Review Article

Efficacy of Different Herbal Sources for Silver Nanoparticle Biosynthesis and its Advantages in Oral Care: A Comprehensive Narrative Review

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ABSTRACT

Oral diseases affect 3.5 billion people globally, with antimicrobial resistance and adverse effects of conventional treatments necessitating novel therapeutic approaches. Green synthesis of silver nanoparticles (AgNPs) using medicinal plants represents a promising strategy combining nanotechnology with traditional herbal medicine for oral healthcare applications. Comparative analysis of major herbal sources reveals substantial variations in AgNP synthesis parameters and therapeutic efficacy. Green tea (Camellia sinensis) demonstrates rapid synthesis (10-20 minutes), the smallest particle size (10-40 nm), and exceptional antimicrobial activity against Streptococcus mutans (MIC 2-8 µg/mL). Neem (Azadirachta indica) exhibits broad-spectrum antimicrobial efficacy with superior anti-inflammatory properties. Turmeric (Curcuma longa) shows outstanding anti-inflammatory and anticarcinogenic activities. Clove (Syzygium aromaticum) demonstrates exceptional antifungal activity against Candida albicans (MIC 4-10 µg/mL). Comparative evaluation reveals synergistic integration of AgNP antimicrobial effects with inherent phytochemical therapeutic properties, including antioxidant, anti-inflammatory, anticariogenic, and wound healing activities. These biosynthesized AgNPs demonstrate applications across preventive dentistry, periodontal therapy, endodontics, restorative dentistry, and oral medicine. Herbal-mediated AgNP synthesis offers sustainable, cost-effective production of biocompatible nanoparticles with multifaceted therapeutic advantages for oral care. Selection of optimal herbal sources depends on specific clinical applications, with standardization protocols and comprehensive clinical validation required for successful translation into commercial products.

Key words: Silver Nanoparticles; Green Synthesis; Phytochemicals; Anti-Bacterial Agents; Oral Health.

Oral diseases represent a significant global public health challenge affecting approximately 3.5 billion people worldwide, with dental caries being the most prevalent condition. The Global Burden of Disease Study 2019 reported 23 million years lived with disability from oral conditions and a substantial economic burden estimated at $544.4 billion annually [1,2]. Severe periodontal disease affects approximately 10% of the global population. Antimicrobial resistance among oral pathogens and the adverse effects of conventional antimicrobials intensify the need for innovative therapeutic solutions [3,4]. Conventional antimicrobial mouth rinses present significant limitations, including tooth staining, taste alteration, mucosal irritation, and emergence of antimicrobial resistance through mechanisms such as efflux pump upregulation and biofilm-mediated protection [5,6].

Nanotechnology offers revolutionary therapeutic approaches through the manipulation of matter at the nanoscale (1-100 nm), where materials exhibit distinctive properties. Silver nanoparticles (AgNPs) demonstrate exceptional broad-spectrum antimicrobial activity through multiple synergistic mechanisms, including cell membrane disruption, reactive oxygen species generation, and interference with DNA replication and protein synthesis [7,8]. This multi-targeted approach significantly reduces resistance development compared to single-target conventional antibiotics [9].

Green synthesis methodologies utilizing medicinal plants for AgNP production have gained prominence due to environmental sustainability, cost-effectiveness, scalability potential, and production of biocompatible nanoparticles without toxic chemical residues [10,11]. Medicinal plants produce diverse bioactive compounds, including polyphenols, flavonoids, alkaloids, terpenoids, and tannins, functioning as reducing agents, stabilizing agents, and capping agents, contributing additional therapeutic properties [12,13]. The integration of nanotechnology with traditional herbal medicine creates innovative therapeutic systems harnessing both AgNP antimicrobial potency and medicinal plants' biological activities.

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Despite extensive research on biosynthesized AgNPs for dental applications, systematic comparative evaluations of different herbal sources remain limited. Each medicinal plant possesses unique phytochemical profiles that significantly influence nanoparticle synthesis parameters, particle characteristics, stability, and therapeutic efficacy [14,15]. This comprehensive review aims to systematically evaluate and compare the efficacy of major herbal sources in AgNP biosynthesis and analyze their therapeutic advantages in oral care applications, providing evidence-based comparative analysis to guide the selection of optimal herbal sources for specific dental therapeutic needs.

2. GREEN SYNTHESIS METHODOLOGY

2.1 Mechanisms of Phytochemical Reduction

Biosynthesis of AgNPs using plant extracts involves complex biochemical processes where phytochemical constituents function as biological reducing agents converting silver ions (Ag^+) to elemental silver (Ag^0) atoms, which subsequently nucleate and aggregate to form nanoparticles [16]. The biosynthesis process involves three distinct phases: (1) Reduction phase where plant phytochemicals (NADH/NADPH) donate electrons to convert silver ions (Ag^+) from $AgNO_3$ to elemental silver (Ag^0), (2) Growth phase involving nucleation and aggregation of silver atoms to form nanoparticles, and (3) Stabilization phase where phytochemical compounds provide capping and stabilization preventing nanoparticle aggregation. The oxidation-reduction cycle ensures complete conversion of silver ions to stable nanoparticles (Figure 1) [17,18].

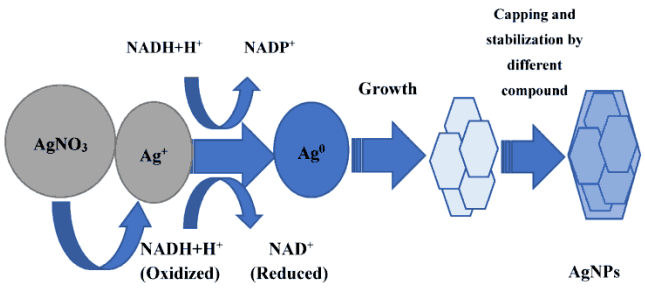


Figure 1. Schematic representation of phytochemical-mediated silver nanoparticle biosynthesis mechanism

Polyphenolic compounds, particularly abundant in green tea and turmeric, serve as powerful reducing agents through hydroxyl groups that donate electrons to reduce Ag^+ ions [19]. Epigallocatechin gallate (EGCG) from green tea exhibits exceptional reducing capacity due to its multiple hydroxyl groups [20]. Flavonoids, including quercetin, kaempferol, and rutin, contribute to metal ion reduction through ketone and hydroxyl functional groups [21]. Alkaloids found in neem participate in reduction reactions through nitrogen-containing heterocyclic structures [22]. Terpenoids in clove and eucalyptus contribute through isoprenoid structures [23]. Proteins and amino acids participate in both reduction and stabilization processes, with amino acids like cysteine and methionine containing sulfur groups that interact with silver surfaces [24].

2.2 Role of Biomolecules in Stabilization and Capping

Following nanoparticle formation, phytochemicals prevent aggregation and provide colloidal stability through electrostatic repulsion and steric hindrance mechanisms [25]. Polyphenols form protective layers on nanoparticle surfaces through coordination bonds between hydroxyl groups and silver atoms, creating negative surface charges that prevent particle coalescence [26]. Proteins adsorb onto nanoparticle surfaces, forming protective coronas providing steric and electrostatic stabilization [27]. Polysaccharides present in aloe vera create thick hydration layers around nanoparticles, enhancing stability in aqueous media [28].

The capping layer composition significantly influences nanoparticle properties, including dispersibility, stability, cellular interactions, and biological activities [29]. Phytochemical-capped nanoparticles demonstrate superior biocompatibility compared to chemically synthesized counterparts due to natural bioactive surface coatings that contribute additional therapeutic properties, including antioxidant, anti-inflammatory, and wound healing activities [30].

2.3 Comparative Synthesis Parameters by Plant Source

Different medicinal plants exhibit substantial variations in synthesis efficiency, reflecting unique phytochemical compositions. Neem leaf extracts demonstrate rapid AgNP synthesis, typically completing within 5-30 minutes at room temperature, attributed to high terpenoid and flavonoid concentrations, producing predominantly spherical nanoparticles in the 5-50 nm range [31]. Green tea extracts enable extremely rapid synthesis within 10-20 minutes due to exceptionally high polyphenol content, particularly Epigallocatechin-3-gallate (EGCG), producing highly uniform spherical nanoparticles typically 10-40 nm with excellent long-term stability [20,32].

Turmeric extracts produce AgNPs within 15-60 minutes with curcumin serving as the primary reducing agent, yielding predominantly spherical particles ranging 10-80 nm [33]. Aloe vera gel extracts demonstrate moderate synthesis rates typically requiring 30-120 minutes, producing spherical to irregular particles in the 15-100 nm range [28]. Clove extracts enable rapid synthesis within 10-40 minutes, attributed to high eugenol content, yielding predominantly spherical particles 5-60 nm [23]. The synthesis parameters of the plant sources for AgNP biosynthesis thus differ from each herbal sources to other in terms of time, optimal $AgNO_3$ Concentration, pH, temperature, particle size, reducing agent, and the stability period. This is given in Table 1.

Table 1. Comparative Synthesis Parameters of Major Herbal Sources for AgNP Biosynthesis

Herbal Source	Synthesis Time	Optimal $AgNO_3$ Concentration	Optimal pH	Temperature Range	Particle Size Range	Primary Reducing Agent	Stability Period
Neem (*A. indica*)	5-30 min	1-5 mM	7-9	25-60°C	5-50 nm	Terpenoids, Flavonoids	6-12 months
Green Tea (*C. sinensis*)	10-20 min	1-3 mM	6-8	25-80°C	10-40 nm	EGCG, Catechins	6-12 months
Turmeric (*C. longa*)	15-60 min	1-10 mM	8-10	40-80°C	10-80 nm	Curcumin	4-8 months
Aloe vera	30-120 min	0.5-5 mM	6-9	30-70°C	15-100 nm	Polysaccharides	6-12 months
Clove (*S. aromaticum*)	10-40 min	1-5 mM	6-8	25-70°C	5-60 nm	Eugenol	4-8 months

Plant materials (neem leaves and other medicinal plants) are boiled for 20 minutes to extract phytochemicals, followed by filtration. The aqueous extract is mixed with $AgNO_3$ solution to synthesize silver nanoparticles, indicated by a color change from clear to brown. The biosynthesized AgNPs undergo comprehensive characterization, including antimicrobial activity testing against oral pathogens (disk diffusion assay), particle size and morphology analysis using various analytical techniques, and stability assessment. The green synthesis workflow of silver nanoparticles from plant extracts is shown in Figure 2.

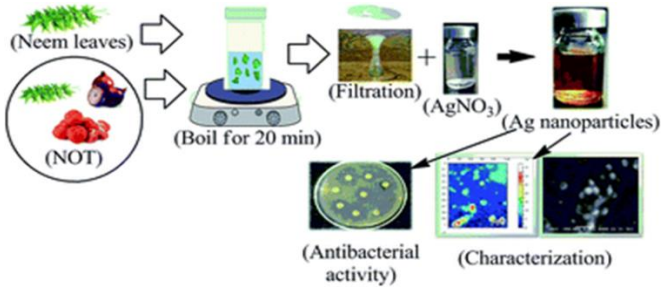


Figure 2. Green synthesis workflow of silver nanoparticles using plant extracts and their characterization.

3. COMPARATIVE ANALYSIS OF HERBAL SOURCES

3.1 Antimicrobial Efficacy Comparison

Against Streptococcus mutans, the primary cariogenic pathogen, green tea-synthesized AgNPs demonstrate exceptional activity with minimum inhibitory concentrations (MIC) of 2-8 µg/mL and zones of inhibition (ZOI) of 18-25 mm, attributed to synergistic effects of EGCG and nanoparticle action [34,35]. Neem-synthesized AgNPs exhibit strong activity with MIC values of 4-12 µg/mL and ZOI of 15-22 mm [36]. Clove-synthesized particles show MIC of 3-10 µg/mL and ZOI of 16-24 mm with eugenol providing additional antimicrobial synergy [23,37]. Against periodontal pathogens Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans, neem-synthesized AgNPs exhibit exceptional activity with an MIC of 3-8 µg/mL, attributed to azadirachtin's anti-inflammatory properties complementing antimicrobial action [38]. For antifungal activity against Candida albicans, clove-synthesized AgNPs demonstrate exceptional activity with MIC of 4-10 µg/mL and ZOI of 18-26 mm, attributed to eugenol's membrane-disrupting properties [37,39]. Thus comparative antimicrobial studies reveal substantial efficacy variations across herbal sources (Table 2).

Table 2. Comparative Antimicrobial Activity of Herbal-Synthesized AgNPs Against Oral Pathogens

Herbal Source	*S. mutans* MIC (µg/mL)	*S. mutans* ZOI (mm)	*P. gingivalis* MIC (µg/mL)	*C. albicans* MIC (µg/mL)	*C. albicans* ZOI (mm)
Green Tea	2-8	18-25	4-10	8-16	15-22
Neem	4-12	15-22	3-8	5-12	16-23
Turmeric	5-15	14-20	6-14	10-18	14-20
Clove	3-10	16-24	5-12	4-10	18-26
Aloe vera	8-20	12-18	8-16	12-20	10-16

3.2 Anticariogenic Properties Comparison

Beyond direct antimicrobial activity, different herbal AgNPs demonstrate varied anticariogenic mechanisms. Green tea-synthesized AgNPs exhibit exceptional glucosyltransferase (GTF) enzyme inhibition, reducing polysaccharide synthesis by 60-85% at concentrations of 10-25 µg/mL, attributed to EGCG's specific enzyme-binding properties [40]. This prevents bacterial adhesion and biofilm formation on tooth surfaces. Additionally, green tea contains natural fluoride (0.3-1.5 ppm) that synergizes with AgNPs for enhanced remineralization [41]. Neem-synthesized AgNPs demonstrate strong acid neutralization capacity, maintaining pH above 5.5 in acidogenic environments, protecting enamel from demineralization [42]. Miswak-synthesized particles provide dual anticariogenic mechanisms through AgNP antimicrobial action and naturally occurring fluoride (8-22 ppm), silica, and

calcium compounds promoting remineralization [43]. Pomegranate-synthesized nanoparticles demonstrate potent anti-biofilm activity disrupting *S. mutans* biofilm architecture by 70-90% through punicalagin's interaction with extracellular polysaccharide (EPS) matrix [44].

3.3 Anti-Inflammatory and Antioxidant Properties Comparison

The anti-inflammatory properties of herbal AgNPs significantly influence efficacy in managing periodontal diseases. Turmeric-synthesized AgNPs exhibit exceptional anti-inflammatory activity through curcumin's potent inhibition of NF-κB pathway, reducing pro-inflammatory cytokines IL-1β, IL-6, and TNF-α by 60-85% at concentrations of 5-20 µg/mL [45,46]. Green tea-synthesized AgNPs demonstrate strong anti-inflammatory effects with EGCG reducing pro-inflammatory mediators by 50-75% while upregulating anti-inflammatory cytokine IL-10 [47]. Neem-synthesized particles exhibit potent anti-inflammatory activity through nimbidin's inhibition of inflammatory pathways, reducing gingival inflammation by 55-70% in experimental models [48].

Antioxidant properties protect oral tissues from oxidative stress implicated in periodontal disease and oral cancer [49]. Pomegranate-synthesized AgNPs demonstrate exceptional antioxidant capacity with DPPH radical scavenging activity of 80-95% at concentrations of 25-50 µg/mL, attributed to high punicalagin and ellagic acid content [50]. Green tea-synthesized particles exhibit strong antioxidant activity with DPPH scavenging of 75-90% due to EGCG and catechin content [47]. Turmeric-synthesized AgNPs show potent antioxidant properties with DPPH scavenging of 70-85% through curcumin's phenolic structure [51]. These properties are compared in Table 3.

Table 3. Comparative Anti-inflammatory and Antioxidant Activities of Herbal-Synthesized AgNPs

Herbal Source	Anti-inflammatory Activity (% Cytokine Reduction)	DPPH Scavenging Activity (%)	Primary Active Compound	Optimal Concentration (µg/mL)
Turmeric	60-85	70-85	Curcumin	5-20
Green Tea	50-75	75-90	EGCG	10-25
Pomegranate	45-60	80-95	Punicalagin	15-30
Neem	55-70	60-75	Nimbidin, Quercetin	10-25
Aloe vera	40-55	50-65	Polysaccharides	20-40

3.4 Anticarcinogenic Properties and Remineralization

Emerging evidence suggests that herbal AgNPs possess anticarcinogenic properties relevant to oral cancer prevention. Turmeric-synthesized AgNPs demonstrate exceptional anticarcinogenic activity against oral squamous cell carcinoma cell lines with IC_{50} values of 8-25 µg/mL, significantly lower than normal keratinocyte cytotoxicity (IC_{50} 40-80 µg/mL), indicating a good selectivity index of 3-6 [52]. Green tea-synthesized AgNPs exhibit potent anticarcinogenic effects with IC_{50} values of 10-30 µg/mL against oral cancer cells while showing minimal toxicity to normal cells [53]. Pomegranate-synthesized AgNPs show promising anticarcinogenic properties with IC_{50} values of 12-35 µg/mL [54].

Dental remineralization represents a critical therapeutic property for early caries management. Miswak-synthesized AgNPs demonstrate exceptional remineralization potential attributed to naturally occurring fluoride, silica, calcium compounds, and chloride that promote hydroxyapatite deposition, with studies showing increased enamel microhardness by 25-40% after 14-day treatment regimens [43]. Green tea-synthesized AgNPs provide moderate remineralization through natural fluoride content and catechin's ability to promote calcium phosphate precipitation, increasing enamel microhardness by 15-30% [41].

3.5 Biofilm Disruption Capacity Comparison

Oral biofilms represent complex microbial communities that resist conventional antimicrobials [55]. Pomegranate-synthesized AgNPs exhibit exceptional biofilm disruption, reducing *S. mutans* biofilm biomass by 75-92% and EPS production by 65-85% at concentrations of 20-50 µg/mL [44]. Green tea-synthesized particles demonstrate strong biofilm disruption, reducing biofilm formation by 70-88% through EGCG's inhibition of quorum-sensing molecules and GTF enzymes [40]. Neem-synthesized AgNPs show potent anti-biofilm activity by reducing biofilm biomass by 65-82% through azadirachtin's interference with bacterial communication systems [36].

4. ADVANTAGES OVER CHEMICAL SYNTHESIS

Biosynthesis using plant extracts offers substantial advantages over chemical and physical synthesis methods. Chemical synthesis requires expensive reducing agents like sodium borohydride and toxic stabilizers, increasing production costs. In contrast, plant-mediated synthesis utilizes inexpensive, readily available medicinal plants requiring minimal processing and operates at ambient conditions, reducing energy requirements by 60-80% [56]. Cost analysis reveals biosynthesis production costs of approximately $5-15 per gram of AgNPs compared to $25-50 per gram for chemical synthesis. Green synthesis aligns with sustainable chemistry principles, minimizing environmental impact, eliminating toxic chemicals, and generating biodegradable byproducts [10]. Phytochemical surface coatings significantly improve biocompatibility compared to chemically synthesized AgNPs, with comparative cytotoxicity studies demonstrating biosynthesized AgNPs exhibiting 30-60% lower toxicity toward mammalian cells [57]. The integration of AgNP's antimicrobial activity with inherent

herbal therapeutic compounds creates synergistic multifunctional formulations [11,13].

AgNPs demonstrate diverse therapeutic functions categorized into three main domains:

(1) Antimicrobial functions, including antibacterial, antifungal, and antiviral activities through multiple simultaneous mechanisms.

(2) Therapeutic functions encompassing anti-caries effects, antibiofilm activity, anti-inflammatory properties, tooth whitening, and tissue regeneration.

(3) Property improvement functions providing reinforcement and protection to dental materials. The multi-targeted approach makes AgNPs suitable for comprehensive oral care formulations, as demonstrated in Figure 3.

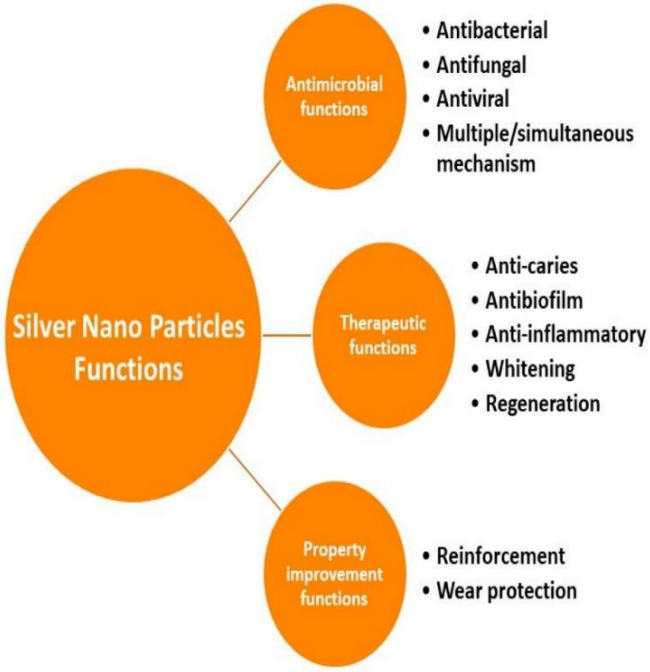


Figure 3. Multifunctional properties of AgNPs for oral healthcare applications

5. MECHANISMS OF ACTION IN ORAL CARE

Herbal AgNPs exert antimicrobial effects through multiple synergistic mechanisms [7,8]. Direct contact between nanoparticles and bacterial cell walls causes physical disruption. The released Ag^+ ions interact with thiol groups in proteins, disrupting cellular metabolism, and represent the primary antimicrobial mechanism [58]. Reactive oxygen species generation causes oxidative stress, damaging proteins, lipids, and nucleic acids [59]. Nanoparticles disrupt the bacterial respiratory chain and interfere with ribosomal function [9]. These mechanisms are illustrated in Figure 4. This multi-targeted approach significantly reduces the likelihood of antimicrobial resistance development compared to conventional single-target antibiotics.

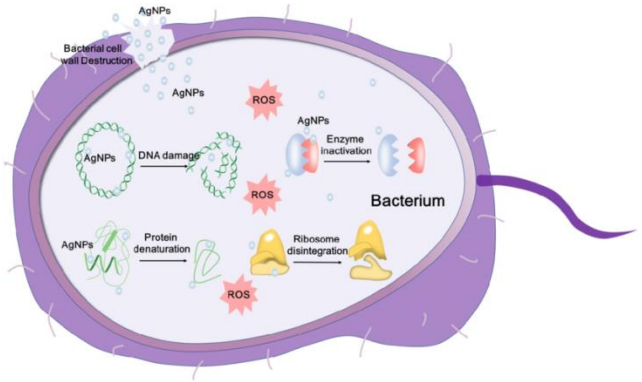


Figure 4. Mechanisms of antimicrobial action of AgNPs **against bacterial cells**

The phytochemicals contribute additional mechanisms: polyphenols disrupt membrane integrity, flavonoids chelate metal ions essential for bacterial metabolism, and terpenoids disrupt membrane lipid bilayers [12]. The anti-inflammatory properties operate through inhibition of NF-κB signaling pathway, cyclooxygenase enzyme inhibition, and matrix metalloproteinase inhibition [45]. Antioxidant activity functions through direct free radical scavenging, metal chelation, and enzyme activation [49]. The anticarcinogenic mechanisms include apoptosis induction, cell cycle arrest, and angiogenesis inhibition [52].

6. CLINICAL APPLICATIONS ACROSS DENTAL SPECIALTIES

The broad-spectrum antimicrobial and therapeutic properties enable AgNPs integration across multiple dental disciplines, as shown in Table 4.

Table 4. Applications of AgNPs in dentistry

1.	Implant treatment	Prevention of peri-implantitis and implant surface modification
2.	Periodontal treatment	Management of periodontal pathogens and inflammation
3.	Orthodontic treatment	Prevention of white spot lesions and bracket coating
4.	Endodontic treatment	Root canal disinfection and biofilm elimination
5.	Restorative treatment	Remineralization and caries prevention
6.	Prosthetic treatment	Denture disinfection and stomatitis management

In preventive dentistry, herbal AgNP mouth rinses serve as daily-use formulations for dental caries and gingivitis prevention [34]. Green tea-synthesized AgNPs demonstrate suitability for combining potent anti-*S. mutans* activity, GTF

enzyme inhibition, and an excellent safety profile enabling long-term use. School-based prevention programs utilizing herbal AgNP rinses demonstrate effectiveness by reducing caries incidence by 30-50% over 12-month periods [60]. Periodontal disease management represents a major application with neem-synthesized AgNP rinses demonstrating efficacy against periodontal pathogens combined with anti-inflammatory effects, reducing pocket depth by 1.5-2.5 mm [38].

Endodontic therapy benefits from clove-synthesized AgNPs demonstrating exceptional efficacy against *E. faecalis* biofilms [37]. In restorative dentistry, remineralization protocols combining herbal AgNP rinses with calcium phosphate delivery systems demonstrate arrest of early caries in 60-75% of cases [61]. Denture-related stomatitis management shows clove-synthesized AgNP rinses reporting 70-85% resolution within 14 days [39]. Orthodontic applications demonstrate a 45-65% reduction in white spot lesion incidence [62]. Oral medicine applications, including recurrent aphthous stomatitis and oral mucositis, show clinical promise [63]. Post-surgical applications demonstrate a 40-60% reduction in surgical site infection rates [64].

7. CHALLENGES AND FUTURE DIRECTIONS

The inherent variability in plant phytochemical composition represents a significant challenge for product standardization [14]. Geographic origin, seasonal variation, plant age, soil conditions, and harvesting methods all influence phytochemical profiles. Establishing standardized sourcing protocols, including specific cultivar selection, defined growing conditions, and controlled post-harvest processing, is essential [15]. The development of international standards specific to phyto-synthesized nanomaterials would facilitate quality assurance. Determining optimal therapeutic concentrations balancing efficacy and safety requires extensive dose-response studies.

Despite promising short-term safety data, long-term safety validation through extended clinical trials is essential. Large-scale randomized controlled clinical trials (RCTs) with adequate sample sizes and extended follow-up periods are needed to establish clinical efficacy definitively. Regulatory classification of herbal AgNP products varies internationally, creating market access challenges. Future research should prioritize advanced synthesis optimization, mechanistic studies, oral microbiome modulation studies, personalized formulation development, combination therapy research, and clinical translation research [65].

CONCLUSION

Different herbal sources demonstrate distinct advantages in AgNP biosynthesis with applications spanning preventive dentistry to oral cancer management. Successful clinical translation requires addressing standardization challenges, comprehensive safety validation, and rigorous clinical trials to establish these innovative formulations as mainstream oral healthcare products.

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