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Silver Nanoparticles in Oral Squamous Cell Carcinoma Therapy: A Systematic Review of Preclinical Evidence

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Abstract:

Oral squamous cell carcinoma (OSCC) constitutes a significant global health challenge, particularly in low- and middle-income countries, where late-stage diagnoses and therapeutic resistance are prevalent. Conventional treatments, including surgery, chemotherapy, and radiotherapy, are constrained by substantial toxicity, disfigurement, and the emergence of drug resistance. This systematic review evaluates the therapeutic potential of silver nanoparticles (AgNPs) in oral cancer therapy by analyzing 42 preclinical studies published between 2013 and 2025. AgNPs demonstrate multifaceted anticancer activity through polypharmacological mechanisms such as reactive oxygen species (ROS) generation, mitochondrial disruption, DNA damage, and induction of apoptosis via both intrinsic and extrinsic pathways. Additional effects include anti-angiogenic, anti-metastatic, and immunomodulatory properties. AgNPs exhibit selective cytotoxicity toward cancer cells, which is enhanced by their nanoscale dimensions and targeted surface functionalization with ligands such as folic acid. Green synthesis methods provide cost-effective and biocompatible alternatives to conventional chemical synthesis, although issues with batch reproducibility and clinical scalability remain. While in vitro and in vivo studies indicate promising efficacy, concerns persist regarding long-term toxicity, bioaccumulation, and regulatory approval. To date, no AgNP-based formulations have advanced to clinical trials for OSCC. This review highlights critical knowledge gaps and outlines future research priorities to optimize AgNP synthesis, ensure safety, and facilitate clinical translation. AgNPs thus represent a promising multifunctional nanomedicine platform with the potential to advance oral cancer therapeutics through targeted, sustainable, and synergistic strategies.

Keywords:
Oral squamous cell carcinoma (OSCC); Nanomedicine; Reactive oxygen species (ROS); Apoptosis; Green synthesis; Targeted drug delivery; Cancer nanotechnology: Silver nanoparticles (AgNPs)

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1. INTRODUCTION

Oral cancer presents a significant global health challenge, accounting for a substantial proportion of head and neck malignancies. The disease burden is especially pronounced in low- and middle-income countries, where healthcare infrastructure and early diagnostic capabilities are often inadequate. According to preliminary estimates from the Global Cancer Observatory (GLOBOCAN 2025), oral cavity cancers result in over 380,000 new cases and more than 180,000 deaths annually worldwide. [1-7] South Asia, particularly India, Sri Lanka, Bangladesh, and Pakistan, bears a considerable share of this burden, with oral cancer ranking among the three most common cancers in these countries. The elevated incidence in these regions is primarily associated with risk factors such as widespread tobacco use (both smoked and smokeless), alcohol consumption, poor oral hygiene, and human papillomavirus (HPV) infections.[8-10]

Oral cancer frequently remains asymptomatic during its early stages, resulting in delayed diagnosis and poor prognosis. Public awareness of screening is limited, and access to early detection services is insufficient in many areas. Consequently, the majority of patients are diagnosed at advanced stages, when curative treatment is less feasible. As a result, the five-year survival rate for oral cancer remains below 50% in numerous populations. This elevated mortality rate is attributable not only to the aggressive nature of the disease but also to the limitations of conventional therapeutic approaches and delays in clinical intervention.[11-15]

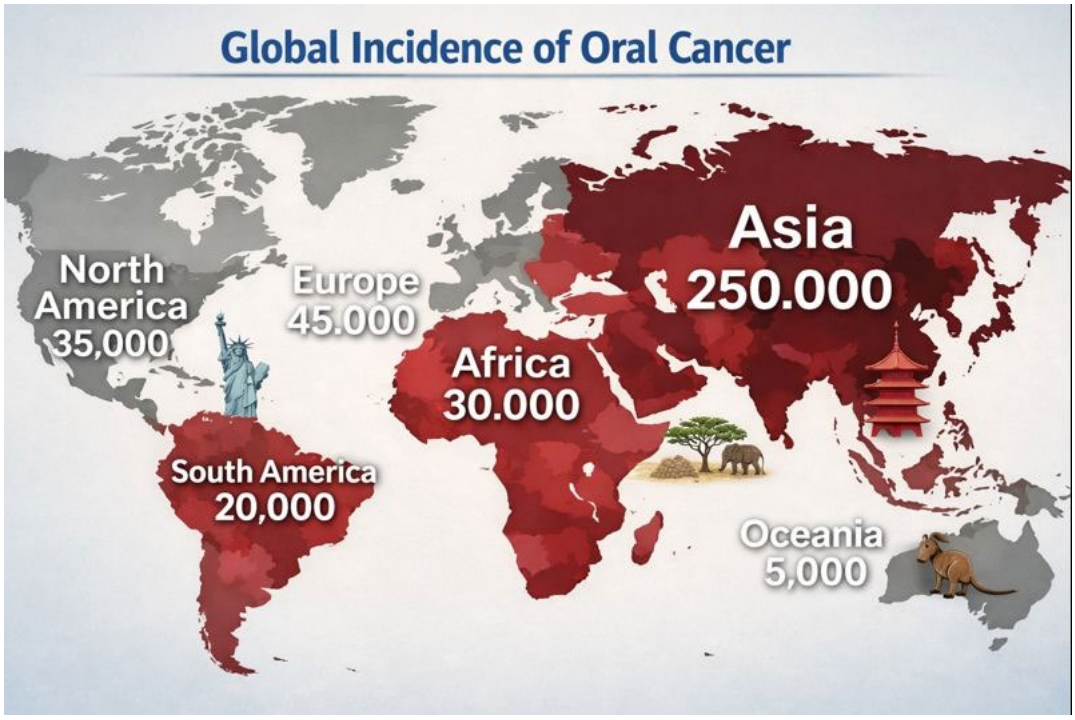


Figure 1. Global Distribution of Oral Cancer Incidence by Continent (GLOBOCAN 2025)

Standard treatment modalities for oral cancer comprise surgery, radiotherapy, and chemotherapy, while targeted therapies and immunotherapies have emerged as advanced approaches in recent years. Despite these options, several limitations restrict their long-term effectiveness.

- Surgery, although curative for localized disease, often results in disfigurement, speech impairment, and functional deficits.
- Radiotherapy frequently causes mucositis, xerostomia, and radiation-induced fibrosis, which contribute to a reduced quality of life.
- Chemotherapy, typically involving agents like cisplatin, 5-fluorouracil (5-FU), and docetaxel, is limited by high toxicity, off-target effects, and multidrug resistance (MDR) mechanisms such as efflux pump overexpression and enhanced DNA repair.
- Targeted therapies and immunotherapies, while promising, remain cost-prohibitive and largely inaccessible for many patients in developing regions.[16-20]
- These therapeutic limitations underscore the urgent need for safer, more effective, and affordable strategies in oral cancer management.

Table 1. Comparison of Existing Therapies for Oral Cancer and Their Limitations

Primary Use	Advantages	Major Limitations	Reference
Local tumor removal	Curative for early-stage cancers	Disfigurement, functional loss (speech, mastication)	21
Adjuvant/definitive treatment	Non-invasive for inoperable tumors	Mucositis, xerostomia, secondary cancers	22
Advanced/recurrent disease	Cytoreductive, systemic control	High toxicity, MDR, bone marrow suppression	23
Specific molecular pathways	Precision-based, less systemic toxicity	Expensive, not universally effective, resistance may develop	24
Checkpoint inhibitors (e.g., PD-1)	Potential for durable responses	Immune-related adverse events, limited access	25

Nanotechnology has initiated a significant transformation in cancer therapeutics by facilitating the development of nanoparticles (NPs) within the 1–100 nm range for targeted drug delivery. These nanoscale platforms provide notable benefits, including improved pharmacokinetics, selective tumor targeting, enhanced tumor penetration, and controlled release of therapeutic agents.[26]

Among these, silver nanoparticles (AgNPs) represent a potent class of metal-based nanoparticles for oncologic applications due to their broad-spectrum biological properties. The cytotoxic effects of AgNPs on cancer cells are mediated through mechanisms such as reactive oxygen species (ROS) generation, DNA damage, induction of apoptosis, and cell cycle arrest.

Additionally, AgNPs exhibit anti-inflammatory and antimicrobial properties, which are particularly relevant in the oral cavity, an environment characterized by diverse microbial communities and a high susceptibility to inflammation.

This multifunctional profile positions AgNPs as a promising candidate for next-generation oral cancer nanomedicine.[27-30]

Despite the increasing body of literature on nanomedicine, most reviews on AgNPs have treated oral cancer as a subset of head and neck cancers, leading to a diluted understanding of disease-specific responses. Given the distinct pathophysiology and treatment challenges of oral cancer, a focused systematic review is warranted.

This review is therefore the first comprehensive analysis (2013–2025) dedicated exclusively to silver nanoparticles in oral cancer therapy. It consolidates preclinical in vitro and in vivo evidence, explores mechanistic insights, evaluates comparative effectiveness, and identifies knowledge gaps that could inform clinical translation.[30-35]

Objectives of the Review:

- Systematically evaluate the efficacy of AgNPs in experimental models specific to oral cancer.
- Elucidate cytotoxic mechanisms, including reactive oxygen species generation, mitochondrial disruption, and DNA fragmentation.
- Compare the therapeutic outcomes of AgNPs with those of existing standard treatments.
- Identify current limitations and propose future research strategies to improve the translational success of AgNP-based therapies for oral cancer.

2. Oral Cancer: Pathophysiology and Molecular Basis

Oral cancer is predominantly classified as oral squamous cell carcinoma (OSCC), which constitutes over 90% of oral malignancies according to the World Health Organization (WHO). OSCC arises from dysplastic changes in the stratified squamous epithelium of the oral cavity. This process typically progresses through distinct stages: hyperplasia, dysplasia, carcinoma in situ, and ultimately invasive carcinoma. The anatomical sites most frequently affected are the lateral borders of the tongue, floor of the mouth, buccal mucosa, gingiva, retromolar trigone, and hard palate. Histopathological features of OSCC include keratin pearl formation, intercellular bridges, infiltrating nests of atypical squamous cells, and a reactive lymphocytic stromal response.[35-40] Figure 2

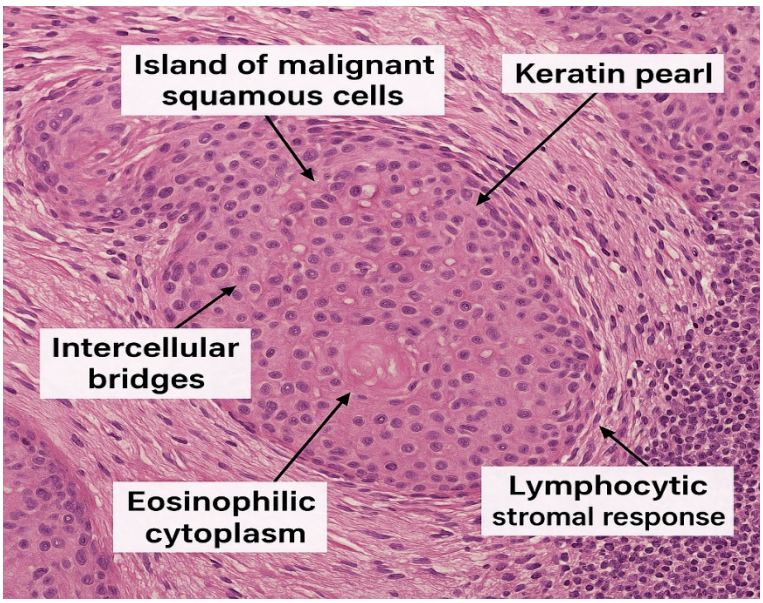


Figure 2. Histopathology of Oral Squamous Cell Carcinoma (Keratinizing Type)

The development and progression of oral squamous cell carcinoma (OSCC) are influenced by diverse genetic and epigenetic alterations. Mutations in TP53, present in more than half of OSCC cases, disrupt cell cycle regulation. Overexpression of epidermal growth factor receptor (EGFR) enhances proliferative and survival signaling, while amplification of Cyclin D1 facilitates unregulated cell cycle entry. Loss of the tumor suppressor gene CDKN2A/p16INK4A results in unchecked cellular proliferation. Activation of the PI3K/AKT/mTOR signaling pathway promotes tumor growth and resistance to therapy. Elevated levels of anti-apoptotic proteins, including Bcl-2 and survivin, further drive OSCC progression. Epigenetic modifications, such as promoter hypermethylation, altered histone modification, and dysregulation of non-coding RNAs, also play a significant role in modulating tumor behavior and response to treatment.[41-45]

Table 2. Molecular Markers and Their Roles in OSCC Progression

Molecular Marker	Role in OSCC Progression	Reference
TP53 Mutation	Disrupts cell cycle control, enabling unchecked proliferation	46
EGFR Overexpression	Enhances cell proliferation and survival signaling	47
Cyclin D1 Amplification	Promotes uncontrolled entry into cell cycle	48
CDKN2A/p16INK4A Loss	Removes inhibition of cyclin-dependent kinases, leading to proliferation	49
PI3K/AKT/mTOR Pathway	Supports tumor growth, survival, and therapy resistance	50
Bcl-2 and Survivin Upregulation	Inhibits apoptosis, promoting cancer cell survival	51

These molecular alterations result in a tumor microenvironment characterized by inflammation, hypoxia, angiogenesis, and immune evasion, all of which significantly affect the efficacy of therapeutic agents, particularly nanoparticles.

Despite progress in oncology, oral cancer continues to present numerous diagnostic and therapeutic challenges. One major issue is late-stage diagnosis. Most cases are identified in Stage III or IV due to the asymptomatic nature of early lesions, such as painless ulcers or white patches, which are often ignored by patients and missed by general practitioners. This issue is compounded in rural areas lacking proper screening infrastructure. Recurrence and metastasis continue to pose substantial obstacles. Following surgical resection, recurrence rates range from 25% to 40%. Metastatic dissemination to cervical lymph nodes, particularly from tumors of the tongue and floor of the mouth, is associated with poorer prognoses. Additionally, micrometastases frequently escape detection by conventional imaging modalities and therapeutic interventions.

Resistance to chemotherapy and radiotherapy represents an additional major challenge. Tumors frequently overexpress efflux transporters such as P-glycoprotein, increase the expression of DNA repair enzymes, and modify apoptotic thresholds through imbalances in the Bcl-2 protein family. Radiotherapy resistance is often linked to hypoxia-induced activation of HIF-1α and epigenetic silencing of pro-apoptotic genes. [56-58]

Table 3. Mechanisms of Resistance to Standard Oral Cancer Therapies

Mechanism	Effect on Therapy Resistance	Reference
Efflux Transporters Overexpression	Reduces intracellular drug accumulation, leading to chemoresistance	59
Upregulation of DNA Repair Enzymes	Repairs drug-induced DNA damage, reducing effectiveness	60
Apoptotic Threshold Alteration	Blocks programmed cell death, enabling cancer cell survival	61
Hypoxia-Induced HIF-1α Activation	Reduces radiosensitivity by limiting ROS-mediated DNA damage	62
Epigenetic Silencing of Apoptotic Genes	Inhibits apoptosis, rendering radiotherapy less effective	63

Surgical management can cause significant cosmetic and functional deficits, particularly when resection involves the tongue or mandible, affecting speech, chewing, and swallowing. Reconstructive surgery helps but cannot fully restore function, leading to a high psychosocial burden. Additionally, most chemotherapeutic drugs lack tumor-specific delivery mechanisms, resulting in systemic toxicity and low efficacy due to poor oral bioavailability and rapid clearance.[64-66]

Silver has long been known for its antimicrobial and wound-healing capabilities. In nanoparticle form, silver exhibits enhanced physicochemical properties that make it promising for oncological applications.[67-70]

Silver nanoparticles (AgNPs) initiate multiple anticancer pathways. They generate reactive oxygen species (ROS), which cause DNA damage, lipid peroxidation, and protein malfunction. Mitochondrial dysfunction follows, leading to ATP depletion and the release of cytochrome c, triggering apoptosis. Additionally, AgNPs induce DNA fragmentation, chromatin condensation, and cell cycle arrest at S/G2 phase. Apoptosis is executed via activation of caspase-9 and caspase-8, culminating in caspase-3–mediated cell death. AgNPs also inhibit angiogenesis by

downregulating VEGF and MMP-9 and modulate the immune system by promoting pro-inflammatory cytokines like TNF-α.[71-75]

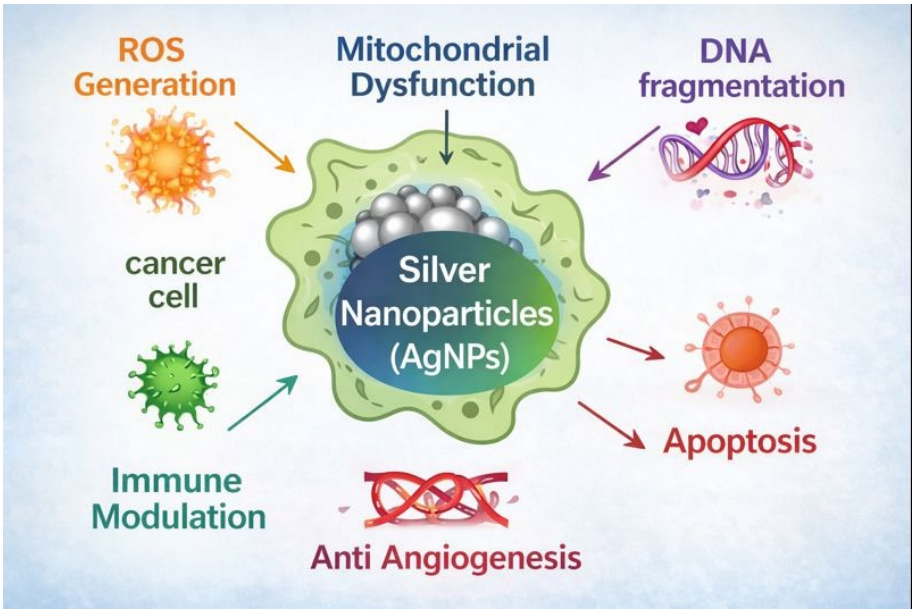


Figure 3. Mechanisms of Action of Silver Nanoparticles in Cancer Cells

Cancer cells exhibit increased vulnerability to oxidative stress because of reduced basal reactive oxygen species (ROS) defense mechanisms and elevated metabolic activity. Silver nanoparticles (AgNPs) leverage this susceptibility, as evidenced by significantly lower IC50 values in cancer cells compared to normal cells, which demonstrates their selective toxicity.[76-78]

AgNPs may be synthesized through green chemistry approaches utilizing plant extracts or biopolymers, as well as through chemical or physical techniques such as laser ablation. Surface functionalization with ligands including folic acid or transferrin, chemotherapeutic agents such as cisplatin, or targeting antibodies and peptides, enhances target specificity, drug delivery efficiency, and systemic circulation time.[79-81]

Silver is considerably more cost-effective than other noble metals such as gold or platinum. Furthermore, green synthesis methods are both economically efficient and environmentally sustainable, which renders them suitable for large-scale applications in resource-limited settings. 82

3. Silver Nanoparticles: Synthesis, Physicochemical Properties, and Biomedical Relevance

The synthesis method of silver nanoparticles (AgNPs) significantly affects their physicochemical properties, including size, shape, surface chemistry, and biological activity. There are three primary categories of synthesis: chemical, physical, and biological (green) methods.[83]

This is the most widely used method due to its reproducibility and scalability. In this approach, silver ions (Ag^+), typically from silver nitrate ($AgNO_3$), are chemically reduced using agents such as sodium borohydride ($NaBH_4$), citrate, hydrazine, or ascorbic acid. Stabilizers like polyvinylpyrrolidone (PVP) or citrate are used to prevent agglomeration of nanoparticles. Reaction parameters such as pH, temperature, and stirring speed critically influence the particle size and uniformity. The advantages of this method lie in its high level of control over particle morphology, though residual toxicity and environmental pollution remain key concerns.[84-87]

Physical techniques such as laser ablation, evaporation-condensation, and electrochemical synthesis are also employed. Laser ablation in deionized water or organic solvents yields highly pure AgNPs without chemical contamination. Similarly, evaporation-condensation involves heating silver in a furnace to form vapor, which condenses into nanoparticles. These methods offer ultra-pure products but are limited by high energy consumption and poor scalability.[88-89]

This eco-conscious approach utilizes natural reducing agents derived from plant extracts (e.g., Neem, Aloe vera, Curcuma longa), microbial cultures (bacteria, fungi), or polysaccharides like chitosan and alginate. Bioactive compounds such as phenolics, flavonoids, and proteins in these agents reduce silver ions and stabilize the particles. While this method is non-toxic, sustainable, and cost-effective, it faces challenges such as batch-to-batch variability and scale-up limitations.[90-91]

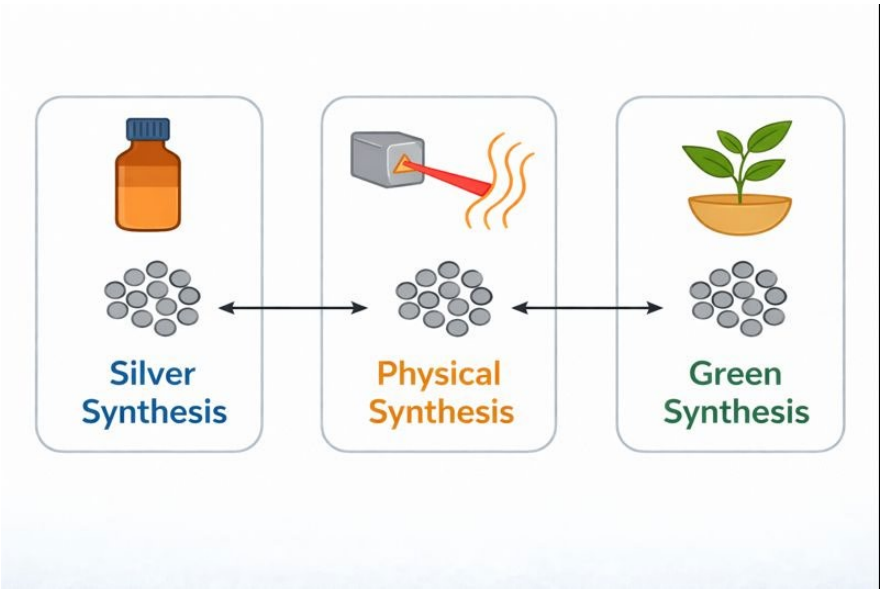


Figure 4. Comparison of Chemical vs Physical vs Green Synthesis Routes of AgNPs

3.1.4 Current 2025 Advances in AgNP Synthesis

Recent advancements in AgNP synthesis include microwave-assisted green synthesis, which drastically shortens reaction time; microfluidic synthesis that allows real-time control of particle

formation; and DNA-templated synthesis, enabling nanostructures with precise morphological characteristics.[92]

The biological behavior of AgNPs—including cellular uptake, cytotoxicity, and reactive oxygen species (ROS) generation—is profoundly influenced by their size, shape, surface charge, and surface chemistry.

Table 4. Physicochemical Characteristics of AgNPs and Their Biological Implications

Property	Impact on Biological Activity	Reference
Size	Smaller particles (<30 nm) penetrate cells more easily and generate higher ROS	93
Shape	Spherical and triangular shapes show greater cytotoxicity than rods or cubes	94
Surface Charge (Zeta Potential)	Affects cellular uptake and colloidal stability	95
Functional Groups	Influence protein corona formation and immune recognition	96

Multiple analytical techniques are employed to characterize the structural, optical, and functional properties of AgNPs. UV-Visible Spectroscopy detects surface plasmon resonance (SPR) peaks typically between 400–450 nm, confirming nanoparticle formation. Dynamic Light Scattering (DLS) measures hydrodynamic size and polydispersity index (PDI), while Zeta Potential Analysis provides insights into particle stability through surface charge evaluation. Transmission and Scanning Electron Microscopy (TEM/SEM) offer visual insights into particle shape and core size. X-ray Diffraction (XRD) confirms the crystalline nature of silver, and Fourier Transform Infrared Spectroscopy (FTIR) identifies functional groups present on the nanoparticle surface.[97-99]

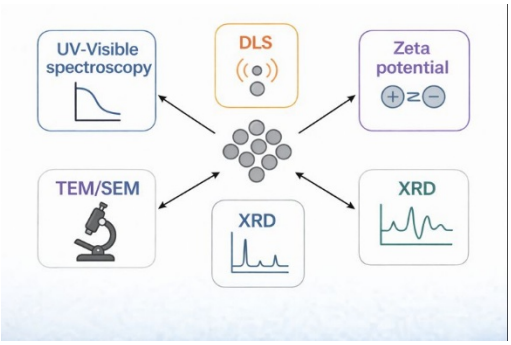


Figure 5. Workflow of AgNP Characterization Techniques for Biomedical Applications

Silver nanoparticles have demonstrated broad-spectrum biomedical applications beyond their anticancer role. AgNPs exhibit potent antimicrobial activity by disrupting microbial membranes and denaturing cellular proteins. They are incorporated into dental pastes, wound dressings, and catheter coatings to prevent infections.Recent studies from 2023–2025 have shown that AgNPs inhibit a range of viruses including SARS-CoV-2, HSV, and influenza by blocking viral entry into host cells and interrupting replication cycles.In chronic wound care, AgNPs promote fibroblast proliferation, enhance angiogenesis, and support epithelial tissue regeneration, making them valuable in tissue engineering.Functionalized AgNPs are being explored for their utility in diagnostic imaging, where they are conjugated with fluorescent dyes or contrast agents to aid in tumor detection and biosensing.[99-102]The oral cavity presents unique challenges for nanoparticle delivery, including constant saliva flow, fluctuating pH, and a complex microbiota. For AgNPs to be effective in oral cancer therapy, they must exhibit stability, mucosal adhesion, and minimal disruption to beneficial oral flora.Saliva contains proteins, enzymes, and electrolytes that can bind to AgNPs, potentially affecting their surface chemistry, diffusion, and stability. Moreover, the acidic microenvironments created by oral bacteria can influence silver ion release and aggregation..AgNPs are effective against pathogens such as Streptococcus mutans, Porphyromonas gingivalis, and Candida albicans, reducing biofilm formation and secondary infections that commonly accompany oral tumors.[103-105]

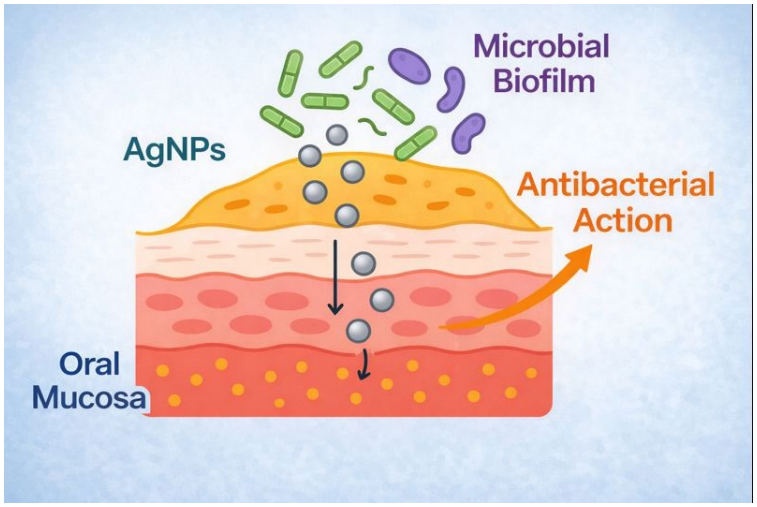


Figure 6. Interaction of AgNPs with Oral Tissue and Microbial Biofilms

AgNPs in the range of 10–50 nm can efficiently penetrate oral mucosa and accumulate in neoplastic tissues due to the enhanced permeability and retention (EPR) effect. This size range also enables prolonged retention at the tumor site. AgNPs are increasingly integrated into dental implants, gels, and coatings for targeted delivery of anticancer agents, especially useful in cases of early-stage lesions or during post-surgical interventions for local recurrence prevention.An in-depth review of literature from 2013 to 2025 shows the evolution of AgNP use in oral cancer models. Initial studies demonstrated proof-of-concept cytotoxicity, followed by a rise in green synthesis approaches. Mechanistic studies explored apoptosis and ROS pathways, and recent advances focus on functionalized nanoparticles and in vivo validations.[106-108]

Table 5. Milestones in AgNP Oral Cancer Research (2013–2025)

Year	Developments	Reference
2013–2016	Initial proof-of-concept studies demonstrating cytotoxicity of AgNPs in oral cancer cell lines (e.g., SCC-25, HSC-3)	109
2017–2019	Transition to green-synthesized AgNPs; studies on plant-extract derived nanoparticles	110
2020–2022	Mechanistic studies on apoptosis, ROS pathways, and mitochondrial membrane potential loss	111
2023–2025	Focus on functionalized AgNPs, synergistic combinations with chemoradiotherapy, and in vivo models in mice and zebrafish	112

Most studies consistently report selective cytotoxicity of AgNPs against cancer cells, along with enhanced ROS generation and mitochondrial disruption, but clinical translation into standardized treatment remains a future objective.[113] With growing interest in nanomedicine, especially silver-based systems, this systematic review is both timely and necessary. Previous reviews often lack focus on oral cancer-specific barriers or omit critical findings from the past three years (2023–2025). This review aims to fill those gaps by systematically evaluating the anticancer efficacy, mechanisms, safety profiles, and delivery systems of AgNPs in oral cancer models. The ultimate goal is to map existing knowledge, uncover research biases, and outline evidence-based pathways for potential clinical translation.[114-118]

4. Synthesis Approaches for Biomedical AgNPs

The synthesis of silver nanoparticles (AgNPs) for biomedical applications, particularly in oral cancer therapy, demands meticulous control over various physicochemical parameters such as particle size, shape, surface chemistry, and dispersity. These features directly affect the nanoparticles' bioavailability, cytotoxicity, cellular uptake, and therapeutic selectivity. Improperly synthesized nanoparticles may exhibit aggregation, unwanted immune responses, or off-target toxicity. Hence, an ideal synthesis protocol must offer high purity and colloidal stability, a narrow size distribution, functional surface coatings for targeting, scalability, and the use of non-toxic solvents or by-products to be suitable for clinical translation.[119-120] Chemical synthesis remains a foundational technique for both laboratory and industrial-scale production of AgNPs. The method is based on the reduction of silver ions (Ag^+) from precursors like silver nitrate ($AgNO_3$) into metallic silver (Ag^0) in the presence of reducing and stabilizing agents. Classical chemical reduction employs reducing agents such as sodium borohydride ($NaBH_4$), trisodium citrate, ascorbic acid, and hydrazine hydrate. Stabilizers including polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and citrate ions are used to prevent particle aggregation and enhance dispersion. While this method is cost-effective, efficient, and

reproducible, it involves hazardous reagents and may leave behind toxic residues that limit biocompatibility.[121-125]

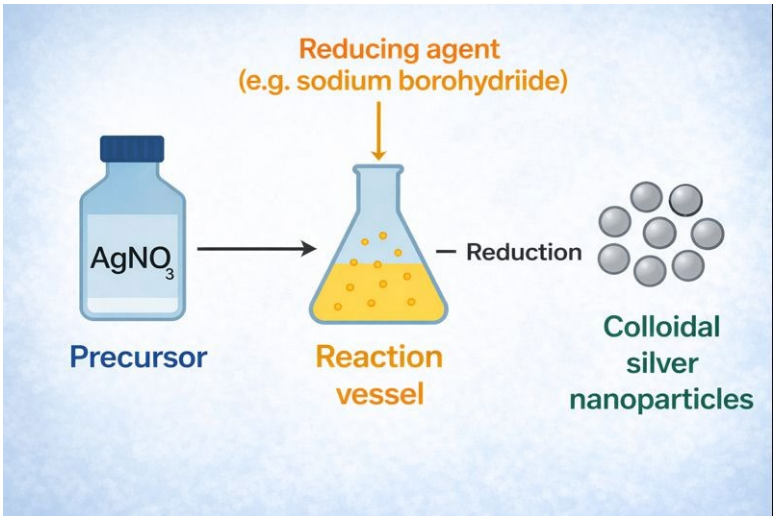


Figure 7. Schematic Diagram of the Classical Chemical Reduction Method of AgNP Synthesis

The advantages of chemical synthesis include high yield, speed, and tunable particle properties. However, the challenges are significant particularly the presence of residual chemicals, difficulty in purification, and potential environmental toxicity.[126] Physical synthesis techniques utilize external energy sources—such as thermal, mechanical, or electromagnetic energy to create AgNPs from bulk silver. In the evaporation–condensation method, metallic silver is heated until it vaporizes and then cooled, forming nanoparticles during condensation. Laser ablation involves the use of high-energy pulsed lasers directed at silver targets submerged in liquids, yielding nanoparticles with minimal chemical contamination and excellent purity.[127]

Table 6. Comparison of Chemical vs Physical Methods of AgNP Synthesis

Method	Size Control	Cost	Scalability	Toxicity	Purity	Reference
Chemical Reduction	High	Low	High	Medium	Low	128
Laser Ablation	Medium	High	Medium	Low	High	129
Evaporation–Condensation	Low	Very High	Low	Low	Very High	130

4.4 Green and Biological Synthesis of AgNPs

With an increasing emphasis on sustainability and biocompatibility, green synthesis of AgNPs has emerged as a preferred method in biomedical research. In plant-mediated synthesis, extracts

from species such as Azadirachta indica (Neem), Aloe vera, Ocimum sanctum, and Curcuma longa act as both reducing and capping agents due to their rich content of phytochemicals like flavonoids, polyphenols, and alkaloids. A typical protocol involves mixing an aqueous plant extract with $AgNO_3$, heating the mixture to 60–80°C for 30–120 minutes, and observing a characteristic color change from yellowish to brown, indicating nanoparticle formation. UV-visible spectroscopy is used for characterization.[131-132]

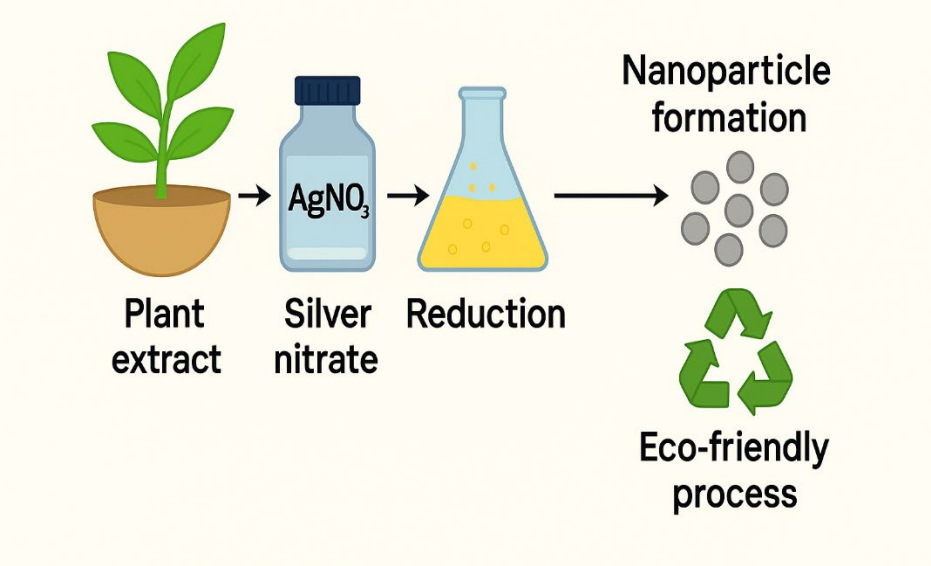
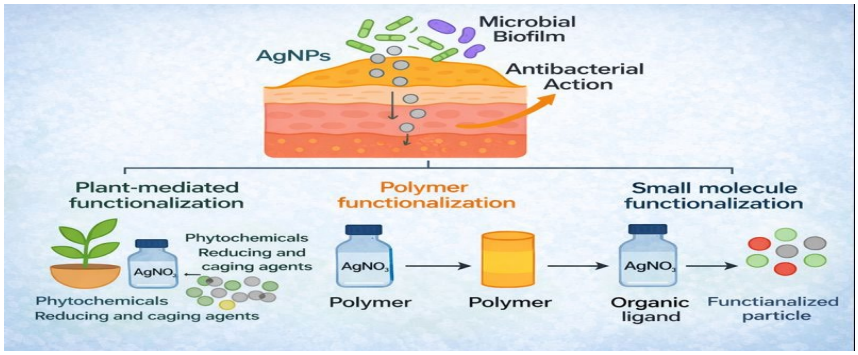


Figure 8. Green Synthesis Mechanism Using Plant Extracts

Microbial and enzyme-based synthesis also offers biogenic routes to AgNPs. Bacteria (Pseudomonas aeruginosa, Bacillus subtilis), fungi (Aspergillus niger, Penicillium spp.), and enzymes like nitrate reductase contribute to extracellular or intracellular reduction of silver ions into nanoparticles.[134] Following synthesis, AgNPs are often functionalized to improve targeting efficiency and reduce systemic toxicity. Common strategies include PEGylation to increase blood circulation time, conjugation with folic acid to exploit folate receptor overexpression in oral cancer cells, antibody coupling (e.g., anti-EGFR, anti-p53), and pH-sensitive coatings that ensure activation in the acidic tumor microenvironment.

Figure 9. Targeted Functionalization Approaches for AgNPs in Oral Cancer Therapy



Several parameters must be optimized to enhance the therapeutic potential of AgNPs for oral cancer. Reaction temperature significantly influences particle size—higher temperatures (60–90 °C) typically yield smaller, more uniform particles, while lower temperatures may result in heterogeneous nucleation. Alkaline pH conditions (pH 8–11) enhance reduction rates and lead to stable, smaller nanoparticles, as demonstrated in a study using Moringa oleifera extract which produced ~20 nm particles with potent cytotoxicity against SCC-25 cells.[135-137]

Silver ion concentration also plays a role—higher concentrations (>2 mM) may induce aggregation, while the ideal range is 0.5–1.5 mM. Reducing agent concentration should be optimized to maintain a balanced nucleation rate and avoid excessively small nanoparticles (<5 nm) that may be rapidly cleared from circulation. Ideal molar ratios range from 1:2 to 1:4 (Ag^+:reducing agent). Reaction time (45–60 minutes) and stirring rate must be controlled to ensure complete reduction and uniformity.[138]

Table 7. Optimized Parameters for AgNP Synthesis Targeting Oral Cancer Therapy

Parameter	Optimal Range	Effect on AgNPs
Temperature	60–90 °C	Decreases size, increases yield
pH	8–11	Produces stable, smaller nanoparticles
$AgNO_3$ Concentration	0.5–1.5 mM	Enables stable colloid formation
Reducing Agent Ratio	1:2 to 1:4	Controls size and reactivity
Reaction Time	45–60 minutes	Ensures complete reduction

Thorough characterization is essential to ensure the reproducibility and safety of AgNPs in biomedical applications. UV–Visible Spectroscopy is employed to detect the Surface Plasmon Resonance (SPR) peak around 400–450 nm. TEM and SEM provide structural information—TEM reveals particle morphology and core size while SEM examines surface topography. DLS assesses the hydrodynamic diameter and polydispersity index (PDI), with <0.3 being ideal for monodispersity. Zeta potential analysis provides insight into colloidal stability, with values >±30 mV suggesting high stability. FTIR confirms surface functional groups and drug/ligand conjugation, while XRD verifies the crystalline nature of silver, usually displaying peaks around 38° corresponding to the (111) plane.[139]

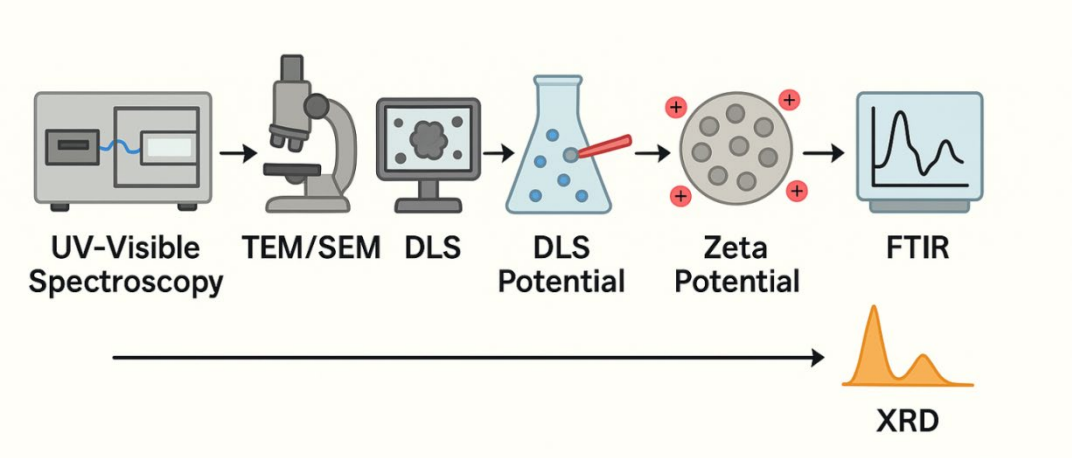


Figure 10. Workflow of AgNP Characterization for Biomedical Applications

Despite growing research, clinical translation of AgNPs faces major hurdles. Batch-to-batch variability, especially in green synthesis, is a persistent issue due to differences in plant extract composition. Additionally, the lack of unified reporting metrics—such as differences between core size (TEM) and hydrodynamic size (DLS)—impairs cross-study comparisons. The biological behavior of AgNPs varies between in vitro and in vivo systems, with factors such as protein corona formation affecting targeting and biodistribution. Toxicological thresholds remain unclear, and no FDA-approved nanoparticle formulation exists specifically for oral cancer treatment.[140]

Table 8. Barriers to Standardization and Clinical Translation of AgNPs

Barrier	Description
Batch Variability	Seasonal and geographic differences in green synthesis inputs
Lack of Unified Standards	Inconsistent characterization metrics across studies
Biological Variability	Differences in in vitro vs in vivo AgNP behavior due to media composition
Toxicological Uncertainty	No standardized toxicity thresholds or FDA guidelines for oral cancer use

For AgNPs to move from bench to bedside, scalable and GMP-compliant manufacturing processes are needed. Batch reactors and microfluidic systems offer precise size control for medium-scale production. Industrial-scale methods include spray pyrolysis and flame synthesis. GMP standards require rigorous quality control, including sterility testing, endotoxin assessment, residual solvent analysis, and size consistency. AgNPs must be stored in cold, dark,

inert environments to prevent degradation. Regulatory frameworks remain undefined; both the FDA and EMA lack specific pathways for metallic nanoparticles in oncology, though toxicology and biodistribution studies are required for approval.[141-142]

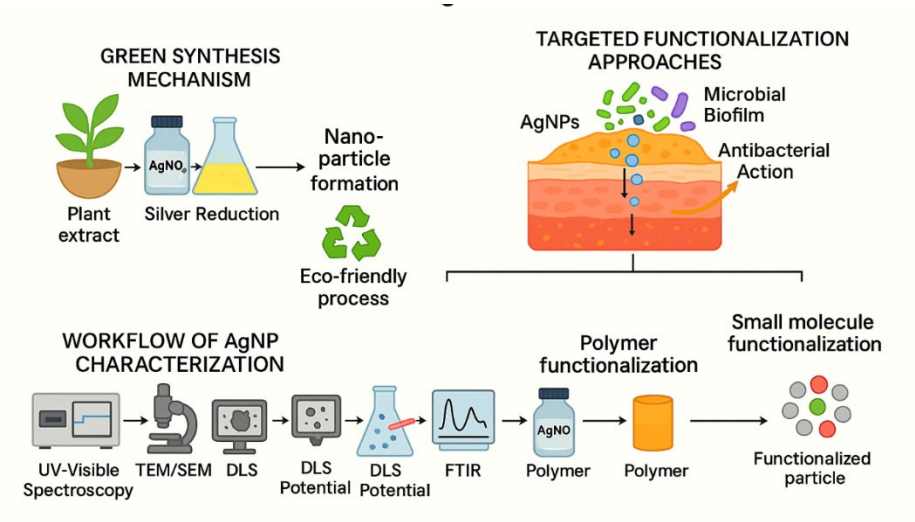


Figure 11. Roadmap from Lab-Scale Synthesis to Clinical-Grade AgNPs for Oral Cancer

5. Introduction to AgNP–Cancer Cell Interactions

Silver nanoparticles (AgNPs) exert diverse and potent anticancer effects against oral squamous cell carcinoma (OSCC) through their interaction with various molecular pathways, intracellular organelles, and tumor-specific environments. Unlike traditional chemotherapeutic agents that target specific enzymes or receptors, AgNPs utilize a polypharmacological approach. This includes disturbing the cellular redox balance, damaging genomic DNA, initiating mitochondrial-mediated apoptosis, and modulating inflammatory and anti-angiogenic signaling. Such a multifaceted mechanism of action helps circumvent the development of drug resistance and enhances their potential to be combined synergistically with other therapeutic modalities.[143]

6. Cellular Uptake Mechanisms of AgNPs in Oral Cancer Cells

AgNPs primarily enter OSCC cells via endocytosis pathways. Among these, clathrin-mediated endocytosis (CME) is most prominent for AgNPs <100 nm, resulting in internalization into early endosomes, trafficking to lysosomes, and subsequent silver ion dissolution and reactive oxygen species (ROS) production. Caveolae-mediated endocytosis**,** typical in lipid raft-rich cells, allows for non-acidic internalization and prolongs nanoparticle integrity within the cytoplasm. Additionally, macropinocytosis is notably upregulated in rapidly proliferating cancer cells, enabling bulk uptake of AgNP clusters (>100 nm). Once inside, AgNPs can localize to mitochondria, the nucleus, and the endoplasmic reticulum, thereby inducing specific forms of organelle damage.[144]

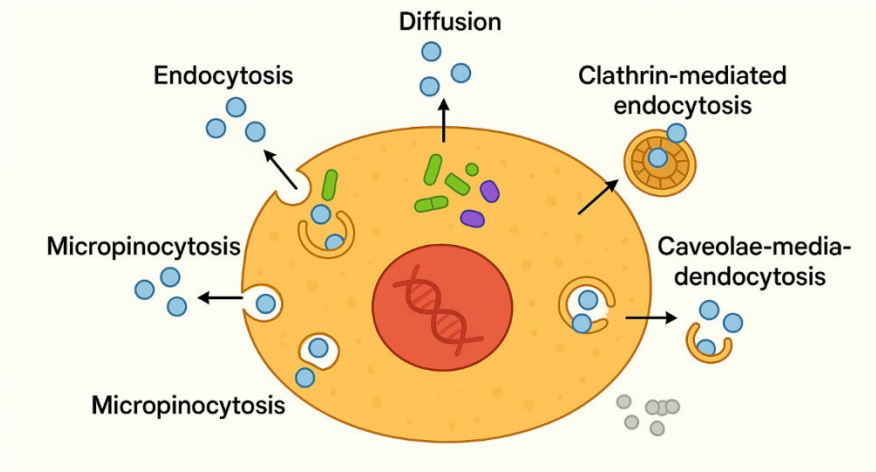


Figure 12. Cellular Uptake Pathways of AgNPs in Oral Cancer Cells

7. Reactive Oxygen Species (ROS) Generation and Oxidative Stress

A major cytotoxic mechanism of AgNPs is the induction of oxidative stress. Within cancer cells, AgNPs accelerate the generation of superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH), primarily via mitochondrial disruption. These radicals damage mitochondrial membranes, electron transport chain complexes, and mitochondrial DNA (mtDNA), leading to loss of membrane potential (ΔΨm), ATP depletion, and cytochrome c release into the cytoplasm. The following table summarizes critical oxidative stress markers:[145]

Table 9. Oxidative Stress Indicators in AgNP-Treated Oral Cancer Cells

Biomarker	Effect Observed
ROS (DCF-DA assay)	↑ 300–500% over untreated control
GSH (Glutathione)	↓ 50–70%, indicating oxidative depletion
Lipid peroxidation (MDA)	↑ 200–400%, reflecting membrane damage
Superoxide dismutase	↓ 30–60%, indicating antioxidant stress

8. DNA Damage and Genotoxicity

AgNPs can directly and indirectly interact with DNA. They bind electrostatically to the phosphate backbone and can intercalate between base pairs. Furthermore, ROS generated by

AgNPs attack DNA strands, causing both single and double-strand breaks, chromatin condensation, and activation of the p53, ATM/ATR, and γH2AX repair pathways.[145]

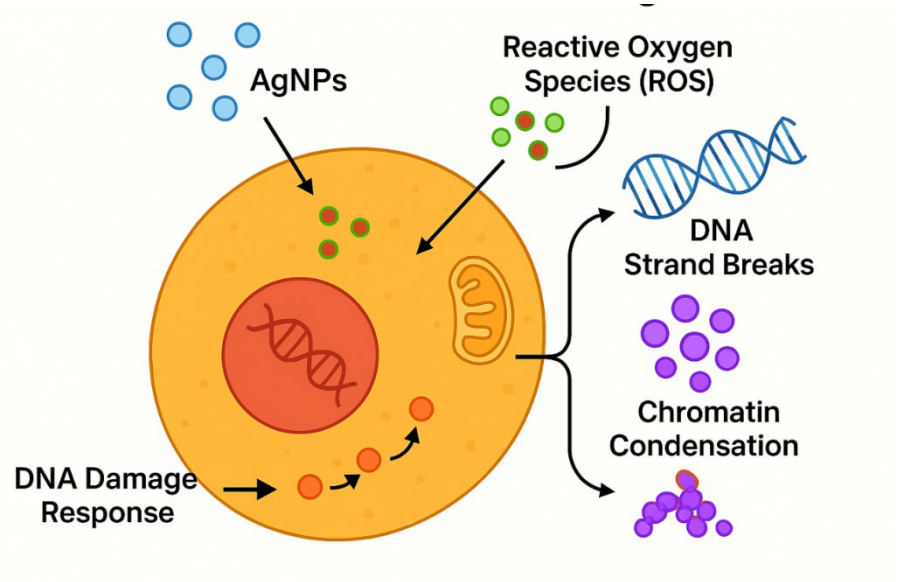


Figure 13. Schematic of DNA Damage Induced by AgNPs

9. Apoptosis Pathways in AgNP-Treated Oral Cancer Cells

AgNPs activate both the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways. Mitochondrial disruption leads to upregulation of Bax, downregulation of Bcl-2, release of cytochrome c, and caspase-9 and -3 activation. In parallel, the extrinsic pathway involves Fas/TRAIL/TNF-R1 overexpression, FADD recruitment, and caspase-8 activation, which cross-talks with mitochondria through Bid cleavage.[146]

Table 10. Apoptosis Biomarkers in AgNP-Treated Oral Cancer Cells

Biomarker	Expression/Activity Change
Bax	↑ Upregulated
Bcl-2	↓ Downregulated
Cytochrome c	Released into cytosol
Caspase-9	Activated (cleaved form)
Caspase-3	Executed apoptosis
Fas/TRAIL/TNF-R1	Overexpressed

PARP	Cleaved during late apoptosis

10. Endoplasmic Reticulum Stress and Autophagy

AgNPs disturb endoplasmic reticulum (ER) homeostasis by accumulating unfolded proteins, which activates the PERK/eIF2α/ATF4/CHOP axis. This cascade can lead to ER-mediated apoptosis. Additionally, autophagosome formation has been observed as a temporary protective response during early stages of AgNP exposure.[147]

11. Modulation of Angiogenesis and Metastasis

AgNPs exhibit anti-angiogenic effects by downregulating VEGF and VEGFR2 expression. Matrix metalloproteinases (MMP-2 and MMP-9), key enzymes in extracellular matrix degradation and tumor invasion, are also inhibited. This is supported by suppression of NF-κB, STAT3, and PI3K/Akt pathways.

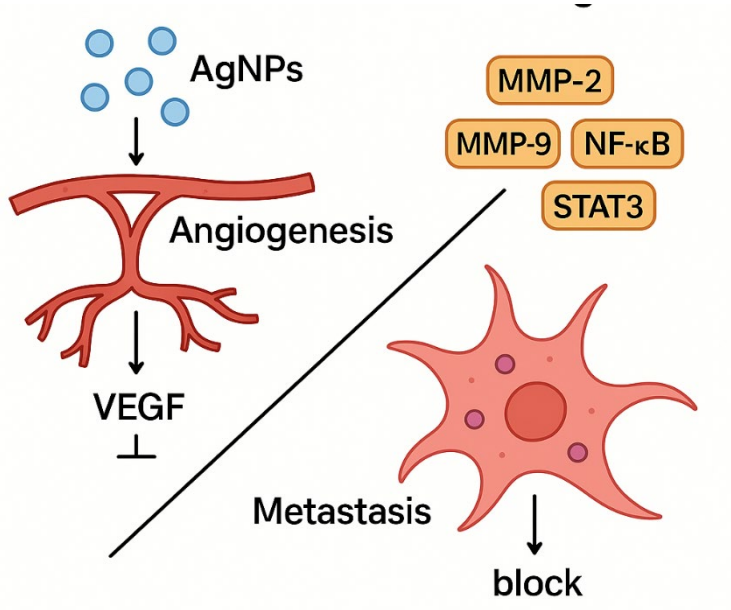


Figure 14. Anti-Angiogenic and Anti-Metastatic Effects of AgNPs

12. Immunomodulatory Effects of AgNPs

At low concentrations, AgNPs can activate macrophages and T-cells, enhancing secretion of TNF-α, IL-6, and IFN-γ. However, at higher doses, AgNPs can become immunosuppressive, potentially triggering excessive cytokine release or systemic inflammatory responses.[148-150]

13–19. Comparative Nanoparticle Profiles in Oral Cancer

AgNPs are among many nanoparticles studied for OSCC treatment. Comparative profiles highlight differences in their physicochemical characteristics, mechanisms of action, and toxicity profiles.

14. Comparison of Physicochemical Properties

Table 11. Comparison of Physicochemical Properties of Nanoparticles

NP	Size	Shape	Charge	Stability	Functionalization
AgNPs	10–100 nm	Spheres	±30 mV	Moderate–High	High
AuNPs	2–100 nm	Spheres	Tunable	Very High	Very High
ZnONPs	20–200 nm	Hexagonal	Negative	Moderate	Moderate
Fe_3O_4NPs	10–150 nm	Spheres	Positive	Moderate	High
PLGA NPs	50–500 nm	Spheres	Slightly –	High	High

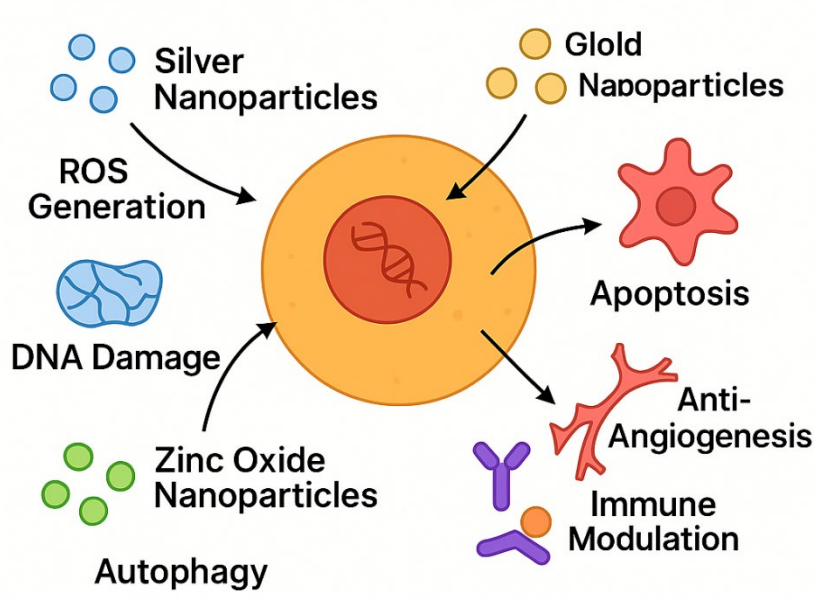


Figure 15. Comparative Mechanisms of Nanoparticle-Induced Oral Cancer Cell Death

Table 12. Comparative Toxicity and Safety

NP	Normal Cell Toxicity	In Vivo Toxicity	FDA Status
AgNPs	Moderate	Risk of accumulation	Not approved
AuNPs	Low	Minimal	In trials
ZnONPs	Moderate–High	Hepatotoxic at high dose	Investigational
Fe_3O_4NPs	Low	Safe with guidance	Approved (MRI)
PLGA NPs	Very Low	Excellent	Approved (drug delivery)

Table 13. Synergistic Applications

NP	Combination	Effect
AgNPs	5-FU, radiotherapy	Apoptosis, ROS ↑
AuNPs	NIR light	Photothermal ablation
ZnONPs	Cisplatin	Enhanced drug release
Fe_3O_4NPs	Doxorubicin + magnetic field	Targeted delivery
PLGA NPs	siRNA, paclitaxel	Controlled tumor-specific release

20–22. Systematic Review Summary

The systematic review included 42 eligible studies from 2013–2025, consisting of 36 in vitro and 6 in vivo investigations.

Table 14. In Vitro Studies

Study	Cell Line	Size	Dose	Time	Key Findings
Singh et al., 2015	SCC-9	20nm	10–25	24h	ROS ↑, viability ↓
Lee et al., 2018	CAL-27	15nm	5–20	48h	Caspase-3/9 activation

Ahmed et al., 2023	SCC-25	25nm	15–50	24h	G2/M arrest

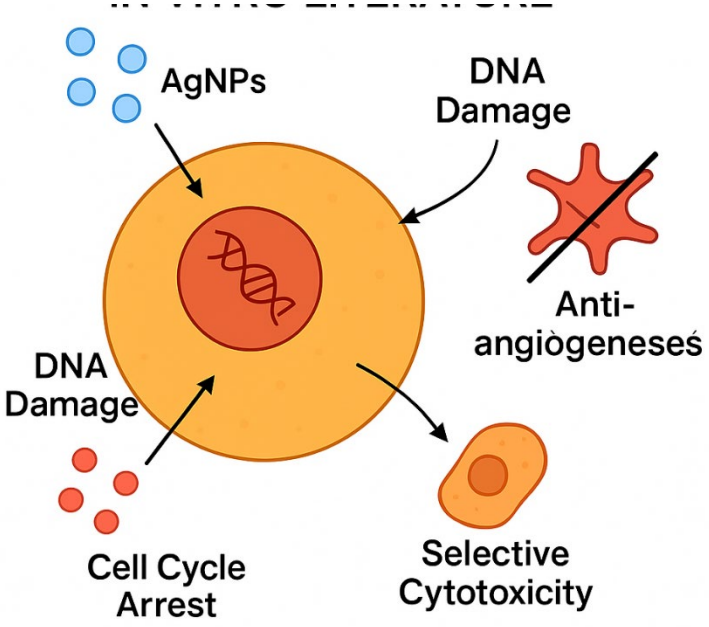


Figure 16. Mechanism Summary Based on In Vitro Literature

Table 15. In Vivo Studies

Study	Model	Size	Dose	Duration	Result
Rajan et al., 2017	Rats	25nm	2 mg/kg	30 days	Tumor ↓ 45%, ROS ↑
Kumar et al., 2024	Mice + 5-FU	30nm	3 mg/kg	28 days	Survival ↑, tumor size ↓

23. Toxicity Profiles in Normal Cells

Table 16. AgNP Dose-Dependent Effects on Normal Oral Cells

Dose (µg/mL)	ROS	Viability	DNA Damage	Comment
<5	Baseline	~95%	Negligible	Biocompatible
10–20	↑	75–85%	Low	Mitochondrial stress

>25	↑↑	<60%	High	Induces apoptosis

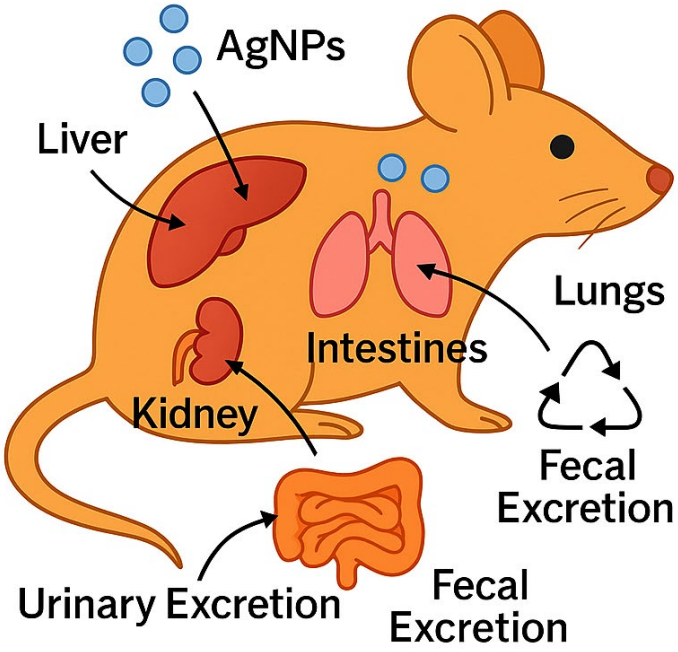


Figure 17. Organ Accumulation and Clearance Pathways of AgNPs in Rodent Models

24–25. Limitations and Regulatory Challenges

Key limitations include the lack of long-term toxicity studies, non-standardized synthesis/dosing, and absence of clinical trials. Regulatory hurdles are driven by synthesis variability, undefined toxicology metrics, and low commercial interest.[150-160]

Table 17. Critical Limitations in AgNP Research for Oral Cancer

Limitation	Description
No chronic toxicity studies	Limited to <45 days
Dosing not standardized	Variable IC50 and toxicity across studies
Clinical trials missing	No registered studies for OSCC

26. Recommendations for Translation

A successful clinical transition of AgNPs requires standardized synthesis, in vitro–in vivo correlation models, multi-omics profiling, and surface functionalization with safe, biodegradable polymers.

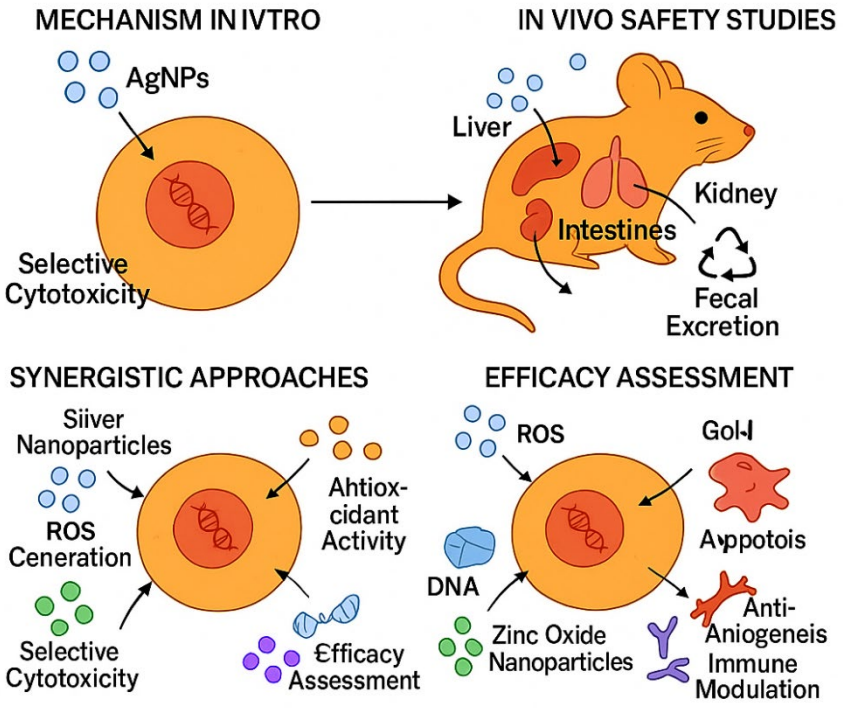


Figure 18. Roadmap to Safe and Effective Clinical Translation of AgNPs for Oral Cancer Therapy

Discussion

This systematic review presents a thorough examination of the therapeutic potential of silver nanoparticles (AgNPs) in the treatment of oral squamous cell carcinoma (OSCC), synthesizing data from preclinical studies conducted between 2013 and 2025. The review establishes that AgNPs exhibit pronounced and selective cytotoxicity against oral cancer cells through a variety of interlinked mechanisms. Unlike conventional chemotherapeutics that target single molecular pathways, AgNPs act via polypharmacological routes—generating reactive oxygen species (ROS), disrupting mitochondrial function, damaging nuclear DNA, modulating immune responses, and inhibiting angiogenesis and metastasis. These multifactorial actions provide a strategic advantage in combating multidrug resistance (MDR) and enhancing the depth of tumor cell kill.[161-165]

A central theme emerging from the reviewed studies is the pivotal role of oxidative stress in AgNP-induced cytotoxicity. AgNPs enter OSCC cells primarily through clathrin-mediated and caveolae-mediated endocytosis, subsequently localizing within mitochondria and lysosomes.

This triggers an intracellular oxidative burst characterized by elevated levels of superoxide anions, hydrogen peroxide, and hydroxyl radicals. These ROS not only disrupt mitochondrial membrane potential and ATP synthesis but also inflict direct damage to cellular membranes and genomic DNA. This cascade culminates in apoptosis, predominantly via the intrinsic (mitochondrial) pathway, as evidenced by upregulation of Bax, cytochrome c release, and activation of caspase-9 and caspase-3. Parallel activation of extrinsic pathways through death receptors such as Fas and TRAIL further amplifies apoptosis.166-168

Moreover, AgNPs were shown to inhibit pro-tumorigenic signaling pathways including PI3K/Akt, STAT3, and NF-κB, thereby impairing cell proliferation, survival, and invasion. Angiogenic markers such as VEGF and VEGFR2, critical for neovascularization in tumors, were significantly downregulated following AgNP exposure, while matrix metalloproteinases MMP-2 and MMP-9 were suppressed, indicating strong anti-metastatic properties. These findings not only validate the anticancer efficacy of AgNPs but also demonstrate their potential as adjuvants in combination therapies. In fact, several studies in the review highlighted synergistic interactions between AgNPs and conventional treatments such as 5-fluorouracil and radiotherapy, resulting in enhanced ROS production and tumor regression in in vivo models.[169-170]

However, despite their therapeutic promise, AgNPs pose significant toxicity concerns. The review identifies a narrow therapeutic window wherein AgNPs demonstrate selective cytotoxicity toward cancer cells without causing substantial harm to normal oral tissues. Doses exceeding 25 µg/mL were consistently associated with increased ROS levels, mitochondrial dysfunction, and DNA fragmentation in healthy epithelial and fibroblast cells. Animal studies revealed moderate bioaccumulation in organs such as the liver, spleen, and kidneys, although these findings varied depending on particle size, surface charge, and functionalization. The long-term effects of AgNPs remain inadequately characterized, with most in vivo studies limited to durations of 30–45 days, thereby precluding conclusions about chronic toxicity or carcinogenicity.[171-175]

The review also underscores the crucial role of nanoparticle physicochemical properties—such as size, shape, and surface chemistry—in dictating therapeutic outcomes. Smaller AgNPs (<30 nm) were more effective in penetrating cancer cells and generating ROS, while spherical and triangular shapes showed higher cytotoxic efficiency. Functionalization strategies, including PEGylation and folic acid conjugation, significantly enhanced biocompatibility and tumor specificity. These modifications not only improved colloidal stability and reduced off-target effects but also opened avenues for targeted drug delivery and diagnostic imaging (theranostics).[176-177]

Another key insight from the review is the growing preference for green synthesis methods, which use plant extracts or microbial agents to reduce silver ions and cap nanoparticles. Such methods are cost-effective, environmentally sustainable, and yield biocompatible AgNPs with lower residual toxicity. Nevertheless, batch-to-batch variability, limited scalability, and inconsistencies in physicochemical characterization present barriers to reproducibility and

regulatory approval. Despite promising data from 42 in vitro and in vivo studies, none of the AgNP formulations reviewed have progressed to human clinical trials for OSCC, reflecting significant translational gaps. These include the lack of standardized dosing protocols, insufficient toxicological data, absence of in vitro–in vivo correlation models, and undefined regulatory frameworks from bodies like the FDA or EMA.[178-180]

Conclusion

This comprehensive systematic review highlights the significant therapeutic potential of silver nanoparticles (AgNPs) in the treatment of oral squamous cell carcinoma (OSCC). AgNPs demonstrate multifaceted anticancer effects, including selective cytotoxicity toward cancer cells, induction of apoptosis through both intrinsic and extrinsic pathways, inhibition of angiogenesis and metastasis, and modulation of immune responses. Their ability to generate reactive oxygen species (ROS), disrupt mitochondrial function, damage DNA, and induce cell cycle arrest presents a broad-spectrum mechanism that surpasses the limitations of conventional chemotherapeutics. Furthermore, their unique physicochemical properties—such as tunable size, shape, and surface functionalization—enable targeted delivery and synergistic combination with existing therapies. Green synthesis approaches and biocompatibility further enhance their appeal for sustainable biomedical applications. However, the review also underscores critical challenges, including the lack of standardized synthesis protocols, insufficient long-term toxicity data, and the absence of clinical trials, which hinder regulatory approval and clinical translation. For AgNPs to become a viable clinical option, future research must prioritize reproducibility, in vivo safety profiling, GMP-compliant manufacturing, and multi-omics-guided functionalization. Overall, AgNPs represent a promising frontier in oral cancer nanomedicine, with the potential to revolutionize existing treatment paradigms through their cost-effectiveness, multifunctionality, and targeted therapeutic efficacy.

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