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Functionalized silver nanoparticles in lung cancer treatment: mechanistic insights and emerging combination strategies

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Nanotechnology has emerged as a transformative frontier in contemporary medicine, offering innovative methodologies for the diagnosis and therapeutic management of diverse malignancies. Among various nanoplatforms, AgNPs have garnered significant research attention due to their distinctive physico-chemical attributes and potent biological activities. This review provides a comprehensive analysis of the therapeutic potential of AgNPs in lung cancer (LC). We examine the recent advancements in AgNP synthesis techniques, surface functionalization strategies, and characterization techniques that modulate their pharmacokinetics and bioreactivity. The tumor-targeting precision of AgNPs is explored in detail through the EPR effect, along with their cellular uptake and cytotoxic action *via* oxidative stress, mitochondrial dysfunction, and DNA damage, culminating in the programmed death of lung cancer cells. Furthermore, the review discusses strategies to enhance biocompatibility and tumor selectivity through surface modification with polymers or targeting ligands. This review also evaluates the synergistic anticancer efficacy of AgNPs in combination with traditional chemotherapeutics and hybrid nanostructures, demonstrating improved therapeutic indices and reduced side effects. Despite these promising results, rigorous *in vivo* investigations and clinical trials remain imperative to validate the long-term safety, optimal dosage, and therapeutic mechanisms of these nanocomposites.

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1. Introduction

Cancer, a disease marked by uncontrolled cell proliferation and division, has several risk factors, categorized as intrinsic and extrinsic.[1–3] According to GLOBOCAN, the cancers that account for the highest mortality rates globally are lung cancer (18%), colorectal cancer (9.4%), liver cancer (8.3%), stomach cancer (7.7%), and breast cancer (6.9%).[4] LC stands as the primary contributor of cancer-related fatalities worldwide, with projections indicating approximately 2.5 million new cases and an estimated 1.8 million deaths in the year 2022.[5] LC is a lethal disease characterized by rapid progression, a high incidence rate, and a limited survival duration. The disease could develop from early to advanced stages within a span of one year after being diagnosed. The patients diagnosed with LC have lower survival rates than those with pancreatic, prostate, colon, and even breast cancers.[6] LC is primarily divided into two main categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Different histological and molecular traits serve as the basis for this classification. The occurrence of both SCLC and NSCLC is closely associated with various risk factors, including air pollution, aging, genetic predispositions, pre-existing respiratory conditions (such as emphysema and chronic obstructive pulmonary disease (COPD)), significant tobacco use, and exposure to harmful substances in the workplace.[7] Additionally, infectious diseases caused by pathogens, such as *Chlamydia pneumoniae*, *Streptococcus pneumoniae*, and human immunodeficiency virus (HIV), contribute to the development of LC.[8,9]

The therapeutic approaches for LC and its subtypes, specifically SCLC and NSCLC, encompass surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy (Fig. 1). The most prescribed standard for LC treatment is surgery, which is not appropriate for advanced-stage and metastatic lung tumors. Historically, the most effective treatment option for lung tumors that cannot be removed due to extensive local invasion or when surgery is unfeasible is the combination of chemotherapy and radiation.[10,11] However, in spite of their potential effectiveness, these interventions carry notable adverse

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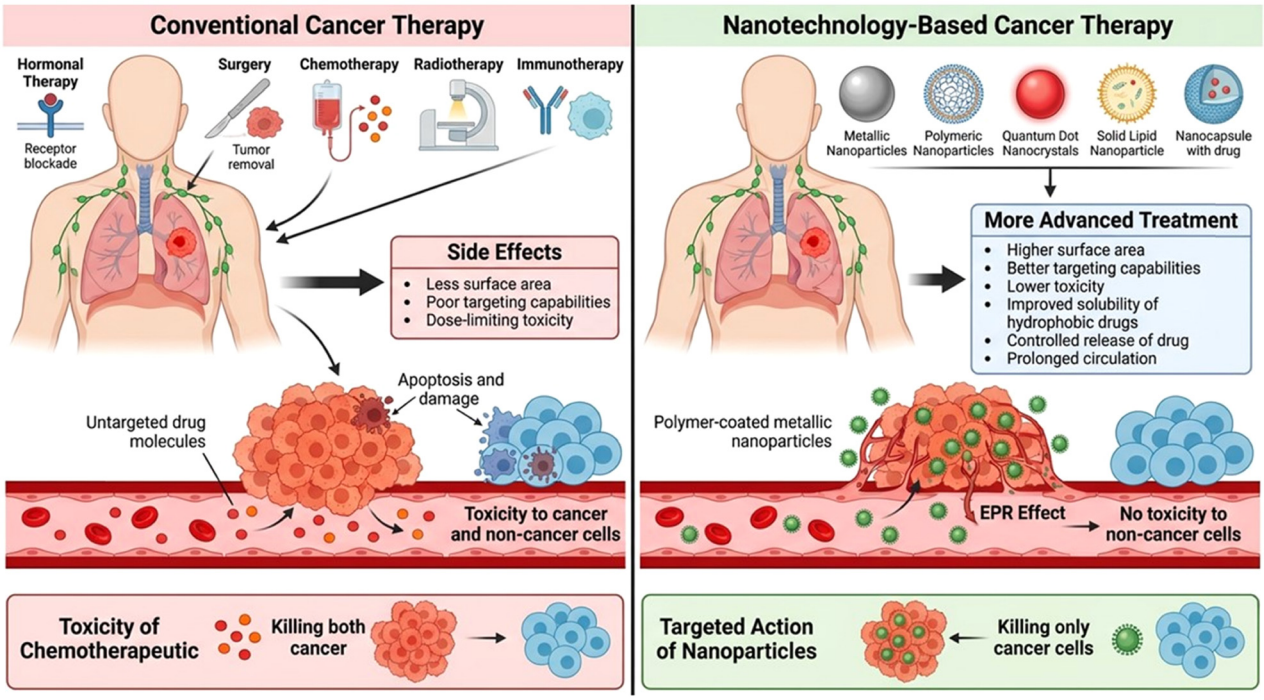

Fig. 1 Overview of the advancements in nanotechnology-based lung cancer treatments compared with conventional therapies.

effects, a lack of target specificity, the development of multi-drug resistance, and the possibility of disease recurrence.[12,13] Additionally, studies revealed that radiotherapy should not be the recommended course of treatment for patients who already have significantly damaged pulmonary systems because it damages the surrounding normal healthy cells, which could result in a loss of lung function.[14,15] Similarly, the drugs used in chemotherapy for the treatment of LC are non-specific and impart toxicity towards the normal cells around the tumor growth, resulting in the death of the patient.[14,16] Hence, there is an urgent need to investigate new and safer treatment alternatives.

A new industry has emerged focusing on the entire modern human production process, specifically the study and development of nanomaterials (NMs), which has been driven by the rapid advancements in nanoscience and nanotechnology.[17,18] NMs can be classified according to their origin (natural or synthetic), chemical composition, material matrix (including carbon-based, inorganic, organic, and composite matrix NMs, or their dimensionality (0-D, 1-D, 2-D, 3-D).[19] NMs, because of their tiny size (1–100 nm), can easily spread throughout the body and pass through biological barriers.[20] This has led to a hopeful outlook that NMs could effectively target disease locations, demonstrating significant promise in the identification and treatment of a range of conditions, such as cancer,[21,22] neurodegenerative diseases,[23] cardiovascular issues,[24] and infections.[25] Metallic NPs represent a specific class of nanostructures made from noble and transition metals, such as silver (Ag), gold (Au), platinum (Pt), copper (Cu) and nickel (Ni). These metal-based NPs have the potential to exhibit various anticancer effects, whether on their own or in combination with drugs or vitamins. A wide variety of nanomaterials, including gold NPs (AuNPs),[26] zinc oxide (ZnO),[27] titanium dioxide (TiO_2),[28] copper oxide (CuO),[29] carbon nanotubes,[30,31] polymeric NPs[32] and superparamagnetic iron oxide NPs (Fe_3O_4 NPs),[33] have been explored for LC therapeutics. Although each NM offers unique benefits, such as high drug-loading capacity (polymeric NPs), strong photothermal conversion (AuNPs), or ROS-mediated cytotoxicity (ZnO, CuO), several limitations remain. For instance, AuNPs suffer from poor biodegradability;[34] CuO NPs often exhibit high intrinsic toxicity;[35] TiO_2 can cause pulmonary inflammation and delayed clearance from the lung, especially at elevated or chronic exposure;[36] bare Fe_3O_4 NPs can be cytotoxic *in vitro*, and surface modification is often needed to improve biocompatibility.[37] Some carbon-based NMs show long-term retention and biopersistence.[38] Therefore, there is a restriction to their widespread therapeutic application.

In biomedical research, AgNPs have drawn attention because of their unique combination of intrinsic biological function and tunable physicochemical properties. Their size, shape, and functionality can be precisely modified through controlled synthesis and surface engineering to improve stability, biocompatibility, and interactions with biological systems.[39] In the realms of nanomedicine and drug development, AgNPs offer distinct advantages over other metal NPs. They show antimicrobial, antioxidant, anticancer, and catalytic activities.[40] Historically, Ag has been utilized in the treatment of skin infections and to preserve drinks in containers for prolonged periods of time. Today, it is being utilized to develop innovative structures designed to fight cancers.[41] Unlike other NMs that primarily function as inert nanocarriers, AgNPs possess intrinsic bioactive properties and can directly contribute to anticancer and antimicrobial effects while serving as platforms

for drug and gene delivery.[39] In contrast to magnetic NPs such as iron oxide, which are widely used for imaging and targeted delivery, AgNPs exhibit stronger direct anticancer effects without requiring external stimuli. The anticancer effects of AgNPs on tumor blood vessels are linked to their 'Enhanced Permeability and Retention' (EPR) effect, leading to their accumulation in tumor tissues.[42] AgNP treatment effectively suppresses the motility of cancer cells by modulating the activity of matrix metalloproteinases (MMPs), thereby halting the cell cycle and inducing various morphological changes.[43,44] AgNPs also inhibit uncontrolled cell growth *via* autophagy, necrosis or apoptosis, engaging pathways like NF-κB, COX-2, and PI3K/AKT/mTOR.[45,46] AgNPs are versatile nanostructures that can be easily manufactured in unique sizes and shapes at comparatively inexpensive costs to Au and Pt. Its synthesis follows standard procedures that do not require sophisticated laboratory equipment, and its surface chemistry can be readily tuned to enable functionalization with targeting ligands, polymers, or drugs.[47,48] The optical and electronic properties of AgNPs further enable their applications in diagnostics, biosensing, and bioimaging, supporting early disease detection and monitoring.[39,49] Additionally, AgNPs are increasingly explored in tissue engineering, where they aid in scaffold modification and infection control. Despite these advantages, challenges related to dose optimization, toxicity, biodistribution, low biodegradability, lower predictability of *in vivo* behavior compared to some alternative NMs and long-term safety must be carefully addressed to enable successful clinical translation, as summarized in the schematic overview (Fig. 2).

A considerable percentage of the studies examined (8.34%) discussed the green synthesis of metal-based NPs, while 3.83% specifically focused on the production of AgNPs. Importantly, 13.03% of the articles were dedicated solely to the cytotoxic effects of green-synthesized AgNPs, whereas 39.78% emphasized their antioxidant properties.[50] Furthermore, 5.29% and 21.8% of the articles investigated the antimicrobial abilities of AgNPs that were synthesized biologically, emphasizing the rising interest in green synthesis for its eco-friendly and less toxic attributes. In contrast, the effectiveness of these NPs against LC and other cancer types was reported in 69.03% of the articles without differentiation.[50] Despite the many reviews about the general biomedical and anticancer uses of AgNPs, many of them are not focused on discussing disease-specific mechanisms and translational relevance. The present review is distinct in that it offers an in-depth understanding of the mechanistic pathways of AgNPs and an LC-based perspective. In addition, it highlights some of the recent gaps and advances in surface-functionalization methods and combination therapies that would improve the selectivity, biocompatibility and therapeutic behavior of AgNPs. By integrating fundamental design principles with emerging clinical evidence, this review aims to bridge the gap between NM research and translational applications in LC therapy. To enhance translational relevance, a clinically viable AgNP formulation for LC treatment should

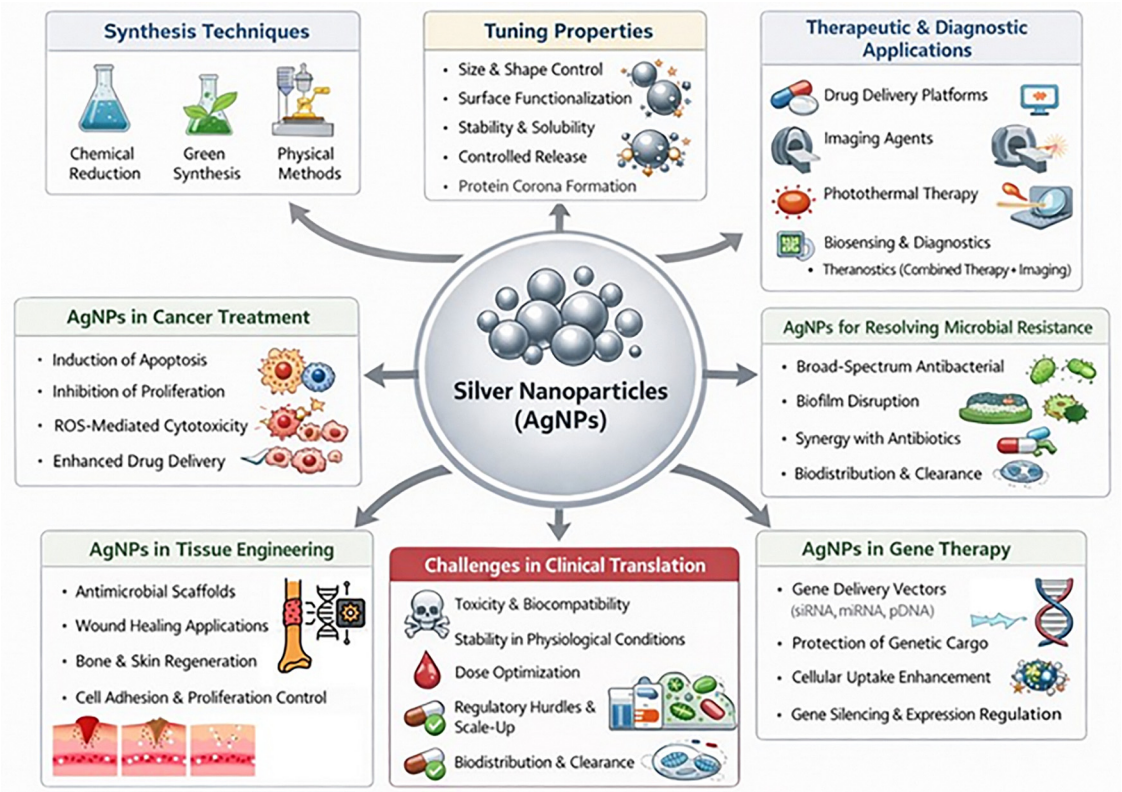

Fig. 2 Schematic of multifunctional AgNPs in diagnostic and therapeutic applications.

meet key criteria, including a controlled size (~20–100 nm), biocompatible surface coating to regulate Ag^+ release, and a clinically feasible route of administration (such as inhalation or targeted intravenous delivery). Additionally, formulations must be scalable under manufacturing standard conditions and demonstrate a favorable therapeutic window with selective tumor toxicity. These parameters serve as a benchmark for evaluating the current experimental systems discussed in this review.

2. AgNPs: synthesis methods, characterization techniques and physicochemical properties

2.1. Synthesis of AgNPs

The different shapes, sizes and properties of AgNPs are achieved through various synthesis methods. These methods can be widely classified into two fundamental approaches: top-down and bottom-up approaches. The top-down method focuses on the reduction of bulk precursors into nanostructures *via* various physical and thermal techniques.[51] This method is also known as the destructive method.[52] The bottom-up method or constructive method involves the synthesis of NMs by assembling atomic and molecular components into larger, more complex nanoscale assemblies through controlled chemical and biological processes.[52] Further, the synthesis techniques can be classified into three main categories: physical, chemical, and green methods. The characteristics of the final NPs are greatly influenced by the technique selection (Fig. 3).

2.1.1. Physical method. The physical method relies on the physical agents, mainly heat, electrical discharge or electromagnetic irradiation,[53] and they eliminate the need for toxic precursors and usually have a rapid processing time. The top-down approach mainly consists of physical methods, such as mechanical milling, nanolithography, sputtering, chemical etching, electro explosion, laser ablation, physical vapor deposition and thermal decomposition.[54] The physical method produces NPs on a large scale with structural homogeneity and elemental purity. However, the absence of a chemical stabilizer or capping agents poses a significant challenge in preventing agglomeration. Also, a major drawback is their high energy consumption, which makes them unsuitable for treating LC. NPs synthesized through physical methods are generally small (size <10 nm), which increases cellular toxicity due to their ability to easily penetrate cells. This is detrimental to the intended medication delivery system as it may impact both cancerous and healthy cells.[55]

2.1.2. Chemical method. Nowadays, chemical synthesis remains the most prevalent approach for the fabrication of AgNPs. They are further subdivided into chemical reduction, pyrolysis, electrochemical, photochemical, microwave-assisted and sonochemical procedures. The three fundamental components required for the synthesis process are metal precursors, a reductant and stabilizing/capping agents. Ag^+ is reduced from the silver precursor to the Ag^0 state during the reactions, which occur mainly in the solution phase. Ascorbic acid, ethylene glycol (ethane-1,2-diol), sodium citrate, borohydride, and hydrazine (also known as diamine) compounds are among the frequently utilized reducing agents.[56] Nucleation and growth are the two stages of the AgNP creation process. The concentration of monomers in the solution quickly surpasses the crucial supersaturation level, causing burst nucleation and precipitation. The nucleus is created by the precipitation of the monomer, and the repeated nucleation process encourages the constant emergence of additional seeds.[57] Following nucleation, the increased monomer addition causes nucleus growth and creates NPs of bigger sizes.[58] Stabilizers, such as polymers and surfactants, are also utilized throughout the production process; they disperse AgNPs and improve their biocompatibility.[59]

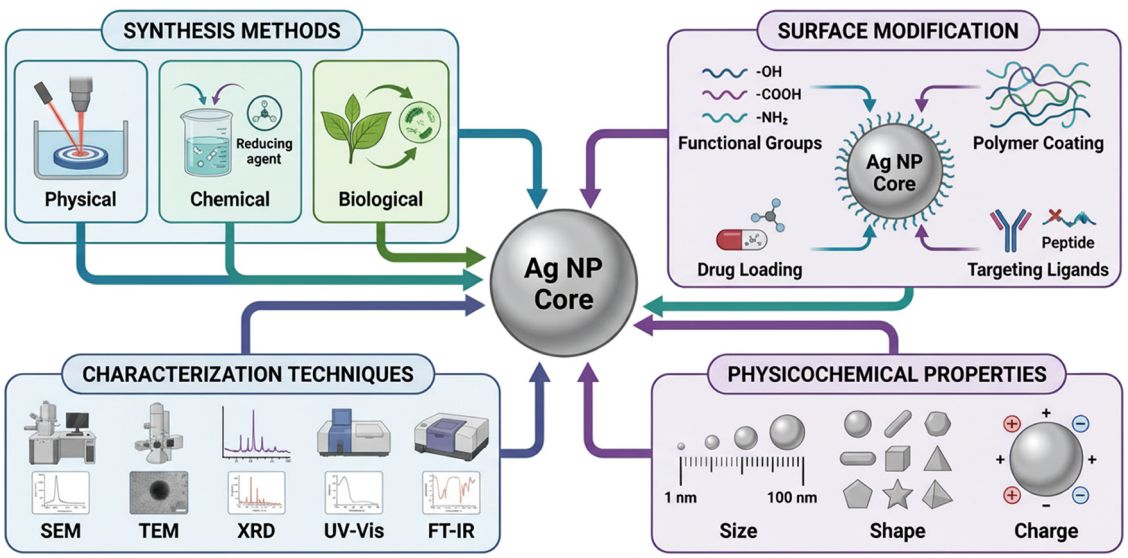

Fig. 3 Schematic representing the synthesis methods, surface modification strategies, characterization techniques and physicochemical properties of AgNPs.

2.1.3. Biological method. Biological synthesis follows the green chemistry principles *via* the utilization of biomolecules, enzymes, various plant materials and microorganisms as reducing and capping agents. It serves as an alternative to other methods that utilize toxic chemical reducing agents and stabilizers. This method has simpler reaction conditions and has almost no environmental toxicity effects, as it uses water as a solvent at normal temperatures and pressures.[60] Altering the pH of the reaction mixture can change the size and shape of the biosynthesized AgNPs. The reducing/capping capabilities and following growth of AgNPs are directly impacted by the pH, which makes it easier to regulate the electrical charges of biomolecules.[61]

2.2. Characterization of AgNPs

A comprehensive array of analytical and spectroscopic techniques is employed to characterize the properties of NPs, including their morphology, elemental composition, surface functionality, colloidal stability, size distribution and dispersity (Fig. 3).

2.2.1. UV-Vis spectroscopy (UV-Vis). An optical analysis of AgNPs is done using this technique, where both qualitative and quantitative information on NPs is provided. It elucidates how surface plasmon resonance affects the size and dispersion of AgNPs. With this method, the sample absorbs UV or visible light, producing distinct spectra. In the 400–500 nm UV region, the AgNPs show high absorption because of the localized surface plasmon resonance phenomena (Fig. 4a).

2.2.2. Fourier-transform infrared spectroscopy (FT-IR). This technique provides information regarding the various functional groups that are available in the sample. The infrared light interacts with the rotational and vibrational modes of the molecules, leading to the stretching and bending vibrations in the 4000–400 cm^{-1} range. It is used to confirm the presence and interaction of the surface functional groups responsible for the reduction, capping, and stabilization of AgNPs, thereby providing insight into their synthesis mechanism and surface chemistry (Fig. 4b).

2.2.3. Scanning electron microscopy (SEM). This method is used for determining the dimensions, shape and surface morphology of the NPs. A beam of electrons is utilized as an imaging probe for scanning across the sample. It provides high-resolution images by detecting reflected or knocked-off electrons from the surface of the sample. The benefit is that a minimal amount of the sample is needed. AgNPs have different morphologies, including spherical, nanowires, nanobars, nanorice, nanorods, nanoprism, nanocubes, nanoflower, and star-shaped[62] (Fig. 4c).

2.2.4. Transmission electron microscopy (TEM). This is another effective imaging tool for the analysis of the shape, size distribution and structural arrangement of NPs. It utilizes a transmitted beam of high-energy electrons to generate images that have higher resolution than SEM images (Fig. 4d).

2.2.5. Dynamic light scattering (DLS). This method is used to ascertain the NPs' hydrodynamic size by passing a monochromatic light source (laser) through a suspension of NPs. Due

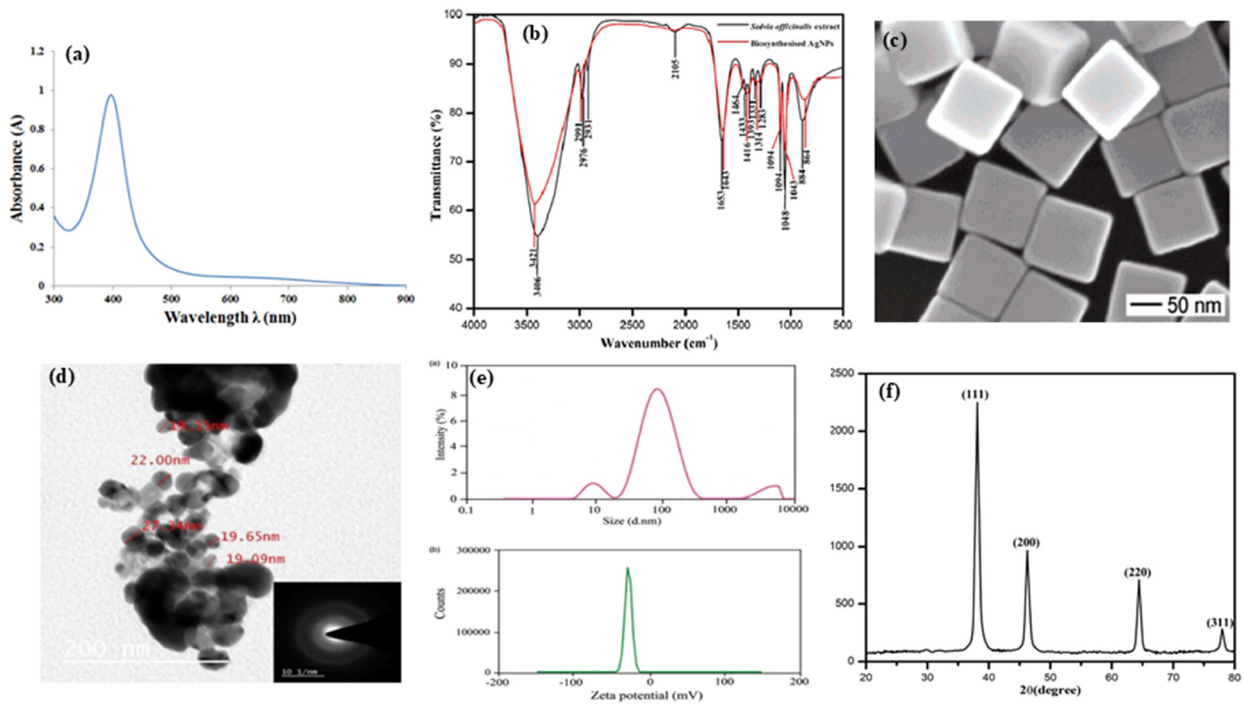

Fig. 4 Characterization of AgNPs. (a) UV-vis spectra, reproduced from ref. 65, with permission from *J Biochem Tech*, copyright 2019. (b) FT-IR spectra, reproduced from ref. 66, with permission from Elsevier, copyright 2020. (c) SEM image of Ag nanocubes, reproduced from ref. 67, with permission from ACS, copyright 2006. (d) TEM image with SAED pattern, reproduced from ref. 68, with permission from Springer Nature, copyright 2019. (e) DLS and zeta potential plots, reproduced from ref. 69, with permission from Taylor and Francis, copyright 2016. (f) XRD pattern, reproduced from ref. 66, with permission from Elsevier, copyright 2020.

to Brownian motion, the particles scatter light with fluctuating intensities, allowing the particle size to be calculated using the Stokes–Einstein equation. Also, this method determines the zeta potential (ζ) of NPs, where a large magnitude, either positive or negative, indicates the electrostatically stabilized NPs, which in turn indicates no aggregation[63] (Fig. 4e).

2.2.6. Powder X-ray diffraction (P-XRD). The crystalline nature, lattice constant, orientation and average size of the particles are provided through P-XRD. Additionally, it gives information on the phase impurity in the samples. It is useful for verifying the alloy structure of the bimetallic NPs. For the AgNPs, the XRD pattern (Fig. 4f) shows the presence of mainly three diffraction peaks, corresponding to (*hkl*) indices of (111), (200), and (220), which represent the face-centered cubic (fcc) structure.[64]

2.3. Properties of AgNPs

The AgNPs' small size and high surface area-to-volume ratio allow them to display unique physicochemical characteristics compared to other NPs.[70] These physicochemical properties are governed by their synthesis methods, size, shape, surface charge, coating, composition and agglomeration (Fig. 3). Due to their nanoscale dimension and enhanced reactivity and interaction, NPs can be used as a catalyst. In biological processes, the small size of NPs permits deep tissue penetration and absorption by target cells, thereby increasing the bioavailability of medicinal compounds.[71] Que *et al.* reported that 13 nm AgNPs significantly inhibit the migration and invasiveness of A549 cells compared to larger-sized NPs.[72] They can be synthesized in different shapes, like spherical, nanocubes, nanorice, nanorods, nanobars, nanoprism, wool-like nanoflower, nanowires, and star-shaped, as shown below in Fig. 5. For the biological systems, the spherical NPs are highly favoured because of the high surface-area-to-volume ratio, and they are capable of releasing Ag^+ ions more efficiently, showing a remarkable antibacterial activity.[73] Additionally, the stability and interaction of AgNPs with other molecules are determined by the surface charge. The surface charge can be adjusted by pH modulation and surface functionalization. In biomedical applications, the surface charge can help in improving uptake, targeting and therapeutic efficiency.[74] Altogether, these characteristics make them exceptional biological agents for wound healing, antibacterial activity, cancer treatment, biosensors, bioimaging, and anti-diabetic effects.[75]

3. Tailoring AgNPs through functionalization for enhanced therapeutic performance

AgNPs have been found to be interesting therapeutic nanocarriers because of their better physical, chemical and biological

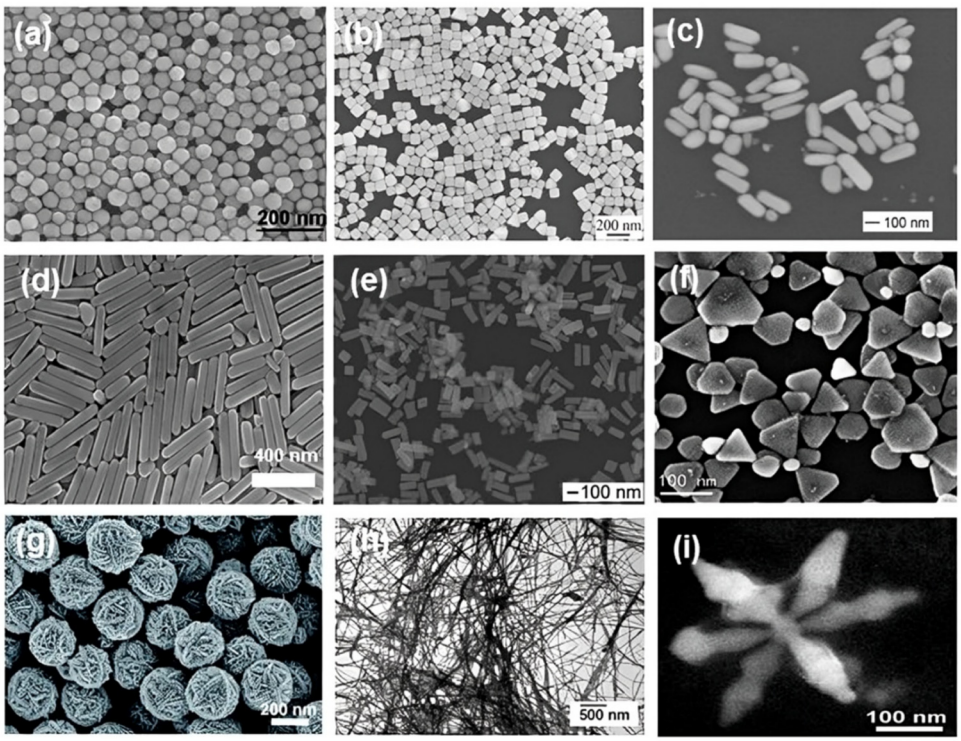

Fig. 5 Representation of electron microscopy images of the synthesized Ag nanostructures: (a) nanospheres, reproduced from ref. 76, with permission from Elsevier, copyright 2019; (b) nanocubes, reproduced from ref. 77, with permission from ACS, copyright 2010; (c) nanorice, reproduced from ref. 78, with permission from ACS, copyright 2007; (d) nanorods, reproduced from ref. 79, with permission from ACS, copyright 2011; (e) nanobars, reproduced from ref. 78, with permission from ACS, copyright 2007; (f) nanoprisms, reproduced from ref. 80, with permission from RSC, copyright 2019; (g) wool-like nanoflowers, reproduced from ref. 81, with permission from RSC, copyright 2022; (h) nanowires, reproduced from ref. 82, with permission from *Wiley*, copyright 2002; and (i) nanostar, reproduced from ref. 83, with permission from ACS, copyright 2013.

properties. However, they are also prone to exhibiting toxicity, limited solubility and stability, which hinder their use in nanomedicine.[84] To enhance their safety profile, surface modification is necessary. The surface functionalization can be done using polymers, peptides, surfactants, aptamers, biomolecules, fluorescent molecules, drugs, *etc.*, as shown in Fig. 6. This can be done *via* adsorption, surface coating, covalent and non-covalent modifications and electrostatic interactions using different physical and chemical methods.[85] Surface modification helps in controlling size and protecting the NPs from the complex biological environments, thereby improving biodistribution, bioavailability and targeting.[45] Improved cellular membrane interactions, regulated drug release, reduced toxicity, increased therapeutic binding, and enhanced biocompatibility are all benefits of the surface alteration.[86] However, despite promising outcomes, many reports remain method-driven with limited mechanistic rigor, but collectively, they provide insights into how surface chemistry shapes therapeutic outcomes in LC treatment. Table 1 summarizes the surface-modified Ag-based nanocomposites and their applications for effective treatment against LC cell lines.

Biopolymer- and plant-extract-derived coatings are among the most frequently explored. Studies involving trimethyl chitosan,[87] chitosan-capped AgNPs synthesized with *Piper betle* and *Sida acuta* extracts,[88,89] and caffeic-acid-functionalized AgNPs[90] consistently show reduced AgNP aggregation and improved selective cytotoxicity toward cancer cells. These systems likely benefit from steric stabilization, controlled surface charge, and the inherent antioxidant or pro-apoptotic activity of natural phytochemicals, although this synergy is often assumed rather than dissected experimentally. Similarly, asparaginase-bound Ag nanocomposites[91] illustrate how enzymatic ligands can enhance selective anticancer responses through increased metabolic stress in LC cells; however, deep investigations into their NP-enzyme conjugation stability or *in vivo* behavior are lacking.

Small-molecule functionalization offers additional therapeutic advantages. Curcumin (Cur)-stabilized AgNPs surface-functionalized with isonicotinic acid hydrazide (INH)[92] demonstrates how dual-function ligands can simultaneously improve particle stability, alter zeta potential, and introduce biologically active sites that modulate ROS-mediated apoptosis. Likewise, AgNPs synthesized using *N*-cholyl D-penicillamine (NCPA)[93] showed enhanced stability and reduced hemolytic toxicity, presumably due to the biosurfactant-like structure of NCPA, which forms a protective interface that limits membrane disruption and excessive ion release. These are some examples of how even simple molecular coatings can remodel intracellular fate, yet mechanistic interrogation remains limited. Synthetic polymers expand functionality further: PVP-coated AgNPs modified with *D. sissoo* and *A. calamus* extracts[94] and PLGA-based paclitaxel-loaded AgNPs[95] underscore the advantages of polymeric shells in controlling Ag^+ dissolution, enhancing drug-loading capacity, and reducing off-target cytotoxicity. However, most drug-loaded systems still lack clear benchmarking against free drugs, obscuring the origin of the improved efficacy, whether from NP-mediated delivery or standard cytotoxic drug action. Similarly, camptothecin-functionalized AgNPs[96] have been shown to demonstrate improved cytotoxicity; however, the study relies primarily on IC_{50} values, without deep mechanistic evidence of improved uptake, intracellular trafficking, or ligand-receptor specificity. Targeted and stimuli-responsive approaches are emerging, although they remain in the early development stages. ACE2 receptor-directed AgCS-CIS-SCRBD nanocomposites[97] and curcumin-loaded photodynamic AgNP conjugates[98] indicate that ligand-mediated uptake and PDT-triggered ROS generation can significantly potentiate

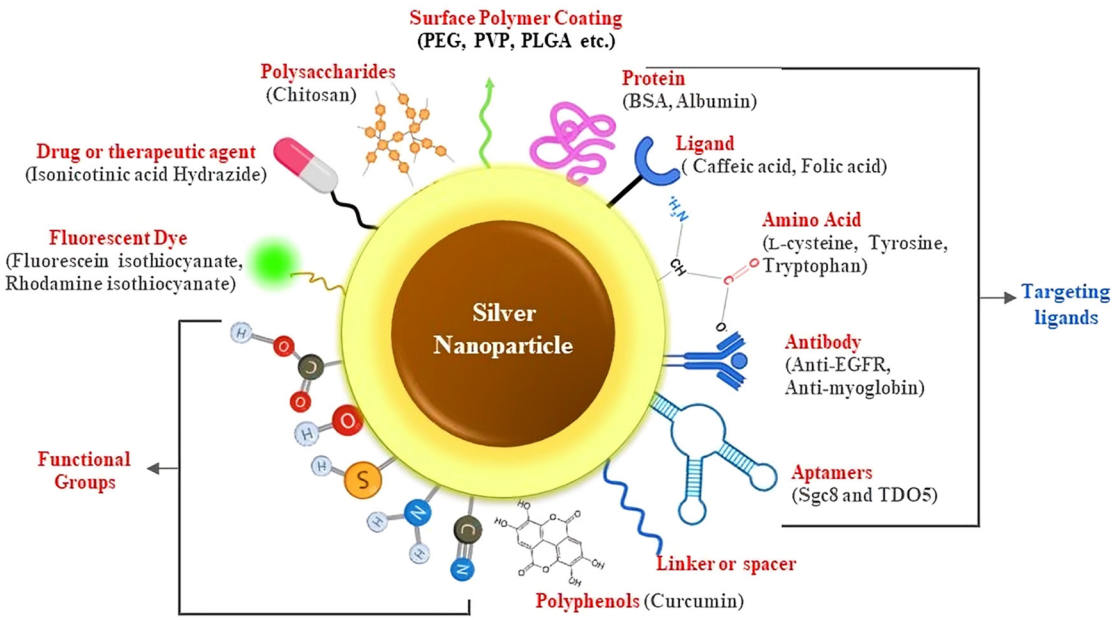

Fig. 6 Surface functionalization of AgNPs with various biological and chemical moieties.

Table 1 Comparative overview of various surface-functionalized Ag nanocomposites evaluated for LC treatment, highlighting their composition, size, IC_{50}/LC_{50} values, and cytotoxicity against LC and normal cell lines

Nanocomposites	Surface functionalization	Category/ description	Size (nm)	Advantage of functionalization	LC cell line and IC_{50}/LC_{50}	Toxicity to normal cell line	Ref.
TMC/Ag	*N*,*N*,*N*-Trimethyl chitosan chloride (TMC)	Polymer	11–17.5	Enhances dispersion, reduces aggregation, and increases uptake *via* positive charge	A549 and 12.3 μg mL^{-1}	WI-38 (357.2 μg mL^{-1})	87
CS@PB-Ag	Chitosan and *Piper betle* extract	Biopolymer and plant extract	28	Polyphenols stabilize AgNPs and induce ROS-mediated apoptosis	A549 and 180 μg mL^{-1}	—	88
CS@Ag	Chitosan and Sida acuta extract	Biopolymer and plant extract	6–45	Enhances biocompatibility and reduces nonspecific toxicity	A549 and 34.5 ± 0.5 μg mL^{-1}	—	89
CA-Ag	Caffeic acid	Ligand	75	Improved solubility and antioxidant protection increase selectivity	A549 and 78 μg mL^{-1}	—	90
ASNase-Ag	Asparaginase	Enzyme	58	Enzyme-mediated metabolic stress and enhanced cancer-specific toxicity	A549	—	91
AgNPs@Cur@INH	Curcumin and isonicotinic acid hydrazide	Polyphenol and antibiotic	—	Improved mitochondrial stress and apoptotic signaling	LK-2	WI38 (<LK-2)	92
Ag-NCPA	*N*-Cholyl D-penicillamine (NCPA)	Biosurfactant	9.1 ± 0.6	Thiol-Ag binding improves colloidal stability and selective uptake	A549 and 50 μg mL^{-1}	—	93
AgPVP, DS@AgPVP, and AC@AgPVP	Polyvinylpyrrolidone (PVP), *D. sissoo* (DS) and *A. calamus* L.	Polymer and plant extracts	10–20	Controlled dissolution and enhanced cellular uptake	A549 and 41.60 ± 2.35, 14.25 ± 1.85, and 21.75 ± 0.498 μg mL^{-1}	WI-38 (420.69 ± 2.87, 408.20 ± 3.41, and 391.80 ± 1.55) μg mL^{-1}	94
PLGA-Pac-Ag	Polylactic-*co*-glycolic acid (PLGA)	Polymer	276 ± 2.7	Slow Ag^+ release; high drug entrapment; and improved stability	A549 and 0.798 μg mL^{-1}	—	95
CMT-Ag	Camptothecin	Alkaloid	10 ± 2	Drug-assisted apoptosis and improved intracellular delivery	A549 and 107.18 μL mL^{-1}	L926 (>100 μl mL^{-1})	96
AgCS-CIS-SCRBD	Chitosan, cisplatin and SCRBD-targeting ligand	Biopolymer, drug and ligand	40–110	Drug delivery + AgNP ROS contributes dual-action cytotoxicity	A549 and 5 μg/100 μL	HEK293 (>50 μg/100 μL)	97
Cum-PEG-BpAg	Thiol polyethylene glycol amine (HS-PEG2K-NH_2)	Polymer	27.8	Prevents aggregation and enables photodynamic ROS burst	A549 and 4.014 μg mL^{-1}	—	98

apoptosis. Yet, these investigations are typically confined to single-cell-line studies and lack the pharmacokinetic or immunological evaluations necessary for translational relevance. Despite these advantages, the field continues to rely heavily on descriptive synthesis reports, UV-Vis spectra, and IC_{50} assays, with limited mechanistic or *in vivo* validation. Greater emphasis on standardized surface chemistry analysis, quantitative mechanistic studies, and reproducible biological models is needed to translate functionalized AgNPs from promising *in vitro* constructs to clinically meaningful anticancer platforms.

The studies summarized in Table 1 reveal several common trends in the assessment of surface-functionalized AgNP systems for LC therapy. Many investigations rely primarily on a single LC cell line, most frequently A549, which limits the broad applicability of the findings across the diverse molecular subtypes of LC. In addition, comparisons with normal lung cells, such as WI-38 or L926, are included in only a limited number of studies, and the absence of appropriate non-cancerous controls in many reports makes it difficult to adequately evaluate cancer selectivity and potential toxicity toward healthy lung tissue. Another notable issue is the use of relatively high dose ranges in several *in vitro* experiments, sometimes exceeding concentrations that may be clinically achievable, thereby complicating the translational relevance of the reported IC_{50} values. Furthermore, although many functionalized AgNP systems demonstrate promising *in vitro* cytotoxicity and mechanistic activity, only a small number have been validated in animal models. Together, these observations highlight a broader gap between NP development studies and the rigorous *in vivo* investigations required to support clinical translation.

A comparative assessment of AgNP functionalization is highly dependent on the nature of the surface modifier, with each strategy offering distinct advantages rather than a single superior approach. Polymer-coated systems (TMC-, PVP-, and PLGA-based AgNPs) consistently exhibit enhanced colloidal stability, controlled Ag^+ release, and improved biocompatibility, often translating into higher anticancer efficacy and lower toxicity towards normal cells. In contrast, AgNPs functionalized with biopolymer (chitosin) and plant extract (*Piper betle*, *Sida acuta* extract, *D. sissoo* and *A. calamus* L.) provide better biocompatibility and reduced nonspecific toxicity but generally show moderate cytotoxicity. Systems functionalized with

ligands (caffeic acid and SCRBD) and small molecules (isonicotinic acid hydrazide) exhibit improved cellular interactions and selectivity, with intermediate therapeutic outcomes. Notably, drug-loaded and -targeted nanocomposites demonstrate the highest potency due to the synergistic effects between the AgNP-induced ROS generation and the drug activity, although their performance is often influenced by the drug component itself. Overall, these findings highlight that the effectiveness of AgNP functionalization is context-dependent, requiring a balance among stability, selectivity, and therapeutic efficacy for optimal design.

4. Administration routes for AgNPs

From a translational perspective, the administration route must align closely with clinically realistic AgNP design parameters, including particle size, surface stability, biodistribution, and safety profile. In this context, inhalation delivery is particularly attractive for lung cancer treatment as it enables direct deposition in the respiratory tract, enhances local drug concentration, and reduces systemic exposure and associated toxicity.[99,100] Alternatively, targeted intravenous delivery remains a viable strategy, especially when supported by surface functionalization to improve tumor accumulation and minimize off-target effects.[101,102] In contrast, commonly used experimental routes, such as intraperitoneal or non-targeted systemic administration, may have limited clinical relevance, underscoring the importance of evaluating AgNP systems within physiologically and clinically feasible delivery frameworks.[103]

4.1. Intraperitoneal (IP)/systemic delivery

IP injection is one of the prevalent approaches used in preclinical tumor models. It enables the introduction of NPs systemically while avoiding the barriers associated with oral drug delivery, and it is less difficult to perform in small animals. In a study that involved the implantation of H1299 human lung cancer cells in SCID mice, green-synthesized AgNPs were prepared using plant extracts and subsequently administered to the mice *via* IP injection in three doses per week at a body weight of 10 μg g^{-1}. This way, the rate of tumor growth in this intervention group was considerably reduced as compared to that in the control group. This approach provided systemic exposure but not localized delivery to lung tissue, and thus, it may not accurately model the pharmacokinetics of localized lung tumors.[104]

4.2. Intravenous (IV) injection

The IV injection technology enables the direct delivery of AgNPs into the bloodstream, where they can circulate and potentially target lung tumors, especially metastases or well-vascularized tumors. However, the systemic application of AgNPs may lead to organ toxicity, inducing adverse effects such as lung inflammation. For instance, a study involving multi-dose IV administration in mice revealed the presence of inflammatory infiltrates and notable structural alterations in lung tissue. Although this method is considered simplistic for systemic delivery, there is a scarcity of direct *in vivo* investigations regarding AgNPs administered *via* IV in LC models (*i.e.*, lung tumors) in the existing literature.[105]

4.3. Intratumoral/local injection

Direct injection into or around a tumor optimizes local bioavailability and reduces the risk of systemic adverse effects. AgNPs have been evaluated in this manner within immune-sensitization and tumor-control models (these metal NPs have the ability to augment necrosis and immune infiltration when administered locally). Although the majority of intratumoral AgNP immunomodulation instances have been observed in models other than LC models, the underlying principle extends to lung tumors that can be accessed through image-guided injections or surgical procedures, thus providing a high local dosage with diminished systemic toxicity. A recent study demonstrated that small citrate-coated AgNPs measuring approximately 5 nm, when injected around the tumor, significantly amplified immune infiltration and enhanced the efficacy of checkpoint blockade in murine tumor models (this illustrates the promising potential of localized AgNP administration in bolstering anti-tumor immunity).[106]

4.4. Inhalation/pulmonary aerosol

Administering AgNPs through aerosolization or inhalation presents the most evident opportunity for targeted treatment of LC. The aerosolized particles settle throughout the airways and alveoli, resulting in elevated local concentrations within the tumor microenvironment while minimizing systemic exposure. Robust methodological examples exist for inhalable nanomedicines in LC (numerous NP types have been developed as aerosols and evaluated in orthotopic/orthotropic lung tumor studies),[107] yet therapeutic investigations specifically employing inhaled AgNPs for lung tumors remain exceedingly scarce.[108]

4.5. Intranasal administration

Non-invasive intranasal dosing is an active way of delivering NPs to the upper as well as lower respiratory tracts. This method has been widely applied in the study of the translocation of substances in the nose into the brain and the pulmonary deposition of Ag nanoarchitectures. It is a viable alternative to the treatment of lung tumors in the small animal setting because it is simple to administer, although, because of anatomical dissimilarities between the rodent and human nasal structures, scaling and validation must be carried out before it can be utilized in a clinical setting. Research into the intranasal fate of Ag shows that pulmonary and systemic redistribution of Ag is important after nasal administration, which means that this route could be considered in future studies for local lung delivery in many tumor models.[109]

4.6. *In vitro* route selection

Several *in vitro* experiments have demonstrated the potent anticancer efficiency of AgNPs against LC cell lines through diverse molecular pathways. Green-synthesized AgNPs have also been

shown to cause concentration-sensitive cytotoxicity and apoptosis in H1299 cells *via* the reduction of the anti-apoptotic Bcl-2 and the enhancement of the caspase-3 activity. Similarly, artificially engineered AgNPs made using *Alangium salvifolium* leaf extract showed a significant anti-tumor effect in xenograft SCID mice by inhibiting the NF-kB signaling pathway through intraperitoneal injection.[110] Likewise, biogenic AgNPs synthesized using *Alangium salvifoliu*m leaf extract exhibited a significant anti-tumor effect on A549, causing G2/M phase arrest, mitochondrion membrane depolarization, and DNA fragmentation.[111] Additionally, AgNPs obtained using *Albizia adianthifolia* caused intrinsic mitochondrial apoptosis in A549 cells through the expression of p53, Bax, and caspases, as well as the inhibition of Bcl-2 and disruption of the mitochondrial potential.[112] In another study, eco-fabricated AgNPs obtained using *Azadirachta indica*, *Gymnema sylvestre*, and *Moringa oleifera* were found to have a high antiproliferative activity against A549 cells *via* the down-regulation of angiogenic (VEGF) and proliferative (Cyclin D1) genes, thus reducing the chance of metastasis.[113] All these findings show that plant-based AgNPs have significant cytotoxic and anti-metastatic impacts on LC cells through apoptotic and oxidative stress signaling. However, the issue of excessive ROS-mediated toxicity, unpredictability in *in vivo* translocation, unclear mechanisms of NP internalization, and oscillations in green production stability are significant barriers to clinical application.

Preclinical evidence demonstrates that AgNPs can be delivered through multiple administration routes, including intraperitoneal, intravenous, intratumoral, inhalation, and intranasal pathways, each offering distinct advantages and limitations. Systemic delivery approaches such as IV and IP administration enable widespread biodistribution but raise concerns regarding off-target toxicity and organ accumulation. In contrast, localized delivery strategies, particularly inhalation or intratumoral injection, may offer higher NP concentrations at lung tumor sites while minimizing systemic exposure. Nevertheless, most existing investigations rely on preclinical animal models or *in vitro* systems, and comprehensive pharmacokinetic and toxicity studies are still required to determine the most effective and safe delivery strategies for clinical translation.

5. Cellular uptake pathways of AgNPs: insights into biological interactions

5.1. Active mechanism

The study of the complex mechanisms of cellular uptake, subcellular localization, and cellular retention is essential for the enhancement of the functionality and design of NM-based materials for medical applications. In the case of LC, AgNPs are taken into cells through receptor-mediated uptake, endosome-mediated uptake, and passive diffusion, all of which are mediated by endocytosis, particularly phagocytosis, macropinocytosis, caveolin-mediated endocytosis (CVME), and clathrin-mediated endocytosis (CME).[114] The absorption of AgNPs in A549 and H1299 cells takes place *via* the non-phagocytic pathway (CME, CVME, or macropinocytosis) predominantly.[115] These mechanisms affect their intracellular trafficking, bioavailability, and cytotoxic effects.[116] The four main endocytic mechanisms covered in this article are clathrin-mediated endocytosis (CME), caveolin-mediated endocytosis (CVME), phagocytosis, and micropinocytosis. Macrophages present in the pulmonary microenvironment are responsible for the uptake of AgNPs *via* phagocytosis. This elucidates the specificity of endocytic processes in terms of cell types and highlights the broader biological importance of AgNP movement in the lung tumor microenvironment, where the cancerous and immune cells interact.[117]

5.1.1. Phagocytosis. Phagocytosis is a cellular process whereby a cell surrounds large particles with a membrane and then ingests and actively absorbs them, as depicted in Fig. 7a. One of the major features of the process, phagocytosis, is the internal vesicles, or phagosomes, which are typically approximately 250 nm in diameter.[118,119] Phagocytosis is done by special phagocytic cells, such as dendritic cells, macrophages, monocytes, neutrophils, and B lymphocytes. Opsonization and adherence of immunoglobulins, *e.g.* antibodies (Abs), as well as complement proteins and other serum proteins, *e.g.* laminin and fibronectin, to the surface of NPs facilitate the elimination of the NPs through the complement system, scavenger, and Fc receptors, prompting a signaling cascade, actin assembly, cell surface extensions and engulfment and internalization.[120] The major receptors that contribute to the process of phagocytosis include the IgG Fc receptor family (includes FcgRI, FcgRIIA and FcgRIIIA), complement receptors (include CR1–CR4) and the a5b1 integrin.[121] Alveolar macrophages and tumor-associated macrophages (TAMs) can internalize AgNPs in lung tissue through the Fc and complement receptor. Such macrophages can be used as a sink, which can cause competition between them and cancer cells in the uptake of NP, or they can be used to complement the redistribution of the NPs once ingested.[122] Surface modifications, including Ab-conjugation or the adsorption of opsonins, can be used to enhance macrophage targeting, which can be beneficial to immunotherapy but may also impair the delivery of cancer-specific NPs.[123]

5.1.2. Receptor-mediated endocytosis (RME). RME is divided into several categories, including CME, CVME, and clathrin-/caveolin-independent endocytosis, which represent the major pathways. The most well-studied mechanism of transporting substances into eukaryotic cells is CME.[124] It is a complex process that involves intercellular signal transduction, membrane recycling and the uptake of nutrients. The vesicle formation relies on a diverse set of proteins and interactions between stimuli and their respective receptors.[125,126] The encapsulation of these vesicles by clathrin results in the creation of clathrin-coated vesicles, as shown in Fig. 7c. The dimensions of clathrin-coated vesicles vary according to the type of cell, generally falling within the range of 70–150 nm.[127] The process of vesicle release from the plasma membrane is controlled by GTPase and dynamin.[125] Following the release of the vesicles, clathrin undergoes degradation facilitated by auxilin- and heat shock cognate 70-dependent proteins.[127]

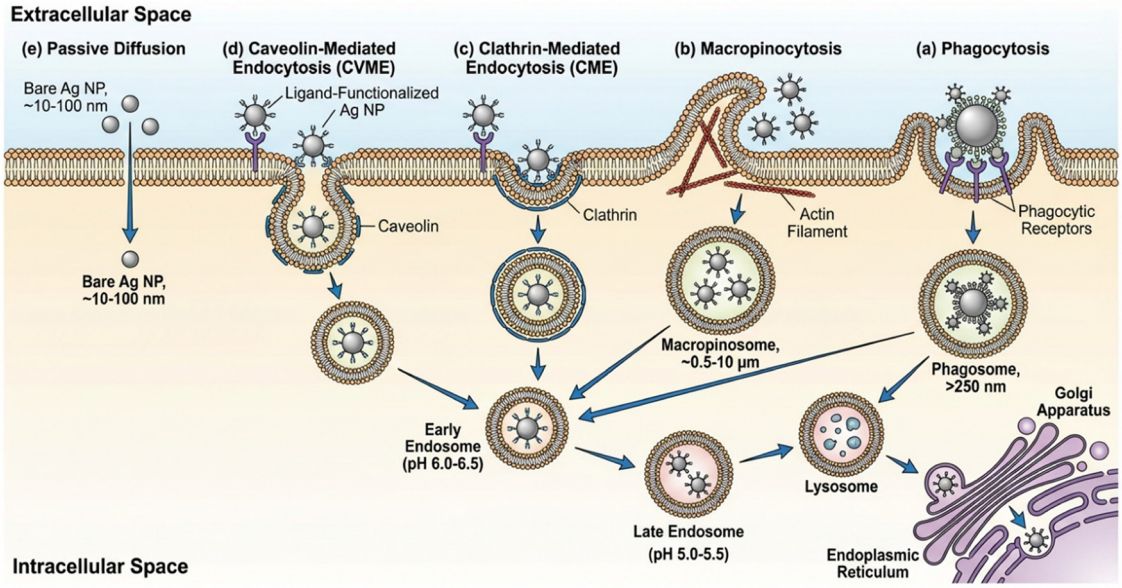

Fig. 7 Schematic of the different cellular pathways of AgNPs uptake between the extracellular and intracellular spaces. The entry into cells can occur by (e) passive diffusion or by endocytic processes, including (d) caveolin-mediated endocytosis, (c) clathrin-mediated endocytosis, (b) macropinocytosis and (a) phagocytosis. After internalization, the NPs are transported *via* early and late endosomes (pH 6.5–5) and lysosomes, and they eventually interact with intracellular organelles, such as the ER and Golgi apparatus.

Some of the components are sent to early endosomes, while some are brought back to the surface of the plasma membrane. Additionally, vesicles may reach later-stage endosomes before moving on to lysosomes and multivesicular bodies (MVBs), as well as other cellular compartments. The majority of receptor-mediated nanoparticle uptake by cells takes place *via* CME. In the A549 and H1299 cells, transferrin- or folate-conjugated AgNPs utilize clathrin-coated pits to gain entry through receptor-mediated endocytosis. Inhibiting transferrin receptors (TfR) or pre-treating the cells with chlorpromazine, a clathrin-assembly inhibitor, significantly diminishes AgNP uptake, thereby confirming the dependence on clathrin-mediated endocytosis.[128]

CVME is recognized as the second most thoroughly studied endocytic pathway, playing a vital role in intracellular transport and mechanosensing within cells. This process is initiated by the ligand-receptor binding, which generates flask-shaped invaginations called caveolae, which measure 60–80 nm in diameter within the plasma membrane,[129] as displayed in Fig. 7d. A variety of proteins are recruited in the endocytic pathway, including caveolin-1, which interacts with cholesterol in lipid rafts; importantly, caveolin-1 remains associated with vesicles even after internalization, in contrast to CME.[130] Vesicle formation is influenced by kinases and phosphatases, such as Src tyrosine kinase and the serine/threonine protein phosphatases PP1 and PP2A.[131] Similar to CME, the protein dynamin is crucial for the detachment of vesicles from the cell membrane, resulting in the formation of caveolin vesicles that can merge with other caveolin vesicles to create multivesicular structures, which then fuse with early endosomes.[132] Depending on the type of cell, these vesicles may subsequently travel to the SER or the Golgi transport network.[133] A549 cells exhibit elevated levels of caveolin-1 and internalize albumin-coated or cholesterol-functionalized AgNPs *via* caveolae-dependent endocytosis.[134] Therefore, caveolin-mediated uptake offers benefits for drug-loaded NPs intended for the treatment of lung adenocarcinoma.

5.1.3. Macropinocytosis. Macropinocytosis is a dynamic process through which cells actively engulf significant amounts of extracellular fluid, resulting in the biogenesis of large vesicles termed as macropinosomes, with diameters ranging from 0.5 to 10 μm[135] (Fig. 7b). This mechanism is commonly employed by macrophages to engulf apoptotic cell debris, other cells, and bacteria. Unlike phagocytosis and RME, macropinocytosis is not strictly governed by specific receptors or other molecular signals. Research has shown that the activation of tyrosine kinase receptors is linked to the induction of macropinosomes during this process.[136] After NMs are internalized *via* macropinocytosis, the pH within macropinosomes gradually decreases. As a result, the acidified macropinosomes can either be fused with the late endosomes, interact with the lysosomes or recycle the contents to the cell membrane.[116] Also, there are clathrin or caveolin-independent endocytosis (CIE) pathways, which encompass the abovementioned processes. It has been indicated that CIE is involved in the process of regulating several processes, which include cell polarization, intercellular signal transduction, cell growth and repair of the plasma membrane.[137] The synthesis of raft proteins is dependent on the formation of vesicles in the endocytosis process that is controlled by RhoA and CDC42.[138] The synthesis of raft proteins is necessary in the endocytosis process, involving various proteins like Arf-6, Rho-A (associated with the IL2Rb-dependent pathway), flotillin, and CDC42.[127] RhoA acts *via* a

dynamin-dependent mechanism and is implicated in the uptake of proteins in immune cells and fibroblasts, such as the interleukin-2 receptor (IL-2R-b).[116,139] However, it is not investigated further because few studies have explored its role in the uptake of NMs. In contrast, CDC42 is involved in a dynamin-independent route that promotes the internalization of CtxB and VacA.[116] The increase in macropinocytosis within metabolically active LC cells, namely A549 cells with KRAS mutations, has a significant impact on cancer biology and nanomedicine in general. The mechanism enables the non-specific absorption of large amounts of extracellular fluid, which may be used to deliver drugs better with the help of special NPs.[140]

5.2. Passive mechanism

Direct cellular entry occurs when NPs can enter the cell plasma membrane *via* different biochemical or physical events, and they include the following: (i) direct translocation, whereby NPs disrupt the plasma membrane to enter without being trapped in endosomes or using energy-dependent transport, as demonstrated in (Fig. 7e); (ii) lipid fusion, in which NPs covered with lipid bilayers merge with the plasma membrane, followed by the direct translocation of their cargo into the cytoplasm; (iii) the method of producing NPs by internalization through electroporation or making holes in the membrane with the help of electrical pulses; (iv) microinjection, which entails the use of special microinjectors to bring NPs to the cytoplasm.[141] Passive entry mechanisms such as membrane fusion, translocation, or electroporation are not commonly seen in physiological contexts, but they can be applied to deliver specifically designed NPs to the pulmonary cytosomal space. For passive crossing, AgNPs smaller than 10 nm have the capacity to cross lipid bilayers passively due to their increased surface energy and possible membrane-disrupting properties. This property explains their concentration in cells even under conditions when active endocytosis is not taking place.[142]

The EPR effect is a vital targeting mechanism for AgNP delivery in the treatment of solid tumors, including LC.[141] NSCLC tends to have aggressive vascular responses, abnormal angiogenesis, and increased metabolic demand conditions, which favor the use of the EPR effect. The fast-growing tumor mass in LC contributes to the formation of dysfunctional blood vessels that have enlarged endothelial gaps, insufficient pericyte cover and disproportionate vessel density. The result of these structural abnormalities is that the vascular permeability becomes enhanced, enabling AgNPs, which are typically between 40 and 400 nm, to passively leave the bloodstream into the tumor interstitium.[143] In parallel, the dysfunctional lymphatic drainage observed in lung tumors prevents the elimination of these NPs and, thus, increases their retention in the Tumor Microenvironment (TME). AgNPs have unique physicochemical properties that enhance their circulation, tumor localisation and cytotoxicity. PEGylation is one of the possible modifications that increase the half-life of NPs by preventing their elimination by the mononuclear phagocyte system (MPS) and the immune system. AgNPs respond to the acidic, hypoxic, and redox-imbalanced conditions inside the lung tumor tissue, after retention into the tissue, releasing Ag^+ ions and consequently forming ROS.[144]

The cellular uptake of AgNPs in LC cells occurs predominantly through energy-dependent endocytic mechanisms, including clathrin-mediated endocytosis, caveolin-mediated endocytosis, macropinocytosis, and phagocytosis. The cellular interactions and intracellular localization also vary depending on shape, and shape changes affect ROS generation and apoptotic responses. Also, surface coating (*e.g.*, PVP or citrate) will have a profound influence on the stability of AgNPs and the dissolution of the ions. The steady leakage of Ag^+ ions in A549 and H1299 cells is a key factor influencing cytotoxicity as these ions react with thiol-containing proteins to disrupt antioxidant defenses and contribute to increased oxidative stress. The effects are also controlled by the particle size, where smaller AgNPs exhibit a higher cellular uptake and higher ion release, thus enhancing the level of mitochondrial dysfunction and DNA damage. A combination of these AgNP-specific properties generates different mechanistic results in A549/H1299 models,[145] which are not so clear in non-ion-releasing or less redox-active NMs. Despite these mechanistic insights, most findings originate from *in vitro* cellular studies, and further investigation is necessary to understand how these pathways operate within the complex tumor microenvironment *in vivo*.

6. Deciphering the cytotoxic pathways triggered by AgNPs in LC cells

HeLa and A549 cells showed the release of intracellular Ag^+ ions following the internalization of NPs, suggesting that the acidic environment of lysosomes promotes particle breakdown and establishes a causal association between ion release and eventual cell death.[146] *In vitro* studies of the anti-cancer effects of the NPs against human LC[147] have shown that they cause toxicity in cancer cells by disrupting the cell cycle, reducing ROS production, impairing mitochondrial function, releasing lactate dehydrogenase (LDH), and activating apoptotic genes like Bax, as well as causing the formation of apoptotic bodies, DNA damage, micronuclei, and chromosomal abnormalities (Fig. 8). Other works have clarified the relations between AgNPs and the immune system, which suggest that AgNPs can cause inflammation in the target cells. The stimulation of inflammatory response occurs due to the synthesis of these NPs by the macrophages, which release TNF-a, inflammatory cytokines, and interleukins (IL-6) upon activation. The effectiveness and efficiency of AgNPs in the production of ROS depend on their size, with smaller NPs being more effective. However, as a result of biological processes, the anti-proliferative effect and anti-angiogenic effect of AgNPs have also been identified.[148]

6.1. Induction of oxidative stress and ROS generation

AgNPs have been shown to be effective in the treatment of cancer, particularly LC, by triggering oxidative stress through the generation of ROS. This begins with the cellular uptake of

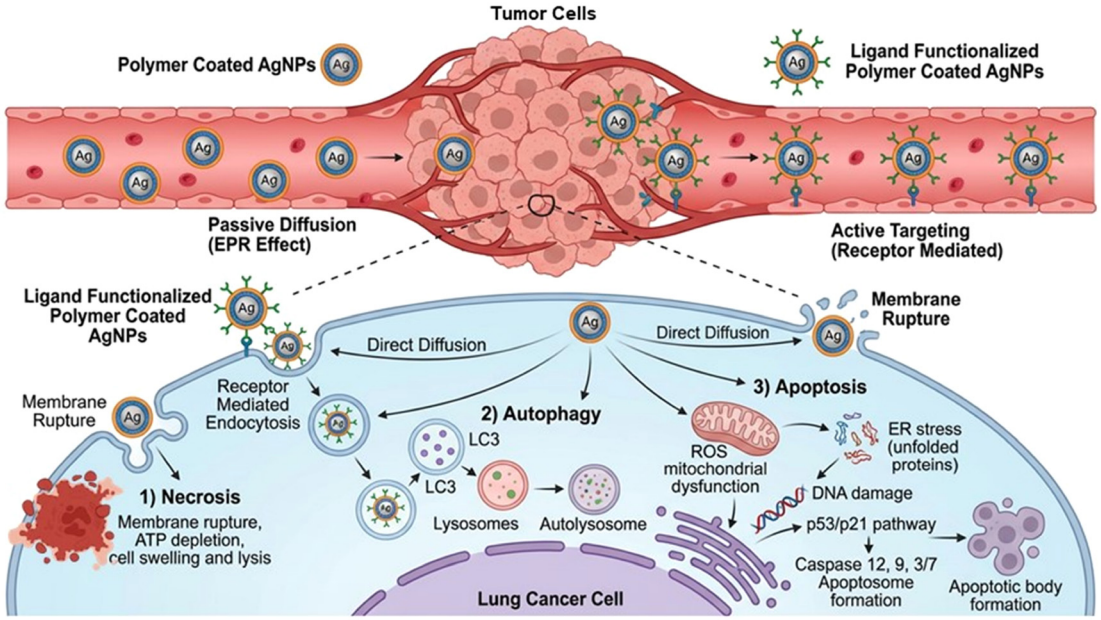

Fig. 8 Mechanism of action of AgNPs in lung cancer cells.

AgNPs (Fig. 7) *via* direct or different endocytic mechanisms. These pathways allow the entry of AgNPs into the cell and their localization in organelles like the lysosome, ER and especially mitochondria, which is the most important in the production of ROS (Fig. 8).[149] AgNPs cause the depolarization of the mitochondrial membrane and the suppression of the electron transport chain within the mitochondria. This imbalance results in the leakage of electrons, whereby the superoxide anions (O_2^-), subsequently, are converted into hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH) by the mitochondrial antioxidant system. The overproduction of these ROS leads to mitochondrial impairment and the destruction of cellular constituents, such as lipids, proteins, and DNA, which adds to oxidative stress.[150] In addition, AgNPs may be localized to lysosomes, damaging the lysosomal membrane and leading to an enzyme and iron leakage. The accumulation of ROS in the cytoplasm and organelles leads to cell damage by oxidative stress, the denaturation of proteins, and the damage to DNA.[151] The peroxidation of lipid molecules by ROS breaks down cell membranes, whereas the oxidation of proteins by ROS can cause enzyme loss of activity and structural damage.[152] The ROS-mediated DNA damage may also cause mutations, breakage of chromosomes, and the initiation of DNA repair. AgNPs increase oxidative stress in LC cells, which already have high concentrations of ROS, pushing the cells to a threshold that induces apoptosis. AgNPs also impair cellular antioxidant defenses, along with ROS generation. The decrease in the antioxidant content (such as glutathione [GSH]) and the inhibition of enzymes (such as superoxide dismutase [SOD] and catalase) reduce the cell's ability to counteract the ROS and, thus, enhance oxidative stress in LC cells.[153] This triggers signaling pathways, including the MAPK and NF-κB pathways, which regulate cell viability, inflammation, and cell death. The excessive ROS produced by AgNPs in LC cells activates intrinsic and extrinsic apoptotic pathways. In the intrinsic pathway, mitochondrial dysfunction induced by ROS causes cytochrome *c* release, which subsequently activates caspase-9 and caspase-3, ultimately resulting in cell death (Fig. 8). In a study on LC cells, AgNPs ranging from 10–50 nm effectively suppressed tumor growth and induced cell death by increasing ROS production, activating mitochondrial signaling cascades, enhancing the activity of apoptotic enzymes such as caspase-3 and caspase-9, inducing morphological alterations including chromatin condensation, and inhibiting key carcinogenic processes.[154] Conversely, in the extrinsic pathway, apoptosis is mediated through ROS-dependent upregulation of death receptor signaling. AgNPs stimulate the formation of ROS by damaging mitochondria, destabilizing the lysosome, and disrupting cellular antioxidant response.[155] This oxidative stress causes cell damage and triggers apoptotic activities in LC cells. AgNPs show selective toxicity towards cancer cells by exploiting their high quantity of ROS levels and inherent sensitivity to oxidative stress. Moreover, the inflammatory and metastatic process modification highlights the therapeutic potential of AgNPs in the treatment of LC. The ability to trigger ROS and disrupt the homeostasis of cancer cells makes AgNPs a strong candidate for targeted treatment, a novel approach to treating LC.[156]

6.2. AgNP-induced mitochondrial dysfunction

The recent study into the cytotoxic effects of AgNPs on LC cells produced valuable results regarding the specific biochemical mechanisms through which these particles exert their impact.[157] The ions in question play a part in the appearance of ROS that disrupt mitochondrial activity and cause cell damage. Mitochondria are essential for the production of energy, regulation

of cellular metabolism, and maintenance of cellular integrity.[148,158] However, when subjected to AgNPs, mitochondrial dysfunction ensues, whereby a time- and dose-responsive increase in mitochondrial ROS and the oxidation of cellular proteins occur (Fig. 8).[159] This mitochondrial perturbation is correlated with the shifts in cell cycle progression, including the G2-phase arrest in sensitive cell lines, such as A549 and Calu-1.[160,161] It is noteworthy that the NCI-H358 cells, which are more resistant to AgNPs, did not show significant mitochondrial ROS and protein oxidation, despite a decrease in cell proliferation under the combination of AgNPs and ionizing radiation. An in-depth examination of mitochondrial respiration revealed that the AgNP exposure caused a reduced ATP level in these cells, particularly in the AgNP-sensitive lines.[162] There was also a rise in mitochondrial respiration that may have been compensatory in nature. Nevertheless, this did not lead to profound alterations in the mitochondrial respiration parameters in the different cell lines. This depleted ATP, together with mitochondrial dysfunction, led to a significant drop in cell viability, especially in the Calu-1 cell line, which underwent an almost complete loss of ATP after prolonged exposure to AgNPs.[163] Factors such as mitochondrial mass and redox condition may be the cause of this susceptibility of different LC cell lines to AgNPs. In particular, Calu-1 cells that are sensitive to AgNPs (obtained by means of the lung pleura) exhibited more mitochondrial dysfunction as compared to NCI-H358 cells (obtained by means of the bronchoalveolar tissue). This implies that the anatomical source of lung cells might have a role to play in their sensitivity to AgNPs,[164,165] and similar *in vivo* studies have shown that exposure to AgNPs causes pleural inflammation and fibrosis in animals. Overall, it can be concluded that the mitochondrial dysfunction and ROS generation caused by AgNPs in LC cells are essential factors influencing cell death, and the cellular response varies across cell types. These findings indicate the need to understand the molecular pathways of AgNP-induced toxicity, which would guide future clinical treatment and risk management regarding the use of AgNPs.

6.3. DNA damage and cell-cycle arrest

Prior research has examined the cell cycle arrest and cytotoxic effects caused by AgNPs.[166–168] As the duration of exposure increases, the impact of AgNPs on the cell cycle and apoptosis increases, thereby exacerbating both cellular and genomic toxicity. Typically, cell cycle checkpoints, such as G2/M, are activated in response to DNA damage, preventing cells from progressing into mitosis (M phase). An elevation in G2/M cell-cycle arrest signifies that a greater proportion of cells are stalled in the G2 phase to facilitate DNA repair. Cells that have been successfully repaired can proceed to mitosis; however, those that sustain irreparable damage experience an irreversible G2/M cell-cycle arrest, followed by apoptosis.[169] Au@Ag nanorods (NRs) can significantly keep HepaRG cells in the G2/M phase, promote late-stage apoptosis, and increase p53 and p21 levels, which are key regulators of the cell cycle.[170] Given that p53 can also trigger apoptosis if DNA repair fails, p21 may play an indirect role in apoptosis through cell-cycle arrest *via* a mechanism dependent on p53, achieved by downregulating the nuclear protein ICBP90, which is involved in DNA replication and cell-cycle control.[171] Additionally, apoptosis and G2/M arrest linked to the p53/p21 pathway have been documented in HepG2 cells treated with garlic extracts.[172] Consequently, it can be deduced that oxidative stress-related damage to DNA and chromosomes may increase the expression of p53 and p21, leading to cell-cycle arrest. Extended exposure to Au@Ag NRs during the replication of DNA and chromosomes could further augment genotoxic effects and apoptosis.[170]

6.4. Autophagic cell death and autophagy

Certain research indicates that AgNPs serve as inducers of autophagy with a protective effect. To delve deeper into this hypothesis, one could employ the well-known autophagy inhibitor, chloroquine, or assess the effects of AgNPs in hypoxic environments, where it is believed that autophagy is induced (Fig. 8).[173–175] Numerous studies have shown that autophagy and apoptosis interact, and their simultaneous activation enhances their antitumor effects.[176] AMPK is a crucial sensor in cellular metabolism regulation. Changes in the ATP to AMP ratio boost its activity, leading to Autophagy Activating Kinase 1 (ULK1) phosphorylation, vital for autophagy initiation; mTOR is the main antagonist of ULK1 and plays a critical role in the proliferation and survival mechanism of cancerous cells.[177] In their 2020 research, Chen *et al.*[178] investigated the regulatory effects of PVP-coated AgNPs on autophagy within the 'PC-3' human prostate cancer cells at non-toxic concentrations. Their flow cytometry analysis showed that AgNP treatment did not induce apoptosis; however, there was a substantial elevation in all autophagic markers. This was coupled with lysosomal impairment, evidenced by reductions in the lysosome count and the protease activity, with a substantial decrease in cathepsin D expression, eventually resulting in the blockage of autophagic flux. Hypoxia, which is characterized by increased concentrations of HIF-1, and an energy deficit caused by the activity of NPs promoted the activation of AMPK and inhibited the expression and phosphorylation of mTOR. Due to this cascade of events, ACC1 (acetyl-CoA carboxylase 1), being an AMPK target, was activated, and S6K, a mTOR target necessary as a protein synthesis factor, cell growth factor, proliferation factor, and survival factor, was inhibited. Protein LC3-I/II is identified as one of the major autophagy markers, and the rise of its expression implies active autophagic activity. In addition, p62/SQSTM1 (sequestosome 1) is a key autophagy receptor that attaches cytoplasmic components for degradation.[179] The significant increase in p62 in the tumor cells after treatment implies that the autophagic flux is probably disrupted. In that regard, AgNPs are found to induce autophagy as the defense response, implying that the inhibition of this route is likely to enhance the antiproliferative effects of AgNPs. Autophagy plays a dual role in AgNP-induced responses in LC models, acting as either a cytoprotective or cytotoxic mechanism depending on the exposure dose and duration. The AgNP-induced oxidative stress and mitochondrial damages in the A549 and H1299 cells commonly trigger autophagy as a mechanism of adaptive cell survival, enabling the clearance of damaged organelles and the

minimization of cellular damage.[180] Protective autophagy is capable of inhibiting apoptotic cell death, consequently diminishing the therapeutic activity of AgNPs, especially at low or sublethal levels. Conversely, during elevated exposure or prolonged stress, overload or dysregulated autophagy can result in a cytotoxic outcome, leading to autophagic cell death. Thus, the balance between protective and destructive autophagy is considered a decisive factor influencing AgNP therapeutic effects, and protective autophagy represents a barrier that could limit the therapeutic effect of AgNPs.

6.5. AgNPs and MAPK pathway

Numerous studies have looked at how NPs affect the regulation of key components in different signaling pathways, highlighting their capacity to affect cellular processes linked to inflammation, stress response, and programmed cell death.[181,182] AgNP synthesis with sinigrin has been studied in relation to the regulation of critical components within different signaling pathways to highlight the pro-apoptotic effect associated with cytochrome *c* release; activation of caspases (-3, -6, and -8); and an increase in levels of p21, p53, and pro-apoptotic proteins, such as Bid, Bax, and Bak.[183] The authors suggest that apoptosis was induced by stress kinases p38 and JNK, which were activated by stressors, including cytokines, osmotic pressure and radiation. Both the kinases and NF-kB were upregulated in HeLa cells that were exposed to AgNPs, despite the combination with camptothecin. On the other hand, the activity of the Akt and the components of the Raf-MER-Erk signaling pathway were found to be reduced, which probably reduced the viability of tumor cells and promoted apoptosis *via* the downregulation of growth factor-related kinases.[184] Liu *et al.*[185] found comparable alterations in the phosphorylation levels of p38, JNK and Erk1/2 in U251 cells (human glioma). The introduction of the GSH antioxidant diminished the activation of these kinases, suggesting that the MAPK signaling pathways are activated through a ROS-mediated mechanism. Enhanced phosphorylation of Erk1/2 has also been reported to correlate with increased cell survival and proliferation, but Erk-mediated pathways have been reported to cause apoptosis.[186] These findings align with previous findings, demonstrating that AgNP treatment significantly downregulates Akt and Erk1/2 expression in human bladder cancer (T24) cells while promoting apoptosis through Erk-mediated signaling pathways.[187] Additionally, ROS triggered the p38 stress kinase in A549 cells, which in turn activated caspase-3;[188] likewise, in several tumor cell lines, such as MDA-MB-231, MCF-7, U251, and MO59K, there was an apparent rise in JNK phosphorylation, along with the increased expression of its direct downstream target, c-Jun. The genotoxic effects of AgNPs have been demonstrated by the increased accumulation of γ-H2AX, a known marker of DNA damage, as well as damage to telomeres. Following AgNP treatment, telomere alterations were noted, which coincided with a decrease in intracellular TRF2 levels, a crucial protector of telomeres, and a downregulation of hTERT, the enzyme telomerase's catalytic component.[189] The phosphorylation of DNA-PKcs, crucial for repairing DNA double-strand breaks, positively influences the expression of JNK. Inhibiting DNA-PKcs resulted in reduced phosphorylation and expression of DNA-PKcs, as well as decreased levels of both phosphorylated and total JNK, which ultimately affected tumor cell survival. These findings indicate that blocking DNA repair pathways, like those involving DNA-PKcs, may amplify the antiproliferative and cytotoxic effects of AgNPs on tumor cells.[190]

Mechanistic studies collectively demonstrate that AgNP-induced cytotoxicity in LC cells primarily arises from ROS generation, mitochondrial dysfunction, DNA damage, and activation of apoptotic signaling pathways, such as MAPK and p53-mediated responses. This exploits the inherent vulnerability of cancer cells to oxidative stress, thereby promoting selective cytotoxic effects relative to normal cells. Particle size, surface chemistry, and intracellular ion release play critical roles in modulating these biological responses. The cytotoxic effects of AgNPs in LC models occur *via* some distinct mechanisms. Through AgNPs, as opposed to other NMs, the release of Ag^+ ions is continuous and attaches to the thiol (-SH) groups of protein,[191] disrupting the antioxidant systems of glutathione and thioredoxin and enhancing oxidative stress.[145] Also, they have a redox-active surface that promotes the generation of ROS, which cause mitochondrial dysfunction, such as membrane potential loss and decreased ATP generation. The AgNPs also tend to accumulate in the lysosomes, resulting in their destabilization, leading to subsequent cell death pathways. All of these, *i.e.*, the constant Ag^+ release, thiol reactivity and the increased redox activity, characterize the unique cytotoxic signature of AgNPs in LC models. While numerous studies confirm these mechanisms in cultured LC cell lines, *in vivo* validation of these pathways remains limited, emphasizing the need for mechanistic studies in physiologically relevant tumor models. Despite the excellent potential of AgNPs as anticancer agents in the context of LC models, it has not been easy to translate the lab findings into actual clinical practices. With lower doses, their efficacy is likely to decrease, whereas with high doses, they may damage normal cells. The results obtained with A549 and BEAS-2B cells[192] indicate that AgNPs are not necessarily selective to tumors. Rather, they tend to cause a general oxidative stress and the dysfunction of lysosomes in cancerous and normal cells,[193] and this prompts concerns regarding unwanted side effects.

7. Silver-mediated combination therapies: enhancing anticancer efficacy through synergistic approaches

NM-based cancer therapy, comprising the combination of NMs with chemotherapeutic drugs, exhibits significantly improved therapeutic efficacy against cancer. In conventional chemotherapy, combination therapy appears to be a standard route to bypass cross-resistance and produce a synergistic therapeutic effect without noticeably increasing adverse toxicities. Among metallic NPs,

Table 2 Summary of various Ag-based multifunctional nanocomposites, along with their physicochemical properties, drug-loading efficiency, and cytotoxic activity against LC and cell lines

Nanocomposite	Chemotherapeutic agents	Size (nm)	% Drug loading	Lung cancer cell line	IC_{50} value ($\mu g\ mL^{-1}$)/nM	Toxicity to normal cell line IC_{50} value ($\mu g\ mL^{-1}$)	Treatment exposure time (hours)	Ref.
Ag-MTX	Methotrexate	13	28%, 31% and 40%	A549	23	—	48	195
Ag-PTX	Paclitaxel	24.36–58.77	—	A549	8.58 ± 0.34	WI-38 (56.07 ± 3.54)	48	196
Ag-Car	Carboplatin	30–40	—	A549	3.58	WI-38 (153.63 ± 3.56)	24	197
Ag-shikonin	Phytochemical naphthoquinone	20	—	A549	2.4 ± 0.11	—	24	198
DsAgN-5FU	5-Fluorouracil	8.32	25.9% ± 3.5%	A549	5	—	48	199
AgNP-RTX	Raltitrexed	20.4 ± 0.4	—	A549	1000 nM	—	72	200
ZnO@Ag	—	—	—	A549	—	—	48	201
ZnO@PDA@Ag	—	10–30	—	H1299	42.42 ± 4	—	48	202
CuO@Ag	—	—	—	A549	15	—	24	203
Fe_3O_4@SiO_2@PDA@Ag	—	10–30	—	H1299	21.52	—	48	204
Ag/Fe_3O_4	—	20–40	—	NCI-H661 NCI-H1975 NCI-H1573 NCI-H1563	183 176 169 125	HUVECs	48	205
In_2O_3@Ag	—	25.10	—	A549	18.01	IMR90 (>100)	24	206
Ag–CuO	—	—	—	A549	2.8 ± 0.05	—	24	207
Fe_3O_4@Alg–Ag	—	20–40	—	NCI-H1975 NCI-H1573 NCI-H1299	194 255 427	HUVECs	48	208
AgZnO	—	11	—	A549	15	BEAS-2B (>90)	24	209

like Zn, Au, Ag, Ti, Cu, and Mg, AgNPs are widely known for their biomedical applications, attributed to their antibacterial, anticancer, antiviral, anti-inflammatory and antifungal activities. However, AgNPs alone exhibit little antibacterial or anticancer effect compared to combination treatments. To avoid undesirable side effects, AgNPs must be taken in combination with an anticancer medication. Also, studies revealed that AgNPs have a well-established ability to improve other NPs' activity when used as a dopant.[194] Table 2 summarizes the studies of combinations of various drugs/NPs with Ag for treating LC effectively.

7.1. Silver combination with anti-LC drugs

AgNPs have been widely explored as carriers for small-molecule chemotherapeutics, where their high surface area and tunable surface chemistry enable efficient drug loading and controlled delivery. In such systems, AgNPs not only act as delivery platforms but also contribute to enhanced cytotoxicity through ROS-mediated mechanisms.

Methotrexate (MTX), a chemotherapeutic folic acid analog, is characterized by its short duration in the bloodstream and high cellular efflux rate, causing many restrictions on its clinical applications. A combination drug of Ag and MTX was synthesized by Rozalen *et al.*, and its anticancer activity against A549 cell lines was tested. The results demonstrate that the conjugation of MTX to AgNPs enhanced its therapeutic effect and thereby lowered the MTX effective dosages needed. However, there was no noticeable reduction in cell viability following treatment with AgNPs alone. Also, an *in vivo* zebrafish assay indicated that AgNP-MTX did not induce significant toxicity or malformations, suggesting a favorable safety profile for further therapeutic applications.[195] Paclitaxel (PTX) is one of the most potent anti-cancer drugs; however, its clinical applications are limited by poor aqueous solubility. Thus, a combination of AgNPs and PTX was prepared, exhibiting significantly enhanced anticancer activity compared to paclitaxel alone across various cancer cell lines, particularly showing an improved selective cytotoxic effect in A549 LC cells. Additionally, the study demonstrated that AgNP-PTX induced DNA fragmentation, leading to increased apoptosis in cancer cells compared to treatment with paclitaxel alone. Further, in the WI-38 healthy cells, low toxicity was observed, which indicates that AgNP-PTX can effectively minimize the side effects commonly associated with cancer therapies, making it a safer alternative for treatment.[196] To reduce the drug-related side effects of Carboplatin (Car), a study utilized AgNPs as a carrier for the drug. The synthesized AgNPs and carboplatin-loaded AgNPs (AgNPs-Car) show significant promise as candidates for treating human lung carcinoma. Interestingly, the combination induced DNA fragmentation and eventually increased the apoptosis of cells due to the release of Ag^+ ions and the formation of radical species, which disrupt critical cellular mechanisms.[197] The synergetic effect of shikonin, a phytochemical naphthoquinone isolated from the roots of the Chinese herbs '*Lithospermum erythrorhizon*' and AgNPs in A549 cells was studied, and they significantly inhibited cell viability and proliferation in A549 cells more effectively than individual components. In this study, Shikonin functioned as a stabilizing and reducing agent in AgNP synthesis, which may contribute to their anticancer properties. AgNPs' ability to liberate Ag^+ is facilitated by the acidic surroundings of cancerous cells, which intensifies their lethal effects on cancer cells in particular. Also, an *in vivo* study conducted on normal mice indicated that shikonin-AgNPs have a potential lung-targeting ability.[198] A novel multicomponent system was created, which uses Generation 5 (G5) PAMAM dendrimers to deliver both AgNPs and the hydrophobic anticancer drug 5-fluorouracil (5-FU) to cancer cells. The combination of 5-FU

and dendrimer-stabilized silver nanoparticles (DsAg NPs) exhibited a synergistic effect in inhibiting the growth of A549, suggesting that this nanocomposite can enhance the anticancer effects compared to using 5-FU alone.[199] Another study demonstrated that covalently attaching Raltitrexed (RTX) to AgNPs produces a synergistic therapeutic effect, where the antifolate activity of the drug and the intrinsic ROS-generating properties of AgNPs jointly enhance cytotoxicity. This direct drug-NP conjugation achieved substantially better anticancer efficacy than the free drug alone.[200]

Overall, these studies frequently report enhanced cytotoxicity and apoptosis in LC cell lines. While these findings suggest potential synergistic effects through mechanisms such as ROS amplification and improved intracellular drug delivery, most investigations remain restricted to single-cell-line models and short-term *in vitro* assays. Robust pharmacokinetic analysis, reproducibility across multiple tumor models, and comprehensive toxicity assessments are still largely absent. Consequently, the current evidence supports the potential of AgNP-based drug combinations but remains insufficient to establish clear translational advantages. Despite enhanced activity, the contribution of Ag *versus* that of the host material is often not systematically distinguished, and toxicity toward normal cells remains underexplored.

7.2. Silver-doped metal oxide combination action on LC treatment

The enhancement and synergistic effects resulting from Ag doping in other NPs have been extensively investigated by various researchers. The Ag-doped ZnO system has been the most extensively studied due to its inherent biocompatibility and superior photocatalytic behavior. Studies by A. Ullah *et al.*[201] showed that Ag doping significantly influences the structural and optical properties of ZnO NMs. Low-level doping (0.3 wt%) significantly enhanced ZnO's anticancer activity against A459 cells, achieving 72.86% inhibition. This improvement can be attributed to the increased production of ROS *via* charge separation, the electrostatic attraction between Ag^{+} and Zn^{2+} ions and negatively charged cancer cell membranes, and the improved crystallinity that facilitates electron-transfer processes.

At high doping concentrations (0.6 wt%), the activity decreased due to structural distortion, indicating the need for an optimal Ag concentration for synergy.[201] A similar work reported the successful synthesis of a novel ZnO@PDA@Ag nanocomposite, where Ag-doped polydopamine (PDA)-coated ZnO produced strong cytotoxicity against H1299 cells (IC_{50} = 42.42 ± 4 μg mL^{-1}) with high biocompatibility, highlighting the combined benefits of Ag doping and PDA-mediated stabilization.[202] In a CuO system synthesized *via* green routes, Ag doping amplified anticancer efficiency by doubling the cytotoxic effect compared to undoped CuO. The 20% Ag-doped CuO NPs triggered 50% cell death at only 15 μg mL^{-1}, attributed primarily to ROS overproduction and the disruption of mitochondrial function. The synergy arises because Ag enhances electron transport, while CuO contributes intrinsic oxidative stress, forming a potent dual-metal oxidative assault on cancer cells.[203]

7.3. Ag-doped magnetic and hybrid combination action on LC treatment

Ag doping also significantly enhances the therapeutic value of magnetic NPs, like Fe_3O_4. The Fe_3O_4@SiO_2@PDA@Ag nanocomposite induced pronounced apoptosis in H1299 cells (IC_{50} = 21.52 μg mL^{-1}), demonstrating how Ag's surface reactivity complements Fe_3O_4 magnetic guidance while maintaining biocompatibility (Fig. 9a).[204] Similarly, the Ag–Fe_3O_4 nanocomposite prepared using *Mentha* extract as a reducing and stabilizing agent displayed strong cytotoxic effects against multiple LC cell lines, NCI-H661, NCI-H1975, NCI-H1573, and NCIH1563 (IC_{50} values: 183, 176, 169, and 125 μg mL^{-1}, respectively).[205] The presence of Ag protected Fe_3O_4 from oxidation and provided additional ROS-mediating sites, contributing to selective cancer targeting.[170] The photodeposition of Ag-doped In_2O_3 NPs achieved a pronounced dose–response increase in anticancer performance. The addition of Ag from 2% to 6% resulted in a drastic decrease in the values of IC_{50} against A549 cells to 75.81 and 18.01 μg mL^{-1}, respectively, in pure In_2O_3 and 6% Ag doped In_2O_3. The enhancement is due to an increased crystallinity, better electron–hole separation and more oxidative radicals. The overall impact of these changes resulted in the oxidative damage of cancer cells, with no effect observed on the biocompatibility of good to normal IMR90 fibroblasts.[206] Bimetallic and hybrid systems also benefit greatly from Ag incorporation. The hybrid silver–copper nanocomposite (Ag–CuO NCs) synthesized with *Ocimum americanum L.* extract exhibited potent antiproliferative activity against A549 cells (IC_{50} = 2.8 ± 0.05 μg mL^{-1}), inducing apoptosis and cell-cycle arrest at the G0/G1 phase (Fig. 9c).[207] Similarly, alginate-modified Fe_3O_4 decorated with Ag (Fig. 9b) displayed strong cytotoxic effects against NCI-H1975, NCI-H1563, and NCI-H1299 LC cells while sparing normal HUVECs, indicating selective toxicity aided by Ag's interaction with malignant cell membranes.[208] Bimetallic AgZnO NPs formed using *Salvia officinalis* extract further confirmed the synergetic action. The combination of Ag and ZnO produced significantly better anticancer activity than AgNPs alone, while the plant-derived capping provided biocompatibility with BEAS-2B normal cells. The bimetallic structure enhanced apoptosis and inhibited the migration of A549 cells.[209]

The above-discussed studies demonstrated the enhanced anticancer activity of AgNPs against LC cells through synergistic mechanisms, such as increased ROS generation and oxidative stress. While several studies report the improved cytotoxicity and selectivity of AgNPs compared with single-component NPs, most of the results are derived from *in vitro* models and vary considerably based on differences in synthesis methods, NP composition, and experimental conditions. Consequently, although these hybrid systems show promising therapeutic potential, further mechanistic studies, standardized characterization, and comprehensive *in vivo* investigations are necessary to confirm their reproducibility and translational relevance.

The hybrid and drug-combination systems summarized in Table 2 above highlight the increasing interest in utilizing AgNPs as multifunctional platforms for synergistic LC therapy. In these reported studies, integrating AgNPs with chemotherapeutic

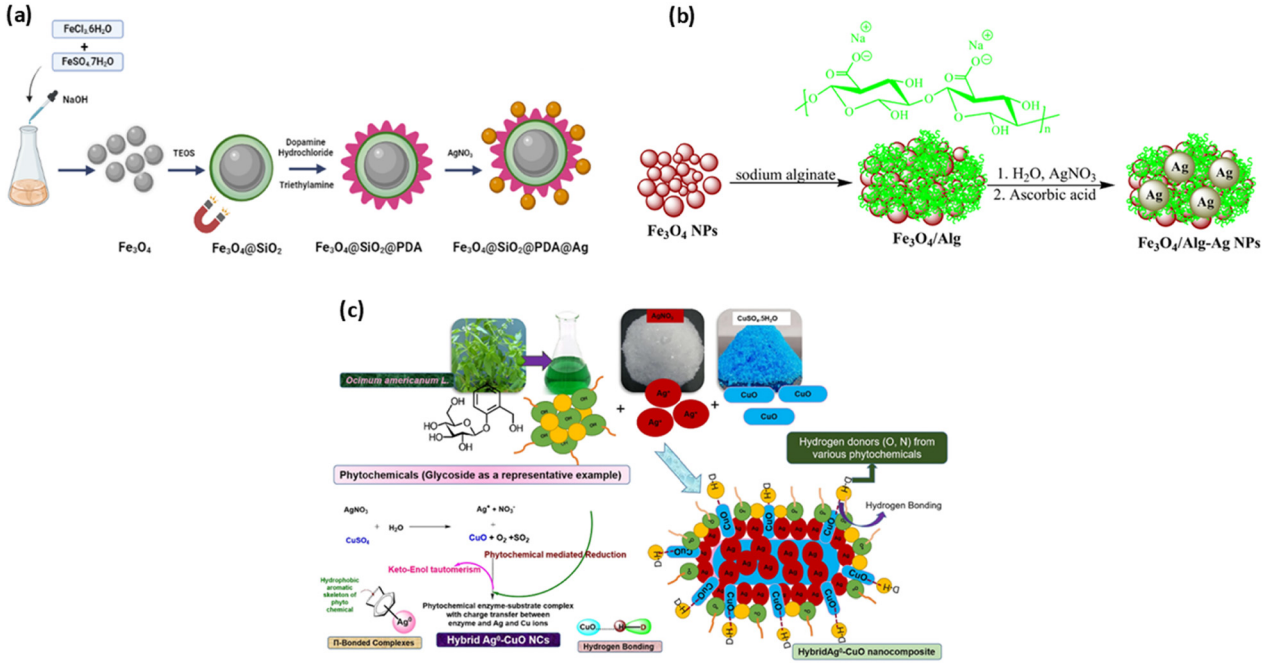

Fig. 9 Synthesis of Ag-doped nanocomposites: (a) Fe_3O_4@SiO_2@PDA@Ag nanocomposite, reproduced from ref. 204, with permission from Taylor and Francis, copyright 2024; (b) Fe_3O_4@Alg–Ag nanocomposite, reproduced from ref. 208, with permission from Elsevier, copyright 2022; and (c) Ag–CuO nanocomposite, reproduced from ref. 207, with permission from Elsevier, copyright 2023.

agents or secondary NMs enhances anticancer efficacy by improving drug delivery, increasing cellular uptake, and amplifying ROS-mediated apoptotic signaling in LC cells. Despite these promising outcomes, several methodological limitations persist. Most investigations assess therapeutic efficacy using a limited number of LC cell lines, predominantly A549 or H1299, without evaluating performance across a broader range of genetically diverse LC models. Furthermore, normal lung epithelial controls are not consistently included, which restricts the clear assessment of cancer selectivity and potential off-target toxicity. In addition, relatively high NP or drug concentrations are frequently used to demonstrate synergistic effects, raising concerns about the clinical relevance of the reported doses. Importantly, only a small proportion of hybrid AgNP systems have been validated in animal tumor models, and comprehensive studies addressing pharmacokinetics, biodistribution, and long-term toxicity remain scarce. Collectively, these limitations emphasize the need for more standardized experimental frameworks, clinically relevant dosing strategies, and rigorous *in vivo* validation to advance Ag-based hybrid nanoplatforms toward translational application.

8. Clinically approved nanoformulations and early clinical investigations of AgNPs

Several nanomedicine formulations have successfully reached the clinical stages, demonstrating the translational potential of NP-based therapies for cancer treatment. Among the FDA-approved nanodrugs, Doxil (liposomal doxorubicin) was the first nanocarrier system approved for ovarian cancer and Kaposi's sarcoma, followed by 'Abraxane' (albumin-bound paclitaxel) for breast and LC, and 'Onivyde' (liposomal irinotecan) for pancreatic cancer. Additionally, Vyxeos (liposomal daunorubicin/cytarabine) represents a successful example of combination nanotherapy with synchronized drug delivery, used to treat specific types of acute myeloid leukemia (AML) in adults and children.[210,211] These formulations exhibit improved pharmacokinetic profiles, enhanced tumor accumulation through the EPR effect, and reduced systemic toxicity compared to their conventional counterparts.

While most of the studies on AgNPs remain at the preclinical stage, recent work has begun to highlight translational efforts specific to Ag-based nanomedicines. A recent review of the clinical translation landscape of AgNPs notes that although Ag-nano constructs have been extensively investigated *in vitro* and *in vivo*, therapeutic clinical trials for cancer applications are still extremely limited. For example, most clinical studies to date have involved topical or antimicrobial use of AgNPs rather than systemic administration for oncology.[212,213] Preclinical studies demonstrate promising anticancer activity; for instance, AgNPs show selective cytotoxicity in aggressive cancers, such as triple-negative breast cancer and lung carcinoma cell lines.[214] However, no registered Phase III clinical trial has been reported for AgNPs in LC therapy. This gap underscores the urgent need to connect the design of AgNP-based systems (*e.g.*, size control, surface functionalization, drug loading) with realistic clinical endpoints, safety profiles, manufacturing scalability, and regulatory pathways.

9. Toxicity, challenges and future directions

In LC, AgNPs have demonstrated the ability to induce cancer cell death, but their therapeutic utility is limited by their toxicity, particularly within the highly sensitive pulmonary environment.[215,216] The respiratory system is highly sensitive to inhaled NPs due to its extensive surface area and thin alveolar-capillary barriers. Achieving targeted delivery through inhalation routes remains difficult. In some studies, AgNPs reportedly caused acute and chronic pulmonary inflammation, pulmonary edema, alveolar wall thickening and fibrosis.[75,217] Although AgNPs show promising anticancer effects against LC in preclinical models, physiological and toxicological issues pose significant barriers to their clinical application.

9.1. Non-specific pulmonary toxicity

Despite the claims of selective toxicity toward cancer cells, another aspect of AgNPs is their detrimental impact on normal pulmonary epithelium and macrophages, activated by oxidative stress and mitochondrial damage, which is evidence of prominent non-selective cytotoxicity.[70,218] Extended exposure triggers fibrotic reactions and inflammatory cytokines (IL-6, TNF-α), suggesting substantial non-specific damage.[219] Future studies should focus on improving the selectivity of AgNPs towards tumor cells by incorporating tumor-targeting ligands and biocompatible surface coatings, such as polyethylene glycol or albumin. Additionally, systematic comparisons between LC cells and normal lung epithelial cells should be performed to better define therapeutic windows and minimize off-target toxicity.

9.2. Biodistribution and Ag^+-ion fate

The physicochemical characteristics of AgNPs, such as size, morphology, agglomeration behavior, and surface charges, also affect their biological interaction, making reproducibility and dose optimization difficult.[220] Their small size permits them to penetrate deep into the alveolar areas, where they can aggregate and produce genotoxic effects, such as DNA strand breaks and chromosomal abnormalities.[215] Past studies have demonstrated the fact that AgNPs have a low clearance rate and are capable of being stored in extrapulmonary organs, such as kidneys, spleen, and liver, among other organs, which raises the issue of longevity and systemic toxicity after lung delivery.[221,222] Such persistence may also raise the question of their ability to induce resistance mechanisms in tumor cells and also their interaction with other drugs that are co-administered or with biological molecules. Poor knowledge of their metabolism, excretion, and the biological fate of released Ag^+ ions further complicates safety studies and long-term toxicological evaluation.[223] Chronic exposure to Ag compounds causes risk known as 'argyria', characterized by permanent blue-gray pigmentation of the skin and eyes. Future research should, therefore, prioritize comprehensive pharmacokinetic and biodistribution studies, including quantitative tracking of Ag^+ ions, to better understand NP metabolism, clearance mechanisms, and potential systemic toxicity.

9.3. Interspecies differences in preclinical models

Differences in the murine and human lung structures and the clearance mechanisms reduce the precision of using *in vivo* findings for human predictions. The lack of extensive pharmacokinetic and biodistribution information, species-specific metabolism, and information on what happens to Ag^+ ions all contribute to impeding the clinical translation. Hence, humanized lung models and specific drug regimens need to be developed to ensure selective delivery, clearance assurance, and safety of future therapy interventions.[224]

9.4. Scale-up and batch variability

In addition to such biological constraints, the scalability and reproducibility of NP synthesis represent other significant hindrances to clinical translation. Techniques optimized in the laboratory may not be reproducible at large scale in terms of uniform morphology and functionalization, and this can cause changes in biological activity and safety. Also, as the cost of large-scale manufacturing is high and no standardized regulatory frameworks and manufacturing protocols exist, implementing quality assurance, risk assessment, and approval procedures for AgNP-based formulations is difficult.[225,226] Future work should, therefore, focus on developing scalable and reproducible NP synthesis strategies, along with standardized characterization protocols to ensure consistent physicochemical properties across production batches.

9.5. Regulatory considerations and future strategies

The absence of standardized regulatory frameworks for NMs further complicates the clinical translation of AgNP-based formulations. High production costs, limited manufacturing guidelines, and insufficient long-term safety data pose significant challenges for regulatory approval.[227] To overcome these barriers, future studies should emphasize internationally standardized toxicity testing protocols, detailed NP characterization, and long-term *in vivo* safety studies. Additionally, strategies, such as controlled release systems for regulated Ag^+ ion delivery, green synthesis approaches, and targeted functionalization, may help reduce toxicity while enhancing therapeutic efficacy. These efforts will be essential to advance AgNP-based nanotherapeutics from experimental research to safe and effective clinical applications for LC treatment.

10. Conclusions

AgNPs are extremely versatile multi-functional platforms that have considerable potential to transform LC nanotherapy due to their outstanding physicochemical properties, including their tunable size and morphology, optimal surface charge, easy functionalization and enhanced anticancer effect. This review highlights the critical role of the synthesis procedures and characterization techniques that enable the accurate

regulation of the morphology and surface functionality of AgNPs, which in turn govern their biocompatibility, solubility, cellular uptake, and biodistribution in LC-targeted nano therapies. AgNPs enter LC cells through passive diffusion or receptor-mediated endocytosis, where they elevate ROS and cause mitochondrial dysfunction, ER stress, and intrinsic apoptosis. Prolonged damage triggers autophagy and G2/M transition arrest governed by p53/p21, which eventually results in apoptosis or necrosis of cancerous cells under extreme stress. In addition, AgNPs demonstrate a strong synergistic effect with established chemotherapeutic agents, natural products, and other NMs, minimizing the adverse side effects without disrupting or preventing the anticancer activity; this makes them the best candidate for use in multifunctional cancer therapeutics. Although AgNPs have the potential to be therapeutically beneficial, they also have extensive off-target effects on normal pulmonary epithelial and immune cells, which pose a major translational barrier. Therefore, several key priorities must be addressed to advance AgNP-based nanotherapeutics towards clinical application. The development and adoption of physiologically relevant *in vitro* lung models, such as air–liquid interface cultures, organoids, and lung-on-chip systems, are essential for more accurate evaluation of efficacy and toxicity. Standardized toxicological and pharmacokinetic frameworks are needed to enable reliable comparison across studies and to better understand biodistribution, clearance, and long-term safety. The establishment of rational design principles balancing therapeutic efficacy with controlled Ag^{+}-ion release and minimized off-target effects will be critical for optimizing the NP performance. Additionally, greater emphasis should be placed on clinically relevant delivery strategies, particularly inhalation-based approaches, to ensure effective and targeted drug deposition in lung tissues. Addressing these priorities will be crucial for bridging the gap between experimental studies and the safe, effective clinical translation of AgNP-based formulations for LC treatment.

Conflicts of interest

The authors declare no conflicts of interest.

Abbreviations

5-FU	5-Fluorouracil
A2780	Ovarian cancer cell line
A549	Human lung adenocarcinoma cells
Abs	Antibodies
AC	*A. calamus* L.
ACC1	Acetyl-CoA carboxylase1
ACE 2	Angiotensin-converting enzyme 2
AFM	Atomic force microscopy
Ag	Silver
AgNPs	Silver nanoparticles
AML	Acute myeloid leukemia
AMPK	AMP-activated protein kinase
Au	Gold
BEAS-2B	Human non-tumorigenic lung epithelial cells
Bp	*Bidens pilosa*
CAPIR	Circulation, accumulation, penetration, internalization, and release
Car	Carboplatin
CIE	Clathrin-independent endocytosis
CIS	Cisplatin
CME	Clathrin-mediated endocytosis
CMT	Camptothecin
COX-2	Cyclooxygenase-2
CS	Chitosan
CuO	Copper oxide nanoparticles
CUR	Curcumin
CVM	Caveolin-mediated endocytosis
DNA PKcs	DNA-dependent protein kinases
DS	*D. sissoo*
ECM	Extra cellular matrix
Fe_3O_4	Ferrite nanoparticles
GLOBOCAN	Global cancer observatory
HS-PEG2K-NH_2	Thiol polyethylene glycol amine
HUVECs	Human umbilical vein endothelial cells
IC_{50}	Half-maximal inhibitory concentration
IMR90	Normal human lung fibroblasts
In_2O_3	Indium oxide
INH	Isonicotinic acid hydrazide
JNK	c-Jun N-terminal kinase
L132	Human embryonic lung epithelial cell line
L929	Adherent type of mouse fibroblast cell line
LC	Lung cancer
LC3	Microtubule associated protein
LK-2	Lung squamous carcinoma
MAPK	Mitogen-activated protein kinase
MPS	Mononuclear phagocyte system
mTOR	Mammalian target of rapamycin
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide
MTX	Methotrexate
MVBs	Multivesicular bodies
NCPA	*N*-Cholyl D-penicillamine
NF-κb	Nuclear factor-Kappa B
NMs	Nanomaterials
NPs	Nanoparticles
NSCLC	Non-small cell lung cancer
PB	*Piper betle*
PDA	Polydopamine
PLGA	Poly lactic-*co*-glycolic acid
Pt	Platinum
PTX	Paclitaxel
PVP	Polyvinylpyrrolidone
RME	Receptor-mediated endocytosis
ROS	Reactive oxygen species
RTX	Raltitrexed
S6K	Ribosomal protein S6 kinase beta-1
SCLC	Small cell lung cancer
SCRBD	SARS-CoV-2 receptor binding domain

SEM	Scanning electron microscopy
SER	Smooth endoplasmic reticulum
SPR	Surface plasmon resonance
SQSTM1	Sequestosome 1
TEM	Transmission electron microscopy
TiO_2	Titanium dioxide
TMC	*N*,*N*,*N*-Trimethyl chitosan chloride
TME	Tumor microenvironment
WI 38	Normal lung cell
ZnO	Zinc oxide

Data availability

The authors declare that the data supporting the findings of this study, including the newly generated figures and tables, are available within the article. Additional datasets are available from the corresponding author upon reasonable request.

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