area, altered electronic characteristics, and enhanced biological interactions. Nanomaterials exhibit superior antimicrobial efficacy, improved drug loading capacity, controlled release behaviour, enhanced penetration into microbial biofilms, and excellent compatibility with polymeric wound dressing matrices. Consequently, nanotechnology-based wound care systems have attracted considerable attention in pharmaceutical sciences, biomedical engineering, and regenerative medicine [4]. Various nanomaterials including silver nanoparticles, zinc oxide nanoparticles, copper nanoparticles, titanium dioxide nanoparticles, silica nanoparticles, lipid nanoparticles, polymeric nanoparticles, and nanofibers have been investigated for wound healing applications. Among these, silver nanoparticles

(AgNPs) have emerged as one of the most extensively studied and clinically relevant nanomaterials owing to their broad-spectrum antimicrobial activity and favourable safety profile [5].

Silver has been recognized as an antimicrobial agent since ancient civilizations, where silver vessels were used to preserve drinking water and prevent microbial contamination. The advancement of nanotechnology has significantly enhanced the biomedical potential of silver through the production of silver nanoparticles. Compared with bulk silver, AgNPs possess an exceptionally high surface-to-volume ratio, allowing greater interaction with bacterial cell membranes and intracellular targets. Traditionally, silver nanoparticles have been synthesized through physical and chemical methods such as laser ablation, evaporation-condensation, chemical reduction, microwave irradiation, photochemical synthesis, and electrochemical techniques. Although these approaches enable controlled nanoparticle production, they often require toxic reducing agents, hazardous organic solvents, elevated temperatures, sophisticated instrumentation, and high energy consumption. Residual chemical contaminants may also compromise nanoparticle biocompatibility and limit their biomedical applications. In response to these limitations, green synthesis has emerged as a sustainable alternative that utilizes naturally occurring biomolecules from plants, microorganisms, algae, fungi, or biopolymers to reduce silver ions into stable nanoparticles. Green synthesis is considered environmentally benign, cost-effective, energy-efficient, scalable, and compatible with biomedical applications because it avoids hazardous chemicals while simultaneously producing biocompatible nanoparticles coated with naturally derived phytochemicals [6,7,8].

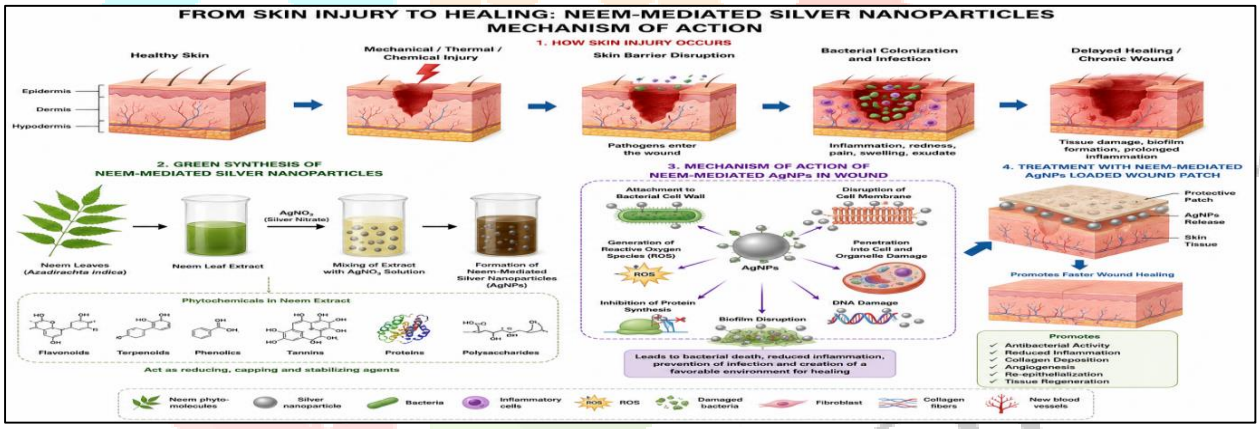

Figure 2: Mechanism of action how to neem mediated nanoparticle patch work on skin infection against bacteria. [6]

Recent investigations have demonstrated that neem-mediated silver nanoparticles possess superior antibacterial activity against both Gram-positive and Gram-negative pathogens compared with crude neem extracts or chemically synthesized nanoparticles. [6,7,8]

II. BOTANICAL PROFILE OF *AZADIRACHTA INDICA:*

Azadirachta indica A. Juss., commonly known as Neem, is a large evergreen tree belonging to the family Meliaceae. It is regarded as one of the most valuable medicinal plants because of its extensive therapeutic properties and diverse phytochemical composition. The generic name *Azadirachta* is derived from the Persian word *Azad-Darakht-e-Hind*, meaning "the free tree of India," while the species name *indica* denotes its Indian origin. Neem has been extensively used in Ayurveda, Siddha, and Unani medicine for more than two thousand years and is popularly referred to as "The Village Pharmacy" owing to the medicinal value of every part of the plant. [9,10]

Morphological Characteristics: *Azadirachta indica* is a medium- to large-sized evergreen tree that generally attains a height of 15–30 m, with a trunk diameter of 1–2.5 m and a broad, dense crown. The tree develops a strong tap root accompanied by an extensive lateral root system, enabling efficient water absorption from deep soil layers and contributing to its exceptional drought resistance. Leaves are alternate, imparipinnate, and compound, measuring approximately 20–40 cm in length. Each leaf consists of 8–19 serrated leaflets with pointed tips and a glossy dark green surface [10-14].

Table 2: Major Phytochemicals Constituents of Neem [10-14]

Sr. No	Phytochemical Class	Representative Compounds	Biological Activity
1	Limonoids	Azadirachtin, Nimbin, Nimbidin, Salannin, Gedunin, Nimbolide	Antimicrobial, anti-inflammatory
2	Flavonoids	Quercetin, Kaempferol, Rutin, Catechin	Antioxidant, antibacterial
3	Phenolic Compounds	Gallic acid, Ferulic acid, Caffeic acid, Chlorogenic acid	Reducing agents, antioxidant
4	Terpenoids	β-Sitosterol, Stigmasterol	Anti-inflammatory
5	Tannins	Hydrolysable tannins	Antimicrobial
6	Alkaloids	Various alkaloids	Antimicrobial
7	Proteins	Amino acid-rich proteins	Capping agents
8	Polysaccharides	Cellulose, pectin derivatives	Stabilizing agents
9	Saponins	Various saponins	Membrane disruption
10	Essential Oils	Neem oil constituents	Antifungal

III. GREEN SYNTHESIS OF SILVER NANOPARTICLES USING *AZADIRACHTA INDICA:*

i) Introduction: Green synthesis of silver nanoparticles (AgNPs) has emerged as an environmentally sustainable and economically viable alternative to conventional physical and chemical methods of nanoparticle production. Traditional methods often rely on hazardous reducing agents such as sodium borohydride and hydrazine, which generate toxic by-products and require high energy consumption. Among the various biological resources, *Azadirachta indica* (Neem) has gained considerable attention because its leaves are rich in flavonoids, phenolic acids, terpenoids, tannins, proteins, polysaccharides,

and reducing sugars. These phytochemicals possess hydroxyl, carbonyl, amino, and carboxyl functional groups capable of donating electrons to silver ions (Ag^+), reducing them to elemental silver (Ag^0), and subsequently stabilizing the newly formed nanoparticles through surface capping. [15]

ii) Principle of Green Synthesis: The biosynthesis of silver nanoparticles is based on the reduction of silver ions (Ag^+) present in an aqueous silver nitrate ($AgNO_3$) solution into elemental silver atoms (Ag^0) by phytochemicals present in neem leaf extract. [16-20]

Initially, silver nitrate dissociates in water: $AgNO3 \rightarrow Ag^{++}NO3^-$

When neem leaf extract is added, phytochemicals such as flavonoids and phenolic compounds donate electrons to Ag^+ ions: $Ag^{++}e^- \rightarrow Ag0$

A visible colour change from colourless to yellowish-brown or dark brown indicates the successful formation of AgNPs due to the phenomenon of Surface Plasmon Resonance (SPR), typically observed at 400–450 nm by UV–Visible spectroscopy. [16]

iii) Step-by-Step Green Synthesis Procedure:

Step 1. Collection of Plant Material: Fresh, healthy neem leaves are collected and thoroughly washed with running tap water followed by distilled water to remove dust, microorganisms, and surface impurities.

Step 2. Preparation of Neem Leaf Extract: Approximately 10 g of finely chopped neem leaves are boiled in 100 mL of distilled water for 10–15 minutes at 60–80°C. The extract is cooled to room temperature and filtered through Whatman No.1 filter paper to obtain a clear green filtrate rich in phytochemicals.

Step 3. Preparation of Silver Nitrate Solution: A 1 mM aqueous $AgNO_3$ solution is prepared by dissolving silver nitrate in distilled water under subdued light to prevent photodegradation.

Step 4. Mixing of Reactants: Neem leaf extract is added dropwise to the $AgNO_3$ solution under continuous magnetic stirring. The reaction is generally maintained at room temperature or 60°C for 30–60 minutes.

Step 5. Formation of Silver Nanoparticles: The solution gradually changes from colourless to yellowish-brown, followed by dark brown, indicating nanoparticle formation due to surface plasmon resonance.

Step 6. Purification: The reaction mixture is centrifuged at 10,000–15,000 rpm for 15–20 minutes. The pellet is washed repeatedly with distilled water or ethanol to remove unreacted phytochemicals.

Step 7. Drying: Purified AgNPs are dried in a vacuum oven at 40–60°C and stored in airtight amber-coloured containers for further characterization and formulation. [16-20]

Table 3: Factor Affecting AgNP synthesis

Sr. No	Factors	Effect on nanoparticles
1	pH	Controls reduction rate, size, and stability
2	Temperature	Influences nucleation and growth
3	$AgNO_3$ concentration	Determines particle yield and size
4	Extract concentration	Provides reducing and capping molecules
5	Reaction time	Affects completeness of reduction

IV. CHARACTERIZATION AND EVALUATION OF NEEM-MEDIATED SILVER NANOPARTICLES

i) **Introduction:** The successful synthesis of silver nanoparticles (AgNPs) using *Azadirachta indica* leaf extract must be confirmed through comprehensive physicochemical characterization. Characterization provides essential information regarding nanoparticle formation, particle size, morphology, crystallinity, elemental composition, surface chemistry, colloidal stability, and biological suitability. Since the physicochemical properties of AgNPs directly influence their antimicrobial efficacy, biocompatibility, stability, and wound-healing potential, accurate characterization is indispensable for biomedical applications. [21]

ii) UV–Visible Spectroscopy:

Principal: UV–Visible spectroscopy is the primary technique used to confirm the formation of silver nanoparticles. Metallic nanoparticles exhibit Surface Plasmon Resonance (SPR), a phenomenon resulting from the collective oscillation of conduction electrons when irradiated with visible light. [22-24]

When neem extract reduces Ag^+ ions into Ag^0 nanoparticles, the reaction mixture changes from colourless to yellowish-brown or dark brown. This colour change corresponds to an SPR absorption band, typically observed between 400 and 450 nm, confirming AgNP formation.

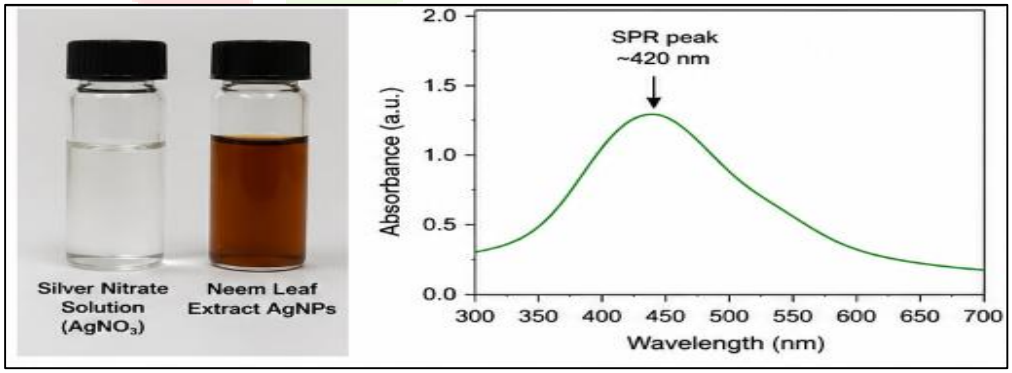

Figure 3: UV Visible Spectroscopy detection of Nanoparticles

Table 4: UV- Visible Spectroscopy Parameters

Sr. No	Parameters	Typical Observations
1	Wavelength range	300–700 nm
2	SPR Peak	400–450 nm
3	Typical Neem AgNP Peak	420 nm
4	Confirmation	Formation of AgNPs

iii) Fourier Transform Infrared Spectroscopy (FTIR)

Principal: FTIR identifies the functional groups present on the nanoparticle surface. Biomolecules from neem extract remain adsorbed on AgNPs and act as natural capping agents. FTIR detects these molecules through characteristic infrared absorption bands. [25]

Table 5: Major FTIR Peaks of Neem-Mediated AgNPs

Sr. No	Wavenumber (cm^{-1})	Functional Group	Source
1	3400	O–H Stretch	Phenolics
2	2920	C–H Stretch	Terpenoids
3	1650	C=O Stretch	Proteins
4	1540	N–H Bend	Amino acids
5	1380	C–N Stretch	Alkaloids
6	1050	C–O Stretch	Polysaccharides

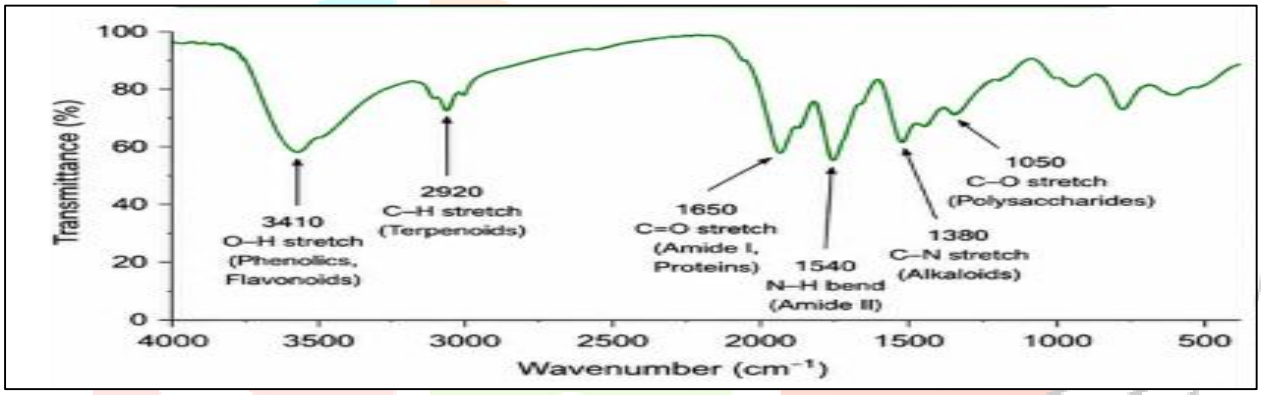

Figure 4: Evaluation of Nanoparticle using FTIR

iv) Scanning Electron Microscopy (SEM)

Principal: SEM produces high-resolution images of nanoparticle surface morphology using a focused electron beam. [26-28]

Table 6: SEM Analysis

Sr. No	Parameters	Observations
1	Shape	Spherical
2	Surface	Smooth
3	Distribution	Uniform
4	Agglomeration	Minimal

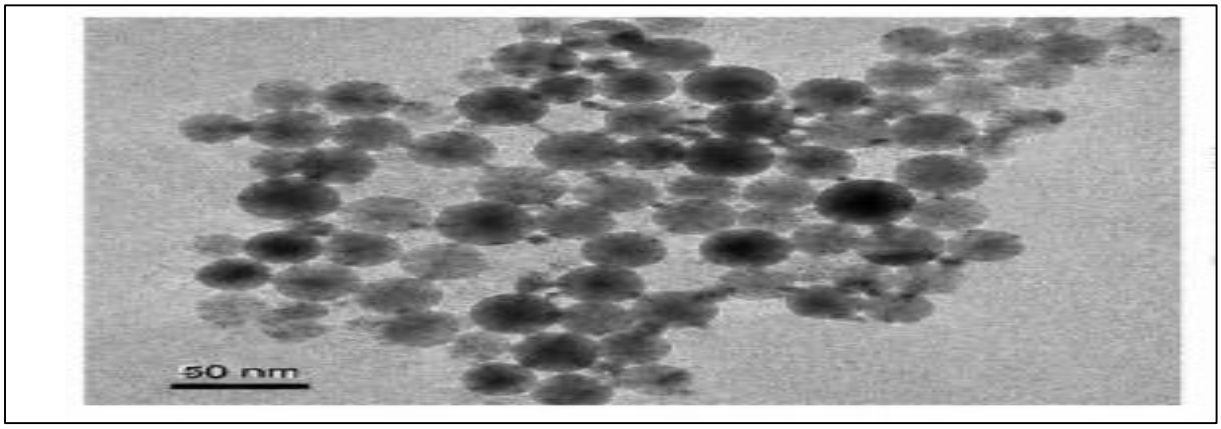

Figure 5: SEM analysis of Nanoparticles [26-28]

V. ANTIBACTERIAL MECHANISM OF NEEM-MEDIATED SILVER NANOPARTICLES (AGNPS)

The antibacterial action of neem-mediated AgNPs involves a series of interconnected molecular and cellular events that ultimately lead to bacterial death**.** [29]

Following is a stepwise mechanism:

Step 1: Adhesion to the Bacterial Cell Surface: AgNPs come into contact with the bacterial surface. Electrostatic interactions between positively charged silver ions released from AgNPs and negatively charged bacterial cell wall components facilitate nanoparticle attachment. In Gram-negative bacteria, AgNPs interact primarily with lipopolysaccharides (LPS), whereas in Gram-positive bacteria they bind to the thick peptidoglycan layer and teichoic acids. This initial interaction destabilizes membrane integrity and increases cell wall permeability, making bacterial cells more susceptible to further damage. [29-34]

Step 2: Membrane Damage: After attachment, AgNPs disrupt membrane architecture by interacting with membrane phospholipids and proteins. Structural damage causes:

- Increased membrane permeability
- Leakage of potassium ions
- Loss of intracellular proteins
- Cytoplasmic leakage
- Collapse of membrane potential

These events compromise bacterial viability and impair essential physiological functions. [30-32]

Step 3: Release of Silver Ions (Ag^+): Silver nanoparticles continuously release Ag^+ ions into the surrounding environment. These ions diffuse through damaged membranes and bind strongly to sulphur-containing proteins and phosphorus-containing biomolecules.

Silver ions inhibit numerous intracellular enzymes involved in:

- Cellular respiration
- ATP synthesis
- Electron transport
- Protein folding

The resulting metabolic dysfunction significantly reduces bacterial survival.

Step 4: Reactive Oxygen Species (ROS) Generation: One of the principal antibacterial mechanisms of AgNPs is the induction of oxidative stress. Interaction between nanoparticles and bacterial cells stimulates excessive production of reactive oxygen species (ROS), including:

- Superoxide radicals ($O_2^{\bullet -}$)
- Hydroxyl radicals (•OH)
- Hydrogen peroxide (H_2O_2)
- Singlet oxygen ($^1O_2$)

Elevated ROS levels oxidize membrane lipids, proteins, and nucleic acids, overwhelming bacterial antioxidant defence systems.

Step 5 DNA Damage: Silver ions and ROS penetrate into the bacterial cytoplasm and interact with chromosomal DNA.

Step 6 Protein Denaturation: Silver ions possess strong affinity for thiol (-SH) groups of proteins.

Step 7 Biofilm Inhibition: Biofilms protect bacteria from antibiotics and immune cells. Neem-mediated AgNPs interfere with Initial bacterial adhesion.

Step 8 Cell Death: The combined effects of membrane disruption, oxidative stress, metabolic inhibition, DNA damage, and protein denaturation ultimately result in irreversible bacterial death. [29-34]

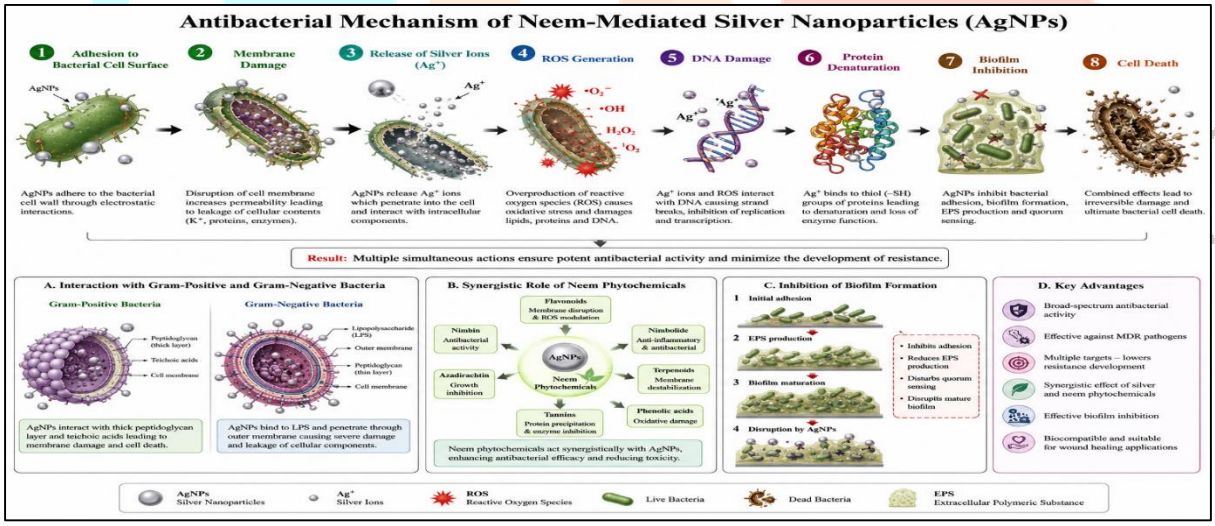

Figure 6: Antibacterial Mechanism of Neem – Mediated Silver Nanoparticles.

VI. PREPARATION OF NEEM-MEDIATED ANTIBACTERIAL WOUND PATCH

Neem-mediated silver nanoparticles (AgNPs) are commonly incorporated into biodegradable polymeric matrices to fabricate antibacterial wound patches. Natural and synthetic polymers such as chitosan, polyvinyl alcohol (PVA), sodium alginate, gelatin, and cellulose derivatives are widely used because of their excellent biocompatibility, biodegradability, mechanical strength, and moisture-retention properties. [35]

The wound patch is generally prepared using the solvent casting method, one of the simplest and most reproducible techniques for polymeric film fabrication. Initially, the selected polymer is dissolved in an appropriate solvent under continuous stirring to obtain a homogeneous polymeric solution. A suitable plasticizer, such as glycerol or polyethylene glycol (PEG), is then added to improve the flexibility of the resulting film. The synthesized neem-mediated AgNPs are uniformly dispersed into the polymer solution under magnetic stirring or ultrasonication to ensure even nanoparticle distribution. [36]

The homogeneous casting solution is poured onto a clean Petri dish or casting plate and allowed to dry under controlled temperature conditions. After complete solvent evaporation, the dried film is carefully peeled off and cut into patches of the desired dimensions. The prepared wound patches are subsequently characterized for their physicochemical, mechanical, and antibacterial properties before biomedical application.

The incorporation of neem-mediated AgNPs into the polymer matrix provides sustained antimicrobial activity, improves mechanical stability, maintains a moist wound environment, and promotes accelerated wound healing. [37]

Table 7: Formulation of a Neem-Mediated Silver Nanoparticle Antibacterial Wound Patch [37]

Sr. No	Ingredient	Concentration	Function
1	Chitosan	2.0% w/v	Primary film-forming polymer
2	Polyvinyl Alcohol (PVA)	1.5% w/v	Improves mechanical strength and flexibility
3	Glycerol	0.5% v/v	Plasticizer
4	Neem-mediated Silver Nanoparticles (AgNPs)	100 µg/mL	Antibacterial active agent
5	Distilled Water	q.s. to 100 mL	Solvent

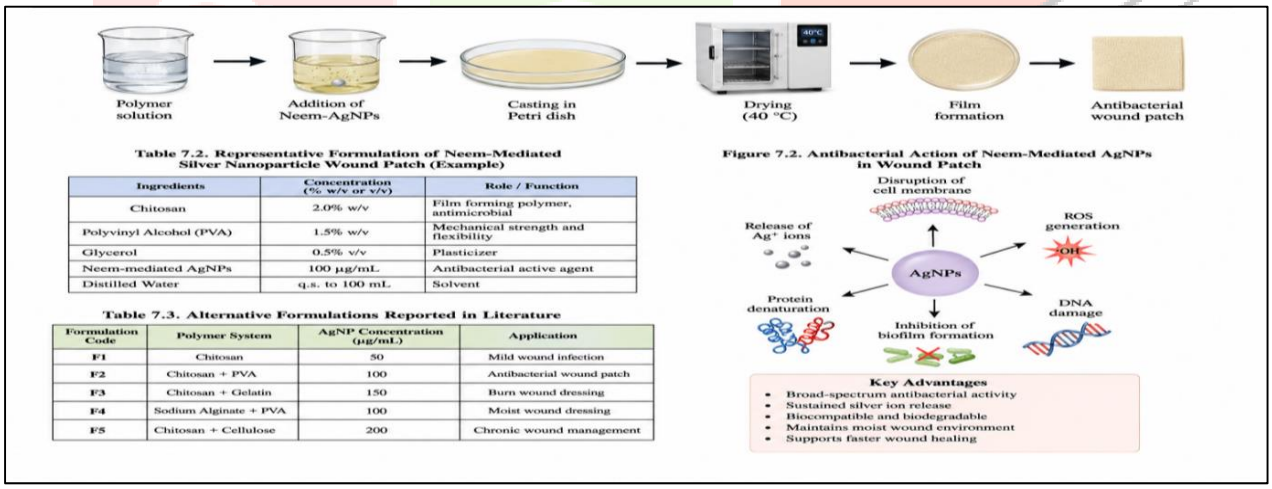

Figure 7: Preparation of Neem Mediated Silver Nanoparticle Patch

VII. EVALUATION OF NEEM-MEDIATED ANTIBACTERIAL WOUND PATCH

i) **Introduction:** The performance of neem-mediated silver nanoparticle (AgNP)-loaded wound patches depends on their physicochemical, mechanical, antimicrobial, and biological properties. Therefore, comprehensive evaluation is necessary to ensure that the wound patch possesses adequate flexibility, mechanical integrity, moisture balance, sustained silver release, biocompatibility, and antimicrobial efficacy. Various characterization methods reported in the literature are summarized below. [38]

ii) **Physical Evaluation:**

Table 8: Physical Evaluation Parameters [39]

Sr. No	Parameter	Purpose	Expected Observation
1	Appearance	Visual examination	Smooth, uniform, bubble-free film
2	Colour	Visual inspection	Light green to brown
3	Thickness	Uniformity of patch	Uniform thickness throughout the film
4	Weight Variation	Dose uniformity	Minimal variation
5	Surface Texture	Surface quality	Smooth and homogeneous
6	Transparency	Visual property	Semi-transparent or opaque

iii) **Mechanical Evaluation:** Mechanical properties determine whether the patch can withstand handling and application without breaking.
EX- Tensile Strength, Folding Endurance, Percent Elongation, Young's Modulus.
A wound patch should possess sufficient tensile strength while remaining flexible enough to conform to the wound surface. [40]

iv) **Antibacterial Evaluation:** The antibacterial efficacy of the wound patch is generally assessed against common wound pathogens.
Common Test Organisms: Staphylococcus aureus, MRSA, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae.
Test Perform: Agar diffusion assay, MIC determination, Time-kill assay. [40]

VIII. CHALLENGES IN THE DEVELOPMENT OF NEEM-MEDIATED SILVER NANOPARTICLE WOUND PATCHES

Despite their significant antibacterial and wound-healing potential, several challenges limit the clinical translation of neem-mediated silver nanoparticles (AgNPs). The major challenge is the **lack of standardized green synthesis protocols**, as variations in plant source, extraction method, pH, temperature, and reaction conditions can affect nanoparticle size, morphology, stability, and biological activity, leading to batch-to-batch variability.

Another concern is the **control of nanoparticle characteristics**, including particle size, shape, and surface charge, which directly influence antimicrobial efficacy and biocompatibility. In addition, the long-term safety of AgNPs requires further investigation, as prolonged exposure may cause oxidative stress, cytotoxicity, or silver accumulation in tissues. [41-45]

The limited availability of clinical studies also restricts their therapeutic application. Most investigations have been conducted under laboratory conditions or in animal models, while well-designed human clinical trials remain scarce. Furthermore, large-scale manufacturing, quality control, nanoparticle stability during storage, and compliance with Good Manufacturing Practices (GMP) present additional challenges for commercialization. [46-48]

Finally, the absence of standardized regulatory guidelines for plant-mediated nanomaterials complicates product approval and clinical translation. Addressing these challenges through standardized synthesis methods, comprehensive toxicological studies, large-scale clinical evaluation, and clear regulatory frameworks will be essential for the successful development of neem-mediated AgNP-based wound dressings. [49-53]

IX. FUTURE PERSPECTIVES

The integration of green nanotechnology with advanced wound care systems offers tremendous opportunities for the development of next-generation antimicrobial wound dressings. Neem-mediated silver nanoparticles represent a sustainable alternative to chemically synthesized nanoparticles because they combine the intrinsic therapeutic properties of neem phytochemicals with the broad-spectrum antimicrobial activity of silver. Future research should focus on improving synthesis reproducibility, optimizing nanoparticle characteristics, and enhancing the clinical performance of AgNP-based wound patches through innovative formulation strategies. [54-56]

One promising direction is the development of smart wound dressings capable of responding to changes in wound pH, temperature, bacterial load, or inflammatory biomarkers. Such intelligent systems could enable controlled and stimuli-responsive release of silver nanoparticles, minimize unnecessary silver exposure while maintain effective antimicrobial activity. Incorporation of biosensors within wound patches may further facilitate real-time monitoring of wound healing and infection status. [57]

Advances in biopolymer engineering are expected to improve the mechanical properties, biodegradability, and controlled-release characteristics of wound patches. Natural polymers such as chitosan, alginate, gelatin, cellulose, silk fibroin, and hyaluronic acid, either individually or in combination, are likely to play an increasingly important role in designing multifunctional wound dressings with enhanced therapeutic efficacy.

Artificial intelligence (AI) and computational modelling may also accelerate the optimization of green nanoparticle synthesis by predicting the influence of synthesis parameters on nanoparticle size, morphology, stability, and biological activity. Machine learning approaches combined with high-throughput experimental screening could significantly reduce development time and improve process reproducibility. [58]

Another emerging area involves combining neem-mediated AgNPs with additional bioactive agents such as antibiotics, growth factors, stem cell-derived exosomes, antimicrobial peptides, essential oils, or natural phytochemicals to achieve synergistic antimicrobial and regenerative effects. Such multifunctional wound dressings may prove particularly valuable for treating chronic wounds, diabetic ulcers, burn injuries, and multidrug-resistant infections. Future investigations should also prioritize comprehensive preclinical and clinical evaluations, including pharmacokinetic studies, biodistribution, long-term toxicity, and randomized controlled clinical trials. These studies will be essential for establishing standardized therapeutic guidelines and facilitating regulatory approval. [59-60]

X. CONCLUSION

Neem-mediated silver nanoparticles represent a promising advancement in green nanotechnology for the development of next-generation antibacterial wound dressings. The phytochemicals present in *Azadirachta indica* not only facilitate the eco-friendly synthesis of stable silver nanoparticles but also enhance their antimicrobial, antioxidant, and wound-healing properties through synergistic biological effects. Incorporation of these nanoparticles into biocompatible polymeric wound patches offers sustained antimicrobial activity, improved moisture retention, and accelerated tissue regeneration. Although challenges related to standardization, large-scale production, long-term safety, and regulatory approval remain, continued research and technological advancements are expected to overcome these limitations. Overall, neem-mediated AgNP-based wound patches provide a sustainable and effective platform for advanced wound management and hold significant potential for future clinical and commercial applications.

XI. CONFLICT OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this review article. The authors have no financial, personal, academic, or commercial relationships that could have influenced the work reported in this manuscript.

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