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Biomedical applications of silica nanoparticle compounds

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ABSTRACT

Silica nanoparticles (SiNPs) consist primarily of silicon dioxide and has many qualities, such as selectable particle size, high surface area, and good biocompatibility that make them ideal for additional biomedical usage. SiNPs are becoming increasingly popular amongst researchers for their ability to retain thermal stability and exist in a variety of platforms, such as chromatography, medicine and optics. Advances and growth in the area of nanobiotechnology have alluded to both function and modification of SiNPs through their surface and as structures. One of the most promising uses of SiNPs is the development of therapeutics to target disease like cancer, respiratory and cardiovascular diseases. One of the additional benefits of SiNPs are the ability to also function as carriers of imaging agents, for enhancing medical imaging and imaging modalities like fluorescent imaging, and possibly imagers of the future for early detection of cancer. Mesoporous silica nanoparticles (MSNs) are a subclass of SiNPs, developed to provide controlled drug release with optimal cellular selectivity. What this research highlights are the versatility of SiNPs as applications and devices in modern biomedicine science approaches.

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1. Introduction

Nanotechnology has been characterized as one of the most advanced technologies [1]. Every nanomaterial shows different (physical, chemical, and biological) characteristic properties than their bulk counterparts because they are so small with a high surface area-to-volume ratio. These unique properties allow nanomaterials to be applied to many fields of science (physics, chemistry, biology, engineering, etc.), and they have significantly altered many of our day to day experiences including healthcare, food, cosmetics, electronics, and energy [2]. Moreover, within the last decade with advances in biomedicine and nanotechnology, nanomedicine has emerged rapidly. Amongst many nanoparticle materials, silica nanoparticles (SiNPs) in particular have many advantageous properties including high surface area, selectable pore size, easy functionalization and high biocompatibility [3].

SiNPs are nanometric, inorganic prototype materials (1 - 100 nm) that are synthetically engineered. SiNPs have high surface area, ease of synthesis and modification, and are quite effective for therapeutic agent delivery [3]. Silica is one of the Earth's most abundant materials, and its nanoscale form, $(SiO_2)_n$, often forms chain-like structures that resemble a three-dimensional solid. In these chains, some silicon atoms may not achieve full fourfold coordination, while others reach three- or twofold coordination with oxygen atoms. For certain sizes ($n > 12$), these chain-like arrangements are particularly prevalent, and dangling bonds may occur, possibly affecting interactions with other species. Its nanoparticles are widely utilized in pharmaceuticals, as in boost formulations and as enterosorbents. Binding sites could be utilized to target localized areas (tumor sites) for treatment [4].

This paper provides an overview of the biomedical implementations of silica nanoparticle compounds and reports on the state of the arts, discusses developments made, areas of concern and consideration still, and future suggestions and modifications for improvement and ultimately multifunctional development for diagnosis, therapy and pro-disease development measures.

2. Properties of silica nanoparticles

2.1. Structure and chemical composition

SiNPs have received ample attention thanks to their remarkable structural pliability and chemical stability [5]. SiNPs essentially have an amorphous silicon dioxide (SiO_2) matrix as their base structure, which can offer notable porosity and thermal stability [6].

SiNPs are largely constituted of an amorphous 3D network of interconnected SiO_4 tetrahedrons that are linked together with Si–O–Si (siloxane) bonds. The disorder within the amorphous structure is attributable to irregular bonding, which accommodates a variety of pore sizes and reactive surface areas. The unique structural heterogeneity of SiNPs introduced silanol and siloxane groups that are critical for surface modifications, ensuing biological interactions, and contributing to the hydrophilic and chemically tunable nature of SiNPs wherein they are aimed at biomedical applications [7].

The surface of SiNPs is composed predominantly of silanol groups (-SiOH), which are imperative for functionalization. The silanol groups allow for hydrophilicity and an array of chemical modifications to achieve multiple functionalities [8]. Surface engineering technology can allow SiNPs to be functionalized with various polar organic groups to improve targeting delivery and biocompatibility/effectiveness. For example, PEG coating can improve circulation time of SiNPs whilst minimizing the immune system detection [9].

Surface modification of SiNPs involves processes that alter their chemical composition. This can be achieved either through physical methods like thermal or hydrothermal treatment, affecting the silanol-to-siloxane ratio, or via chemical methods that directly change the surface's chemical properties [10]. Fig. 1. shows schematic of antibodies, peptides, enzymes, aptamers, DNA fragments, etc. for functionalizing the SiNP surface.

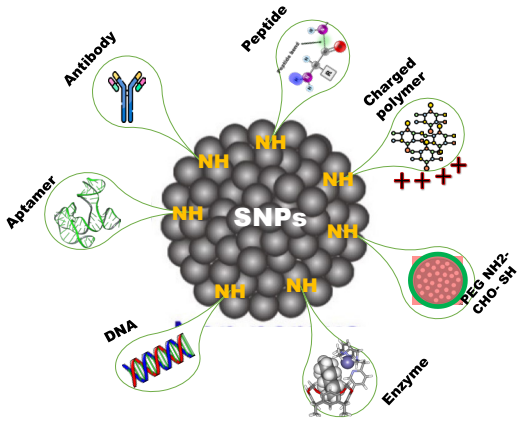

Fig. 1. Schematic of antibodies, peptides, enzymes, aptamers, DNA fragments, etc., for functionalizing the SiNPs surface.

Uniform SiNP spheres can be synthesized through controlled hydrolysis and condensation of alkoxysilanes like TEOS under alkaline conditions, known as the Stöber method. By adjusting variables such as ammonia concentration, solvent, and temperature, the particle size can be precisely tailored [11].

The link between structure and properties is essential, as mesostructured SiNPs can be shaped into spheres, rods, or ellipsoids, affecting how they are taken up by cells and distributed in the body. Overall, SiNPs combine stable SiO_2 frameworks, surface silanol chemistry, and customizable porosity, making them highly adaptable for diverse applications [9].

2.2. Physical and chemical properties

SiNPs offer distinct advantages for adsorption applications over other materials, owing to their stable structure, high surface area, adjustable porosity, surface silanol groups that facilitate easy modification, eco-friendliness, simple synthesis, and low production cost [12].

SiNPs exhibit a high surface area, tunable size and porosity and acceptable biodegradability from the perspective of specifically addressing their physical characteristics. The sizes, volumes, and surface chemistry of SiNPs all contribute to their flexibility in many applications.

The density of SiNPs depends on its condensation, measuring around 2 g/cm³, and the refractive index is 1.43, which confers possible utility in optical technologies [6].

Chemically, SiNPs are characterized by passive compatibility, heat resistance, and good chemical properties in addition to their mesoporous structure. Combining all three facilitates drug loading and controlled release in a biomedical context [13]. Even when their chemical properties appear strong, mesoporous SiNPs can

also be biodegraded into biological settings such as by gradual dissolution to $Si(OH)_4$, which is especially beneficial in the biomedical application context[13]. Rahman et al., [14] showed that adjusting from approximately 130 nm SiNPs to 7 nm SiNPs augments the apparent surface area, silanol content, and apparent density. These reductions also cause nanoscale impulse changes as a result of SiNPs, such as decreased Si–O–Si bond angle and defect creation (i.e., E centers and oxygen deficient), and allow optical and physicochemical properties to differ greatly from bulk silica. SiNPs have the advantage of demonstrating optical transparency, chemical inactivity, and retention in physiological environments this enables imaging to be a consistent advantage [9, 15].

2.3. Biomedical properties of silica nanoparticles

MSN-based nanomaterials are applied across multiple disease areas: anti-infective therapy (bacterial infections), antioxidant therapy (Alzheimer's disease), metabolic disease therapy (osteoporosis) and tumor therapy. Fig. 2 focuses on these disease areas and the application of MSNs. Specific MSN strategies include but are not limited to enzyme-like catalytic therapy, radiotherapy, thermotherapy, chemotherapy, dynamic therapy, multimodal synergistic therapy, immunotherapy and gene therapy. In this context, the wide range of strategies embraces the flexibility of MSN systems to deliver diverse therapeutic modalities through a targeted, controlled, and combinatorial approach [16]. Additionally, a rich research domain has explored methods of surface modification to improve targeting efficiency and biocompatibility of silica nanoparticles for application in biomedicine. Specific ligands (antibodies, peptides, or small molecules) can be attached to the nanoparticle surface, ultimately allowing silica nanoparticles to actively target tumor cells compared to non-targeted nanoparticles, while limiting off-target interactions and increasing therapeutic precision [17]. In cancer treatment, for instance, mesoporous silica nanoparticles are often designed to be stimuli responsive, where stimulus-responses can be engineered to release the therapeutic payload following tumor-specific conditions, e.g. acidic pH, redox gradients, or enzyme activity. Stimulus-mediated release limits systemic toxicity while improving the efficacy of the treatment [18]. Silica nanoparticles also have an important role in diagnostic imaging applications. When doped with fluorescent dyes or magnetic materials, silica nanoparticles are useful in new multimodal imaging techniques such as MRI, fluorescence imaging, and PET. With this multi-functionality, there is potential for real-time imaging of biodistribution and therapeutic outcome of nanoparticles which dynamically combines diagnosis with therapy [19].

As new therapeutic strategies evolve, the simultaneous assembly of drug and gene within a single silica nanoparticle platform has emerged. The co-delivery could provide a synergistic effect against cancer therapies, and in general, it provides a versatile and multi-functional therapeutic modality.

A critical aspect when utilizing silica nanoparticles for biomedical applications is their biodegradability. Biodegradable particles are slowly biodegradable into non-toxic silicic acid reducing long-term toxicity [13].

A number of studies have stated that biodegradable nanoparticles degradation and longevity will rely on factors like size, porosity, and surface coatings that impact distribution, accumulation, and clearance profiles in vivo [20]. The subsequent clearance of nanoparticles is paramount for the clinical safety of silica nanoparticles. In general, particles or smaller than about 5.5 nm can be excreted through the kidneys, which greatly decreases the likelihood of nanoparticles from accumulating in other organs in the body, however larger or non-degradable nanoparticles will be retained by the liver and spleen at a greater risk. The FDA, along with many other regulatory organizations, emphasizes prompt clearance of injectable agents. Therefore, it appears SiNPs that are biodegradable and renally excretable can be more acceptable clinically due to diminished bioaccumulation and enhanced biocompatibility [13]. To back up these claims, Bimbo et al. [21] showed that thermally hydrocarbonized porous silicon nanoparticles had good in vivo stability, and low levels of cytotoxicity and immunogenicity. In animal studies, irrespective of delivery method, oral delivery of particles appeared to pass intact through the GI tract, and when injected intravenously caused rapid accumulation in the liver and spleen, suggesting they could be safe and promising carriers for oral drug delivery.

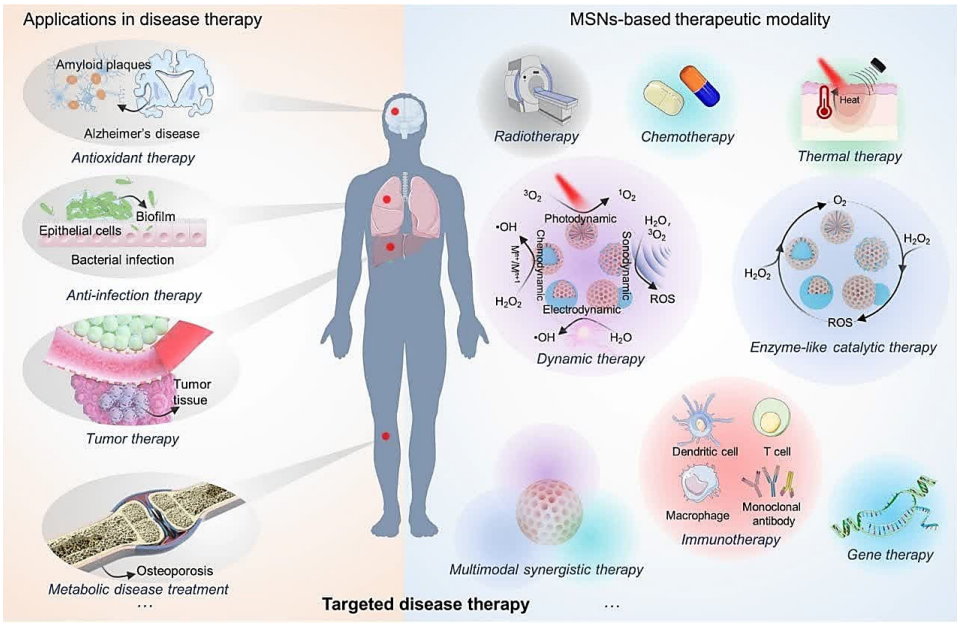

Fig. 2. MSNs for disease treatment: anti-infective, antioxidant, metabolic, and tumor therapies. Current MSN approaches include enzyme-like catalysis, radiotherapy, thermotherapy, chemotherapy, dynamic therapy, multimodal therapy, immunotherapy, and gene therapy [16].

3. Synthesis techniques for silica nanoparticles

3.1. Chemical methods

3.1.1. Sol-gel method

The sol-gel process is a common method used to synthesize SiNPs. It involves the transformation of a colloidal suspension (sol) into a gel network structure. A sol is a liquid medium containing nanoscale colloidal particles (1–100 nm) and gel is a structure with a continuous interconnected solid network that contains sub-micron pores and polymeric chains. The sol-gel process can be categorized into two sections based on the type of precursor materials used, inorganic precursors like chlorides, nitrates, sulfides, and alkoxides [22]. Fig. 3 shows schematic of the sol-gel chemical method for silica formation.

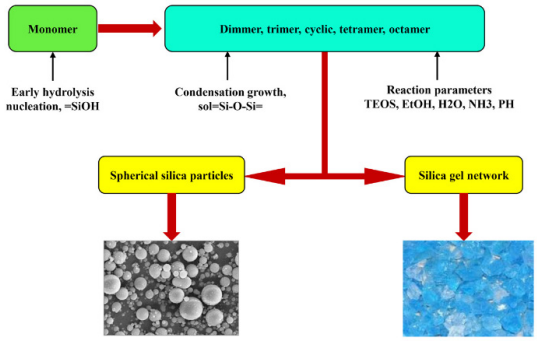

Fig. 3. Schematic of the sol-gel chemical method for silica formation [23].

Tetraethyl orthosilicate (TEOS) is a frequently used precursor in sol-gel potentially producing silica-based nanoparticles. The TEOS precursor undergoes hydrolysis, producing silanol functional groups (Si–OH) that can condense and polymerize either with one another or ethoxy groups to form siloxane functional groups (Si–O–Si). Siloxane functional groups are a core unit in producing the overall silica network [24]. Jafarzadeh and co-workers [25] developed a modified sol-gel method for the preparation of silica nanoparticles, and materials formed using sol-gel methods can exhibit different properties depending on the order of the mixing components and the drying method. The authors used a Mode-A mixing method in which TEOS and ethanol were mixed before adding water, and this method produced monodispersed particles with an average size of 10.6 nm. They additionally determined that freeze-drying not only preserved the surface morphology of the nanoparticles formed but also increased pore size, pore volume, and water desorption efficiencies ultimately improving the quality of the produced powders. Additional work by Dabbaghian [26] used a sol-gel precipitation method to investigate how different synthesis parameters affect the size of the produced nanoparticles and examined the effects of ethanol concentration, temperature, TEOS quantity, and the presence of ammonia. In the study, it was found that ethanol has the largest effect on particle size, and increased temperature generally decreased particle size. They also determined that the nanoparticles had the most uniform size distribution at the smallest nanoparticle dimensions, emphasizing how precisely controlled conditions are critical for achieving size uniformity in SNPs synthesis.

3.1.2. Microemulsion technique

The technique of water-in-oil (W/O) microemulsion has become a robust and popular technique for synthesizing nanoparticles with controlled morphology and uniform size. A W/O microemulsion system is an isotropic, thermodynamically stable, single-phase mixture, composed of water, oil, and surfactant, an amphiphilic molecule to reduce the interfacial tension between the water and oil phase to allow for the formation of a transparent solution. Within this system, nanodroplets of water that are suspended in the oil phase serve as nanoscale reactors for particle formation. These droplets typically form spherical waters pools, and the size defined (usually defined by the W_0 value: water to surfactant molar ratio) will determine the size of the resulting nanoparticles, where larger W_0 values will usually give larger particle sizes [27].

Because of the confined nanoscale environment, this W/O microemulsion is a great media for environmentally friendly, controlled size and shape synthesis of functional and structured nanoparticles. In the recent years this method has shown diverse silica nanostructures such as core-shell and homogeneous dispersions, frequently within one system [28].

A research study, espoused by Darbandi et al. [29] utilized a somewhat different variation of this methodology and in this case, an oil-in-water (O/W) microemulsion method where cyclohexane was the oil phase and Synperonic NP-5 was used as the surfactant. This study produced monodispersed, luminescent silica nanoparticles that had quantum dots in the core. The results showed that reaction time, temperature, and concentration could all effect particle properties. This study showed great possibilities as a simple and effective approach, compared to other sol–gel methods, especially relating to photonics and biolabeling applications. A number of other studies have also demonstrated the versatility of the W/O microemulsion method to achieve silica coatings on magnetic ferrite nanoparticles. One study revealed the silica-coated magnetite (Fe_3O_4) and cobalt-ferrite ($CoxFe_{3-}xO_4$) nanoparticles in a W/O microemulsion reaction method. The core particles were approximately 8–14 nm; the silica shells were approximately 14 nm thick. Cobalt ions added into the solution greatly improved the magnetic coercivity of particles; showing that the composition and structure for both can be tuned using this approach [30, 31].

In another related investigation, Fe_3O_4 and silica-coated Fe_3O_4 nanoparticles were synthesized using a W/O microemulsion system containing Tween-80 and SDS as surfactants. The silica coating led to reduced particle agglomeration and resulted in slightly larger, more uniformly distributed nanoparticles (~16 nm) compared to their uncoated counterparts. Structural analysis confirmed their spinel phase, and further testing showed that both coated and uncoated nanoparticles exhibited antibacterial activity, with the coated ones showing significantly improved effects [32].

3.1.3. Stöber method

The Stöber method, first introduced in the 1960s, is a well-established chemical technique for synthesizing SiNPs via controlled hydrolysis and condensation of alkoxide precursors, such as tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS). Typically performed in alcoholic media at room temperature, this process involves a nucleophilic attack by hydroxide ions on the alkoxysilane molecules, producing silanol intermediates that subsequently condense to form siloxane bonds. The overall result is the formation of colloidal silica particles. The method's simplicity and reproducibility have made it one of the most frequently used protocols in nanoparticle synthesis [33, 34].

The original work by Stöber et al. (1968) demonstrated that particle size could be fine-tuned (from tens to hundreds of nanometers) by adjusting parameters such as ammonia concentration, alcohol type, and precursor ratios. This tunability has contributed to the method's popularity in both academic and

industrial applications, as evidenced by its extensive citation record [34].

A more recent advancement by Ren et al. [35] combined microchannel technology with microwave-assisted synthesis based on the Stöber approach. Their results showed accelerated nucleation and growth, producing silica nanoparticles with controlled sizes between 15 to 400 nm. The microwave-assisted approach yielded larger, more uniform particles and higher output than microchannel-only methods.

Another modification of the Stöber method enabled the synthesis of rough-surfaced spherical SiO_2 nanoparticles using a ternary mixture of TEOS, ethanol, and water. After a cooling treatment, particles around 177 nm in size with high surface area (~85 m^2/g) were obtained. Key factors influencing particle morphology included pre-reaction time, temperature, and ammonia concentration. These particles were later functionalized with gold for use in catalytic applications [36].

In the work by Pradhan et al., [37] the Stöber process was coupled with spin coating to deposit silica nanoparticles onto p-type silicon substrates. The resulting layers exhibited quasi-superhydrophobic surfaces with a contact angle of approximately 130°, suggesting their potential in self-cleaning surface technologies.

A comparative study between commercial fumed silica and Stöber-derived silica nanoparticles highlighted differences in surface hydroxyl group content. The Stöber particles, possessing higher –OH group density, showed better surface reactivity and more significant ζ-potential shifts (from −35.5 mV to +26.2 mV) upon functionalization with 3-aminxopropyltriethoxysilane (APTES). This suggests their enhanced suitability for surface modifications in chemical and energy-related applications [38].

In study by Larsen et al., [39] a modified Stöber method was employed to coat iron oxide nanoparticles (IONPs) using a combination of TEOS and APTES. Tuning the TEOS/APTES ratio allowed control over particle size (60–100 nm), morphology, and amine surface functionalization. Higher concentrations of APTES led to aggregation, while optimized ratios resulted in well-dispersed amine-functionalized silica-coated IONPs, exhibiting improved magnetic response and surface properties desirable for biomedical applications.

3.2. Physical methods

3.2.1. Laser ablation

Laser ablation is a technique that uses laser energy, short for "light amplification by stimulated emission of radiation," to remove material from solid targets. In this method, intense energy is focused on a specific point of the surface, causing light-absorbing materials to evaporate. The term "ablation" denotes the elimination of surface atoms and involves both single-photon chemical bond disruption and multiphoton-induced thermal evaporation [40]. This method has gained popularity among physical approaches for producing non-toxic nanomaterials, as it avoids foreign compounds and allows control over the three-dimensional size of particles. Its versatility and simplicity make it suitable for synthesizing a broad range of nanomaterials with diverse applications [41].

Although laser ablation enables the production of high-purity nanoparticles, since purity depends primarily on the target material and surrounding medium, it traditionally suffers from limited control over particle size distribution, agglomeration, and crystallinity. This is mainly due to the random Brownian motion involved in particle formation [40]. To address this, advanced variations of laser ablation techniques have been developed to better control particle morphology. A significant advancement came in 2010, when researchers developed a laser ablation method for synthesizing silica-metal nanoparticles by irradiating a metal target submerged in an aqueous metal salt solution. This single-step process enabled the fast fabrication of silica-stabilized nanoparticles such as silver, gold, and their alloys. During ablation, silica is simultaneously generated, acting as a stabilizing agent and reducing the toxicity of the metallic components. This hybrid approach effectively combines physical and chemical synthesis routes, providing both stability and biocompatibility [42]. In a separate approach, core–shell silica nanoparticles were synthesized through a two-step laser-assisted ablation technique. Initially, a silicon wafer was ablated in water, and subsequently, silver nitrate was added to the solution. The resulting redox reaction produced silver nanoparticles encapsulated by porous silica shells. Key synthesis parameters such as laser pulse energy, wavelength, ablation duration, and the concentration of silver ions, were shown to significantly affect the size and optical properties of the final particles. These nanoparticles were thoroughly analyzed using UV–VIS-NIR spectroscopy, XRD, and high-resolution TEM, confirming their structural and optical characteristics [43].

3.2.2. Ultrasonication

Ultrasonication has proven to be a powerful physical tool in the synthesis of silica nanoparticles, especially in sol–gel and microemulsion-based processes. The introduction of ultrasound energy not only accelerates the chemical reactions but also has a pronounced impact on particle size, morphology, and dispersion stability [44, 45].

For instance, Nam et al. conducted a study using both the Stöber and reverse microemulsion methods under ultrasonic conditions at 40 kHz. The resulting nanoparticles demonstrated uniformity in structure and a low relative standard deviation, along with a stable zeta potential of approximately −30 mV. Notably, there was a linear correlation between particle concentration and light scattering intensity, suggesting excellent colloidal stability. These characteristics point toward high potential for application in agriculture and other fields. Interestingly, in a separate approach, ultrasonication was introduced not during synthesis, but during the aging phase of the precursor solution. This gentle pre-synthesis treatment (~1 mW) was found to extend the induction period, increase the size of the silica spheres, and significantly enhance monodispersity. Together, these findings highlight that both pre-synthesis and in-process ultrasound applications can distinctly influence nucleation and growth behavior [44, 46].

In other investigations, researchers focused on modifying the traditional Stöber method using high-power ultrasound probes to significantly enhance synthesis efficiency. By optimizing several parameters like the concentrations of TEOS, ammonia, water, reaction temperature, ultrasound intensity, and insonation time, they successfully reduced the reaction time from 270 to only 10 minutes, while simultaneously achieving smaller nanoparticle sizes. Characterization through DLS and TEM revealed particles ranging from 6 to 153 nm in diameter, accompanied by stable zeta potentials, confirming the method's consistency and precise control. Similarly, another study employed a Taguchi experimental design to optimize ultrasound-assisted sol–gel synthesis. The analysis emphasized that ammonia concentration was the most critical factor affecting particle size. Under optimized sonication settings, uniform silica nanoparticles with an average diameter of 13 nm were obtained. The structural integrity and morphology of the particles were confirmed through XRD, FTIR, light scattering, and SEM, validating the effectiveness of the approach [47, 48].

3.2.3. Evaporation-condensation (vapor phase synthesis)

In vapor-phase nanoparticle synthesis, the system is intentionally brought to a thermodynamically unstable state to facilitate vapor-to-solid phase transition. This state typically involves supersaturated vapor in which the reactants are condensed through chemical reactions. First, homogeneous nucleation occurs, and then particle growth continues by vapor condensation on the initial particles. To produce smaller nanoparticles, rapid and intense nucleation must occur, and then particle growth must be stopped quickly to prevent excessive growth. These processes are very rapid and uncontrolled, and are more suitable for continuous or semi-continuous production, unlike colloidal synthesis, which is time-consuming and batch-wise [49, 50].

Gas-phase or aerosol technologies have enabled the synthesis of industrial nanomaterials such as carbon black and fumed silica for over a century. These methods, which have evolved from early experiments, now include multiscale process design and advanced diagnostic tools, providing precise control over particle size, shape, and composition, controls that are typically difficult to achieve with wet chemical methods.

In high-temperature syntheses, processes such as coagulation and sintering determine the final shape and properties of the particles, creating fractal structures with predictable sizes. The physical principles of this technology allow for simple modeling. Modern technologies such as flame spray pyrolysis have wide applications in catalysis, sensors, and biomedical engineering, contributing to the rapid growth of these fields [51].

Gas-phase or aerosol technologies have been used for over a century to synthesize industrial nanomaterials like carbon black and fumed silica. These methods have advanced to include multiscale process design and sophisticated diagnostics that allow precise control over particle size, shape, and composition. In high-temperature processes, coagulation and sintering shape particles into fractal structures with predictable sizes, guided by easily modeled physical principles. Modern techniques like flame spray pyrolysis have broad applications in catalysis, sensors, and biomedical engineering, driving rapid progress in these fields.

3.2.4. Ball milling

Mechanical milling, particularly the high-energy ball milling technique, has emerged as an effective physical method for synthesizing and dispersing silica nanoparticles. This approach is capable of producing fine, amorphous silica particles and enables their efficient integration into composite systems. The process relies on mechanical forces generated by moving balls to crush raw materials into much smaller particles. Although this method can be scaled relatively easily for industrial use, its time-consuming nature often limits its practicality in laboratory-scale studies focusing on silica nanoparticle fabrication [52].

In a study conducted by Salavati-Niasari [53], high-energy planetary ball milling was used to synthesize amorphous silica nanoparticles from rice husk ash at room temperature. After 6 hours of milling, uniformly spherical particles with an average diameter of around 70 nanometers were obtained. The research also revealed that increasing the milling time or rotational speed could further reduce the particle size. Moreover, when these nanoparticles were evaluated as drug carriers for Penicillin-G in simulated body fluid, they demonstrated a sustained-release behavior, underlining their potential application in controlled drug delivery systems.

In a separate investigation by Hedayati [54], surface-modified silica nanoparticles were embedded into a poly(ether ether ketone) (PEEK) matrix using the same high-energy ball milling method. Before milling, the silica particles were functionalized with 3-glycidoxypropyltrimethoxysilane, and the mixture was milled for 15 hours under an argon atmosphere. Transmission electron microscopy (TEM) confirmed a homogeneous dispersion of silica within the polymer matrix. Additionally, differential scanning calorimetry (DSC) analysis showed that the milling process and the presence of silica nanoparticles both contributed to a reduction in the crystallinity and melting point of the PEEK matrix, showing the influence of nanosilica on the thermal properties of polymer-based materials [54].

3.3. Biological methods

3.3.1. Plant extract mediated synthesis

Due to the silica and silicon-based nanomaterials multifunctionality, there is a growing demand for synthesis methods that are not only cost-effective, safe, and scalable, but also environmentally friendly. To address this, researchers are increasingly focusing on green synthesis approaches that make use of sustainable agricultural bio-resources, including rice husk ash, coffee husks, sugarcane residues, wheat husk, and corn cob ash [55].

3.3.2. Microbial synthesis

To establish a milder and more environmentally friendly method for producing amorphous silica from rice straw, an enzymatic hydrolysis strategy was applied. In this approach, rice straw was initially hydrolyzed using either a specific fungal strain (Trichoderma reesei TISTR 3080) or a mixed microbial community (referred to as LDD1). Following enzymatic treatment, the material underwent thermal processing at 500 °C for 8 hours. The decomposition rates of rice straw by T. reesei and LDD1 reached 59.6% and 45.2% of the original mass, respectively. Thermogravimetric analysis revealed ash contents of 12% and 23% for the two treatments. Structural characterization through X-ray diffraction and transmission electron microscopy confirmed the presence of amorphous silica as the dominant component in the ash, with particle sizes ranging between 50 and 80 nanometers. The silica purity was found to be 82.5% in the T. reesei-treated sample and 73.6% in the LDD1-treated sample. However, both types of ash also exhibited relatively high levels of impurities such as manganese and phosphate, likely originating from microbial activity during the hydrolysis stage [56].

3.3.3. Diatom extraction

Diatoms are unicellular photosynthetic algae that inhabit virtually all aquatic environments and play a fundamental role in sustaining life on Earth. Their cell walls, known as frustules, are remarkable natural examples of intricate three-dimensional (3D) architectures, constructed primarily from nanopatterned silica. These structures not only provide mechanical strength but also possess a variety of physicochemical properties valuable for technological applications [57].

Among natural sources, diatoms represent the most abundant and efficient biological producers of porous silica. Their frustules exhibit high surface area, thermal resistance, excellent biocompatibility, and the potential for customizable surface modifications. These attributes, combined with the ease of cultivating diatoms under artificial conditions and the widespread availability of fossilized diatom frustules (diatomite), position diatoms as a sustainable and low-cost alternative to synthetic materials, particularly in the development of advanced drug

delivery systems [58]. Diatoms convert dissolved silicon into silica through biosilicification. At neutral pH, silicon mainly exists as orthosilicic acid; once solubility limits are reached, it forms biosilica via an intracellular pathway. Orthosilicic acid is transported into biosilica deposition vesicles, where biomolecules such as long-chain polyamines, silaffin proteins, and silacidin drive its transformation into hydrated amorphous silica. In this process, long-chain polyamines influence nanoparticle size, silaffins boost silica synthesis, and silacidins promote self-assembly by interacting with positively charged species [59].

Recent research has emphasized the potential of diatom biosilica as a promising alternative to synthetic porous silicon in the creation of next-generation, nature-inspired nanocarriers for biomedical applications. These naturally derived materials offer an eco-friendly and economically viable platform for developing controlled drug delivery systems.

For instance, Diatomite, a natural sedimentary material of fossilized diatom shells, was purified by thermal and acidic treatments to yield biocompatible medical-grade silica. It was then mechanically processed into 100–300 nm nanoparticles via crushing, sonication, and filtration, functionalized with 3-aminopropyltriethoxysilane, and labeled with tetramethylrhodamine isothiocyanate for bioimaging. Confocal microscopy confirmed efficient cellular uptake and uniform distribution within cancer cells, indicating strong potential as nanocarriers for drug delivery [60].

Diatomaceous earth–based mesoporous silica nanoparticles (dMSNs) were engineered for multimodal cancer therapy. They co-loaded lanthanide ions for ROS generation under near-IR light (PDT) and dual MRI/fluorescence imaging, and fucoidan (from Sargassum oligocystum) as a chemotherapeutic agent. The combined treatment reduced cancer cell viability to 47.7%, versus 57.4% with fucoidan alone, highlighting the enhanced efficacy of diatom-based multimodal nanoplatforms [61].

4. Biomedical applications of silica nanoparticles

Although silicon was initially regarded as a highly toxic substance, this assumption was later reconsidered following the discovery of several of its naturally benign characteristics. Today, silicon is recognized as an essential trace element in the human body, ranking just after iron and zinc in abundance. Consequently, various silica-based materials, such as bioglasses, star gels, mesoporous silica, and solid silica nanoparticles, have attracted attention due to their high effectiveness in a wide range of applications, such as biomedicine, controlled and targeted drug delivery, tissue regeneration, and diagnostic imaging. However, to ensure their performance and safety, precise control over the physicochemical properties of these engineered silica materials is crucial [62, 63].

The special physicochemical properties such as biocompatibility, large surface area, and tunable porosity of nanosilicates have also been investigated in medical applications, especially in cancer treatment, making nanosilicates promising candidates for the development of therapeutic and diagnostic tools in modern medicine. Moreover, due to the surface properties of silica particles, it facilitates surface modification and enables the attachment of various biomolecules such as nucleic acids and proteins [64].

4.1. Cancer theranostics and targeted drug delivery

Nanotechnology's ability to alter drug pharmacokinetics has led to its use in various biomedical applications, especially targeted drug delivery. Targeted drug delivery increases the concentration of the drug in target tissues and reduces the side effects of the drug, increasing the effectiveness of the treatment [65]. This method can help the drug molecule reach the target tissue more specifically, reducing the dosage and side effects. Of course, targeted drug delivery is different from targeted therapy, which is the interaction of the drug with a specific receptor [66, 67].

Mesoporous silica nanoparticles have been shown to be very effective in cancer treatment due to their excellent structural properties like high porosity, large surface area, tunable size and specific mineral compositions [68, 69]. These nanoparticles can deliver chemotherapeutic drugs to the tumor in a highly targeted manner, which both increases the efficacy of the treatment and reduces side effects. By using targeting ligands and the sensitivity of the materials to stimuli, the precision of MSNs in delivering anticancer drugs has been improved. The researchers investigated that the biocompatibility of MSNs can be improved by modifying the surface of the nanoparticles, and generally show less toxicity than colloidal silica, which may cause cytotoxicity under oxidative stress [69-72].

MSNs encapsulate chemotherapeutics like doxorubicin and paclitaxel and can be actively targeted to breast and liver cancers using ligands such as EpCAM aptamer, folic acid, GPC-3 peptide, and HER2/neu antibodies, enhancing uptake, efficacy, and reducing side effects. These features also boost diagnostic imaging contrast, notably in ultrasound. Preclinical breast cancer studies show improved pharmacodynamic and pharmacokinetic profiles when drugs are delivered by MSNs. The mesoporous structure also supports non-invasive imaging and the integration of diagnostic and therapeutic functions, making MSNs valuable for simultaneous cancer diagnosis and treatment [62, 73, 74].

4.2. Medical imaging

Nanomaterials have attracted attention in various fields, especially in imaging as molecular probes and contrast enhancers, due to their improved properties compared to traditional materials [72]. SiNPs with tunable size, biocompatibility, and easy surface modification are widely used for tissue and cancer cell imaging, via surface modification or doping, in vivo and in vitro. For example, FSiNPs fuse silica nanoparticles with fluorescent dyes (FSiNPs), enabling bright, photostable cancer cell imaging. They are synthesized by sol-gel and water-in-oil microemulsion methods, trapping fluorescent molecules in the silica matrix and shielding them. To improve dispersion and biomolecule binding in aqueous environments, FSiNP surfaces are bioconjugated with cancer-targeting groups (e.g., aptamers, antibodies, folic acid). These features make FSiNPs precise tools for tumor imaging [75].

In recent developments, MSNs have made significant progress as multimodal imaging agents in ultrasound, fluorescence, photoacoustic, MRI, and CT, increasing the accuracy of preoperative tumor detection and visualization for hepatocellular carcinoma (HCC) [70, 76].

In a study, a nanocomposite consisting of mesoporous silica nanoparticles decorated with superparamagnetic magnetite nanocrystals was synthesized for magnetic resonance imaging (MR) with contrast capability. The dye molecule in the silica structure enhances the optical imaging quality, and the aggregation of magnetite nanocrystals on the silica surface resulted in an increase in the MR signal, which is due to magnetic synergy. The anticancer drug doxorubicin (DOX) was able to penetrate the pores of the nanoparticles and cause cell death. The successful delivery of DOX and the maintenance of its anticancer properties were the result of passive targeting and concentration at the tumor site and the apoptosis process in the tumor tissue of mice, which were also confirmed by MR and fluorescence imaging [77].

4.3. Antibacterial and antiviral applications

SiO_2 nanoparticles are known as one of the effective agents against viral and bacterial infections due to their specific physicochemical properties. Their high surface-to-volume ratio allows for better adsorption onto microbial membranes and disruption of their integrity. Also, when exposed to light or heat, these nanoparticles generate reactive oxygen species (ROS) and cause oxidative damage to microorganisms. However, SiO_2 as antimicrobial agents should consider possible toxic effects on human cells and the environment [78].

Silica nanoparticles were coated with a silver/ polyrhodanine composite in which metallic silver nanoparticles with a diameter of about 7 nm were regenerated on the silica surface. This composite, with structural confirmation through microscopic and spectroscopic methods, showed strong antibacterial activity and long persistence against Staphylococcus aureus and Escherichia coli bacteria due to the combined antimicrobial effects of silver nanoparticles and polyrhodanine [79]. Nanoparticles bind to viral surfaces, disrupting virus–host cell interactions and inhibiting entry by agglutinating surface proteins. Porous silica nanoparticles aggregated upon exposure to the H1N1 influenza virus, and this aggregation was demonstrated by TEM analyses, as reported by Sminkina and colleagues, with validation in vitro [80].

Labau and colleagues [81] developed lipid-coated mesoporous silica nanoparticles (LC-MSNs) loaded with the antiviral drug ML336. The liposomal coating increased the circulation time, drug persistence, and biocompatibility. LC-MSNs loaded with ML336 dose-dependently inhibited Venezuelan equine encephalitis virus (VEEV) in vitro and sustained drug release after endocytosis, enhanced therapeutic efficacy. In vivo mouse safety studies showed that therapeutic doses (0.11 g / kg) were nontoxic and that the nanoparticles significantly reduced viral load in the brains of VEEV-infected mice [81]. Table 1 shows the summary of studies on Silica nanoparticles and silica composites.

5. Conclusion

This study investigated biomedical applications and properties of silica nanoparticle compounds and synthesis techniques for silica nanoparticles. Silica nanoparticles have gained significant attention in the biomedical field such as drug and gene delivery, regenerative medicine, tissue engineering, cancer diagnostics and treatment due to their unique properties such as adjustable particle size, large surface area, excellent biocompatibility, and tunable pore structures. These features make them highly suitable for a variety of biomedical applications, particularly in drug delivery, diagnostics, and therapeutic interventions. This comprehensive progress positions silica nanoparticles as key nanotechnology tools in future biomedical innovations. This review also discusses the future prospects of SiNPs in clinical trials and their potential in precision medicine and advanced therapeutic strategies, with the goal of safer, more efficient nanomedicines.

Table 1
The summary of studies on Silica nanoparticles and silica composites.

Silica nanoparticles and composites	Synthesis method	Key findings	Application	Ref.
Thermally hydrocarbonized porous silicon NPs	Thermal carbonization	Excellent in vivo stability,low cytotoxicity, nonimmunogenic, rapid liver and spleen uptake	Oral drug delivery	[21]
Mesoporous silica nanoparticles (MSNs)	Sol-gel + surface modification	High cellular uptake, sustained release, high cytotoxicity on SCC7 cells	Chemophotodynamic therapy	[82]
MSNs-HA (Hyaluronic Acid-conjugated)	Amidation	Excellent dispersity, enhanced cytotoxicity on HeLa cells	Targeted cancer therapy (CD44+)	[83]
CurNQ-loaded mesoporous silica nanoparticles	Sol-gel loading	pH-responsive fluorescence and cytotoxicity; targeted release in acidic tumor environment	Ovarian cancer theranostics	[84]
Dye-loaded MSNs with cavitation nuclei	Sol-gel + ultrasound	Ultrasound-enhanced extravasation of MSNs; improved tumor tissue penetration	Enhanced tumor penetration	[85]
Curcumin-loaded MSNs in PCL/Gel nanofibers	Sol-gel + electrospinning	Sustained release; preserved stemness and proliferation of hADSCs over 28 days	Stem cell therapy / Cancer	[86]
Lectin-conjugated MSNs for bone cancer	Sol-gel + lectin functionalization	pH-responsive DOX release; ~100× higher cytotoxicity in SaOS-2 (osteosarcoma) cells vs normal cells	Targeted bone cancer therapy	[87]
Dendronized MSNs	Sol-gel + PAMAM dendron grafting	Endosomal escape via PAMAM buffering; low cytotoxicity; efficient intracellular release	Cytosolic drug delivery / Gene therapy	[88]
Redox-responsive MSNs loaded with siRNA/DOX	Sol-gel + disulfide gating	Dual delivery overcame drug resistance; triggered siRNA/DOX release; suppressed MDR1 expression	MDR cancer chemotherapy	[89]
Aminopropyl-modified MSNs (MCM-41 type)	Co-condensation (TEOS/APTES)	Surface morphology and pore structure tuned via APTES content; enhanced uptake in LNCaP cancer cells	Active targeting (folate receptor)	[90]
Dye-loaded MSNs + polymeric cavitation nuclei	Sol-gel + ultrasound-activated cavitation	Ultrasound-enhanced nanoparticle extravasation; improved release in tumor models	Tumor-targeted drug delivery	[91]
Fe_3O_4@SiO_2 core-shell MSNs with zwitterionic coating	Sol-gel + core-shell + MPC silanization	Low protein fouling, co-delivery of siRNA + daunorubicin; significant ovarian cancer cell silencing/killing	Ovarian cancer theranostics	[92]
Gold-core@mesoporous silica (AuNR@MSN)	Seed-mediated AuNR + silica shell	Combined nitric oxide and levofloxacin release under NIR; ~90% biofilm reduction via PTT	Antimicrobial & biofilm photothermal therapy	[93]
Eudragit-coated MSNs for oral corticosteroid delivery	Sol-gel + polymer coating	pH-triggered colonic release of budesonide; improved colitis symptom reduction in mouse model	Inflammatory bowel disease (IBD) therapy	[94]

Author contributions

Fatemeh Sharifjafari: Conceptualization, Writing – original draft, Writing – review & editing; **Darya Nejadkoorki:** Investigation, Writing – original draft, Writing – review & editing**; Sogand Bahadori:** Writing – review & editing; **Reza Khoda dadi:** Writing – original draft, Writing – review & editing.

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Data availability

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