Endocytosis pathway of mesoporous silica versus silver nanoparticles: a comparative review for targeted therapeutics

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Endocytosis is a critical cellular process for the internalization of nanoparticles (NPs), which play a vital role in clinical and biomedical applications such as targeted drug delivery, gene therapy, and diagnostics. In this review, a comprehensive comparison is made between the endocytosis mechanisms of two types of nanoparticles widely used in many applications: the first is mesoporous silica nanoparticles (MSNs), and the second one is silver nanoparticles (AgNPs). MSNs have the characteristics of high surface area, and tunability of the surface properties, and are also safe and tissue-compatible, making them suitable for targeted drug delivery. The primary endocytosis mechanism is by receptor-mediated endocytosis, as clathrin- and caveolae-mediated pathways. On the other hand, AgNPs, known for their antibacterial and anti-malignant properties, are, through a combination of clathrin-mediated endocytosis and macropinocytosis. With clear therapeutic potential, AgNPs show cytotoxicity due to silver ion release and generation of reactive oxygen species (ROS). This review highlights how particle shape, size, surface charge, and surface functionalization affect the uptake mechanisms and intracellular fate of these NPs. Also, the impact of NPs properties on toxicity, interaction, and targeted drug delivery efficiency is clarified. Understanding those factors is important for optimizing NPs design and supporting their applications in diagnostics and nanomedicine. This review concludes that MSNs have superior properties for drug delivery and low toxicity levels while the AgNPs have potent effects on cancer therapeutics and antimicrobial use.

Keywords: Endocytosis, mesoporous silica nanoparticles, silver nanoparticles, targeted therapeutic, drug delivery

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INTRODUCTION

Endocytosis is a crucial cellular process in which cells internalize extracellular materials, including (NPs), by invaginating the plasma membrane to form intracellular vesicles [1]. The endocytosis mechanism plays an important role in nutrient regulations and cellular uptake, receptor recycling, and cell responses to external factors. With improvements in nanotechnology, understanding the mechanisms of endocytosis has become widely important for diagnostics and therapeutics applications for example targeted drug delivery, and gene therapy, [2][3][4].NPs, have small size and tunable surface properties, and mimic biological structures, making them ideal for cellular interaction research and targeted therapeutic applications [5][6]. The pathway by which NPs are entering the cell significantly affects their intracellular fate, cell biological functions, and biotherapeutics efficiency [7][8]. Endocytic pathways are under the category of clathrin-mediated endocytosis (CME), caveolae-mediated endocytosis, macropinocytosis, clathrin, and caveolae are independent pathways [9]. The pathways have a specific process of vesicle formation and specialized transportation pathways inside each cell [10]. The particle's physical characteristics such as the shape, size, surface charge, and functionalization of NPs greatly affect the cellular uptake mechanisms [11][12]. For instance, positively charged NPs undergo enhanced cellular uptake due to electrostatic interactions with the negatively charged cell membrane [13]. Also, the particle size plays an important role in selectively choosing which NPs are internalized through clathrin-coated pits or macropinocytosis [14]. Understanding these interactions is critically important for designing NPs with tailor-made biological responses. NPs based drug delivery systems often exploit specific endocytic pathways to achieve the targeted cell delivery, minimize off-target effects, and improve therapeutic efficiency [15]. Studies have demonstrated that changing the surface chemistry of NPs and directing them toward a specific endocytic pathway, the precision and delivery efficacy [16]. Studying intracellular trafficking and fate, including intra-cellular degradation, exocytosis, and interactions with different intracellular targets, is very important for optimizing nanomedicine strategies [7]. This comprehensive investigation into NPs endocytosis highlights the importance of the cellular uptake mechanisms to improve the design and development of effective NPs based therapeutics [15].

OVERVIEW

Endocytosis is a vital process by which NPs enter the cells to perform different and specific functions, which may include targeted drug delivery and diagnostic imaging while using contrast media. MSNs and AgNPs are two widely used types of NPs due to

their easy formation and applicable changes of their chemical and physical properties. MSNs have a porous structure, which offers high surface area also tunability for controlled drug delivery such as slow release, while AgNPs are known for their strong antimicrobial and anticancer properties [17][18]. Both types of NPs can be internalized into cells through different endocytosis processes, the mechanisms and efficiency of uptake can greatly vary between them which affects the choice decision between the two types. The internalization of MSNs occurs via receptor-mediated endocytosis, such as clathrin or caveolae-mediated pathways, affected by their surface modifications [19]. On the other hand, AgNPs usually enter cells through a combination of clathrin-mediated endocytosis and macropinocytosis, with their size and surface charge playing a crucial role [20]. While MSNs are generally considered cell-safe, tissue biocompatible, and biodegradable and could be safely excreted, AgNPs can exhibit cell toxicity due to the release of the silver ions, which generate a reactive oxygen species (ROS) and damage the cellular structures [21]. Understanding the differences in endocytosis mechanisms between MSNs and AgNPs is critically important for optimizing their design and improving their effectiveness in different aims in biomedical applications [19].

THE DIFFERENT FACTORS AFFECTING THE ENDOCYTOSIS MECHANISMS OF MSNS AND AGNPS

The particle structure and surface properties and its effect on endocytosis

Particle properties of MSNs MSNs are characterized by a very high surface area, porosity, and tunable surface properties. These properties allow for functionalization with different ligands or polymers, enhancing their interactions with specific cellular receptors [22]. MSNs are in general neutral or have slight negative charge, which affects their interaction with the cell membrane and affects the cellular uptake efficiency [23].

Particle properties of AgNPs Are spherical in shape and have a great antimicrobial property. They can be modified with the use of many surface coatings to enhance their stability and prevent agglomeration [24]. AgNPs may be differently charged (negative or positive), and the surface charge acts as a key role in their interaction with cell membranes and cellular uptake [25].

Cell entry Pathways and trafficking

Cell entry pathway of MSNs MSNs is primarily internalized through receptor-mediated endocytosis mechanisms. The two main mechanisms are clathrin-mediated endocytosis, caveolae-mediated endocytosis, and phagocytosis [17]. Changing the surface properties by modifying with a surface coating such as polyethylene glycol (PEG) coating or targeting ligands enhances the specificity and regulates the rate of internalization into the cells. For example, PEG surface-coated NPs can prevent opsonization and extend circulatatory time in vivo [18].

The cell entry pathway of AgNPs AgNPs enter the cells through a combination of different endocytotic pathways, which include clathrin-mediated endocytosis, caveolae-mediated endocytosis, and macropinocytosis [19]. AgNPs' surface charge and small particle size often allow for easy cellular entry, also the uptake is affected by the type of the cell or the presence of different extracellular proteins such as the protein corona [20].

The effect of the size and shape of the particles on the cellular uptake

Size and shape effect of MSNs uptake The size of MSNs greatly affects their cellular uptake, with smaller NPs less than 100 nm exhibiting more efficient endocytosis [21]. The shape of MSNs such as spherical or rod-like can also affect the internalization process and the cellular uptake efficiency, with the elongated particles having less uptake efficiency than spherical particles [22].

Size and shape effect of AgNPs uptake The size and shape of AgNPs are very important for the determination of their cellular uptake as well. The Smaller the AgNPs the more likely to be caught up by the cells, while the larger particles may need different uptake mechanisms [23]. The surface-to-volume ratio of AgNPs also affects their reactivity and interaction with the cell membrane [24].

Cellular Interaction and Toxicity

Toxicity of MSNs MSNs are in general considered biocompatible and less likely to have toxic effects when compared to to AgNPs. MSNs porous structure allows the controlled release of loaded drugs or other bioactive agents, which reduces the risk of cytotoxicity [25]. However, when large amounts are internalized into the cell, or if the surface properties are not properly tuned, MSNs can still cause cell stress and are not safe [26].

Toxicity of AgNPs The endocytosis process of AgNPs is associated with the release of silver ions Ag+, which cause toxicity by the generation of reactive oxygen species (ROS) and the induction of oxidative stress in

the cells [27]. AgNPs toxicity is a great concern, especially on long-term use and exposure, the release of silver ions can damage cellular components, including DNA, proteins, and lipids [28]. But we still need that toxicity when dealing with killing cancer cells or microbial infections.

Endosomal escape and drug delivery

Endosomal escape it and drug delivery by MSNs Escape from the endosomes after cell entry is a great advantage of MSNs in drug delivery. This allows for the release of the encapsulated drugs into the cytoplasm, greatly enhancing the therapeutic outcomes [29]. Undertaken surface modifications, such as the use of pH-sensitive or thermal-responsive surface coatings, could facilitate endosomal escape [30].

Endosomal escape and drug delivery by AgNPs AgNPs are not suitable for carrying drugs or therapeutic agents. AgNPs primary function in medicine is usually for antimicrobial or anticancer uses [31]. But still, many studies have suggested that AgNPs can also be used for targeted drug delivery, where the particles can release silver ions inside the cell to induce cytotoxicity and planned cell death [32] (Figure 1).

Biological Implications for MSNs and AgNPs

MSNs implications MSNs are widely studied for their use in drug delivery and imaging. Their tunable properties make them highly versatile and manipulative, allowing for targeted therapy, reduced systemic toxicity, and controlled drug release [34]. Their biocompatibility and ability to be biodegraded in vivo make them the most suitable for clinical use.

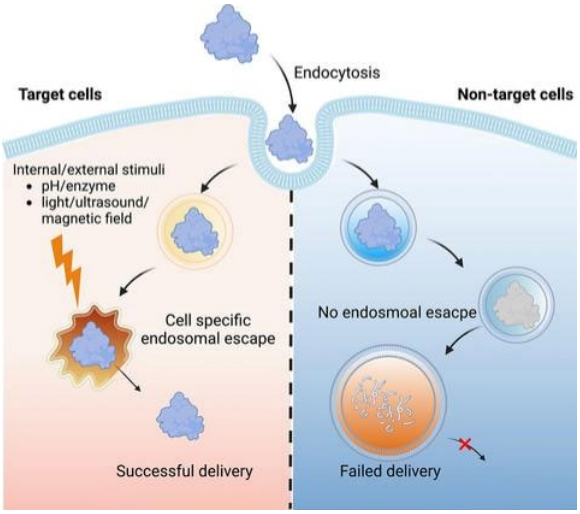

Figure 1 Shows the endosomal escape and non-endosomal escape endocytosis process cited from reference [33].

AgNPs implications AgNPs, on the other hand, have significant anticancer and antimicrobial power, but their cytotoxicity limits their widespread in biomedical application. The potential for Ag^{+} ion release and oxidative damage makes a great risk for healthy cells [35]. Furthermore, much research has been focused on minimizing toxicity while enhancing the benefits and therapeutic effects of AgNPs [36].

TARGETED THERAPEUTICS OF MSNS

MSNs have promising features for targeted drug delivery due to their unique structure and multifunctional properties, including a high surface area, tunable pore size, large pore volume, and easy surface modification. MSNs' framework can be encapsulated with a variety of therapeutic agents, for example, small molecule drugs, peptides, and nucleic acids, for controlled drug release [34] (Table 1).

Mechanism of Action

Drugs are loaded into the mesopores of MSNs by diffusion or using covalent bonding. The porous network provides wide spaces for drug loading. MSNs are functionalized with targeting ligands such as antibodies, peptides, folic acid, or aptamers to recognize and bind specific cell receptors on the targeted cell, such as cancer cells [36]. MSNs enter cells primarily through endocytosis Pathways such as (clathrin-mediated, caveolae-mediated, or macropinocytosis) [37]. The release of the drug may be different with different stimuli and different cell responses as MSNs can be engineered to respond to stimuli like changes in PH, redox conditions, enzyme release, and change in temperature. In cancer treatment, pH-responsive MSNs release drugs in an acidic tumor environment while remaining stable at neutral pH [38]. Functionalization with fusogenic peptides or pH-sensitive polymers helps MSNs to escape the endosome preventing degradation of the drug cargo [39]. Once inside the cytoplasm, the encapsulated drugs are released to exert their therapeutic effects, such as inducing cancer cell apoptosis or inhibiting tumor growth (Figure 2).

Clinical applications

Cancer therapy uses MSNs to deliver chemotherapeutic agents targeting only tumor cells, enhancing efficacy and reducing the systemic toxicity of the chemotherapy [41]. Also, Gene therapy by MSNs encapsulates and delivers the siRNA or DNA for gene silencing and expression regulation and modulation [42][43]. Antibiotics and antimicrobial therapy have a great concern that MSNs can release

Table 1 Comparison of Endocytosis for Silver Nanoparticles vs Mesoporous Nano Silica

Feature	(AgNPs)	(MSNs)
Structure	Solid metallic NPs	Porous silica framework with a high surface area
Size Range	1-100 nm	50-300 nm (commonly used)
Surface Properties	Reactive, can be functionalized	Chemically modifiable, hydrophilic, or hydrophobic depending on surface modification
Surface Charge	Typically, negative or positive, dependent on coatings (e.g., citrate, PVP)	Generally negative but tunable through surface modification
Endocytosis Pathways	Clathrin-mediated, caveolae-mediated, macropinocytosis	Clathrin-mediated, caveolae-mediated, phagocytosis
Cellular Uptake Efficiency	High, dependent on size and coating	Moderate to high, dependent on pore size and surface properties
Biocompatibility	Can be cytotoxic and induce oxidative stress	Generally biocompatible, low toxicity without functionalization
Degradation	Slow or non-degradable	Biodegradable under physiological conditions
Intracellular Fate	Accumulates in lysosomes, potential for long-term cellular retention	Degrades into biocompatible silica over time
Drug Delivery Potential	Limited due to lack of porosity; used mainly for antimicrobial effects	High due to mesoporous structure allowing high drug loading
Toxicity Concerns	High, induces reactive oxygen species (ROS) and genotoxicity	Low toxicity but dependent on surface functionalization and dose
Applications	Antimicrobial agents, biosensors, imaging	Drug delivery, gene delivery, biosensors, imaging
Endosomal Escape	Challenging, limited by NPs rigidity	Enhanced potential with functionalization (e.g., pH-responsive coatings)

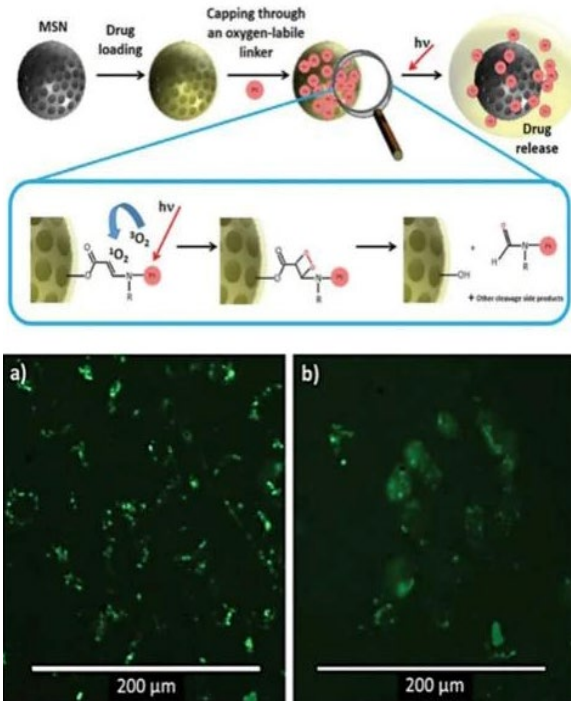

Figure 2. (A) Schematic representation of MSNs engineered for endosomal escape by reactive oxygen species (ROS). A visible light-sensitive porphyrin is grafted to the surface through a ROS-responsive linker that is cleaved when upon light irradiation, triggering endosomal escape and drug release. (B) Calcein assay for assessing endosomal escape: Calcein is a membrane-impermeable dye that is unable to cross the lipid bilayer of the endo-lysosomes in the dark. When light is applied, ROS generated destabilizes the membrane, and calcein diffuses into the cytoplasm [40].

antibiotics in a controlled way to the targeted bacterial infections [44][45]. The combination therapy and diagnostic Codelivery of drugs and contrast agents allows both therapy and diagnostics (theranostics) [46][47]. Despite their potential, challenges such as long-term safety, biodistribution, excretion, and clearance need further investigations to ensure clinical viability.

TARGETED THERAPEUTICS PROPERTIES OF AGNPS

AgNPs are increasingly explored for targeted therapeutic applications due to their unique physicochemical properties, such as a large surface-to-volume ratio, high stability, and easy functionalization. These properties make AgNPs available to deliver therapeutic agents effectively while minimizing out-of-target effects [48].

Mechanism of Action

AgNPs can be loaded with therapeutic agents such as anticancer drugs, antibiotics, or even genetic materials. Surface modifications include attaching targeting ligands such as antibodies, peptides, or folic acid to improve specificity toward the target cells [49]. The uptake of AgNPs is taken up by cells primarily through endocytosis mechanisms, such as clathrin-mediated, caveolae-mediated, and macropinocytosis. The uptake efficiency depends on the size, surface charge, and surface coating of the NPs [50]. Targeting Specificity Functionalized AgNPs can be directed to specific cells by recognizing the over-expressed receptors or biomarkers, such as those found in tumor

cells or on bacteria [51] release of reactive oxygen species (ROS) once inside the cell, AgNPs generate reactive oxygen species (ROS), which induce oxidative stress triggering cell apoptosis. This mechanism is useful in cancer therapy, in that AgNPs are used to selectively attack tumor cells [52]. Endosomal escape of AgNPs as it can escape the endosomal level after internalization by alteration of pH, ensuring that the therapeutic cargo is released inside the cytoplasm. This mechanism is enhanced when NPs coated with pH-sensitive polymers [53]. Therapeutic action after internalization is that the AgNPs either release their drug cargo in a controlled way or interact with a cellular component to exert antimicrobial or anticancer effect. In antimicrobial therapy, AgNPs act by disrupting the bacterial cell membrane and causing bacterial cell death [54][55].

Clinical applications

In cancer therapy AgNPs are used to deliver chemotherapeutics, targeting cancer cells and reducing side effects by avoiding healthy tissue [56]. Also, in antimicrobial therapy, the AgNPs have potent antibacterial, antifungal, and antiviral effects. They disrupt microbial cell walls, leading to microbial death [57]. Gene therapy AgNPs can deliver genetic material like DNA or RNA to specific cells, allowing gene silencing or gene delivery to various therapeutics into the cell [58]. The powerful wound-healing properties of medications with silver-based nanomaterials were observed to accelerate burn healing and wound healing by inducing cell proliferation and reducing the risk of infection [59]. Even the promising clinical applications, challenges such as toxicity, biocompatibility, and long-term stability still need to be addressed for clinical use (Figure 3).

Biodegradability and intracellular fate

Biodegradation and Intracellular Fate of MSNs

Biodegradation MSNs degrade in aqueous environments breaking down into silicic acid ($Si(OH)_4$), which is water soluble and can be excreted through the kidneys [61]. The rate of degradation depends on many factors such as particle size, pore shape and structure, surface area, and chemical modifications [62]. Smaller NPs tend to degrade faster due to their higher surface area-to-volume ratio [63]. In addition, the presence of phosphate ions and an acidic environment, such as in lysosomes, may accelerate the degradation process [64]. Functionalization with organic molecules can enhance or inhibit the MSNs degradation process depending on the hydrophilic or hydrophobic characteristics of the coating [65].

Intracellular Fate MSNs enter cells through endocytosis and are trafficked to endosomes and lysosomes. In the acidic compartments, the degradation of MSNs is induced, and drug release occurs [66]. The release of silicic acid can be metabolized or cleared by the renal system without significant nephrotoxicity [67]. However, prolonged exposure to non-degradable or poorly degradable MSNs may trigger different inflammatory responses and tissue oxidative stress [68]. Surface modifications can be used to affect the uptake pathway and intracellular trafficking, So control the degradation process and drug release [69]. Many studies indicate that MSNs generally have low cytotoxicity levels and have high cell tolerance in vitro and in vivo, although the particle accumulation and long-term effects require more investigation [70]. Optimizing the particle properties for controlled degradation is critically important for enhancing the therapeutic efficacy and biocompatibility of MSNs in biomedical and clinical applications [71] (Figure 4).

BIODEGRADATION AND INTRACELLULAR FATE OF AGNPS

Biodegradation of AgNPs AgNPs degrade by oxidation or releasing the silver ions (Ag^+) in aqueous and biological environments [72]. The rate of degradation depends on many factors, including particle size, surface coating, and environmental conditions such as pH and the presence of different biomolecules [73]. The smaller particles degrade faster as they have a higher surface area [74]. In biological fluids, the chloride ions can form insoluble silver chloride, while proteins may stabilize the NPs or affect their chemical properties such as dissolution kinetics. Surface coatings like polyethylene glycol (PEG) or citrate can regulate the rate of biodegradation by decreasing the Ag^+ release [75].

Intracellular Fate of AgNPs After entering cells via endocytosis, AgNPs are localized in the endosomes and lysosomes . The low pH in these compartments (acidic media) accelerates the oxidation process of AgNPs, inducing the release of toxic Ag^+ [76]. These ions can chemically interact with thiol groups in the proteins and DNA, altering cellular functions and promoting oxidative stress. AgNPs can also be sequestered in vesicles or degraded into ionic forms that diffuse through cellular cytoplasm . Even with their antimicrobial beneficial effect, excessive or prolonged exposure to AgNPs will lead to cytotoxicity,

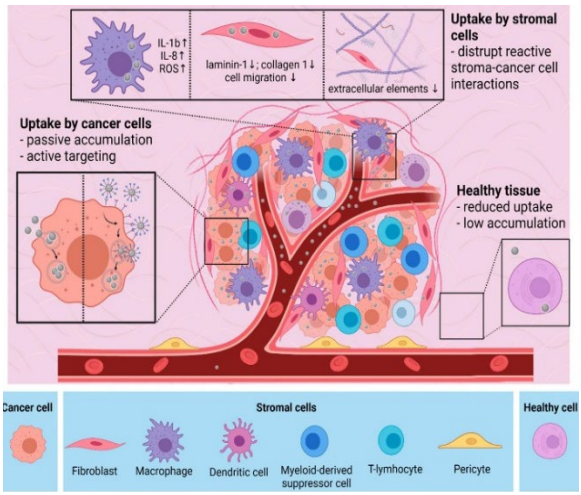

Figure 3 . Interactions of AgNPs with cancer and stromal cells of the tumor tissue and with healthy cells. AgNPs accumulated in tumor tissue passively or can be targeted to the tumor actively. AgNPs affect stroma-cancer cell communication. Reduced accumulation of nanoparticles in healthy tissue cells [60].

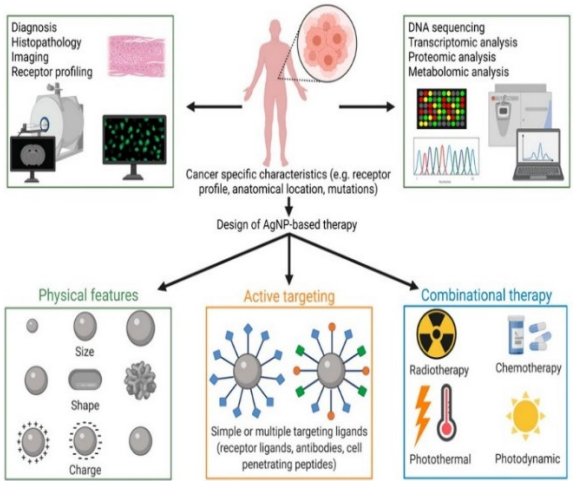

Figure 4. Merging modern diagnostic approaches provided by personalized cancer management and rational AgNP design can improve the anti-cancer effect of AgNPs. A tumor phenotyping based on imaging and traditional histology techniques, together with high-throughput molecular characterization methods, can aid in selecting and designing the ideal nanoparticle candidate with optimal shape and size, targeting the moiety and therapeutic combinational way for each patient [60].

altering mitochondrial functions and inflammatory reactions [77]. Many studies suggested that modification of the surface properties of AgNPs can reduce the cytotoxic effects and improve their biocompatibility [78]. Controlled biodegradation is crucial to balancing their therapeutic efficacy and minimizing toxicity .

CONCLUSION AND FUTURE PERSPECTIVES

The endocytosis of MSNs and AgNPs is greatly affected by their structural and surface properties and characteristics. In general, MSNs have safer biocompatibility behavior and are better suited for targeted drug delivery and cell-saving biomedical applications, with good cellular uptake and controlled release mechanisms. On the other hand, AgNPs exhibit strong therapeutic properties, especially in antimicrobial and anticancer applications; their endocytosis is accompanied by significant cytotoxicity due to the release of silver ions that are intended to kill bacteria or cancer cells. Understanding these differences is critical for optimizing their design and enhancing their clinical application in medicine. This review's findings can be concisely summarized as utilizing MSNs for delivery and safe application while using AgNPs to kill microorganisms and/or cancer cells. Future research work in nanotechnology is expected to focus on enhancing the functionality, biocompatibility, and clinical applications of AgNPs and MSNs, while also addressing biodegradability and long-term toxicity. This research aims to translate findings into commercially viable medical products under the umbrella of regulatory approvals to maximize benefits, efficacy, and safety.

ABBREVIATIONS

AgNPs silver nanoparticles, ROS reactive oxygen species, NPs nanoparticles, MSNs mesoporous silica nanoparticles.

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