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Review Article

Green Synthesis of Silver Nanoparticles from Indonesian Medicinal Plants: Antibacterial and Biomedical Applications

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Abstract

Antimicrobial resistance is a pressing public-health threat, and plant-mediated (green) synthesis of silver nanoparticles (AgNPs) offers a low-toxicity alternative to chemical routes. Indonesia's biodiverse medicinal flora is a promising source of bio-reductants and capping agents, but the evidence remains scattered. This review integrates and positions the Indonesian and global literature on green-synthesised AgNPs from Indonesian medicinal plants. Methods. A semi-systematic, PRISMA-guided review of Scopus, PubMed, ScienceDirect, Google Scholar, Garuda and SINTA (2015–2025) was conducted, applying explicit inclusion/exclusion criteria and structured quality appraisal. Main findings. Flavonoids, phenolic acids, tannins, saponins, and terpenoids dominate Ag^{+}-to-Ag^{0} bio-reduction, giving spherical 5–50 nm nanoparticles with SPR at 400–460 nm. Smaller, phenolic-capped particles show the lowest MICs (5–100 µg/mL), broad-spectrum and anti-biofilm activity, and synergy with conventional antibiotics against ESKAPE pathogens. Gaps. Testing against clinical multidrug-resistant isolates, in vivo and pharmacokinetic data, raw-material standardization, and ecotoxicity/environmental risk assessment are largely missing from the Indonesian literature. Prospects. Multidisciplinary programmes combining green chemistry, phytochemistry, and biomedical sciences can translate plant-mediated AgNPs into reproducible, clinically and environmentally responsible antimicrobial tools.

Keywords: silver nanoparticles; green synthesis; Indonesian medicinal plants; antibacterial activity; anti-biofilm; biosynthesis mechanism

1. Introduction

Infections caused by antibiotic-resistant bacteria are a major and growing cause of global mortality: the most recent systematic analysis estimates 4.71 million deaths associated with bacterial antimicrobial resistance and 1.14 million deaths directly attributable to it in 2021, with reference-scenario forecasts reaching 8.22 million associated and 1.91 million attributable deaths per year by 2050 unless sustained countermeasures are implemented [1], and the World Health Organization has repeatedly flagged ESKAPE pathogens—*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.—as the organisms most urgently in need of new therapeutic options [2,3].

In its 2024 bacterial priority pathogens list, the WHO classified methicillin-resistant *Staphylococcus aureus* (MRSA) as a high-priority pathogen, while carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant Enterobacterales, and third-generation cephalosporin-resistant Enterobacterales were placed in the critical-priority tier, underscoring the urgency of developing alternative antimicrobial strategies [2]. The economic and clinical burden is amplified in low- and middle-income tropical countries such as Indonesia, where high antibiotic consumption, large reservoirs of community and hospital-acquired multidrug-resistant strains, and limited access to last-line antibiotics combine to make alternative antimicrobial strategies an immediate public health priority [1,4].

Nanotechnology offers a way around several of these limitations. Silver has been used as an antimicrobial since antiquity, and silver nanoparticles (AgNPs) in the 1–100 nm range show antibacterial activity that can be an order of magnitude stronger than bulk silver or ionic silver salts because the very high surface area-to-volume ratio drives faster ion release and more intimate contact with the bacterial envelope [5,6,7]. Conventional chemical synthesis of AgNPs, however,

relies on reductants such as sodium borohydride or hydrazine and on capping agents that may be toxic or environmentally persistent [8]. This is where green chemistry enters: plant extracts contain natural reductants (polyphenols, flavonoids, reducing sugars, ascorbate, certain amino acids) and natural capping ligands (proteins, tannins, terpenoids) that can, in a single pot and at mild conditions, convert Ag^+ to Ag^0 and then stabilize the resulting particles [9,10,11]. Plant-mediated synthesis is also more reproducible than microbial routes and avoids the biosafety concerns associated with handling pathogenic micro-organisms during scale-up [12,13]. The conceptual overview of this plant-mediated synthesis process is presented in Figure 1.

Indonesia is particularly well-positioned to contribute to this field. The archipelago is one of the most biodiverse tropical regions in the world, with an estimated 30,000 plant species, several thousand of which are used in jamu and other traditional medicine systems [14]. Many of these species have already been characterized for their phenolic, flavonoid, and alkaloid content, and a small but growing body of Indonesian work has begun applying them to AgNP biosynthesis [15,16,17]. Local research groups have demonstrated the feasibility of using endemic species such as *Cratoxylum glaucum* (pucuk idat) [15], *Phyllanthus niruri* (meniran) and *Orthosiphon stamineus* (kumis kucing) [16], *Calotropis gigantea* from the Aceh geothermal manifestation [17], *Garcinia mangostana* (manggis) rind waste [18], and *Curcuma longa* (kunyit) leaf together with land-snail shell waste [19], showing that single-pot, low-energy biosynthesis is achievable with locally available material.

Despite this momentum, the literature remains scattered across plant species, laboratory protocols, and biological readouts. Existing reviews of plant-mediated AgNPs are either global in scope and organized by mechanism or application—for example, the green-synthesis and antimicrobial syntheses of Vanlalveni et al. [9], Huq et al. [10], and Ahmed et al. [11], the mechanistic account of Dakal et al. [5], and the biomedical-applications review of Simon et al. [72]—or focus on the chemistry of single species, and none has consolidated the Indonesian evidence base as a coherent body or positioned it against this global mechanistic picture. To substantiate this gap, Table 1 maps the scope, plant coverage, methodological rigour, and environmental focus of the principal prior reviews against the present work, showing that no existing review combines an Indonesia-specific plant inventory, a semi-systematic methodology, and an explicit treatment of ecotoxicity and environmental risk. This review addresses that gap by integrating, rather than merely compiling, the Indonesian and global evidence. It first maps the phytochemical groups in Indonesian medicinal plants that are most relevant to AgNP biosynthesis, then walks through the biochemical mechanism of bio-reduction and capping, summarizes how the resulting nanoparticles are characterized, surveys the antibacterial activity reported for plant-mediated AgNPs (with an emphasis on biofilm inhibition and ESKAPE pathogens), and closes with the most promising biomedical applications and the outstanding research gaps that Indonesian laboratories are well placed to address.

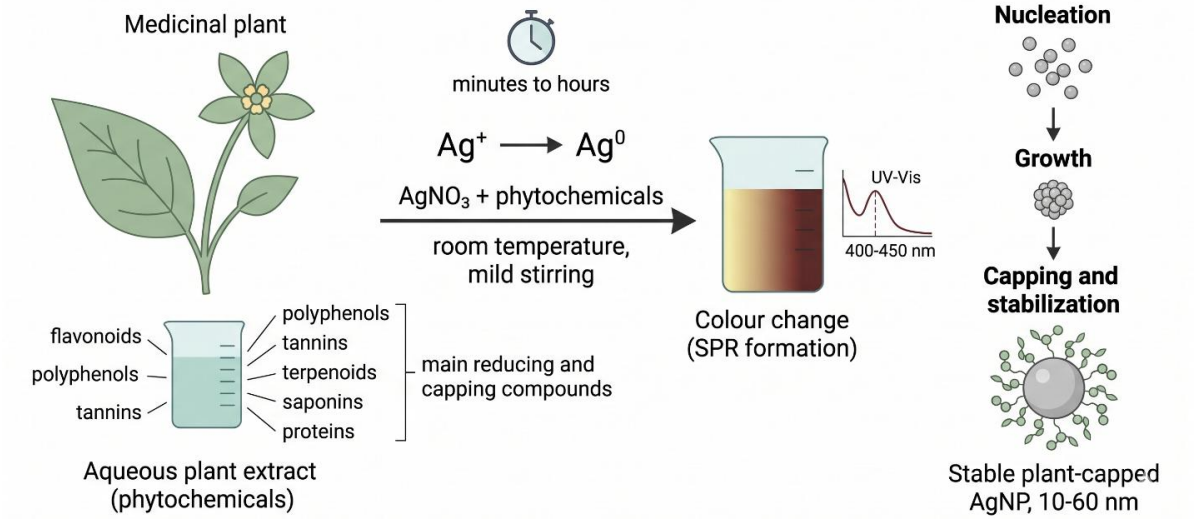

Figure 1: Plant-mediated biosynthesis of silver nanoparticles. Phytochemicals in the aqueous plant extract (flavonoids, polyphenols, tannins, terpenoids, saponins, and proteins) reduce Ag^+ to Ag^0, and the same molecules then act as capping agents that stabilize the resulting nanoparticle. The characteristic colour change from pale yellow to reddish-brown is the visual fingerprint of surface plasmon resonance (SPR), which appears as a single, symmetric band in the UV-Vis spectrum at 400–450 nm.

2. Methods

This work was conducted as a semi-systematic (integrative) review. Because the aim is interpretive synthesis across heterogeneous study types rather than the pooling of comparable effect sizes, a full systematic meta-analysis was not appropriate; however, to meet contemporary review standards the search, screening, and appraisal followed the structure and reporting principles of the PRISMA 2020 framework, adapted for a narrative synthesis. The study-selection process is summarized in the PRISMA-style flow diagram in Figure 6.

Information sources and search strategy. Literature was retrieved between January and March 2026 from five international databases (Scopus, PubMed, ScienceDirect, Web of Science, and Google Scholar) and the two Indonesian national repositories Garuda and SINTA, the latter included specifically to capture nationally indexed Indonesian work that the international databases under-represent. The core Boolean search string was: ("green synthesis" OR "biosynthesis" OR "plant-mediated") AND ("silver nanoparticle*" OR "AgNP*") AND ("plant extract" OR "medicinal plant" OR "Indonesia*") AND ("antibacterial" OR "antimicrobial" OR "anti-biofilm" OR "antifungal" OR "biomedical"). Search terms were applied to title, abstract, and keyword fields, and the reference lists of included articles were hand-searched (backward citation tracking) for additional sources.

Eligibility criteria. Records were eligible for inclusion when they (i) were peer-reviewed articles published in English or Bahasa Indonesia between 2015 and 2025; (ii) reported the direct experimental use of a plant extract as bio-reductant for AgNP synthesis, or were reviews of the underlying mechanism or applications; and (iii) characterized the resulting nanoparticles with at least one standard technique (UV-Vis, FTIR, XRD, SEM, TEM, EDX, DLS, or zeta potential). Records were excluded when they (i) used non-plant biological routes (bacterial, fungal, or algal synthesis) without a plant component; (ii) were opinion pieces, conference abstracts, theses, or preprints lacking full experimental data; (iii) reported no characterization or no biological/biomedical readout; or (iv) were duplicate reports of the same dataset. A limited number of foundational pre-2015 studies were retained where they were necessary to anchor the mechanistic discussion; these are clearly identified as such and were not counted toward the screened pool.

Study selection. The database and repository searches returned 420 records. After removal of 95 duplicates, 325 records were screened at the title and abstract level, of which 180 were excluded as off-topic (non-silver nanomaterials, non-plant routes, or no antimicrobial/biomedical relevance). The remaining 145 full-text articles were assessed for eligibility, and 65 were excluded for absent nanoparticle characterization, insufficient methodological detail, or duplicate datasets, yielding the 80 sources synthesized in this review. Records were screened independently by two authors, and disagreements were resolved by discussion with the third author.

Quality appraisal and bias minimization. Because no single validated appraisal instrument exists for green-synthesis studies, each included experimental article was appraised against a set of pre-defined methodological-quality indicators: completeness of synthesis reporting (precursor concentration, extract-to-salt ratio, pH, temperature, and reaction time), the number and appropriateness of characterization techniques, the use of recognized antimicrobial standards (e.g., CLSI-based MIC/MBC or zone-of-inhibition assays with stated controls), the inclusion of appropriate positive and negative controls, and the reporting of replication. Studies meeting more of these indicators were weighted more heavily in the interpretive synthesis, and weaker single-technique reports were used only as supporting rather than primary evidence. To minimize selection and reporting bias, searches were not restricted to high-impact journals, Indonesian-language and nationally indexed sources were deliberately included alongside international ones, and both positive and null or inconsistent findings (for example, the contradictory reports on Gram-selectivity discussed below) were retained and reported. The review is nevertheless subject to the usual limitations of a semi-systematic design, including potential publication bias toward positive antimicrobial results and the absence of a quantitative meta-analysis.

Table 1: Positioning of the present review against representative prior reviews of plant-mediated silver nanoparticles.

Review (ref.)	Scope / focus	Indonesia-specific plants	Stated methodology	Ecotoxicity / environmental risk
Vanlalveni et al. [9]	Global; green synthesis & antimicrobial activity	No	Narrative literature review	Not a focus
Huq et al. [10]	Global; bioactive AgNPs & antibacterial use	No	Narrative literature review	Not a focus
Ahmed et al. [11]	Global; plant-extract AgNPs, antimicrobial	No	Narrative literature review	Not a focus
Dakal et al. [5]	Global; antibacterial mechanism of AgNPs	No	Mechanistic review	Not a focus
Simon et al. [72]	Global; biomedical applications of plant AgNPs	No	Narrative literature review	Not a focus
This review	Indonesia-focused; synthesis, mechanism, antibacterial, biomedical & environmental	**Yes**	**Semi-systematic, PRISMA-guided**	**Explicitly discussed**

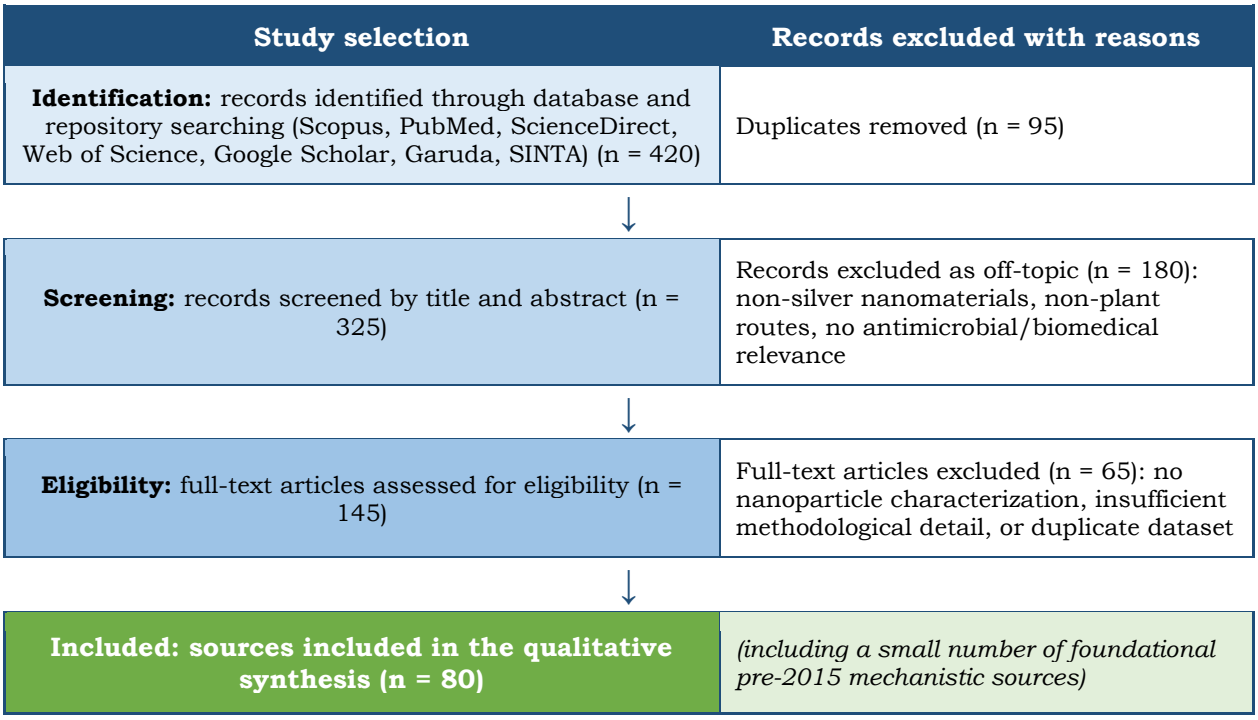

Figure 6: PRISMA-style flow diagram of the study-selection process. The left column shows the four stages (identification, screening, eligibility, included) with record counts; the right column shows records excluded at each stage with reasons.

3. Results and Discussion

3.1. Phytochemistry of Indonesian medicinal plants relevant to AgNP synthesis

Terminology. For consistency, this review uses the following conventions throughout. "AgNPs" denotes silver nanoparticles, with the term defined at first use and the abbreviation used thereafter. "Green synthesis" is used as the umbrella term for environmentally benign, plant-mediated routes, while "biosynthesis" refers specifically to the biochemical bio-reduction and capping reactions carried out by extract phytochemicals; the two are not treated as interchangeable. "Antibacterial" is used when the reported activity is against bacteria specifically, and the broader term "antimicrobial" is reserved for activity spanning bacteria together with fungi and/or viruses.

The reducing capacity of a plant extract is not an intrinsic property of the species but a function of its secondary-metabolite profile. Five broad chemical classes account for most of the documented Ag^{+}-to-Ag^{0} reduction events: flavonoids, phenolic acids, tannins, saponins, and terpenoids [9,20,21]. Flavonoids dominate the literature because the hydroxyl groups on their B-ring and the keto group at C4 together provide both electron-donating capacity and a chelation pocket for the silver ion [21,22,23]. Pure quercetin in aqueous medium can reduce Ag^{+} to Ag^{0} at neutral pH and produce stable nanoparticles in the 10–30 nm range, with the rate and final size strongly dependent on the protonation state of the 3-OH and 7-OH groups, and antibacterial potency improving by an order of magnitude relative to free quercetin [21,23]. The same chemistry underlies the activity of plant extracts in which quercetin and structurally related flavonoids (kaempferol, rutin, dihydroquercetin) are abundant.

Among Indonesian medicinal plants used for AgNP biosynthesis, *Moringa oleifera* (kelor) has been the most studied. Kelor leaf extracts are rich in polyphenols, flavonoids (including quercetin and kaempferol derivatives), and proteins, and these together are sufficient to reduce 1–3 mM silver nitrate within a few hours at 60–80 °C and to stabilize the resulting nanoparticles through surface capping [20,24]. *Curcuma longa* (kunyit) provides a different chemotype dominated by curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin) together with sesquiterpenes such as α- and β-turmerone; the diketone moiety of curcumin is a strong reductant at slightly alkaline pH [19,25]. *Phyllanthus niruri* (meniran) and *Orthosiphon stamineus* (kumis kucing), which carry high total phenolic and flavonoid loads together with characteristic lignans (phyllanthin, hypophyllanthin) and rosmarinic acid derivatives, have been compared in a head-to-head Indonesian study and gave the smallest, most stable AgNPs at 0.5% extract loading [16]. *Garcinia mangostana* (manggis) is unusual in that its principal bioactive class is the prenylated xanthones (α-mangostin, γ-mangostin), which, together with phenolic acids in the rind, enable a single-pot biosynthesis even at room temperature [18,26]. *Calotropis gigantea* from the Ie Seu-Um geothermal area in Aceh contains cardenolides and flavonoids that yielded AgNPs with broad-spectrum

antimicrobial activity against *E. coli*, *S. aureus*, and *Candida albicans* [17].

Cratoxylum glaucum (pucuk idat) from Bangka Island, *Crassocephalum crepidioides* (sintrong), *Areca catechu* (pinang) peel, and *Baccaurea racemosa* (kepundung) fruit peel are less widely known outside Indonesia but have already been used as effective bio-reductants in local studies [15,27,28]. *Annona muricata* (sirsak) extracts, which contain alkaloids (annonaceous acetogenins), megastigmanes, and flavonol glycosides, have produced AgNPs with both antibacterial activity and a strong apoptosis-inducing profile in cancer cell lines, illustrating the dual biomedical potential characteristic of Indonesian endemic flora [29,30]. Beyond flavonoids and phenolics, plant saponins stabilize the colloidal suspension by adsorbing at the metal–water interface, while proteins and amino acids from the extract contribute long-term capping through thiol and amine groups [20,24,31]. The diversity of phytochemicals available across the major plant families used in jamu (Zingiberaceae, Moringaceae, Phyllanthaceae, Lamiaceae, Clusiaceae, Annonaceae) is summarized in Figure 5.

3.2. Biosynthesis mechanism: from Ag^+ to a capped nanoparticle

Mechanistically, green synthesis of AgNPs proceeds in three overlapping stages: reduction, nucleation, and growth, with capping acting throughout. In the reduction step, the phenolic or flavonoid hydroxyl group transfers an electron to Ag^+, yielding Ag^0 and the corresponding quinone or semi-quinone [9,21,22]. For flavonoids such as quercetin or kaempferol, this reaction is most efficient at pH 8–10, where the 3-OH and 7-OH groups are partially deprotonated and therefore more reactive [21,22]. Spectrophotometric studies of pure flavonoid–silver systems have shown that quercetin, dihydroquercetin, rutin, and morin all generate a sharp surface plasmon resonance band at 415 nm, while non-3-hydroxylated flavonoids such as chrysin and naringenin do not, providing direct chemical evidence that the 3-OH group of the flavonoid C-ring is critical for electron transfer to silver [23]. The freshly reduced Ag^0 atoms form clusters that reach a critical radius and nucleate into seed particles; further Ag^0 adds to these seeds in the growth stage. Simultaneously, the same extract molecules adsorb onto the forming nanoparticle surface, preventing uncontrolled aggregation.

FTIR spectra of plant-mediated AgNPs consistently show shifts in the bands assigned to O–H, C=O, C–N, and amide I vibrations, confirming that hydroxyl and carbonyl groups from polyphenols, proteins, and terpenoids are in direct contact with the metal surface [25,31,32]. The protein component of the capping corona is increasingly characterized by LC-MS/MS, which has identified specific extract-derived proteins that remain surface-bound on the final nanoparticle and contribute to its colloidal stability and biocompatibility [31]. The three-stage reduction–nucleation–growth process and the role of the capping corona are summarized schematically in Figure 1.

The three process parameters that dominate the final particle size and morphology are pH, extract concentration, and temperature. Higher pH accelerates the reaction and generally produces smaller, more uniform nanoparticles by boosting nucleation rate, though very high pH can trigger aggregation once capping ligands become overwhelmed [13,33]. Extract volume sets the ratio of reducing and capping equivalents to Ag^+: too little extract leaves particles under-capped and polydisperse, whereas too much extract coats the particles too heavily, reducing their later biological activity [16]. Temperature speeds up reduction but can also disrupt heat-sensitive proteins; most plant-mediated protocols converge on 60–80 °C as a practical optimum, although room-temperature protocols with extended reaction times have also been used successfully for thermolabile extracts [18,34]. Reaction time is typically 1–24 h, followed by the visual appearance of a surface plasmon resonance (SPR) colour ranging from pale yellow to deep brown in small, dispersed nanoparticles [25,32]. Optimization studies on Indonesian plants have shown that an extract-to-$AgNO_3$ ratio of 1:3 to 1:10 and a final concentration of 1–3 mM $AgNO_3$ typically provide the best balance of yield, particle size, and stability [16,17,19].

3.3. Characterization of plant-mediated AgNPs

Standard characterization of AgNPs rests on a well-defined toolkit, and the Indonesian literature is increasingly aligned with international practice. UV-Vis spectroscopy is used as the first, low-cost confirmation: plant-mediated AgNPs typically exhibit a single, symmetric SPR band between 400 and 450 nm, with the exact position shifting to longer wavelengths as the average particle diameter increases [5,32]. FTIR identifies the functional groups from the plant extract that remain bound to the surface, providing indirect evidence of the capping chemistry. XRD provides the crystal structure and, via the Scherrer equation, a first estimate of crystallite size; plant-mediated AgNPs exhibit the four characteristic peaks of face-centred cubic silver at $2\theta \approx 38°$, 44°, 64°, and 77° [19,32].

SEM and TEM provide direct images of particle size and shape and remain the gold standard; particles from plant extracts are commonly spherical, but pseudospherical, hexagonal, and triangular shapes have been reported for specific extracts [5,12,35]. Energy-dispersive X-ray spectroscopy (EDX) confirms the elemental identity of the silver core through its characteristic peak at ~3 keV, and X-ray photoelectron spectroscopy (XPS) provides the oxidation-state distribution at the surface, useful to verify that reduction to Ag^0 has gone to completion rather than leaving residual Ag_2O or AgCl phases [19]. DLS measures the hydrodynamic diameter (always larger than the TEM core diameter due to the capping layer and solvation sphere) and the polydispersity index (PDI), which should ideally remain below 0.3 for a pharmaceutical-grade formulation [13]. Zeta potential values more negative than −30 mV (or more positive than +30 mV) indicate electrostatic stability and resistance to aggregation during storage. The

standard characterization workflow, from first optical confirmation to biological evaluation, is summarized in Figure 2.

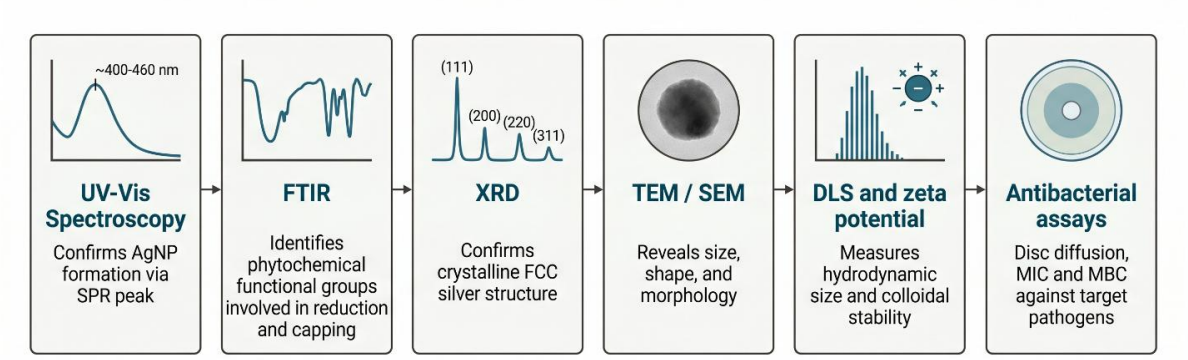

Figure 2: Standard characterization workflow for plant-mediated AgNPs. UV-Vis confirms nanoparticle formation through the surface plasmon resonance peak (400–460 nm); FTIR identifies the phytochemical functional groups involved in reduction and capping; XRD confirms the crystalline face-centred cubic (FCC) structure through the (111), (200), (220) and (311) planes; TEM and SEM reveal size, shape, and morphology; DLS and zeta potential assess hydrodynamic diameter and colloidal stability; and antibacterial assays (disc diffusion, minimum inhibitory concentration, MIC; minimum bactericidal concentration, MBC) evaluate biological performance.

3.4. Indonesian medicinal plants as bio-reductants: case studies

Moringa oleifera leaf extract is the most widely used bio-reductant for AgNP synthesis among Moringa-producing tropical countries, including Indonesia, yielding small, highly active AgNPs (representative data in Table 2) [24]. Gel formulations of *M. oleifera*-AgNPs at 30% w/w have shown stronger inhibition of *Cutibacterium acnes* than standard topical antibiotic controls, a finding relevant to the growing problem of antibiotic-resistant acne [36]. *Curcuma longa* rhizome and leaf extracts produce small, curcumin-coated AgNPs that retain the antioxidant signature of curcumin itself and show antibacterial activity against oral pathogens at sub-microgram-per-millilitre concentrations [25,37,38]. An elegant Indonesian application combined kunyit leaf extract with biogenic hydroxyapatite from land-snail (*Achatina fulica*) shell waste to produce an Ag/HA antibacterial nanocomposite (5–25 nm Ag domains; activity profile in Table 2), illustrating how green synthesis can simultaneously valorize agricultural and food-industry waste streams [19].

Areca catechu peel extract has been used in Indonesia to produce AgNPs active against *E. coli* and *S. aureus*, using an agricultural by-product that is otherwise discarded [27]. *Garcinia mangostana* rind extract, also a fruit-processing waste, has been used to make AgNPs as the active ingredient in environmentally friendly liquid disinfectants targeting *E. coli* and *S. aureus* at extract: precursor ratios optimized to 1:1 [18]. *Calotropis gigantea* aqueous leaf and flower extracts from the Aceh geothermal area produced AgNPs with broad-spectrum antimicrobial activity (parameters in Table 2) [17].

Phyllanthus niruri (meniran), in a head-to-head comparison with *Orthosiphon stamineus* (kumis kucing) and *Curcuma longa*, gave the smallest, most tightly distributed particles at 0.5% w/v extract concentration (Table 2), and is the recommended bio-reductant for further development of topical formulations for diabetic foot ulcers in the Indonesian context [16]. *Cratoxylum glaucum* and *Baccaurea racemosa* extracts have been reported locally to exhibit SPR bands within the expected range and to remain stable for at least 30 days [28,39]. *Annona muricata* (sirsak) leaf extract has produced AgNPs with broad-spectrum antibacterial activity and a documented apoptosis-inducing effect in cancer cells, with multiple independent groups confirming reproducible nanoparticle formation (Table 2) and storage stability of several weeks [29,30,40]. Key plant–phytochemical pairings underlying these case studies are visualized in Figure 5.

Across these cases, three consistent themes emerge: smaller particles (<20 nm) tend to be produced by extracts with higher total phenolic and flavonoid content [41]; antibacterial potency scales with both size reduction and the density of phenolic capping; and the most active formulations reported to date are those obtained at mildly alkaline pH (8–10) with extract-to-$AgNO_3$ ratios in the range 1:3 to 1:10 [9,16,20,24].

Table 2: Summary of plant-mediated silver nanoparticles: synthesis, characterization, and antibacterial activity against common bacterial pathogens. Abbreviations: $AgNO_3$, silver nitrate; CCD, central composite design; CLSI, Clinical and Laboratory Standards Institute; FCC, face-centred cubic; HR-TEM, high-resolution transmission electron microscopy; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant

Staphylococcus aureus; RT, room temperature; SPR, surface plasmon resonance; ZOI, zone of inhibition; ζ, zeta potential.

Plant (common/scientific name, part)	Synthesis conditions	SPR (nm)	Size (nm)/shape	Bacteria tested & antibacterial activity	Reference
Kelor / *Moringa oleifera* (leaf)	1 mM $AgNO_3$; 1:10 extract:salt; RT, 5 d; dark	434	17–60; spherical/semi-spherical	ZOI at 1000 µg/mL: *E. coli* 19.0 ± 0.5 mm; *S. aureus* 20.0 ± 0.5 mm; *K. pneumoniae* 14.6 ± 0.6 mm (well diffusion)	[42]
Kelor / *Moringa oleifera* (gum)	1:1 gum:$AgNO_3$; autoclaved 120 °C, 2 min	— (brown colour)	~50; spherical (SEM)	ZOI: *E. coli* 21 ± 2 mm; *S. aureus* 20 ± 3 mm; MRSA 16 ± 3 mm. MIC 10 µg/mL (Kirby–Bauer)	[43]
Kunyit / *Curcuma longa* (rhizome)	Aqueous rhizome extract + 1 mM $AgNO_3$; RT	415–423	6.3 ± 2.6 (TEM); 16 crystallite (XRD); spherical, FCC	Broth dilution vs *S. aureus*, *E. coli*, *B. subtilis*, *P. aeruginosa*; MIC reduced markedly vs free extract	[25,38]
Kunyit + cangkang bekicot / *Curcuma longa* + *Achatina fulica* (Ag/HA composite)	Microwave 15 min; Ag 1.0–2.4% wt on hydroxyapatite	— (composite)	5–25 (TEM); spherical, dispersed in HA matrix	ZOI dose-dependent vs *E. coli*, *S. aureus*, *K. pneumoniae*, *S. pyogenes*; activity rose with Ag content	[19]
Manggis / *Garcinia mangostana* (rind)	0.01 M $AgNO_3$; 1:1 extract:precursor; RT	~420	82.3 (PSA); spherical	Active vs *S. aureus* and *E. coli*; suitable as active ingredient in liquid disinfectant	[18]
Biduri / *Calotropis gigantea* (leaf and flower)	Aqueous extract + $AgNO_3$; 48 h dark incubation	410–460	87.85–256.7 (SEM-EDS); spherical, agglomerated; ζ −41.8 to −25.1 mV	ZOI: *E. coli* 12.05 ± 0.58 mm; *S. aureus* 11.29 ± 0.45 mm; *C. albicans* 9.02 ± 0.10 mm (Kirby–Bauer)	[17]
Meniran / *Phyllanthus niruri* (aerial parts)	0.5% extract + $AgNO_3$; alkaline NaOH	380–420	Smallest among Indonesian set; spherical, FCC	Recommended bio-reductant for diabetic foot ulcer formulations; smallest particle size and tightest distribution at 0.5% extract	[16]
Jahe + Kunyit / *Zingiber officinale* + *Curcuma longa* (rhizomes)	Synergistic aqueous extracts + $AgNO_3$; reflux	350–430	20–51 (TEM); 42–61 (SEM); spherical	Cytotoxicity confirmed against HT-29 (IC_{50} 150.8 µg/mL); broad antibacterial activity reported	[44]
Mimba / *Azadirachta indica* (leaf)	Aqueous leaf extract + $AgNO_3$; optimized pH & temperature	400	~33; spherical (TEM/SEM), FCC	ZOI at 1000 µg/mL: *E. coli* 18.7 mm; *S. aureus* 17.7 mm; *B. cereus* 17.7 mm; *P.*	[45]

Sirih / *Piper betle* (leaf)	2 mM $AgNO_3$; 1:4 extract; pH 9; sunlight 40 min	420–460	6–20; spherical (TEM), FCC; stable >6 months	*aeruginosa* 10.3 mm. MIC/MBC 390–780 µg/mL ZOI: *S. aureus* 32.8 ± 0.6 mm; *S. typhi* 29.6 ± 0.5 mm; *E. coli* 27.1 ± 0.4 mm; *P. aeruginosa* 22.0 ± 0.5 mm (disc diffusion)	[46]
Cengkeh / *Syzygium aromaticum* (flower bud)	Aqueous bud extract + $AgNO_3$; RT	400–500 (peak ~450)	4–16 (HR-TEM); 7–15 (TEM); quasi-spherical; ζ −28 mV	ZOI 2–4 mm vs *S. mutans*, *S. aureus*, *E. coli*, *E. faecalis*, *C. albicans* (oral pathogens)	[47]
Lidah buaya / *Aloe vera* (leaf gel)	2.2 mM $AgNO_3$; pH 11.9; ~3 h; RT (CCD optimized)	420	15–70; spherical, octahedral possible	2- to 4-fold higher activity than conventional antibiotics vs Gram-positive/Gram-negative strains (disc diffusion, CLSI)	[48]
Sirsak / *Annona muricata* (peel/leaf)	Aqueous peel extract + $AgNO_3$; RT	~420–435	10–60; spherical	Apoptosis-inducing in cancer cells; broad-spectrum antibacterial; NLRP3 inflammasome inhibitor	[29,30]

Table 2 provides a cross-sectional synthesis of representative plant-mediated AgNP systems drawn from the global and Indonesian literature. Several patterns are visible. First, SPR maxima cluster tightly between 400 and 460 nm regardless of plant species, confirming the diagnostic value of the SPR band for first-pass confirmation of AgNP formation. Second, particle size varies much more widely—from <10 nm (*Piper betle*, *Syzygium aromaticum*, *Curcuma longa* rhizome) to 50–250 nm (*Moringa oleifera* gum, *Calotropis gigantea*, *Garcinia mangostana* rind disinfectant formulations)—and this variability tracks with phenolic and flavonoid content, post-synthesis processing, and the use of agglomeration-prone extracts more than with extract pH or temperature alone. Third, antibacterial potency, measured as either the zone of inhibition or MIC, is strongest against Gram-positive cocci (*S. aureus*) and most Gram-negative rods, with *Piper betle*- and *Moringa oleifera* gum-mediated AgNPs producing zones of inhibition comparable to or exceeding those of standard antibiotics. Fourth, Indonesian-led studies are increasingly turning to agricultural waste streams (mangosteen rind, areca peel, kepundung peel, snail shells) as feedstocks, aligning the work with circular-economy principles and reducing raw-material costs.

3.5. Antibacterial activity and molecular mechanisms

The antibacterial activity of plant-mediated AgNPs arises from several overlapping mechanisms rather than a single site of action [49,50,51]. First, the nanoparticle adheres to the bacterial envelope through a combination of hydrophobic interactions, ligand–receptor binding between surface capping molecules and membrane proteins, and van der Waals forces; plant-mediated AgNPs typically carry a negative zeta potential (commonly −20 to −45 mV) imparted by the phenolic and protein capping layer, so attachment is driven by these non-electrostatic interactions rather than by simple cation–anion attraction. Once attached, the particle disrupts membrane integrity, causes leakage of cytoplasmic contents, and depolarizes the proton gradient needed for ATP synthesis [5,31,49]. Second, the continuous release of Ag^+ ions from the particle surface, inside or near the cell, inactivates thiol-containing enzymes in the respiratory chain and forms complexes with DNA bases, thereby interfering with replication [50,52].

Third, both the particle and the released ions catalyse the formation of reactive oxygen species (superoxide, hydrogen peroxide, hydroxyl radical) that oxidize lipids, proteins, and nucleic acids; controlled mechanistic experiments have shown that AgNPs reproducibly elevate intracellular ROS, deplete reduced glutathione, and increase the level of reactive nitrogen intermediates in *E. coli*, *S. aureus*, and *P. aeruginosa* cultures, with antibacterial potency tracking the magnitude of this oxidative stress [51,52,53]. Fourth, AgNPs and the Ag^+ ions they release interact directly with DNA, causing strand breaks, base intercalation, and arrest of replication; biochemical assays of bacteria treated with biosynthesized AgNPs have documented increased DNA fragmentation and elevated lipid

peroxidation, in parallel with disturbed kynurenine metabolism, indicating broad oxidative damage to multiple macromolecule classes [51,52]. This ROS pathway is particularly effective against antibiotic-resistant strains because the bacterial defences that evolved against β-lactams or fluoroquinolones do not overlap significantly with ROS defences [13,53]. The four mechanisms act cooperatively and are summarized schematically in Figure 3.

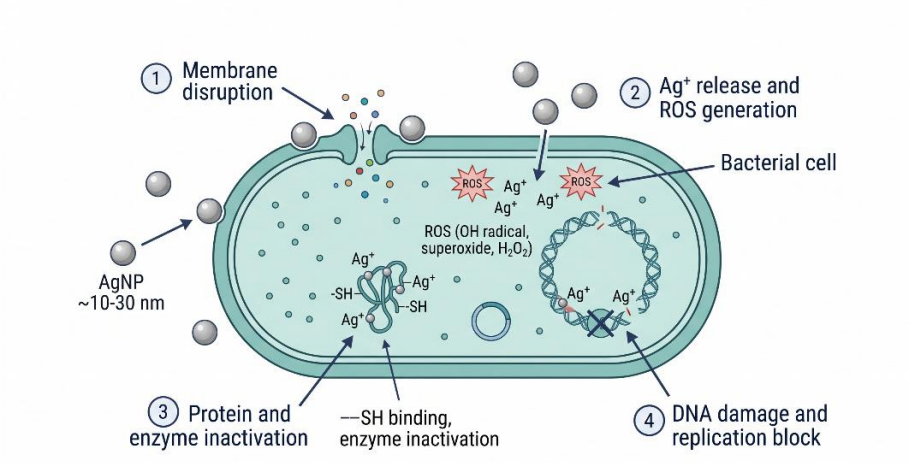

Figure 3: Proposed antibacterial mechanisms of plant-mediated AgNPs. Four routes contribute cooperatively: (1) direct adhesion and disruption of the bacterial cell wall and membrane, leading to loss of permeability and leakage of intracellular contents; (2) dissolution into Ag^+ ions that generate reactive oxygen species (ROS, including •OH, $O_2•^-$ and H_2O_2) and induce oxidative stress; (3) binding of Ag^+ to thiol groups on respiratory and metabolic enzymes, leading to protein misfolding and inactivation; and (4) interaction with DNA, causing strand breaks and arresting replication. This multi-target action is a key reason why bacterial resistance to AgNPs develops more slowly than to conventional antibiotics.

Gram-negative and Gram-positive bacteria respond differently. The thick peptidoglycan layer of Gram-positive species such as *S. aureus* can initially retard penetration, but the absence of a lipopolysaccharide outer membrane means that once AgNPs cross the wall, they reach the cytoplasmic membrane directly. Gram-negative species such as *E. coli* and *P. aeruginosa* have a thinner peptidoglycan layer but an outer membrane whose porins and negatively charged lipopolysaccharide can concentrate AgNPs at the surface [5,49]. Reports on which group is more susceptible are inconsistent: some studies find Gram-negative species more sensitive because of the thinner cell wall and LPS-mediated adsorption, whereas others report Gram-positive species such as *S. aureus* to be equally or more affected once Ag^+ reaches the cytoplasmic membrane [12,13].

The data in Table 2 illustrate this variability: *Piper betle*- and *Moringa oleifera*-mediated AgNPs give larger zones of inhibition against *S. aureus* than against *P. aeruginosa* or *K. pneumoniae*, whereas other systems show the opposite pattern. The practical implication is that the Gram classification alone is a poor predictor of AgNP potency; particle size, phenolic capping density, and the specific strain matter more [5,13,49,50]. Minimum inhibitory concentration (MIC) values reported for plant-mediated AgNPs typically fall within the 5–100 µg/mL range, with smaller particles and those capped with phenolic-rich extracts showing the lowest values [31,49,50]. A consistent observation is that combination treatment with sub-inhibitory doses of conventional antibiotics produces clear synergy: AgNPs combined with β-lactams, fluoroquinolones, or aminoglycosides achieve fractional inhibitory concentration (FIC) indices below 0.5 against MRSA and other ESKAPE pathogens, restoring activity of antibiotics that the resistant strains otherwise inactivate [54,55,56].

Two cross-study relationships deserve a more critical reading than a simple compilation of activity values allows, while keeping in mind that the underlying studies differ in bacterial strain, assay format, and the way "size" is reported (TEM core versus DLS hydrodynamic diameter). First, on the **particle-size–activity relationship**, the systems compiled in Table 2 are broadly consistent with the expectation that smaller nanoparticles are more active: the sub-20 nm *Piper betle* (6–20 nm) and *Syzygium aromaticum* (4–16 nm) preparations sit at the high-activity end, whereas the larger, agglomeration-prone *Calotropis gigantea* (88–257 nm) and *Garcinia mangostana* rind (~82 nm) preparations give smaller zones of inhibition. This is mechanistically expected, because the dissolution rate that supplies antibacterial Ag^+ scales with surface-area-to-volume ratio. The relationship is not monotonic across the dataset, however: the largest particles in Table 2 are not always the least active, and zone-of-inhibition data obtained at a single high test concentration (for example, 1000 µg/mL) are not directly comparable to MIC-based values, so the size–activity trend should be read as a tendency rather than a strict quantitative law. Second, on the **influence of phytochemical composition**, the most active preparations tend to derive from phenolic- and flavonoid-rich extracts, consistent

with the dual role of these molecules as both reductants (yielding smaller particles) and bioactive capping ligands that contribute their own antibacterial action; this confounds any attempt to attribute potency to size alone, since the same chemistry that reduces size also adds intrinsic activity. The within-genus comparison of three *Curcuma* species, which produced graded biological effects despite a shared genus, is direct evidence that phytochemical profile, not taxonomy, drives activity [69]. Taken together, these observations argue against the common overgeneralization that "green AgNPs are broadly antibacterial": potency is governed by an interacting set of factors (size, capping chemistry, dissolution, and strain), and claims should be tied to the specific formulation and test organism rather than asserted for plant-mediated AgNPs as a class.

A further caveat applies to the strength of the antibacterial evidence itself. Almost all of the values discussed above derive from in vitro assays—disc or well diffusion, broth microdilution, and biofilm staining—which measure activity under nutrient-rich, protein-poor, static conditions that differ substantially from an infection site. Diffusion-based zone measurements are influenced by nanoparticle size and agglomeration (large particles diffuse poorly through agar, which can understate the activity of otherwise potent preparations), inter-laboratory differences in inoculum, medium, and incubation make absolute MIC values difficult to compare across studies, and in vitro potency may not translate to in vivo efficacy because serum proteins, physiological chloride, and the host matrix can sequester Ag^+ and form sparingly soluble AgCl. These limitations do not negate the consistent antibacterial signal reported across many independent groups, but they mean that the in vitro data establish promise rather than clinical efficacy, and they reinforce the need for standardized assay conditions and the in vivo studies identified later as a key gap.

3.6. Anti-biofilm activity of plant-mediated AgNPs

Biofilm-forming pathogens are responsible for a disproportionate share of chronic and device-associated infections, and biofilms are intrinsically less susceptible to antibiotics than planktonic cells because the extracellular polymeric substance (EPS) matrix limits diffusion and the dormant subpopulation of cells inside biofilms tolerates concentrations far above the planktonic MIC [57,58,59,60]. Plant-mediated AgNPs combine three mechanisms that make them well suited as anti-biofilm agents: their small size and high surface area let them penetrate the EPS matrix; their continuous Ag^+ release damages biofilm-resident cells in situ; and their phytochemical capping layer brings additional anti-biofilm activity, particularly against quorum-sensing pathways.

In a head-to-head study using AgNPs synthesized with three Indian medicinal plant extracts, biofilm formation by *P. aeruginosa*, *E. coli*, and *S. aureus* was inhibited by more than 95% at AgNP-to-extract ratios of 3:1 and remained strongly inhibited even at low concentrations (10–100 µg/mL), with the plant-mediated nanoparticles outperforming chemically synthesized counterparts and free plant extract in all three species [57]. Biogenic AgNPs in combination with polymyxin B have been shown to disrupt established biofilms of carbapenem-resistant *Acinetobacter baumannii*, an organism for which therapeutic options are otherwise critically limited [58]. AgNPs combined with oregano-derived essential oil components (carvacrol, thymol) showed additive-to-synergistic antibiofilm activity against carbapenem-resistant *Klebsiella pneumoniae*, reducing fimbrial production, swarming motility, and quorum-sensing molecule release [59]. Plant-mediated AgNPs from *Tamarindus indica* leaf extract have been formulated into hydrogels for chronic wound applications and have shown the ability to disrupt established *P. aeruginosa* biofilms in vitro by inhibiting pyocyanin production and EPS synthesis [61]. Importantly, the magnitude of anti-biofilm activity is strongly dependent on the synthesis route: in comparative studies, plant-mediated AgNPs typically inhibited biofilm formation by 80–95% at concentrations at which chemically synthesized AgNPs achieved only 40–60% inhibition, an advantage attributed to the synergistic action of the phytochemical capping layer [57]. The molecular mechanisms by which plant-mediated AgNPs inhibit biofilm formation, mature biofilm dispersal, and quorum-sensing signalling are summarized in Figure 4.

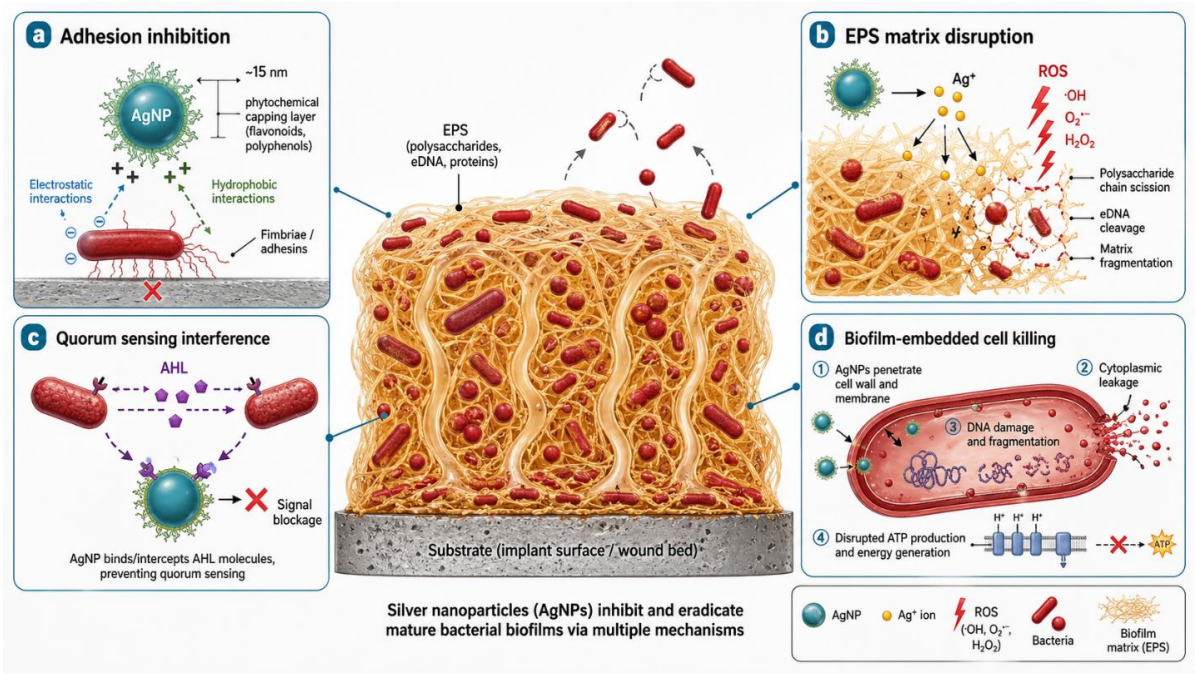

Figure 4: Anti-biofilm mechanisms of plant-mediated AgNPs. (a) Inhibition of bacterial adhesion through electrostatic and hydrophobic interactions with the substrate-binding proteins; (b) disruption of the extracellular polymeric substance (EPS) matrix by Ag^+ release and ROS generation; (c) interference with quorum-sensing signalling molecules (acyl-homoserine lactones in Gram-negative species, autoinducing peptides in Gram-positive species); and (d) killing of biofilm-resident cells through the same multi-target action shown in Figure 3. Unlike antibiotics, AgNPs maintain activity against the dormant subpopulation that is otherwise tolerant to growth-dependent drugs.

3.7. Activity against ESKAPE pathogens and antibiotic synergy

ESKAPE organisms (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, *Enterobacter* spp.) are the principal targets of new-antimicrobial development [2,3]. Plant-mediated AgNPs have been tested against all six and have shown consistent inhibition, with several formulations restoring the activity of antibiotics that are otherwise ineffective against the resistant phenotype. Against MRSA specifically, *Moringa oleifera* gum-mediated AgNPs gave inhibition zones of 16 ± 3 mm at 10 µg/mL [43]; liquorice-decorated AgNPs accelerated wound healing and produced higher procollagen-I synthesis than silver sulfadiazine in a rabbit MRSA wound model [54]; and bacteriocin-encapsulated AgNPs reduced MRSA biofilm biomass by 80–90% [55]. Against *P. aeruginosa* and MRSA isolated from the sputum of COVID-19 patients, biogenic AgNPs from *Fragaria ananassa* leaves prepared by co-sedimentation exhibited SPR at 420 nm, a particle size of ~53 nm, and inhibited both pathogens at clinically relevant concentrations [62]. Studies of AgNPs combined with β-lactams or carbapenems against multidrug-resistant ESKAPE strains have repeatedly reported synergy, with FIC indices below 0.5 and activity restored against vancomycin-resistant enterococci, carbapenem-resistant Enterobacterales, and pan-drug-resistant *K. pneumoniae* [54,55]. The plant-mediated route is favoured for ESKAPE applications because the phytochemical capping layer brings independent antibacterial activity and reduces aggregation, both of which improve activity in complex biological matrices [55,62].

3.8. Biomedical applications beyond antibacterial use

The antibacterial story is the most mature, but plant-mediated AgNPs are being evaluated in several other biomedical contexts. **Wound healing** is the application closest to clinical translation: AgNP-loaded dressings and hydrogels combine topical antimicrobial action with stimulation of fibroblast migration and modulation of pro-inflammatory cytokines, shortening healing time in both burn and chronic wound models [54,63,64,65]. Liquorice-decorated AgNPs significantly increased procollagen-I deposition relative to silver sulfadiazine and accelerated re-epithelialization in a rabbit MRSA-infected wound model [54]. Plant-mediated AgNPs maintain over 80% fibroblast viability at concentrations ≤50 µg/mL while delivering MIC-level antibacterial activity, indicating an acceptable therapeutic window for topical use [66].

Anticancer activity has been demonstrated in vitro for AgNPs synthesized with curcuma, moringa, sirsak (*Annona muricata*), and other extracts against breast, cervical, colorectal, and lung cancer cell lines, with reported IC_{50} values spanning from a few µg/mL to more than one hundred µg/mL depending on the cell line, extract source, and particle characteristics [29,31,67,68]. *Annona muricata* extract-mediated AgNPs induced apoptosis in cancer cells through both intrinsic (mitochondrial, caspase-9/3 activation) and extrinsic (death receptor)

pathways and additionally inhibited NLRP3 inflammasome activity via enhanced autophagy, suggesting an anti-inflammatory role complementary to direct cytotoxicity [29]. *Zingiber officinale*/*Curcuma longa*-mediated AgNPs gave an IC_{50} of approximately 150.8 µg/mL against HT-29 colon carcinoma cells through ROS-driven apoptosis and mitochondrial dysfunction [44], and Curcuma-mediated AgNPs across three species (*C. longa*, *C. aromatica*, *C. caesia*) produced graded cytotoxicity in HT-29 cells, demonstrating that within-genus phytochemical variation translates into biological differences in the resulting nanoparticles [69]. The general molecular signature of biogenic AgNP-induced cancer cell death includes upregulation of p53, p21, caspases-3/7/9, PARP1, JNK, cytochrome c, and the autophagy proteins beclin-1, LC3-II, ATG5 and ATG7, together with downregulation of Bcl-2 and the AKT/Src kinase axis [31,67,70].

Drug delivery is an emerging application in which AgNPs serve as carriers for hydrophobic drugs such as curcumin itself, taking advantage of surface functionalization to extend circulation and target tumour tissue [71]; a recent Indonesian-relevant example combined turmeric leaf extract with bacterial cellulose and silk to produce an antibacterial face covering with synergistic activity against respiratory pathogens [26,72]. **Diagnostic applications**—AgNP-based colorimetric sensors for heavy metals or for biomarkers in saliva and urine—have also been reported from Indonesian groups, although these are still at the proof-of-concept stage [28].

3.9. Antifungal and antiviral activity

Although bacterial pathogens dominate the AgNP literature, plant-mediated AgNPs are increasingly being evaluated for activity against fungi and viruses, both of which are clinically relevant in tropical settings. AgNPs synthesized with *Encephalartos laurentianus* leaf extract showed minimum inhibitory concentrations of 8–256 µg/mL against clinical isolates of *Candida albicans*, significantly reduced biofilm formation, and downregulated the expression of biofilm-associated genes assessed by qRT-PCR; they also accelerated wound re-epithelialization in vivo without granulation or inflammation, indicating dual antifungal and wound-healing utility [73]. Green-synthesized AgNPs from *Ocimum tenuiflorum* and *Ocimum gratissimum* incorporated into a dental varnish achieved a dose-dependent zone of inhibition against *C. albicans* and induced cytoplasmic and protein leakage, validating the membrane-disruption mechanism for the antifungal action [74]. Comparative work with *Psidium guajava* and *Tamarindus indica* leaf extracts produced spherical AgNPs of 5–53 nm and 12–91 nm, respectively, both with strong antifungal activity against *Fusarium oxysporum*, *Aspergillus niger*, and *Aspergillus flavus*, the latter group being responsible for spoilage of stored agricultural products and important targets in the Indonesian tropical climate [61].

Antiviral activity has been less extensively studied, but a head-to-head evaluation of AgNPs synthesized with *Phyllanthus niruri*, *Andrographis paniculata*, and *Tinospora cordifolia* extracts against chikungunya virus showed that *A. paniculata*-mediated AgNPs were the most effective, raising cell viability of infected cells from 25.7% to 80.8% at the maximum non-toxic dose; *P. niruri*- and *A. paniculata*-derived AgNPs additionally have anti-inflammatory activity in vitro [75,76]. These findings support an expanded therapeutic role for plant-mediated AgNPs in tropical fungal and viral infections that disproportionately affect Indonesia.

3.10. Cytotoxicity, in vivo toxicity, and standardization

Against these opportunities, the field has real risks. AgNPs are not biologically inert: their cytotoxic effect on cancer cells is, in principle, the same effect they exert on healthy cells, and dose-response data in normal human fibroblasts and keratinocytes show overlap with the antibacterial MIC range [13,72,77]. Selectivity has to be demonstrated rather than assumed. Hemolysis assays of plant-mediated AgNPs across multiple plant species typically show negligible hemolytic activity at antibacterial concentrations, suggesting that the phytochemical capping layer reduces erythrocyte interaction relative to chemically synthesized AgNPs, but exceptions exist and need to be characterized for each formulation [13,66].

In vivo toxicity studies are sparser. Sub-chronic oral exposure of Sprague–Dawley rats to PVP-coated AgNPs at 50–200 mg/kg/day for 90 days produced silver accumulation in the ileum, liver, and spleen but no significant changes in haematological or biochemical parameters [78,79]. Lower-dose, longer-term studies have nevertheless detected hepatic mitochondrial dysfunction at very low doses, an effect that is reversed by N-acetylcysteine pre-treatment and is therefore mechanistically attributable to oxidative stress [77,78].

Studies with positively charged CTAB-capped AgNPs over 18 days at concentrations comparable to those leached from food-contact products produced lethargy, hepatomegaly, splenomegaly, and altered immune responses, illustrating that surface charge and capping chemistry strongly modulate in vivo toxicity [80]. The most consistent finding across studies is that AgNPs accumulate in the liver and spleen following oral or intravenous administration, with smaller particles more readily distributing to the brain and reproductive organs, raising questions about long-term exposure that have not yet been answered for plant-mediated AgNPs specifically [77,78,80]. The lack of standardization in plant extraction, synthesis conditions, and batch testing is the single largest barrier to translation: a Moringa-AgNP formulation made by one laboratory at 30 °C with a 1:1 extract-to-silver ratio can have a completely different particle size and safety profile from one made by another laboratory at 80 °C with a 3:1 ratio [13,16]. Quality-by-design approaches, including factorial design of experiments to map the effect of pH, temperature, and extract concentration on particle size and biological activity, are beginning to address this gap and should be adopted as standard practice in Indonesian laboratories [16,23].

Environmental fate remains an open question, as AgNPs that leak from medical or consumer products accumulate in wastewater and can affect non-target organisms [77].

3.11. Environmental chemistry, sustainability, ecotoxicity, and environmental risk assessment

For a journal of environmental chemistry, the green credentials of plant-mediated AgNPs warrant explicit, rather than assumed, scrutiny. The sustainability case rests on three features of the green route relative to conventional synthesis: it replaces hazardous reductants and stabilizers such as sodium borohydride and hydrazine with renewable plant phytochemicals, it operates in water at mild temperatures with low energy input, and it can valorize agricultural and food-processing residues that would otherwise be discarded. Several Indonesian studies illustrate this circularity directly, using mangosteen rind [18], areca peel [27], kepundung peel, and land-snail shell waste combined with turmeric leaf [19] as feedstocks, thereby coupling nanoparticle production to waste reduction. Plant-mediated AgNPs also have documented environmental applications beyond medicine, including catalytic degradation of organic dyes, which positions them as potential tools for water remediation [30]. These benefits are real but should be quantified rather than asserted: a rigorous sustainability claim would require life-cycle thinking that accounts for solvent and water use, the energy of extract preparation and downstream purification, the silver precursor itself, and end-of-life fate, none of which is currently reported for Indonesian preparations.

The same properties that make AgNPs useful antimicrobials also make them potential environmental contaminants, so an environmental risk assessment perspective is essential. Silver is toxic to a broad range of non-target aquatic organisms, and nanoparticles released from medical or consumer products can enter wastewater streams and accumulate in the environment [77]. Once released, AgNPs do not persist unchanged: their environmental behaviour is governed by transformation reactions—oxidative dissolution to Ag^+, complexation with chloride and natural organic matter, sulfidation to poorly soluble Ag_2S, and aggregation—which together determine bioavailability and toxicity to bacteria, algae, invertebrates, and fish. The capping chemistry that distinguishes plant-mediated AgNPs is therefore environmentally relevant, because the phytochemical corona influences dissolution rate, surface charge, and aggregation state, and hence ecotoxicity. Direct ecotoxicity data for biogenic AgNPs remain scarce, but they are beginning to appear: a biogenic silver–silver chloride nanoparticle preparation from *Annona muricata* leaf extract, for example, was evaluated for eco-toxicity alongside its antibacterial and dye-degradation activity, an approach that should become routine rather than exceptional [30]. A framework for assessing the environmental risk of these materials should pair characterization of the released species and their transformation products with standardized ecotoxicity testing against representative trophic levels (for example, a bacterium, a green alga, and a crustacean such as *Daphnia*), so that the environmental cost can be weighed against the antimicrobial benefit. Embedding this risk-assessment thinking into Indonesian green-synthesis research would both strengthen the field's environmental-chemistry credentials and pre-empt the regulatory questions that any scale-up will eventually face. Importantly, the same Indonesian research teams active in plant-based nano-synthesis are already demonstrating environmental-chemistry competence in adjacent applications: *Echinodorus palaefolius*, deployed in a constructed-wetland system, removed 95.98% of iron from Jatibarang landfill leachate within seven days [81], illustrating that the green-chemistry expertise and the environmental-monitoring infrastructure are already present and can be redirected towards assessing the fate and risk of plant-mediated AgNPs in the same aquatic and soil environments.

3.12. Challenges, gaps, and future directions for Indonesian research

Six gaps stand out in the Indonesian literature. First, most published studies use one or two standard laboratory strains (typically ATCC *E. coli* and *S. aureus*) and stop there; testing against clinical multidrug-resistant (MDR) isolates, including MRSA, carbapenem-resistant Enterobacterales, and extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* from Indonesian hospitals, would make the findings directly relevant to local clinical needs [55,62]. Second, in vivo studies remain rare; without animal models of wound infection, systemic infection, or tumour growth, the field cannot move toward pre-clinical trials [54,78,80]. Third, there is almost no work on the pharmacokinetics and biodistribution of plant-mediated AgNPs, which are basic safety requirements before any clinical use [77,78,80]. Fourth, anti-biofilm activity has been consistently identified as a strength of plant-mediated AgNPs in international studies but remains under-investigated in Indonesia, despite its direct relevance to chronic wounds, tuberculosis-associated infections, and oral diseases that are highly prevalent locally [57,58,59,61]; plant-extract formulations tested locally against skin pathogens—including green tea (*Camellia sinensis*) cream preparations that inhibit *Staphylococcus epidermidis* and *Propionibacterium acnes* [82]—confirm the phytochemical basis is available, but nanoparticle-enabled delivery and standardization remain to be addressed. Fifth, standardization of the plant raw material—by defining geographic origin, harvest season, post-harvest processing, and a reference phytochemical fingerprint—is essential for reproducible results across laboratories and batches [13,16]. Sixth, the environmental dimension is almost entirely absent: ecotoxicity testing against non-target organisms, characterization of environmental transformation products, and any form of life-cycle or environmental risk assessment are rarely reported for Indonesian plant-mediated AgNPs, even though these data are needed to

substantiate the "green" label and to anticipate the regulatory questions that scale-up will raise [30,77]. Research programmes that combine biomedical sciences departments with chemistry, pharmacy, and public-health groups are therefore particularly well placed to make progress—recent fabrication of triterpenoid nanoparticles from *Gynura procumbens* with selective *S. aureus* activity [83] illustrates the type of phytochemistry-to-nanomaterial translation that, when combined with rigorous microbiological validation, can accelerate the field—and the green-chemistry positioning of this research makes it an excellent fit for Indonesian journals working at the chemistry–biology–health interface.

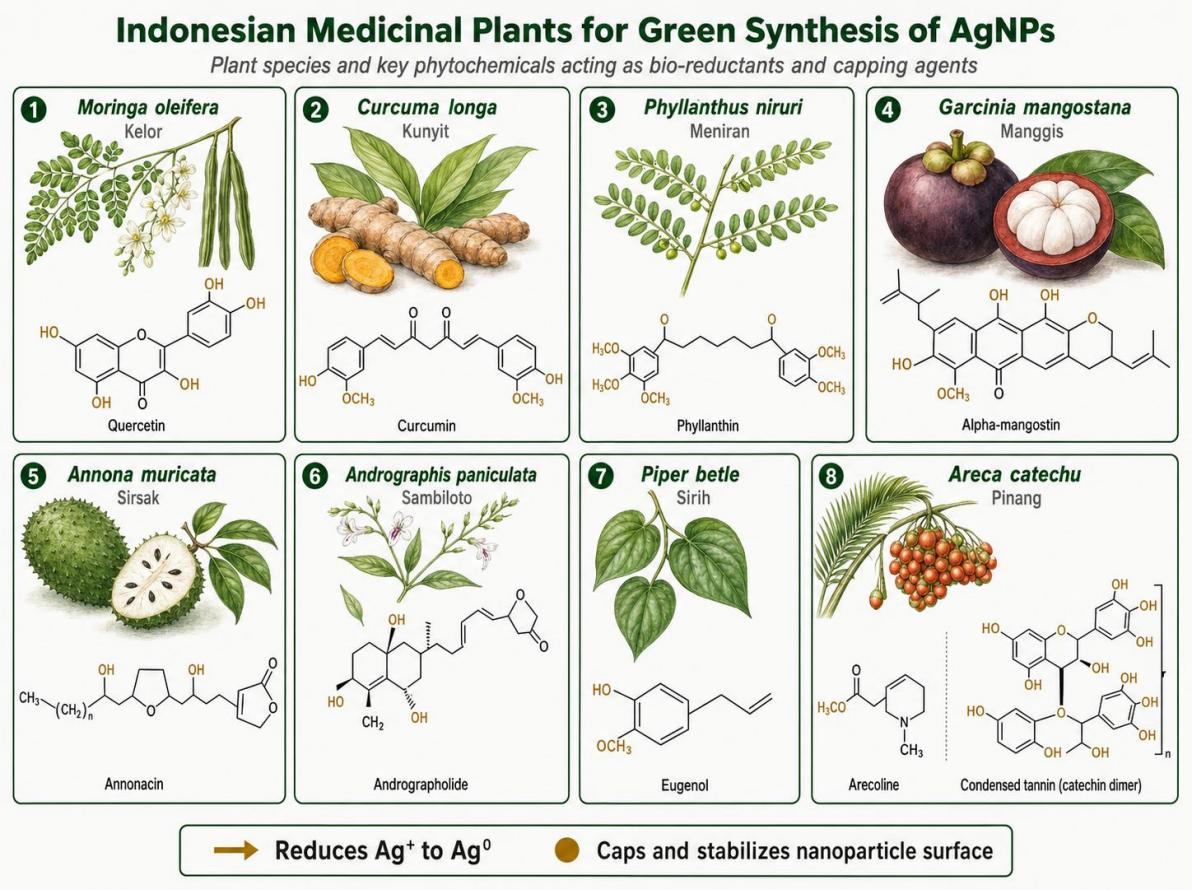

Figure 5: Indonesian medicinal plants frequently used as bio-reductants for green AgNP synthesis, paired with their principal phytochemical classes. Top row, left to right: Moringa oleifera (kelor) — flavonoids and proteins; Curcuma longa (kunyit) — curcuminoids and turmerones; Phyllanthus niruri (meniran) — lignans and phenolic acids; Garcinia mangostana (manggis) — prenylated xanthones (α-mangostin). Bottom row: Annona muricata (sirsak) — annonaceous acetogenins, alkaloids; Andrographis paniculata (sambiloto) — andrographolide, diterpenoids; Piper betle (sirih) — phenylpropanoids, eugenol; Areca catechu (pinang) — alkaloids and tannins. The diverse phytochemical landscape of Indonesian flora provides a deep pool of natural reductants and capping agents for next-generation green AgNP synthesis.

4. Conclusion

This review is, to our knowledge, the first to consolidate the Indonesian evidence on plant-mediated AgNPs into a single integrative synthesis, positioned explicitly against the existing global reviews (Table 1) and conducted through a semi-systematic, PRISMA-guided methodology rather than as a narrative compilation. Green synthesis of silver nanoparticles using Indonesian medicinal plants is a small but rapidly growing field that sits at the intersection of green chemistry, phytochemistry, and biomedical sciences. Indonesian species such as *Moringa oleifera*, *Curcuma longa*, *Phyllanthus niruri*, *Garcinia mangostana*, *Calotropis gigantea*, *Areca catechu*, *Annona muricata*, and several endemic plants have been successfully used as single-pot bioreductants and capping agents, producing AgNPs with broad-spectrum antibacterial activity. The underlying mechanism—membrane disruption, Ag^+-mediated enzyme inactivation, ROS-driven oxidative damage, and DNA interaction—offers clear advantages against antibiotic-resistant ESKAPE pathogens, and biomedical applications in wound healing, cancer therapy, drug delivery, and antifungal action are beginning to emerge. Anti-biofilm activity, in particular, is an underexplored strength of plant-mediated AgNPs that aligns directly

with the clinical priorities of tropical countries. Progress from benchtop to clinic depends on standardizing plant raw material (geographic origin, harvest season, and phytochemical fingerprinting), harmonizing synthesis protocols and characterization workflows, expanding testing to clinical multidrug-resistant isolates from Indonesian hospitals, and completing the in vivo pharmacokinetic, biodistribution, and toxicity studies that are currently missing from the Indonesian literature, and substantiating the "green" label with quantitative sustainability metrics and ecotoxicity and environmental risk assessment. Addressing these gaps in coordinated, multi-disciplinary programmes will be essential if plant-mediated AgNPs are to translate from academic demonstrations into reproducible, clinically relevant, and environmentally responsible antimicrobial tools.

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Author Contributions

F.A.P. conceived the review, conducted the literature search and synthesis, and drafted the manuscript. M.O.S.K.S. and M.B.H. contributed to the phytochemistry and characterization sections and critically revised the manuscript. All authors have read and approved the final version for submission.

Conflict of Interest

The authors declare no competing financial or personal interests that could have influenced the work reported in this review.

Data Availability

No new data were generated for this review. All information synthesised here is drawn from the published sources listed in the reference list.

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