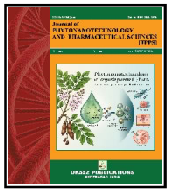
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Phytochemical mediated green nanoparticles from forest trees: Molecular mechanisms, pharmacological activities and future perspectives

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Abstract

Forest trees are a vast and still underexploited reservoir of secondary metabolites, including polyphenols, flavonoids, tannins, terpenoids, alkaloids and saponins, that can simultaneously reduce metal ions and stabilise the resulting nanoparticles (NPs). Phytochemical mediated, or green, synthesis therefore offers a single step, low energy and solvent sparing alternative to physical and chemical routes for producing silver, gold, zinc oxide, copper oxide and other metallic NPs with biofunctional surfaces. This review summarises current knowledge on the synthesis of NPs using leaf, bark, fruit, seed, resin and gum extracts of forest tree species such as *Azadirachta indica* A. Juss, *Eucalyptus globulus* Labill., *Pinus eldarica* Medw., *Terminalia chebula* Retz., *Syzygium cumini* (L.) Skeels, *Cinnamomum camphora* (L.) J. Presl, *Moringa oleifera* Lam., *Ginkgo biloba* L. and *Cassia fistula* L.. The molecular basis of ion reduction, nucleation and capping is discussed together with the key reaction parameters and characterisation techniques. The pharmacological activities of these NPs; namely, antibacterial, antifungal, antiviral, anticancer, antioxidant, anti-inflammatory, antidiabetic, wound healing and larvicidal effects, are described with emphasis on cellular and molecular mechanisms such as reactive oxygen species (ROS) generation, membrane disruption, mitochondrial dysfunction, caspase activation and NF-κB suppression. Finally, challenges relating to batch-to-batch reproducibility, toxicity, environmental fate, sustainable harvesting and regulatory approval are examined, and a translational roadmap is proposed. Standardised extracts, mechanism driven design and rigorous *in vivo* validation will be essential to move forest tree derived green NPs from the laboratory to the clinic

1. Introduction

Nanotechnology has changed the way drugs are designed, delivered and targeted. Nanoparticles (NPs), typically defined as particles with at least one dimension between 1 and 100 nm, display size and shape dependent optical, electronic, catalytic and biological properties that differ markedly from those of the bulk material (Nel *et al*., 2006). Metallic NPs of silver (Ag), gold (Au), zinc oxide (ZnO), copper oxide (CuO) and iron oxide have attracted particular attention in biomedicine because of their large surface area to volume ratio, tunable surface chemistry and intrinsic antimicrobial or cytotoxic activity (Rai *et al*., 2009; Sharma *et al*., 2009).

Conventional physical (laser ablation, evaporation condensation) and chemical (borohydride or citrate reduction) methods of NP synthesis are often energy intensive and rely on hazardous reducing agents and organic solvents that leave toxic residues on the particle surface, limiting biomedical use (Kharissova *et al*., 2013). Green synthesis, which uses biological entities such as bacteria, fungi, algae and plants, has therefore been proposed as an ecofriendly alternative. Among biological systems, plants are especially attractive because extracts are readily available, safe to handle, scalable, and rich in biomolecules that act as both reductants and capping agents in a one pot reaction (Iravani, 2011; Mittal *et al*., 2013; Raveendran *et al*., 2003).

Forest trees deserve a distinct focus within plant-mediated nanotechnology. Trees accumulate large amounts of structurally diverse secondary metabolites in leaves, bark, heartwood, fruits, seeds and exudates as chemical defence against herbivores, pathogens and abiotic stress. Many of these species have a long ethnomedicinal history, for example neem (*A. indica*), arjuna (*T. arjuna*), jamun (*S. cumini*), amla (*P. emblica*, syn. *E. officinalis*), *Eucalyptus* and camphor, and natural products remain a principal source of new therapeutic leads (Newman and Cragg, 2020). Furthermore, bark, leaf litter, pruning residues and fruit pericarp from forestry and agroforestry operations are renewable by-products that can be valorised, so that nanoparticle synthesis can be coupled to circular bioeconomy approaches.

Although several reviews have covered plant mediated NP synthesis in general (Ahmed *et al*., 2016; Kuppusamy *et al*., 2016; Singh *et al*., 2016; Salem and Fouda, 2021), few have concentrated on forest trees and linked the phytochemical profile of the tree to the molecular events of NP formation and to downstream pharmacological

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mechanisms. This review therefore: (i) catalogues forest tree species used for green NP synthesis and their active phytochemicals, (ii) explains the mechanisms of reduction, nucleation and capping, (iii) summarises characterisation approaches, (iv) discusses pharmacological activities with their molecular targets, and (v) identifies research gaps and future directions.

2. Forest trees as phytochemical factories for nanoparticle synthesis

2.1 Plant parts and extraction

Leaves are the most frequently used material owing to their abundance and high content of phenolics and flavonoids; however, bark, fruit, seed, flower, gum and resin extracts have also been successfully employed. Pine bark extract, for instance, yielded silver NPs with antibacterial activity (Iravani and Zolfaghari, 2013), whereas the fruit extracts of *T. chebula* and *E. officinalis* have been used to produce silver and gold NPs, respectively (Ankamwar *et al*., 2005; Kumar *et al*., 2012). Aqueous extraction by boiling or maceration is most common because it is simple and solvent free; hydroalcoholic, microwave assisted and ultrasound assisted extractions can increase the yield of polyphenols and shorten reaction time (Ali *et al*., 2015). The choice of plant part, tree age, season of collection and extraction method all alter the phytochemical profile and hence the size, shape and yield of NPs.

2.2 Key phytochemical classes and their functional roles

Phytochemicals contribute to NP formation through several functional groups. Phenolic hydroxyl groups of tannins, flavonoids and phenolic acids donate electrons and protons to reduce metal ions; carbonyl and carboxyl groups, together with proteins and polysaccharides, coordinate surface atoms and give steric and electrostatic stabilisation; and terpenoids and saponins act as amphiphilic capping agents (Makarov *et al*., 2014; Kuppusamy *et al*., 2016). Table 1 summarises the major classes of phytochemicals in forest trees and the roles they play.

Table 1: Major phytochemical classes from forest trees involved in green nanoparticle synthesis

Phytochemical class	Representative compounds	Typical tree sources	Role in NP synthesis
Hydrolysable and condensed tannins	Gallic acid, ellagic acid, chebulinic acid, proanthocyanidins	*Terminalia* spp., *S. cumini*, *E. officinalis*, *Acacia* spp.	Strong reductants (multiple -OH); chelate metal ions; capping through polyphenol-metal complexes
Flavonoids	Quercetin, kaempferol, catechin, luteolin, rutin	*G. biloba*, *Eucalyptus* spp., *M. oleifera*	Keto-enol tautomerisation releases reactive hydrogen; reduction of Agz/Au³z ; capping
Phenolic acids and stilbenes	Caffeic, ferulic, chlorogenic acid, resveratrol	*Pinus* spp., M. *alba*, *Eucalyptus* spp.	Electron donation; stabilisation through carboxylate groups
Terpenoids and essential oils	Limonene, 1,8-cineole, camphor, azadirachtin, nimbin	*A. indica*, *C. camphora*, *Eucalyptus globulus*	Reduction by aldehyde/ketone groups; hydrophobic capping layer
Alkaloids	Isoquinoline and indole alkaloids	*A. scholaris*, *Holarrhena* spp.	Coordination through N-donor groups; capping
Saponins and glycosides	Triterpenoid saponins, cardiac glycosides	*S. mukorossi*, *A. concinna*	Surfactant-like stabilisation; prevent aggregation

2.3 Forest tree species reported for green nanoparticle synthesis

A wide range of tree species have been explored. Early reports showed that extracts from neem leaves could produce bimetallic Au-Ag nanostructures (Shankar *et al*., 2004), camphor-tree leaf broth yielded Ag and Au NPs of various shapes (Huang *et al*., 2007), and leaf extracts of pine, persimmon, ginkgo, magnolia and plane tree rapidly reduced silver ions to NPs, with particle size controlled by extract concentration and temperature (Song and Kim, 2009). Subsequent studies extended this approach to several medicinal trees and demonstrated biological activity; selected examples are listed in Table 2.

Table 2: Selected forest and agroforestry tree species used for phytochemical-mediated nanoparticle synthesis and their reported bioactivities

Tree species (family)	Part used	NP	Principal phytochemicals implicated	Reported activity/ remarks	References
A. indica (Meliaceae)	Leaf	Au-Ag; Ag	Flavanones, terpenoids, proteins	Bimetallic nanostructures; antibacterial activity	Shankar *et al*., 2004; Tripathi *et al*., 2009
C. camphora (Lauraceae)	Leaf	Ag, Au	Polyols, terpenoids (camphor)	Shape-controlled spherical and triangular particles	Huang *et al*., 2007
C. zeylanicum (Lauraceae)	Bark	Ag	Cinnamaldehyde, polyphenols	Nanocrystalline Ag; bactericidal activity	Sathishkumar *et al*., 2009
Pinus, *Ginkgo*, *Magnolia*, *Platanus*, *Diospyros*	Leaf	Ag	Flavonoids, phenolics, terpenoids	Rapid synthesis; size depends on extract concentration and temperature	Song and Kim, 2009
P. eldarica (Pinaceae)	Bark	Ag	Proanthocyanidins, phenolic acids	Antibacterial activity	Iravani and Zolfaghari, 2013

E. globulus (Myrtaceae)	Leaf	Ag	Flavonoids, cineole, phenolics	Microwave assisted synthesis; antibacterial and antibiofilm activity on clinical isolates	Ali *et al*., 2015
T. chebula (Combretaceae)	Fruit	Ag	Chebulinic acid, gallic acid, ellagic acid	Room-temperature synthesis; antimicrobial activity	Kumar *et al*., 2012
S. cumini (Myrtaceae)	Leaf, seed	Ag	Tannins, anthocyanins, flavonoids	Characterised Ag NPs; extract dependent size	Kumar *et al*., 2010
E. officinalis (Phyllanthaceae)	Fruit	Au, Ag	Ascorbic acid, ellagitannins	Phase transfer and transmetallation studies	Ankamwar *et al*., 2005
M. oleifera (Moringaceae)	Leaf	Ag	Flavonoids, glucosinolates, phenolic acids	Antimicrobial activity	Prasad and Elumalai, 2011
M. alba (Moraceae)	Leaf	Ag	Flavonoids, phenolics	Antimicrobial NPs	Awwad and Salem, 2012
C. fistula (Fabaceae)	Stem bark	Au	Anthraquinones, flavonoids, polysaccharides	Hypoglycaemic activity in diabetic rats	Daisy and Saipriya, 2012
S. aucuparia (Rosaceae)	Leaf	Ag, Au	Flavonoids, phenolic acids	Stable nanocolloids	Dubey *et al*., 2010

3. Molecular mechanisms of phytochemical-mediated nanoparticle formation

The formation of metallic NPs by plant extracts is generally explained by a three-stage process: (i) reduction of metal ions and nucleation, (ii) growth of nuclei with thermodynamic stabilisation, and (iii) termination by capping (Makarov *et al*., 2014). In the activation phase, metal ions such as Ag^{+} or Au^{3+} form complexes with phenolic and carboxylic groups of the extract and are reduced to zero-valent atoms through electron transfer, the polyphenol being oxidised to the corresponding quinone. For flavonoids, keto-enol tautomerisation of the heterocyclic ring has been proposed to release a reactive hydrogen atom that reduces the metal ion (Kumar and Yadav, 2009). Aldehyde and ketone groups of terpenoids, reducing sugars and enzymes such as nitrate reductase-like proteins may supplement this activity (Iravani, 2011).

The zero valent atoms then collide and form nuclei. During the growth phase, small nuclei merge, by Ostwald ripening and coalescence, to form larger crystalline particles, and the final size, shape and crystal facets depend on the relative rate of nucleation and growth. When reduction is fast, as with high concentrations of polyphenols at elevated temperature or alkaline pH, many nuclei form and small, spherical particles result; slower reduction favours anisotropic structures such as triangles, hexagons and rods (Mittal *et al*., 2013). In the termination phase, phytochemicals adsorb on the particle surface through -OH, $-COO^{-}$, -NH, and C=O groups, creating a corona that limits aggregation and defines the surface charge. This corona is important pharmacologically because it determines colloidal stability, protein adsorption, cellular uptake and biodistribution (Figure 1 and 2).

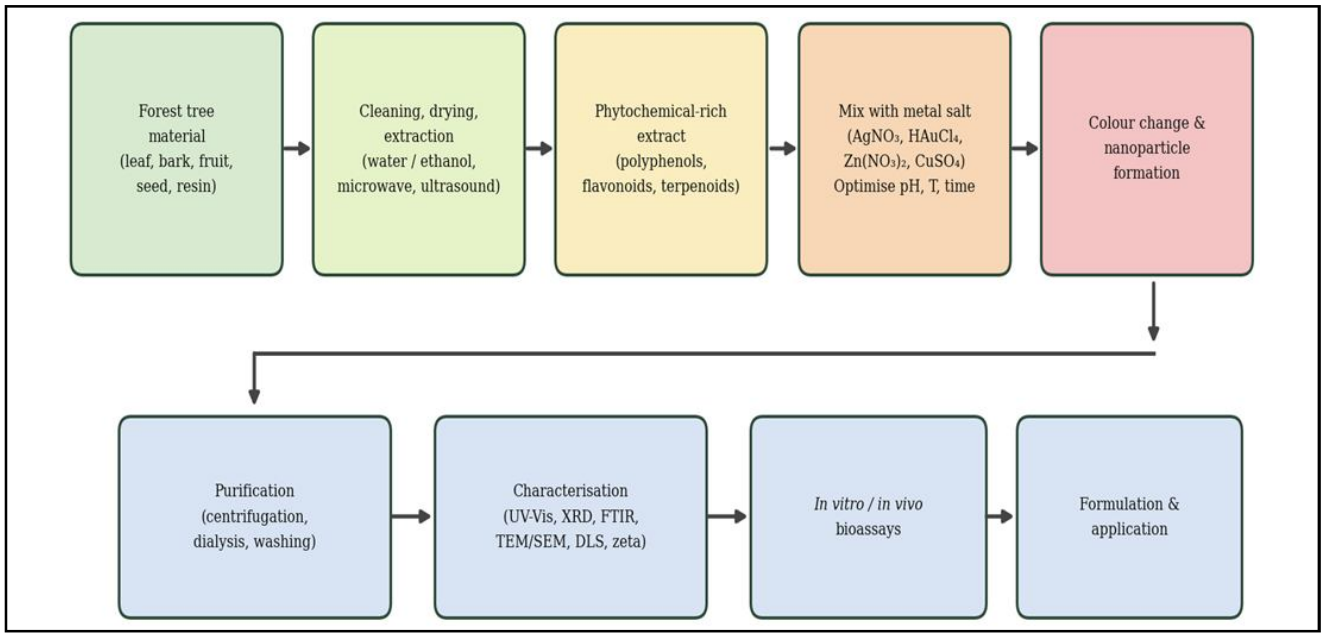


Figure 1: Schematic workflow for the phytochemical mediated green synthesis of metallic nanoparticles from forest tree material, from extraction to application.

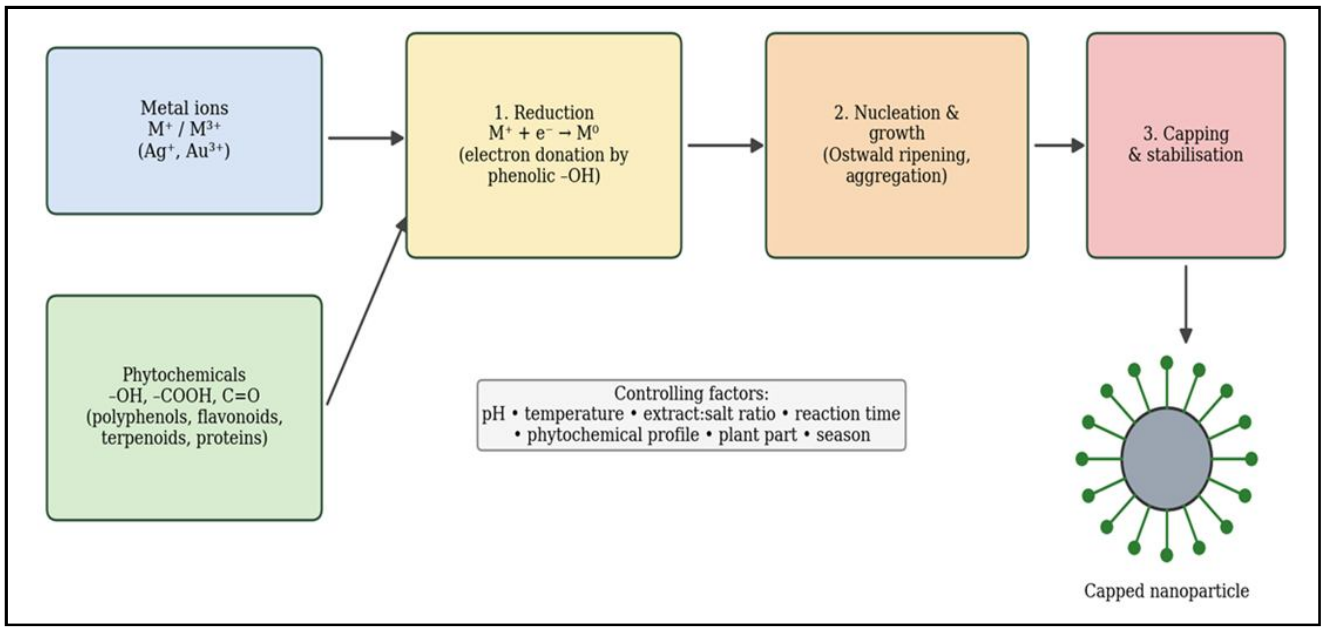


Figure 2: Proposed stages in the formation of capped metallic nanoparticles: reduction of metal ions by phenolic and related groups, nucleation and growth, and capping by phytochemicals, together with the principal controlling factors.

3.1 Factors governing size, shape and yield

i. pH: acidic conditions usually favour larger, aggregated particles because the phenolic groups remain protonated and less able to donate electrons, whereas neutral to alkaline pH accelerates reduction and promotes smaller, monodisperse particles.

ii. Temperature: higher temperature increases the rate of nucleation, and microwave heating gives rapid and uniform synthesis (Ali *et al*., 2015).

iii. Extract-to-salt ratio: excess extract generally provides more capping molecules and smaller particles, whereas excess metal salt leads to larger particles.

iv. Reaction time: surface plasmon resonance (SPR) intensity increases until the metal ions are depleted and may then red-shift if ageing causes aggregation.

v. Plant part and genotype: variation in secondary metabolite content between provenances and seasons is a major cause of poor reproducibility (Singh *et al*., 2016).

Table 3: Common techniques for characterising phytochemical-mediated nanoparticles

Technique	Information obtained	Remarks for plant-derived NPs
UV-Vis spectroscopy	Formation and SPR band; indication of size and aggregation	Quick monitoring of kinetics; broad bands suggest polydispersity
XRD	Crystalline phase, lattice parameters, mean crystallite size (Scherrer equation)	Face-centred cubic peaks for Ag and Au; extra peaks may arise from organic residues
FTIR	Functional groups of capping phytochemicals	Shifts in OH, C=O and C-O bands indicate involvement in reduction and capping
TEM/SEM (± EDX)	Particle size, morphology, elemental composition	Sample drying can induce aggregation; count adequate particles for size distribution
DLS and zeta potential	Hydrodynamic diameter, polydispersity index, surface charge	Hydrodynamic size includes the organic corona and is larger than TEM size
AFM	Three-dimensional topography	Complements electron microscopy
TGA/DSC	Organic coating content, thermal stability	Quantifies phytochemical corona
ICP-MS/AAS	Metal content, ion release	Required for dose normalisation and dissolution studies
XPS	Oxidation state and surface composition	Distinguishes metallic and oxidised species
HPLC/LC-MS of extract	Chemical fingerprint of the reducing/capping phytochemicals	Essential for standardisation and reproducibility

SPR: surface plasmon resonance; XRD: X-ray diffraction; FTIR: Fourier-transform infrared spectroscopy; TEM: transmission electron microscopy; SEM: scanning electron microscopy; EDX: energy-dispersive X-ray spectroscopy; DLS: dynamic light scattering; AFM: atomic force microscopy; TGA: thermogravimetric analysis; DSC: differential scanning calorimetry; ICP-MS: inductively coupled plasma mass spectrometry; AAS: atomic absorption spectroscopy; XPS: X-ray photoelectron spectroscopy; HPLC: high-performance liquid chromatography; LC-MS: liquid chromatography-mass spectrometry.

4. Characterisation of green nanoparticles

Comprehensive characterisation is required to link physicochemical properties to biological activity. A typical workflow starts with visual colour change and UV-Vis spectroscopy, where the SPR band of Ag NPs usually appears at about 400-450 nm and that of spherical Au NPs at about 520-560 nm, and proceeds through crystallographic, spectroscopic and microscopic analysis (Table 3). FTIR of the extract before and after reaction identifies the functional groups that take part in reduction and capping, while zeta potential indicates colloidal stability; values more negative than about -30 mV generally suggest a stable dispersion.

5. Pharmacological activities and underlying molecular mechanisms

Green NPs exhibit biological activity arising from the metallic core, the adsorbed phytochemical corona, or, most often, their synergy. Table 4 gives an overview of the main activities, molecular mechanisms and the trees associated with them, and Figure 3 illustrates the multi-target action.

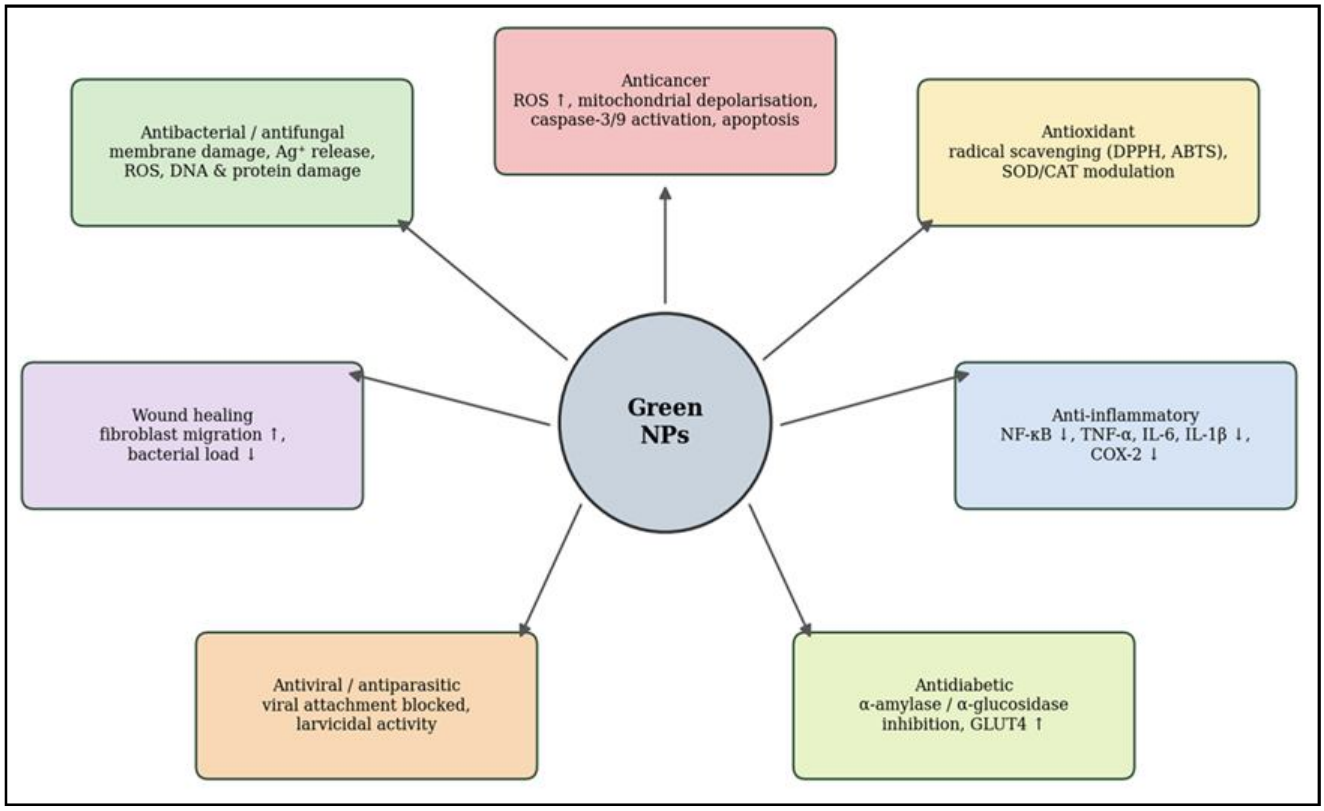


Figure 3: Overview of the pharmacological activities of forest-tree-derived green nanoparticles and the principal molecular events proposed for each (ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GLUT4, glucose transporter 4).

5.1 Antibacterial and antifungal activity

Silver NPs are the best studied antimicrobial nanomaterial. Several mechanisms act in parallel, which is why resistance develops less readily than to single target antibiotics. NPs attach to the bacterial envelope, form pits and increase membrane permeability (Sondi and Salopek-Sondi, 2004; Morones *et al*., 2005). Released Agz ions bind to sulfhydryl groups of membrane and respiratory enzymes, uncoupling electron transport, and may interact with phosphorus containing DNA, hindering replication (Dakal *et al*., 2016). Concurrently, ROS such as superoxide and hydroxyl radicals are generated, causing lipid peroxidation and protein oxidation (Kim *et al*., 2007). Size and shape strongly influence potency, with smaller particles and certain facets showing greater activity (Pal *et al*., 2007). In green synthesised particles, the phytochemical corona can add its own antimicrobial effect; *Eucalyptus* derived Ag NPs, for example, inhibited biofilm formation by clinical isolates (Ali *et al*., 2015), and neem and pine bark derived particles were active against both Gram-positive and Gram-negative bacteria (Tripathi *et al*., 2009; Iravani and Zolfaghari, 2013).

5.2 Anticancer activity

Plant derived Ag and Au NPs have been reported to be cytotoxic to a range of cancer cell lines. Particles accumulate in tumour tissue passively through the enhanced permeability and retention (EPR) effect (Matsumura and Maeda, 1986) and enter cells primarily by

endocytosis. Inside the cell, dissolution and interaction with mitochondria raise ROS, depolarise the mitochondrial membrane and trigger release of cytochrome c, with subsequent activation of caspase-9 and caspase-3 and apoptotic DNA fragmentation (AshaRani *et al*., 2009; Jeyaraj *et al*., 2013). Silver NPs have also been shown to inhibit VEGF-induced angiogenesis through the PI3K/Akt pathway (Gurunathan *et al*., 2009). Phytochemicals on the surface, such as flavonoids and tannins, may act synergistically by inhibiting survival signalling or by sensitising cells to oxidative stress. A key concern is selectivity; because the same ROS dependent mechanisms also damage normal cells, therapeutic windows must be established using non-malignant cell lines and animal models.

5.3 Antioxidant and anti-inflammatory activity

The antioxidant activity of green NPs is attributed to capping polyphenols that retain radical scavenging capacity, and has been evaluated mainly with DPPH, ABTS and ferric-reducing assays. Paradoxically, the metallic core may be pro-oxidant in some biological contexts; the net redox effect depends on dose, cell type and the proportion of phytochemical corona. Anti-inflammatory activity has been linked to down-regulation of NF-κB signalling, with reduced production of proinflammatory cytokines and matrix metalloproteinases (Nadworny *et al*., 2010), a property that may contribute to wound healing outcomes (Tian *et al*., 2007).

Table 4: Pharmacological activities of green nanoparticles from forest trees and proposed molecular mechanisms

Activity	Proposed molecular mechanism (s)	Example tree sources	Key references
Antibacterial/antibiofilm	Adhesion to and pitting of the cell wall; membrane depolarisation and leakage; Agz release binding thiol groups of respiratory enzymes; ROS-induced DNA and protein damage; interference with biofilm matrix	*A. indica*, *E. globulus*, *P. eldarica*, *T. chebula*, *C. zeylanicum*	Sondi and Salopek-Sondi, 2004; Morones *et al*., 2005; Dakal *et al*., 2016
Antifungal	Disruption of fungal membrane integrity and ergosterol-related processes; ROS generation	*S. cumini*, *M. oleifera*	Kim *et al*., 2007; Kumar *et al*., 2010
Antiviral	Binding to viral surface glycoproteins and blocking attachment/entry	Silver NPs (general)	Lara *et al*., 2010
Anticancer	ROS accumulation, mitochondrial membrane depolarisation, release of cytochrome c, caspase-3/9 activation, DNA fragmentation, cell-cycle arrest; anti-angiogenic action	Plant-derived Ag/Au NPs	Gurunathan *et al*., 2009; Jeyaraj *et al*., 2013; AshaRani *et al*., 2009
Antioxidant	Hydrogen/electron donation by surface phenolics scavenges DPPH, ABTS and hydroxyl radicals; metal-chelation	*S. cumini*, *E. officinalis*, *T. chebula*	Ankamwar *et al*., 2005; Kumar *et al*., 2012
Anti-inflammatory	Reduced NF-κB signalling and cytokine release (TNF-α, IL-6, IL-1β); decreased matrix metalloproteinase and COX-2 activity	Ag NPs (general); polyphenol-rich extracts	Nadworny *et al*., 2010
Antidiabetic	Inhibition of α-amylase and β-glucosidase; improved glucose uptake and antioxidant status	*C. fistula*	Daisy and Saipriya, 2012
Wound healing	Antimicrobial effect, reduced inflammation, promotion of fibroblast-to-myofibroblast differentiation and re-epithelialisation	Ag NPs (general)	Tian *et al*., 2007
Larvicidal/antiparasitic	Interference with cuticle and digestive enzymes; oxidative stress in larvae and ticks	Plant-derived Ag NPs	Marimuthu *et al*., 2011

5.4 Antidiabetic, antiviral and vector control activities

Gold NPs prepared from *Cassia fistula* stem bark extract lowered blood glucose and improved lipid profile in diabetic rats, suggesting that both the extract derived phytochemicals and the gold core contribute to the hypoglycaemic effect (Daisy and Saipriya, 2012). Silver NPs interact with viral glycoproteins and block attachment to host cells, as demonstrated for HIV-1 (Lara *et al*., 2010), but data on forest tree derived particles are limited. Plant mediated silver NPs have also shown larvicidal and acaricidal action against vectors and parasites, offering a prospective ecofriendly alternative to synthetic pesticides (Marimuthu *et al*., 2011).

6. Toxicity, environmental fate and safety considerations

Biocompatibility is not guaranteed merely because a synthesis is green. Silver NPs have been shown to cause cytotoxicity and genotoxicity in human cells through oxidative stress and mitochondrial damage (Asha Rani *et al*., 2009), and the relative contribution of particle and released ion remains debated (Beer *et al*., 2012). Toxicity depends on size, shape, surface charge, dose and exposure route, and

it is therefore essential to compare efficacy with toxicity in the same experimental system (Marambio-Jones and Hoek, 2010; Prabhu and Poulose, 2012). Moreover, the presence of the phytochemical corona may reduce toxicity by limiting ion release or may increase it by promoting cellular uptake, and both effects must be tested. Once released into the environment, NPs undergo transformations such as sulfidation, aggregation and dissolution that change their bioavailability and toxicity to aquatic and soil organisms (Lowry *et al*., 2012). Life cycle assessment and ecotoxicity testing should therefore accompany pharmacological development.

7. Challenges and future perspectives

Despite encouraging results, translation of forest tree derived green NPs is limited by several gaps (Table 5). Foremost is reproducibility: the chemical composition of tree extracts varies with species, provenance, age, tissue, season and extraction conditions, and this variability leads to differences in NP size and bioactivity between laboratories (Singh *et al*., 2016; Hussain *et al*., 2016). Most reports also rely on crude extracts without identifying the active reductant, so that the structure-activity relationship is unclear.

Table 5: Key challenges and proposed research directions for forest tree derived green nanoparticles

Challenge	Current limitation	Future perspective
Reproducibility and standardisation	Variable phytochemical composition; unreported extraction details	Chemical fingerprinting (HPLC, LC-MS); use of isolated compounds as model reductants; designof experiments and quality by design optimisation; reporting guidelines
Mechanistic understanding	Mechanisms largely inferred from FTIR and cell-based assays	Omics (transcriptomics, proteomics, metabolomics), molecular docking and DFT modelling of polyphenol metal interactions
Scale up	Batch laboratory scale synthesis	Continuous-flow and microwave reactors; process analytical technology; GMP compatible extracts
Toxicity and biodistribution	Short term *in vitro* studies; few *in vivo* data	Long term *in vivo* toxicity, pharmacokinetics, protein corona studies, immunotoxicity and genotoxicity assessment
Targeted delivery	Passive accumulation only	Surface functionalisation with ligands (folate, peptides, antibodies); stimulus responsive and theranostic systems; combination with standard drugs
Sustainability and ethics	Risk of over harvesting wild trees; unequal benefit sharing	Use of renewable parts (leaves, pruning residues, fruit waste); cultivation of elite chemotypes; compliance with the Nagoya Protocol and benefit sharing with local communities
Regulation and clinical translation	No harmonised regulatory pathway for botanical nanomedicines	Early dialogue with regulators; adoption of nanomaterial characterisation standards; well-designed clinical trials

DFT: density functional theory; GMP: good manufacturing practice.

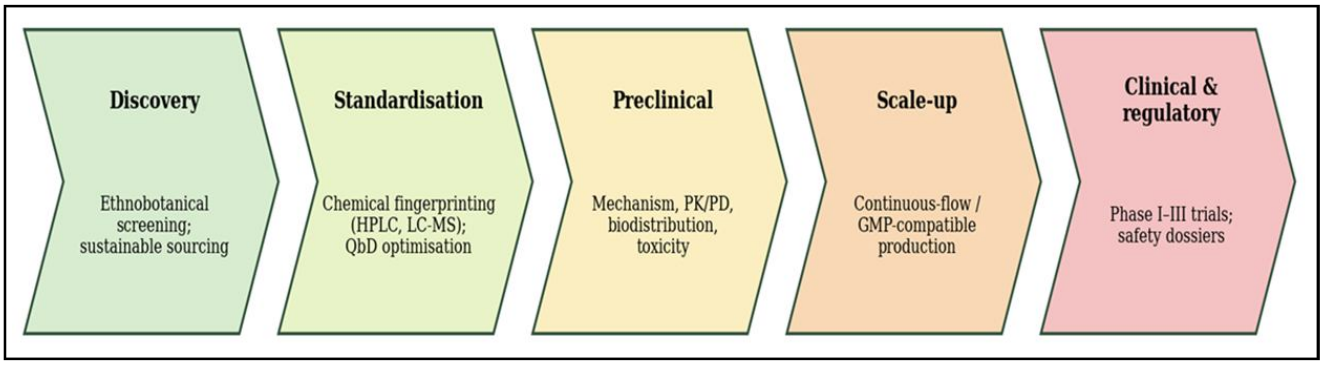


Figure 4: Proposed translational roadmap for the development of forest-tree-derived green nanoparticles from discovery to clinical and regulatory evaluation.

Future work should integrate three strands. First, mechanism-driven design: identifying the dominant reducing and capping compounds in each tree species would allow rational tuning of NP properties and facilitate the use of purified or semi-synthetic phytochemicals, and computational chemistry can support this by modelling polyphenol-metal binding. Second, safety by design and

standardisation: harmonised protocols, validated reference materials and long-term *in vivo* evaluations are needed so that results from different laboratories can be compared. Third, sustainable and equitable sourcing: because many valuable tree species are slow-growing and sometimes threatened, synthesis should focus on renewable biomass, such as leaves, pruning residues and fruit by-products, and on cultivated material, with biodiversity safeguards and benefit-sharing arrangements. Beyond silver and gold, forest tree extracts could also be used for the green synthesis of ZnO, CuO, iron oxide, selenium and bimetallic particles, and for hybrid nanocomposites with polymers such as chitosan for wound dressings and drug delivery. Combination of green NPs with conventional antibiotics or chemotherapeutics may restore the efficacy of drugs against resistant pathogens and tumours. A proposed translational roadmap is shown in Figure 4.

8. Conclusion

Forest trees provide a diverse, renewable and pharmacologically relevant source of reducing and capping phytochemicals for the green synthesis of metallic nanoparticles. The reported particles display promising antibacterial, antifungal, anticancer, antioxidant, anti-inflammatory, antidiabetic and vector control activities through multitarget mechanisms centred on ROS generation, membrane and mitochondrial damage, apoptosis induction and suppression of inflammatory signalling. However, most evidence comes from *in vitro* studies using poorly defined extracts. Standardisation of extracts, thorough physicochemical and toxicological characterisation, mechanistic elucidation and well-designed *in vivo* and clinical studies, combined with sustainable and ethical sourcing of tree material, are required before these nanomaterials can be developed as safe and effective phytomedicines.

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Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

S. Vennila and S. Kala: Conceptualization, academic oversight, critical review and validation of scientific content; **H. B. Roghan**: Data curation.

Consent for publication

All authors gave full consent for publication and submission to this journal.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest relevant to this article.

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