PRODUCTION AND BIOMEDICAL POTENTIAL OF SILICA NANOPARTICLES

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Abstract
Silica nanoparticles (SiNPs) are extensively utilized in the biomedical space as a result of their greater biocompatibility, thermal steadiness, as well as the capability to easily functionalize their surfaces. Nevertheless, the studies of the toxicity of SiNPs are still at their initial levels and the mechanisms of the toxicity of SiNPs are not completely known yet. This paper is a review of the latest developments in manufacturing silica nanoparticles, focusing especially on green and sustainable techniques, such as thermal and wet methods. It is also an analysis of the structural diversity of SiNPs, including solid, mesoporous, shaped, and etched nanoparticles, and the discussion of their toxicological assessment to help justify the safe and effective use of SiNPs in biomedicine.

Keywords: Silica nanoparticles, biomedical application, structural diversity, toxicity

Introduction

Silicon dioxide/silica (SiO_2) is among the common widespread substances over the crust of the earth. It is produced naturally by the silicate minerals, and it is also present in cereals and plants (Diab *et al.,* 2017). Silica occurs in the form of sand and clay in construction materials (bricks and concrete). Silica, which is sand, is the major raw material in the production of different kinds of glass with different characteristics. Moreover, silica has a variety of biomedical and industrial applications (Prabha *et al.,* 2021).

Nanomaterials also have special physicochemical properties, including optical, mechanical, electrical and magnetic, which are not similar to the bulk materials. These features are ascribed to surface effects and quantum confinement (Da Silva Bruckmann *et al.,* 2020; Da Silva Bruckmann *et al.,* 2022), which strongly affect the extensive surface area-to-volume ratio. The increased surface area increases the textural qualities, including ability to absorb fluid. Due to these modified characteristics, nanomaterials have been given great attention with regard to biomedical uses such as bioimaging, cellular imaging, as well as drug delivery.

Nanomaterials have been used in clinical diagnostics and therapeutic applications in a wide variety of nanomaterials nowadays: carbon-based nanomaterials (CBNs), metallic nanoparticles and nanocomposites to name but a few (Chandra and Segal, 2016; Mandal *et al.,* 2018). Gold and silver nanoparticles have been utilized as metallic nanoparticles in the purification of water, whereas the use of gold nanoparticles (GNPs), also known as the gold magic bullets, have demonstrated potential use in treating cancer (Lin *et al.,* 2013; Mahato *et al.,* 2019). Also, CBNs have exhibited high capability for drug delivery as well as biosensing (Chandra *et al.,* 2011).

Although nanoparticles (NPs) are popular, there are concerns about their possible toxicity because these unique properties are the reason behind the popularity of nanoparticles in science and technology (Bondarenko *et al.,* 2021). Silica nanoparticles (SiNPs), as a different nanoparticle system, have received much research interest owing to their distinctive features like extensive surface area, control of pore size, high biocompatibility, capacity to enclose hydrophilic and hydrophobic molecules, as well as scalable production (Almatroudi, 2025). These beneficial features have made their usage possible in various industries including agriculture, energy storage, photovoltaics, and the food industry; most of the research work has however focused on biomedical applications (Devi and Balachandran, 2016; Liberman *et al.,* 2014).

The ability to have a specific control over size of particle, morphology, porosity, crystallinity; and the availability of nanosilica in various structural shapes, such as hollow and core-shell structures, rod-shaped nano-particles and silica gels; have further increased applications (Priti and Sameer, 2019). Specifically, silica nanorods and nanospheres with different aspect ratios are actively studied in diagnosis and therapeutic works (Knopp *et al.,* 2009). Although nanoparticle size and shape have a greater impact on cellular uptake and biodistribution, porosity is a more important factor to consider when it comes to loading payload and efficiency of delivery. Due to their widespread application in medicine, pharmaceuticals, pigments, humidity detectors, and medical insulation materials, silica nanoparticles, or silicon quantum dots, are viewed more attentively in medical research than bulk silicon materials (Maity and Polshettiwar, 2017; Na *et al.,* 2019).

Although silica nanoparticles have made great strides in the research field, their toxicity mechanisms are not fully comprehended, especially in the context of long-term effects and their influence with the biological arrangements. Thus, the recent developments in the production of silica nanoparticles are reviewed, with an emphasis on the environmentally friendly and sustainable ways of preparation, such as thermal and wet techniques. It also investigates the structural diversity of SiNPs i.e. solid, mesoporous, shaped and etched and compares the toxicological profile of the same to justify their efficiency.

## Methods of Obtaining Silica-Based Nanoparticles

The capability to regulate the structure of nanoparticles has become a key field of study in nanomaterials (Brinker and Scherer, 2013). It has been shown that adjustment of the main reaction parameters (pH, temperature, surfactant behaviour and structure, condensation rate of silica precursors) can be used to produce nanoparticles with desired dimensions, morphologies, and surface properties. These tuneable characteristics and the presence of nanosilica in various forms have led to the increasing popularity of nanosilica in an extensive variety of applications: solid (Shirshahi and Soltani, 2014), mesoporous (Bolong *et al.,* 2023), shaped (Parul *et al.,* 2023), and etched architectures (Albert *et al.,* 2021). Additionally, the further comprehension of the synthesis and preparation strategies is needed to achieve high performance of nanoparticles, especially those that can find use in medical diagnostics and therapeutic interventions (Hu *et al.,* 2025).

Solid Silica Nanoparticles

Amorphous silica nanoparticles (solid SiNPs) have found extensive applications in enzyme encapsulation, imaging, drug delivery and therapeutic formula use, frequently in a stabilizing role, among other applications in technology. Such nanoparticles are associated with a characteristic internal structure and are usually non-morphological (Rangararajan and Venkatachalam, 2018; Okoturo-Evans *et al.,* 2013; Machizuki *et al.,* 2021). Two popular methods are usually used to produce solid silica nanoparticles, namely, thermal and wet methods, which are described in the following sections.

Thermal method

Silica nanoparticles produced through the thermal procedure are generally known as fumed or pyrogenic SiNPs (Yang *et al.,* 2014; Di Cristo *et al.,* 2016). Silicon tetrachloride ($SiCl_4$) is burned in a hydrogen-oxygen flame reactor over a temperature above 1000 °C to produce silicon dioxide fumes (SiO_2). The silica particles made are usually between 5 and 50 nm. This is regarded as the aerosol route and consists of creating aerosols via an atomizer (Dossel *et al.,* 2014; Mebert *et al.,* 2017). In the cooling process, particles of pyrogenic silica are gathered into agglomerates, and off-gas with hydrochloric acid (HCl) is removed, after that the solid substance is segregated. Another step of deacidification eliminates HCl covered on the particle surfaces. The reaction parameters (e.g. composition of feedstock and flame conditions) can be carefully adjusted to give nanosilica of a desired physicochemical nature (Rasmussen *et al.,* 2013).

$$2H_2 + O_2 \longrightarrow 2H_2O \qquad\qquad 1$$
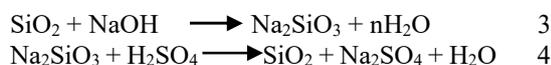$$SiCl_4 + 2H_2O \longrightarrow SiO_2 + 4HCl \qquad 2$$
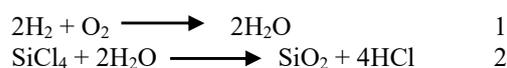
Wet method

The wet method of synthesis of nanoparticles of silica produces hydrated or colloidal particles of silica unlike silica produced using thermal methods. The wet method is more frequently used in the preparation of SiNPs compared to the thermal methods due to its relatively mild conditions of reaction. The method involves various paths of synthesis such as; sol-gel chemistry, Stober synthesis, acid precipitation, and microemulsion.

Acid precipitation method

The given method presupposes the acidification of an alkali metal silicate solution with a diluted acid to create a gelatinous precipitate, which is further filtered, washed to eliminate residual salts, dried, and ground to achieve colourless and microporous silica particles (Rasmussen *et al.,* 2013; Younes *et al.,* 2018). Acid precipitation is also a common technique of harvesting SiNPs from silicon-rich biomass sources including bamboo leaves (Rangararaj and Venkatachalam, 2018), sugarcane bagasse (Athinarayan *et al.,* 2017), paddy straw (Uba *et al.,* 2021), and other biological materials.

Essentially, the biomass undergoes high temperature calcination in which ash is obtained, followed by the treatment with 2.5 N sodium hydroxide (NaOH) stirred on a mixer at about 100 °C for 2 – 3 hours. The silicate-containing supernatant is thereafter titrated gradually using 5 M sulphuric acid to bring the pH into the range of precipitation. The resulting product is then dried under controlled temperature normally about 80 °C. In the pH adjustment the system passes through the sol – gel step. The reaction mechanism is the same, however, different studies have varied synthesis conditions, such as the concentration of NaOH, temperature of the calcination, pH, and temperature of drying.

$$SiO_2 + NaOH \longrightarrow Na_2SiO_3 + nH_2O \qquad 3$$
$$Na_2SiO_3 + H_2SO_4 \longrightarrow SiO_2 + Na_2SO_4 + H_2O \qquad 4$$

Chemical sol-gel method

In contrast to silica nanoparticles synthesized by thermal processes, hydrated or colloidal silica is originally produced by the wet method of synthesis. Due to its relatively mild reaction conditions, wet method is more generally used to fabricate SiNPs compared to thermal methods. This method involves multiple synthesis pathways, which are sol-gel chemistry, Stober synthesis, acid precipitation, and microemulsion.

Stöber synthesis

This is virtually the common physicochemical way of preparing silica nanoparticles, initially reported in 1968. This is done by adding controlled quantities of tetraethyl orthosilicate (TEOS), or other silicate precursors to a stirred as well as a water mixture, ethanol and ammonia. Proportion of these three components is the main determinant of the particle size (Priti *et al.,* 2019). As an example, Mao et al.

(2018) used fly ash as a silica source, which is a byproduct of coal combustion in thermal power plants, n-butanol as a solvent, and cetyltrimethylammonium bromide (CTAB) as a catalyst. The strategy minimizes both the cost of disposal and environmental impact.

Several researches have been carried out on the kinetics and mechanisms of the Stöber process so as to obtain a narrow control of particle size, morphology and uniformity. Nozawa et al. (2005) also noted that the percentages of addition of TEOS have direct impact on the size of particle with high addition rates facilitating greater nucleation and the production of smaller particles (Delville, 2005). More research has found out that solvent to TEOS ratio is a key determinant that controls the size of the particle during Stöber synthesis (Shimura and Ogawa, 2007).

Microemulsion method

Microemulsion technique can be employed for the synthesis of monodisperse SiNPs. Water in oil (w/o) microemulsion is a clear, isotropic, thermodynamically stable system, which is made up of water, oil, and a surfactant (Arriagada *et al.,* 1999). Natalia et al. (2018) used this method to prepare SiNPs through the sol-gel method, where methanol was adopted as a co-surfactant, TEOS was used as a silica source, poly (oxyethylene tert-octyl phenyl ether) (Triton X-100) was used as a surfactant, and cyclohexane was used as an oil phase. Once the w/o microemulsion had been formed, TEOS was added and all molar ratios of the components were taken care of. Ethanol was then integrated to dissect the microemulsion of the surfactant after which the nanoparticles were washed and centrifuged to extract them.

Reverse micelles in this system are created when polar head groups of the surfactant are turned to make water-filled nanocavities. The dissolution of the surfactant molecules is carried out in the organic solvent to create spherical micelles and the silica hydrolysate and condensation is done at the interface of the micelles. In the presence of a controlled environment and the addition of silicon alkoxide and catalyst, nanoparticles are grown in these confined cavities.

A common method involves the mixing of Triton X-100, hexanol and cyclohexane to create the microemulsion. Aqueous ammonia is subsequently integrated to acts as the source of water and catalyst

for hydrolysis of TEOS. Nanoparticles of varied sizes can be achieved by varying the concentration of ammonia (Bagwe *et al.,* 2004). This is also applicable in the generation of dye-doped nanosilica that finds considerable application in bioimaging since it exhibits substantial fluorescence and high photostability (Barrabino, 2011).

Synthesis by microemulsion is relatively fast, and provides reasonable control over nanoparticle formation but is expensive due to the use of surfactants, organic solvents and additional recovery and purification processes are needed, especially when it comes to large scale synthesis. Conversely, the Stöber approach is more popular and offers more opportunities of additional improvements.

Mesoporous Silica
Porosity is categorized based on size of pore (Table 1; Barrabino, 2011). In mesoporous silica, porosity refers to a periodically ordered arrangement of uniformly sized pores embedded within an amorphous silica framework (Prabha *et al.,* 2021). In 1992, Mobil Oil Corporation reported the detection of the M41S family of mesoporous silica materials, characterized by pore diameters ranging from 2 to 10 nm (Prabha *et al.,* 2021). Among these, Mobil Composition of Matter (MCM) materials—specifically MCM-41 and MCM-48 are the most widely studied, featuring two-dimensional hexagonal and three-dimensional cubic pore architectures, respectively (Tzankov *et al.,* 2014; Caras, 2011).

Mesoporous silica nanoparticles (M-SiNPs) exhibit a range of advantageous physicochemical properties, including tuneable sizes of pore categorically range from 2 and 30 nm, large pore volume, large specific surface area, narrow pore size distribution, uniform mesoporosity, adaptable morphology, and excellent biocompatibility and biodegradability. These features make M-SiNPs suitable in bioimaging, catalysis, as well as delivery of drug (Liu *et al.,* 2018). In addition, the pore environment and aperture dimensions can be engineered to selectively accommodate target molecules (Lu *et al.,* 2007), and M-SiNPs can also serve as models or samples for the synthesis of other nanomaterials (Ren *et al.,* 2021).

The internal architecture of mesoporous silica nanoparticles is commonly directed using amphiphilic molecules as structure-directing agents. Depending on synthesis conditions, two principal mesostructures can be obtained: the two-dimensional hexagonal MCM-41 and the three-

dimensional cubic MCM-48. Early mesoporous silica materials were initially developed for catalytic applications (Prabha *et al.,* 2021). For biomedical use, smaller particle sizes and uniform morphology are essential to improve biocompatibility. For example, a modified Stöber method was employed in 1997 to synthesize submicrometer MCM-41 particles (Grün *et al.,* 1997). Subsequent dilution of surfactant solutions enabled the production of approximately 100 nm MCM-41 particles (Cai *et al.,* 2001), while dialysis techniques yielded particles smaller than 50 nm (Suzuki *et al.,* 2004). Averagely, M-SiNPs possess high surface area and pore capillarity that can be readily synthesized with a range of chemical groups for theranostic applications.

Table 1: Classification of porous material (Prabha *et al.,* 2021)

Type of porous material	Diameter of pores (nm)
Microporous	pore diameter < 2
Mesoporous	2 < pore diameter < 50
Macroporous	pore diameter > 50

Shaped Silica Nanoparticles
The shape of nanoparticle is critical in deciding the in vivo performance. Strategies that are commonly employed to regulate the morphology of nanoparticles comprise the incorporation of shape-directing templates and dopants in the synthesis process, and making significant changes to reaction constraints like temperature and pH. Indicatively, Reiter *et al.* (2007) reported the preparation of nanocomposites made out of a nanoscale metal-organic framework (NMOF) core with a silica shell. Single, multilayered silica shells of separate thickness, aspect ratio and size were made by depositing a series of silica layers onto the NMOFs, and then discarding the core by reducing the pH. Similarly, Han *et al.* (2013) used two soft templates, i.e., cetyltrimethylammonium bromide (CTAB) and C12-OH, to synthesize silica nanoparticles with various morphologies, i.e., spherical, rugby-shaped, peanut-like, hollow, and yolk-shell silica nanoparticles. These varies shapes were acquired through the changing reaction temperature and the concentration of C12-OH.

Wang *et al.* (2017) adopted a new technique in the development of single-micelle epitaxial growth strategy which relied on a low-surfactant oil-water

biphasic system to produce virus-like nanoparticles with a spike and tubular surface of mesoporous silica nanoparticles (MSNs). They stated that this virus-mimicking morphology improved cellular uptake, preferred certain internalization pathways and extended blood circulation time ($t_{1/2}$ = 2.16 h) by far than the conventional MSNs ($t_{1/2}$ = 0.45 h).

Etched silica nanoparticles
Etched silica nanoparticles are produced by removing certain chemical structures or elements selectively by physical or chemical treatment from nanoparticles. This approach involves the development of hollow mesoporous structures by taking advantage of the silica particles differences between the core and shell where the interior can be selectively removed and the shell can be retained (Chen *et al.,* 2009). The large percentage of the Si-OH groups to the Si-O-Si groups in the solid silica core compared to the mesoporous shell is a basis of selective etching which usually results in increased condensation during the growth of mesoporous particles. This method allows one to prepare uniformly distributed hollow mesoporous silica with the size of the pore under control.

Chen *et al.* (2019) synthesized homogenous mesoporous silica nanoparticles (MSNs) of an ellipsoidal and uniform shape by synthesizing solid silica followed by deposition of mesoporous layers onto an ellipsoidal and core of iron oxide nanocrystals. It was also shown in the study of Rosu *et al.* (2016) that porous silica particles without a template can be etched with a 3 mM aqueous solution of sodium hydroxide. Aside from alkaline etching or hydrothermal etching, Yu *et al.* (2011) utilized acidic etching using either HCl or H_2SO_4, frequently coupled with hydrothermal treatment, to form hollow or yolk-shell structures. Figure 1 displays some of the different of ways through which silica nanoparticles can be synthesized.
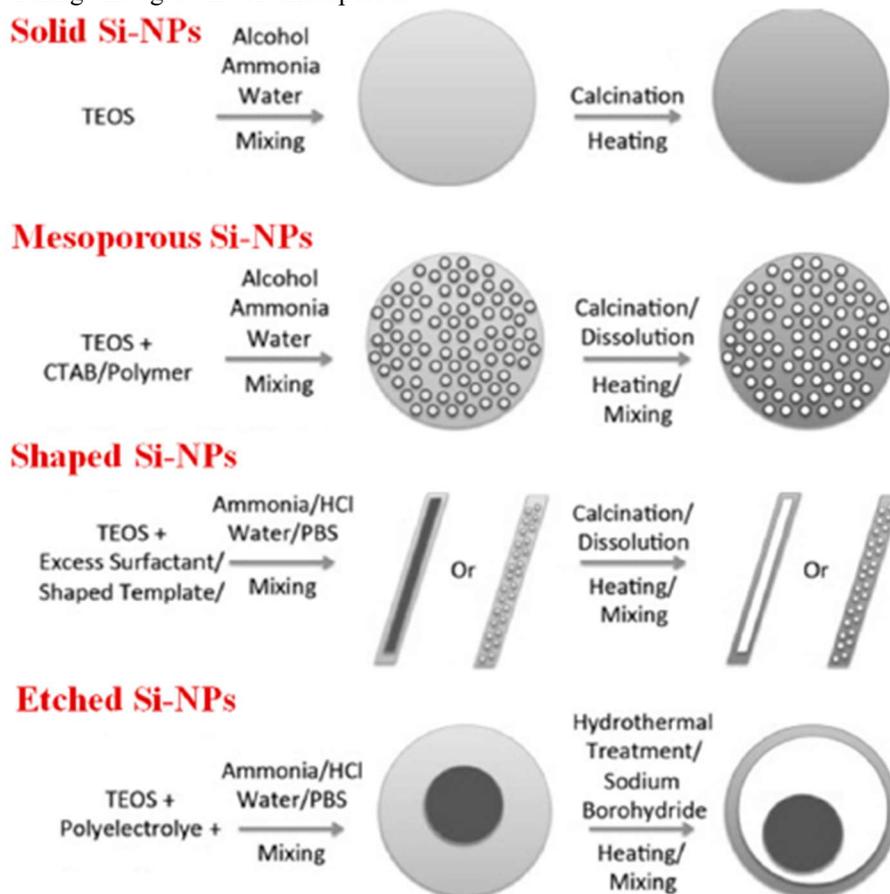

Fig. 1. Different technique of producing silica nanoparticles. Adapted from Liberman *et al.* (2014).

Biomedical Applications

Biosensor

Sensors are analyzing machines that consist of a transducer and an active sensing unit (Kuswandi, 2019). They can be broadly categorized as chemical sensors and biosensors, and the latter are used to recognize biological molecules, such as enzymes, antibodies, nucleic acids, cells, and tissues (Verma, 2017; Yogeswaran and Chen, 2008). Combination of biocompatible and highly conductive nanomaterials, including gold nanoparticles (GNPs), carbon nanotubes (CNTs), and quantum dots (QDs), has improved biosensors performance significantly (Yang *et al.,* 2015; Mahato *et al.,* 2016).

Promising materials within the electrocatalysis and electrochemical sensing are porous silicate materials, such as MCM-41 and SBA-15, which have ordered porous structures, extensive surface area, limited distributions of pore sizes, and can tune their pore sizes (Melde and Johnson, 2010). In particular, mesoporous silica nanoparticles (MSNs) can carry high concentrations of biomolecules, including antibodies, mediators, and enzymes, in their high pore volume and vast surfaces, and can respond quickly and detect small amounts of analytes (Tu *et al.,* 2016). Consequently, the electrochemical biosensors have increased in detecting different analytes, such as cysteine (Amiri *et al.,* 2017), cholesterol (Hui *et al.,* 2015), glucose (Saei *et al.,* 2013), hydrazine (Liu *et al.,* 2016), dopamine (Huang *et al.,* 2015), hydrogen peroxide (Ju and Chen, 2015), and kanamycin (Qin et al.).

Optical biosensors are also greatly appreciated because of their sensitive detection and they are common in the fields of environmental monitoring, pharmaceuticals, healthcare, homeland security and defense (Amiri *et al.,* 2017). As an example, Huang and Li (2013) came up with a non-enzymatic hydrogen peroxide (H_2O_2) sensor made with a hybrid of graphene oxide and silica nanoparticles. Amperometric examination indicated that this composite improves electrochemical action in alkaline mediums attaining low-detecting threshold of 2.6 mM and outstanding reproducibility. Tan *et al.* (2017) also proved that functionalized mesoporous silica may be used to treat heart failure and H_2O_2 detection in the same time. The mesoporous silica nanoparticles were besotted with captopril, a medication used in cardiac arrest in their system, and an H_2O_2 -sensitive probe was connected to the particles surface. Luminol/H2O2 chemiluminescence was used to detect the component, and the platform had high loading capacity and release of the component (Chen *et al.,* 2016). All in all, the findings draw a conclusion that MSNs have great potential in the future as early disease diagnosis, pathogen detection, and electrochemical biosensing.

Drug delivery

Silica nanoparticles (SiNPs) have gained wide recognition as drug and gene delivery vectors for nanomedicine. Nevertheless, the biodistribution, toxicity and immune response of silica and functionalized derivatives of silica need to be considered (Biju, 2014). SiNPs tend to be further categorized as surface-functionalized nanoparticles and mesoporous nanoparticles, the latter being especially common in drug delivery (Chowdhury, 2018). Surface silanol groups allow functionalization of mesoporous SiNPs, which can be loaded and release drugs under control (Vallet-Regi *et al.,* 2007). Their special properties are allowed to carry out the transportation either in the blood or through epithelial barriers to the target tissues with delivery of therapeutic agents.

Zhou *et al.* (2020) made an erlotinib-loaded hollow mesoporous SiNPs to create a gel at moderate room temperature to deliver a sustained release of drugs for the treatment of non-small-cell lung cancer. On the same note, Chen *et al.* (2019) included the anticancer agents, doxorubicin and cyclosporin, in photoluminescent graphene quantum dot-coated mesoporous SiNPs to trigger the breakage of the DNA in the lung cancer cells. According to Madajewski *et al.* (2020), ultrasmall (<8 nm) core-shell SiNPs conjugated with a gefitinib-dipeptide linker exhibited increase dose of drug, dose of drug potency and decreased dose-limiting toxicity. In a second study, Sun *et al.* (2018) took bevacizumab and loaded it into SiNPs to attain sustained release and a long residence time in the vitreous during antiangiogenic therapy by nanocasting. The delivery of drugs using silica has also been used in ophthalmology. SiNP eye drops that contained sodium nitroprusside caused the production of nitric oxide (NO) in the canal (Schlemm) and the trabecular meshwork and triggered soluble guanylate cyclase-activation and lowered the intraocular pressure (IOP) and was used to treat primary open-angle glaucoma. Liao *et al.* (2017) showed that mesoporous SiNPs functionalized with gelatin and loaded with pilocarpine had a high loading capacity and also maintained their release over 36 days after intravitreal injection. Mesoporous SiNPs conjugated with epithelial cell adhesion

molecule (EpCAM) have been used in retinoblastoma (RB) based on a rare retinal cancer (Dimaras *et al.,* 2015). This strategy tremendously enhanced the expression level of caspase-3 over free carboplatin because of receptor-mediated endocytosis (Qu *et al.,* 2017). Silica based on biomass has been used in other drug delivery systems. As an example, the silica nanoparticles made out of rice husks and integrated into the polycaprolactone nanofibers have been used in the delivery of allantoin (Ke *et al.,* 2016). In a different paper, 5-fluorouracil was immobilized using biomass silica nanoparticles that were coated with chitosan; this relatively inexpensive and biocompatible system was applicable to cancer cells lines (MCF-7 and A549) (Dhinasekaran *et al.,* 2020).

Bioimaging

Silica nanoparticles (SiNPs) have become useful in the delivery of drug delivery and contrast imaging agents (Baeza and Vallet-Regi, 2020), providing useful information about the disease condition and its evolution (Fig. 2). They are easily modified to work in diverse modalities of molecular imaging, such as optical imaging, magnetic resonance imaging, radionuclide imaging, computed tomography, photoacoustic imaging, ultrasound and Raman imaging (Tang and Cheng, 2013). As an example, the Prieto-Montero *et al.* (2020) synthesized a functionalized SiNP with rhodamine 101, which allows covalent fixation or mechanical fixation of HeLa cells and enables their visualization. In a different study, Rao *et al.* (2018) prepared reactive oxygen species (ROS)-responsive mesoporous SiNPs (M-SiNPs) by the synthesis of a gadolinium (Gd)-DOTA complex to serve as a gatekeeper and PEG-conjugated chlorin e6 to serve as the responsive element to increase the intensity of T1 MRI signal.

Fluorescent conjugated with bio-derived silica nanoparticles are also being used to form biocompatible imaging probes (Pandey *et al.,* 2014). An example of this is the mesoporous silica nanoparticles prepared using rice husk that were loaded with green fluorescent carbon dots, giving rise to a composite with both high fluorescence and drug-loading capacity compared to unmodified carbon dots, therefore, making them appropriate for theranostics. Likewise, biogenic silica-based composites that are doped with rare earth elements (europium and gadolinium) were prepared through microwave-based combustion (Araichimani *et al.,* 2020). These silica doped matrices showed the possibility of T1-weighted MRI and the fluorescence of these materials, which means that bioengineered silica composites produced by biogenic sources have the possibility to reduce cost in the creation of bioimaging contrast agents.
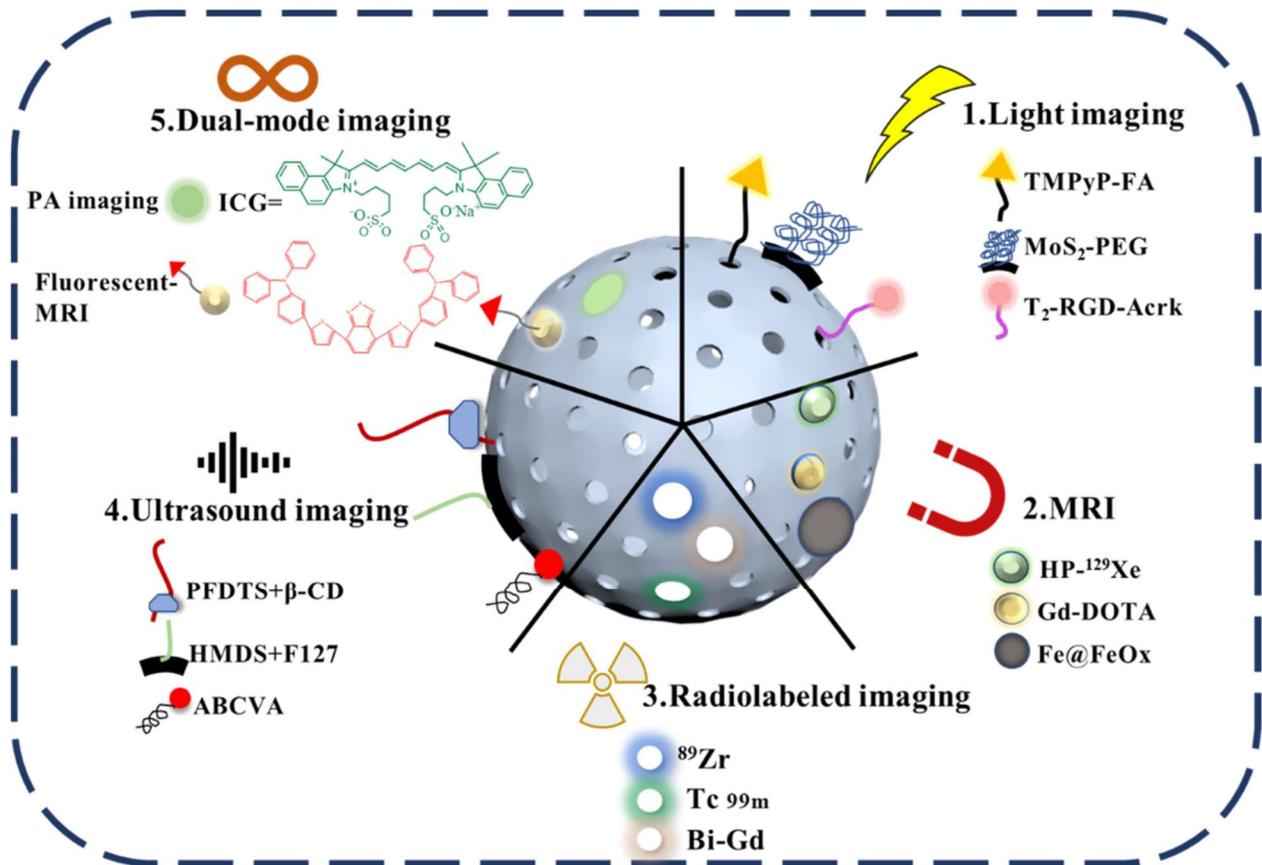
Fig. 2. Medical diagnosis using functionalized SiNPs. (1) Imaging with light. (2) MRI contrast substances. (3) Radiosensitizers for radiolabeled imaging (4) Ultrasound imaging in real time. (5) Dual-mode imaging using fluorescence MRI and PA imaging. (Yang *et al.,* 2020)

Toxicological Assessment of Silica Nanoparticles

Nanomaterials have tremendous potential in biomedical uses as they have unique physical and chemical characteristics. The SiNPs have various benefits over other nanomaterials such as large surface areas, surfaces that can be easily manipulated, uniform cylindrical mesopores, variable particle sizes and varied morphologies. These advantageous structural properties have contributed to increasing their application in biomedicine. It is therefore necessary to evaluate the biocompatibility of solid and mesoporous silica on a molecular, cellular, and tissue scale. Despite many systematic investigations, carried out to comprehend and assess the possible negative impacts of MSNs on the biological systems, their biocompatibility is still a point of debate. The current literature shows conflicting results, as it points to the necessity of obtaining more comprehensive data regarding the potential risks that can be caused by silica to integrate it in its safe clinic-to-clinic translation.

Effect of Size

An important physicochemical parameter that is mostly linked to the toxicity of materials is the nanoparticle size (Feliu and Fadeel, 2010). Since nanomaterials are comparable in diameter to the biological molecules, there is a general assumption that they tend to be more readily absorbed by cells. They also have an extensive surface area to volume ratio which increases the available surface in interacting with the cellular components. Upon nanoparticles being introduced into biological systems they normally undergo a coating effect, known as protein corona, whereby cytosolic proteins adsorb onto the surface which may have an effect on various cellular processes.

Vallhov *et al.* (2007) compared the behaviour and cells uptake of MSNs of varying sizes. They found that bigger MSNs tended to get out of endolysosomes as compared to smaller ones. The paper by Lu et al. (2009) also looked into size-dependent uptake in HeLa cells and reported uptake hierarchy of 50 nm above 30 nm above 110 nm above 280 nm above 170 nm and the uptake of 50

nm particles were 2.5 times greater than 30 nm particles. Hu *et al.* (2011) reported a study that measured the effects of particle diameter on migration and adhesion in human dermal fibroblasts by exposing the cells to MSNs of 80 and 500 nm and discovered that the bigger the size of particle, the more it was taken up by the cell.

There are some studies indicating that smaller MSNs having similar surface areas demand higher cellular energy to be internalized that might enhance cellular damage and cell death. He *et al.* (2011) compared the biodistribution and excretion of mesoporous SiNPs of 80 to 360 nm into the body and in the urine after intravenous injection. Nanoparticles did not cause any serious toxicity or inflammatory effect in the tissues, but accrued in the organs as arranged: liver > spleen > lung > kidney/heart. It accumulated within the first five days of injection but reduced by a big margin after one month. Also, the urine on 30 minutes post-injection had a higher concentration of larger particles which serves to indicate that the reticuloendothelial system (RES) is more efficient in clearing larger nanoparticles than smaller particles.

Li *et al.* (2012) evaluated the cytotoxicity of porous silica particles with the sizes of 190, 420, and 1220 nm, they noted that the 190 and 420 nm particles had great cytotoxicity as the assiduousness increased to 25 mg/mL, while on the contrary the 1220 nm particles showed lower cytotoxicity because of the decrease in endocytosis. Moreover, to investigate size-dependent haemolysis, Lin and Haynes (2010) synthesized MSNs of 25 to 225 nm and showed that size dependence of haemolytic activity was dependent on particle size and dose.

Effect of Morphology

According to Geng et al. (2007) nanomaterials are capable of taking different shapes such as sphere, cylinders, filament, ellipsoids, planar surfaces and other shapes. The morphology of the particles is also very vital in the intensity of toxicity when the nanoparticles come in reaction with the structures of the cells. Certain researchers indicate that nanoparticles when taken in high aspect ratios have the potential to destabilize cell membrane pores and disrupt ionic homeostasis across the cell wall. Indicatively, Trewyn et al. (2007) prepared MSNs, which are spheres and rod-shaped to have similar surface charge, surface area and size of the pores but had different cellular transport characteristics. The more rapid internalization involved the introduction of the spherical particles in the cytoplasm but the rod-shaped particles demonstrated low internalization. In order to understand this disparity, a theoretical framework that was proposed in 2005

came up with the concept of wrapping time whereby the rate at which endocytosis depends on wrapping speed of membranes (Dasgupta *et al.,* 2014).

Morphologies of MSN are different and possess varied interactions with cell membranes which induces their different intracellular signalling pathways on uptake. According to Huang et al. (2010), MSNs of high aspects ratio were found to enter cells faster than lower aspect ratio MSNs. Mesoporous silica nanoparticles with aspect ratios of 1:1; 2:1 and 4:1 were also produced and were identified to result in more cytoskeletal disruption and cytotoxicity in higher aspect ratio. On the same note, Yu et al. (2011) examined the impact of different types of silica nanoparticles namely silica nanorods with an aspect ratio of 2, 4, and 8; MSNs (120 nm, AR 1); as well as nonporous Stober silica (115 nm) on lung carcinoma cells, erythrocytes and macrophages. After comparing the toxicity pattern on cellular interaction and toxicity, they concluded that surface modification and particle porosity particle porosity had a significant influence on the toxicity pattern, with amine-modified mesoporous silica or amine-modified Stober being less toxic than nonporous Stober or mesoporous silica (AR 1-AR 4).

Tang and Cheng (2013) assessed silica toxicity in immunocompetent mice and found the maximum tolerable doses of silica of different types. Amino modified Stober silica (45mg/kg) was found to be most tolerated with mesoporous silica (AR 1, 2, 8) having tolerances of 30/65mg/kg. Even greater tolerances of up to 100 to 150 mg/kg were seen with amine-modified mesoporous silica (AR 1, 2, 8). Chauhan et al. (2013) also investigated the biological reaction of various mouse organs such as the lungs after being exposed to MCM-41 and calcified SBA-15 200 mg/ ml particles at various time points. They did not find any important changes in the tissue microstructure or bioenergetics that would indicate that the calcined MSNs are biocompatible when taken at the correct doses.

Huang *et al.* (2011) examined the clearance and biodistribution of the rod-shaped mesoporous silica nanoparticles with an aspect ratio of 1.5 and 5 in mice labeled with FITC. The liver, spleen, and lungs had high fluorescence signals, which meant that they were taken up by the reticuloendothelial system (RES). It was interesting to note that the movement of the particles with higher aspect ratios lasted longer than 24 hours but those with lower aspect ratios were eliminated faster which suggests that large aspect ratio rod-shaped mesoporous silica

nanoparticles are able to circulate longer than short rods (Huang *et al.,* 2011; Yu *et al.,* 2012).
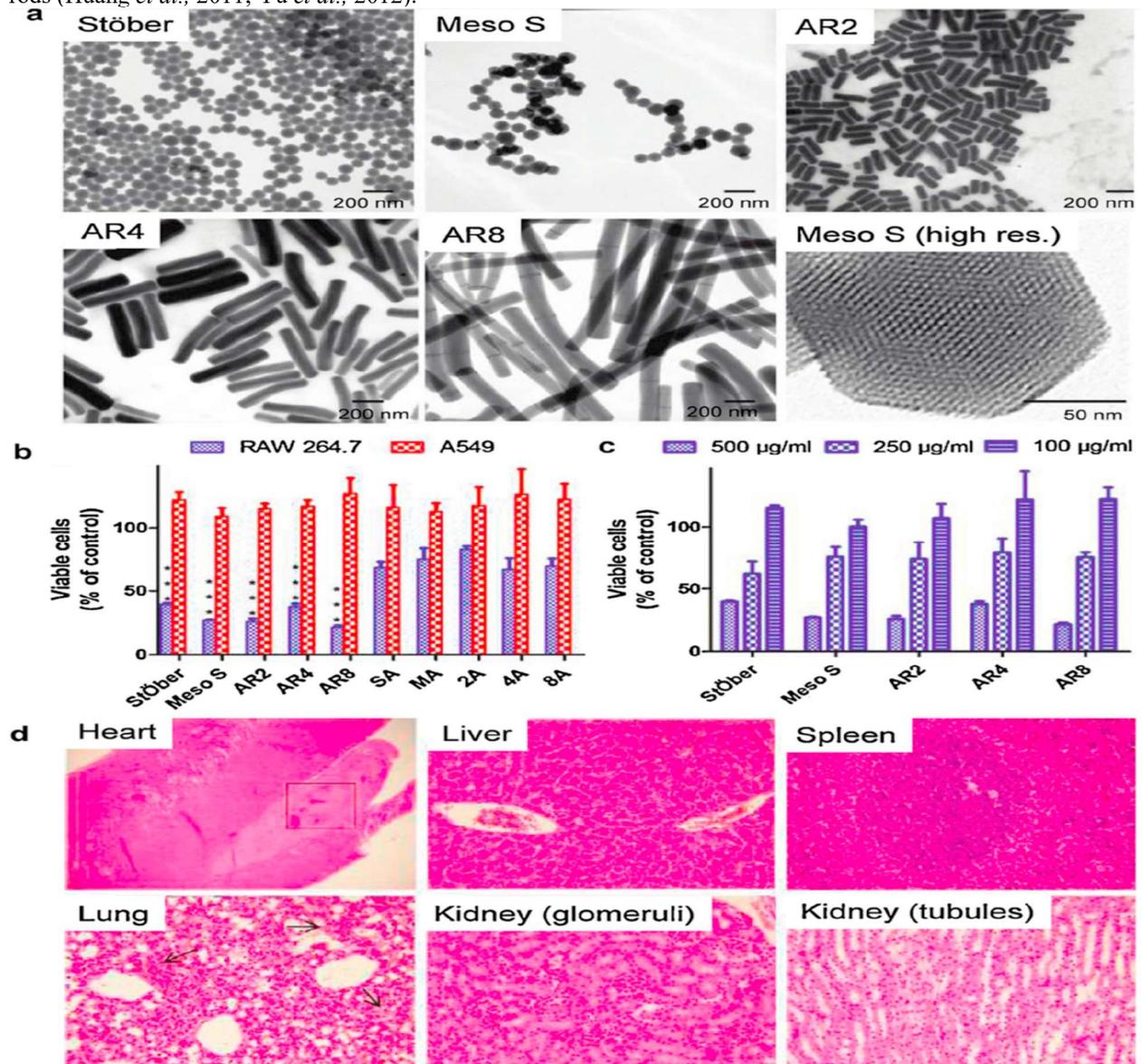

Fig. 3. Effects of SiNP size, shape and surface characteristics on toxicity. (a) Transmission electron microscopy (TEM) images of Stober silica nanoparticles (average diameter =115 nm), mesoporous silica nanoparticles (the Meso S, average diameter=120 nm) and mesoporous silica nanorods (NRs) with aspect ratio (AR) of 2 (AR2), 4 (AR4), and 8 (AR8), and a high-resolution image of a single Meso S particle. (b-c) The outcome of acute cytotoxicity tests conducted using the dissimilar forms of SiNPs. Reprinted by permission of the American Chemical Society, Yu et al, (2011) panels (a-c). (d) Light microscopy records at organ recovery following administration of Stober SiNPs (dose = 600mg/kg). Cited in Yu et al. (2011) with the permission of the American Chemical Society, 2012.

Effect of Surface Properties

Nanomaterials particles with neutral and positive surface charges possess higher chances of interacting with cell membranes compared to negatively charged particles (Chen *et al.,* 2010). Therefore, the surfaces of MSN are often altered to become more cellular and have better biocompatibility. Lin *et al.* (2011) functionalized MSNs with different groups, such as, guanidinopropyl (GP), 3-aminopropyl (AP), 3-[N (2-guanidinoethyl)-guanid]inepropyl (GEGP) and N-folate 3-aminopropyl (FAP). They determined that the uptake of HeLa cells was directly proportional to surface charge as follows: MCM-41

< AP-MCM-41 < GP-MCM-41 < GEGP-MCM-41 < FAP-MCM-41. In addition, cells with folate receptors, demonstrated superior internalization of FAP-modified MSNs, which denoted affinity through a receptor.

Polyethylenimime (PEI), polylysine, chitosan, polyamidoamine dendrimers, and endosome-disrupting peptides are polycationic materials that are frequently used to surface MSNs and enhance cellular uptake and endosomal escape (Slowing *et al.,* 2006). PEI, specifically, is also a good "proton sponge" as it is amine high in concentration, which neutralizes acidification of the endosomes and allows escape as the pH rises (Chen *et al.,* 2011). Also, the use of photosensitive porphyrins on MSN surfaces permits photo-specific release to the endosome enhancing efficiency of delivery (Zhao *et al.,* 2010). PEGylation can also be commonly used to enhance surface hydrophilicity and decrease nonspecific interactions (Chang *et al.,* 2007; Chung *et al.,* 2007).

This indicated that solid silica nanoparticles are more cytotoxic than 100 nm round MNS and nonporous silica reported a high haemolytic activity than porous silica. The reason behind this difference is to a large extent on the effective contact surface area: that is total surface area of mesoporous silica nanoparticles is high, but the porous structure of the material means that the contact surface with cell membranes, proteins, and other cellular components is less common, resulting in decreased cytotoxicity.

Conclusion

The growing need for high-quality materials in different spheres, especially biomedicine, has promoted active research on silica nanoparticles (SiNPs). Some of the synthesis methods have been summarized in this review and they included etching methods, mesoporous silica, shaped silica nanoparticles and solid silica synthesis. The other determinants of biocompatibility of SiNPs that we studied include size of the particle, cell type, shape and surface charge distribution. The advancement in the synthesis as well as surface engineering of SiNPs is significantly important, as they will be used in the future in the biomedical sphere, providing a universal platform of multifunctional therapeutic and diagnostic carriers.

References

Albert, G-C., Sina, S., Tom, A. J. W., Relinde, J. A. V-D-M., Ramakrishna, K., Maarten, B., Alfons, V-B., and Marijn A.V-H. (2021), In situ study of the wet chemical etching of sio$_2$ and nanoparticle sio$_2$ core−shell nanospheres, *ACS Appl. Nano Mater.*, 4,1136−1148.

Amiri, M., Salavati-Niasari, M., and Akbari, A. (2017), A magnetic CoFe$_2$O$_4$/SiO$_2$ nanocomposite fabricated by the sol-gel method for electrocatalytic oxidation and determination of L-cysteine. *Microchim Acta*, 184(3), 825–833.

Araichimani, P., Prabu, K., Kumar, G.S., Karunakaran, G., Van Minh, N., Karthi, S., Girija, E., Kolesnikov, E. (2020), Rare-earth ions integrated silica nanoparticles derived from rice husk via microwave-assisted combustion method for bioimaging applications, *Ceram Int* 46(11),18366–18372.

Arriagada, F. J., and Osseo-Asare, K. (1999), Synthesis of nanosize silica in a nonionic water-in-oil microemulsion: effects of the water/ surfactant molar ratio and ammonia concentration. *J. Colloid Interface Sci.*, 211,210−220.

Baeza, A., and Vallet-Regi, M. (2020), Mesoporous silica nanoparticles as theranostic antitumoral nanomedicines, *Pharmaceutics*, 12 (10).

Bagwe, R. P., Yang, C., Hilliard, L. R., and Tan, W. (2004), Optimization of dye-doped silica nanoparticles prepared using a reverse microemulsion method. *Langmuir*, 20, 8336−8342.

Barrabino, A. (2011). Synthesis of mesoporous silica particles with control of both pore diameter and particle size. Master's thesis

Biju, V. (2014), Chemical modifications and bioconjugate reactions of nanomaterials for sensing, imaging, drug delivery and therapy, *Chem Soc Rev*, 43(3),744–764.

Bolong, X., Shanshan, L., Rui, S., and Huiyu L. (2023), Multifunctional mesoporous silica nanoparticles for biomedical applications, *signal transduction and targeted therapy*, 8,435

Bondarenko, O., Mortimer, M., Kahru, A., Feliu, N., Javed, I., Kakinen, A., and Zhao, Y. (2021), Nanotoxicology and

nanomedicine: the yin and yang of nano-bio interactions for the new decade, *Nano Today,* 39,101184.

Brinker, C.J., and Scherer, G.W. (2013). Sol-gel science: the physics and chemistry of sol-gel processing, *academic press*, New York

Cai, Q., Luo, Z.S., Pang, W.Q., Fan, Y.W., Chen, X.H., and Cui, F.Z. (2001), Dilute solution routes to various controllable morphologies of MCM-41 silica with a basic medium. *Chem Mater,* 13(2),258–263.

Caras, A. (2011). Glucan particle delivery of mesoporous silicadrug nanoparticles, *UMASS Medical School.*

Chandra, P. and Segal, E. (2016). Nanobiosensors for personalized and onsite biomedical diagnosis, *2nd ed., The Institution of Engineering Technology*, 637.

Chandra, S., Das, P., Bag, S., Laha, D., and Pramanik, P. (2011). Synthesis, functionalization and bioimaging applications of highly fluorescent carbon nanoparticles. *Nanoscale*, 3,1533−1540.

Chang, J. S., Chang, K. L. B., Hwang, D. F., and Kong, Z. L. (2007), In vitro cytotoxicitiy of silica nanoparticles at high concentrations strongly depends on the metabolic activity type of the cell line. *Environ. Sci. Technol.,* 41, 2064−2068.

Chauhan, V. P., Popović, Z., Chen, O., Cui, J., Fukumura, D., Bawendi, M. G., and Jain, R. K. (2011), Fluorescent nanorods and nanospheres for real-time in vivo probing of nanoparticle shape-dependent tumor penetration. *Angew. Chem., Int. Ed.*, 50, 11417−11420.

Chen, D., Li, L., Tang, F., and Qi, S. (2009), Facile and scalable synthesis of tailored silica "nanorattle" structures. *Adv. Mater.,* 21,3804−3807.

Chen, F., Zhang, H., Jiang, L., Wei, W., Liu, C., and Cang, S. (2019). Enhancing the cytotoxic efficacy of combined effect of doxorubicin and cyclosporin encapsulated photoluminescent graphene dotted mesoporous nanoparticles against lung cancer cell-specific drug targeting for the nursing care of cancer patients, *J. Photochem. Photobio. B*, 198,111578.

Chen, J., Qiu, X., Ouyang, J., Kong, J., Zhong, W., and Xing, M. M. (2011), pH and reduction dual-sensitive copolymeric micelles for intracellular doxorubicin delivery, *Biomacromolecules*, 12, 3601−3611.

Chen, Y., Chen, H., Zeng, D., Tian, Y., Chen, F., Feng, J., Shi, J. (2010), Core/shell structured hollow mesoporous nanocapsules: a potential platform for simultaneous cell imaging and anticancer drug delivery, *ACS Nano*, 4, 6001.

Chen, Z., Tan, Y., Xu, K., Zhang, L., Qiu, B., Guo, L., Lin, Z., and Chen, G. (2016), Stimulus-response mesoporous silica nanoparticlebased chemiluminescence biosensor for cocaine determination. *Biosens Bioelectron*, 75,8–14.

Chowdhury, M.A. (2018), Silica materials for biomedical applications in drug delivery, bone treatmentor regeneration, and MRI contrast agent. *Rev J Chem*, 8(2),223–241.

Chung, T. H., Wu, S. H., Yao, M., Lu, C. W., Lin, Y. S., Hung, Y., Huang, D. M., *et al.* (2007), The effect of surface charge on the uptake and biological function of mesoporous silica nanoparticles in 3t3-ll cells and human mesenchymal stem cells. *Biomaterials*, 28, 2959−2966.

Da Silva Bruckmann, F., Zuchetto, T., Ledur, C.M., Dos Santos, C.L., Da Silva, W.L., Fagan, S.B., Da Silva, I.Z., and Rhoden, C.R.B. (2022), Methylphenidate adsorption onto graphene derivatives: theory and experiment, *New J. Chem.*, 46,4283–4291.

Dasgupta, S., Auth, T., and Gompper, G. (2014), Shape and orientation matter for the cellular uptake of nonspherical particles. *Nano Lett.*, 14, 687−693.

Devi, M.G., and Balachandran, S. (2016), A review on synthesis, characterization, and applications of silica particles international. *Journal of advanced. Eng Technol*, 4,249–255.

Dhinasekaran, D., Raj, R., Rajendran, A.R., Purushothaman, B., Subramanian, B., Prakasarao, A., Singaravelu, and G. (2020), Chitosan mediated 5-Fluorouracil functionalized silica nanoparticle from rice husk for anticancer activity. *Int J Biol Macromol*, 156,969–980.

Di Cristo, L., Movia, D., Bianchi, M.G., Allegri, M., Mohamed, B.M., Bell, A.P., Moore, C, Pinelli, S., Rasmussen, K., Riego-Sintes, J., Prina-Mello, A., Bussolati, O., and Bergamaschi, E. (2016), Proinflammatory effects of pyrogenic and precipitated amorphous silica nanoparticles in innate immunity cells. *Toxicol. Sci.* 150 (1), 40–53.

Diab, R., Canilho, N., Pavel, I.A., Haffner, F.B., Girardon, M., and Pasc, A. (2017), Silica-based systems for oral delivery of drugs, macromolecules and cells. *Adv. Colloid Interface Sci.* 249,346–362.

Dimaras, H., Corson, T.W., Cobrinik, D., White, A., Zhao, J., Munier, F.L., Abramson, D. H., Shields, C.L., Chantada, G.L., Njuguna, F., and Gallie, B.L. (2015), Retinoblastoma.*Nat. Rev. Dis. Prim.*, 1,15021.

Feliu, N., and Fadeel, B. (2010), Nanotoxicology: no small matter. *Nanoscale*, 2, 2514−2520.

Geng, Y., Dalhaimer, P., Cai, S., Tsai, R., Tewari, M., Minko, T., and Discher, D. E. (2007), Shape effects of filaments versus spherical particles in flow and drug delivery. *Nat. Nanotechnol.*, 2, 249−255.

Grün, M., Lauer, I., and Unger, K.K. (1997), The synthesis of micrometer and submicrometer-size spheres of ordered mesoporous oxide MCM-41. *Adv Mater*, 9(3), 254–257.

Han, L., Zhou, Y., He, T., Song, G., Wu, F., Jiang, F., and Hu, J. (2013). One-pot morphology-controlled synthesis of various shaped mesoporous silica nanoparticles. *J. Mater. Sci.,* 48,5718−5726.

He, Q., Zhang, Z., Gao, F., Li, Y., and Shi, J. (2011), In vivo biodistribution and urinary excretion of mesoporous silica nanoparticles: effects of particle size and pegylation. *Small*, 7, 271−280.

Hu, C., Sun, J., Zhang, Y., Chen, J., Lei, Y., Sun, X., and Deng, Y. (2018), Local delivery and sustained-release of nitric oxide donor loaded in mesoporous silica particles for efficient treatment of primary open-angle glaucoma. *Adv. Health Mater.,* 7 (23),e1801047

Hu, L., Mao, Z., Zhang, Y., Gao, C. (2011), Influences of Size of Silica Particles on the Cellular Endocytosis, Exocytosis and Cell Activity of HepG2 Cells. *J. Nanosci. Lett.,* 1, 1−16.

Huang, Q., Lin, X., Lin, C., Zhang, Y., Hu, S., and Wei, C. (2015), A high performance electrochemical biosensor based on Cu 2 O–carbon dots for selective and sensitive determination of dopamine in human serum. *RSC Adv*, 5(67), 54102–54108.

Huang, X., Li, L., Liu, T., Hao, N., Liu, H., Chen, D., and Tang, F. (2011), The shape effect of mesoporous silica nanoparticles on biodistribution, clearance, and biocompatibility in vivo, *ACS Nano*, 5,5390−5399.

Huang, X., Teng, X., Chen, D., Tang, F., and He, J. (2010), The effect of the shape of mesoporous silica nanoparticles on cellular uptake and cell function. *Biomaterials*, 31, 438−448.

Huang, Y., and Li, S.F.Y. (2013), Electrocatalytic performance of silica nanoparticles on graphene oxide sheets for hydrogen peroxide sensing. *J Electroanal Chem*, 690,8–12.

Hui, N., Wang, S., Xie, H., Xu, S., Niu, S., and Luo, X. (2015), Nickel nanoparticles modified conducting polymer composite of reduced graphene oxide doped poly (3, 4-ethylenedioxythiophene) for enhanced nonenzymatic glucose sensing, Sensors Actuators, *B Chem*, 221,606–613.

Ju, J., and Chen, W. (2015), In situ growth of surfactant-free gold nanoparticles on nitrogen-doped graphene quantum dots for electrochemical detection of hydrogen peroxide in biological environments. *Anal Chem*, 87(3),1903–1910.

Ke, M., Wahab, J.A., Hyunsik, B., Song, K.H., Lee, J.S., Gopiraman, M., and Kim, I.S. (2016), Allantoin-loaded porous silica nanoparticles/polycaprolactone nanofiber composites: fabrication, characterization, and drug release properties, *RSC Advances*, 6(6),4593–4600.

Knopp, D., Tang, D., and Niessner, R. (2009), Review: bioanalytical applications of biomolecule-functionalized nanometer-sized doped silica particles. *Analytica Chimica Acta*, 647(1), 14–30.

Kuswandi, B.J.E.C.L. (2019), Nanobiosensor approaches for pollutant monitoring. *Environ Chem Lett*, 17(2),975–990

Li, Z., Barnes, J. C., Bosoy, A., Stoddart, J. F., and Zink, J. I. (2012), Mesoporous silica nanoparticles in biomedical applications. *Chem. Soc. Rev.*, 41, 2590−2605.

Liao, Y.T., Lee, C.H., Chen, S.T., Lai, J.Y., and Wu, K.C. (2017), Gelatin-functionalized mesoporous silica nanoparticles with sustained release properties for intracameral pharmacotherapy of glaucoma. *J. Mater. Chem. B*, 5(34),7008–7013

Liberman, A., Mendez, N., Trogler, W.C., and Kummel, A.C. (2014), Synthesis and surface functionalization of silica nanoparticles for nanomedicine. *Surf Sci Rep.,* 69(2),132–158.

Lin, M., Pei, H., Yang, F., Fan, C., and Zuo, X. (2013), Applications of gold nanoparticles in the detection and identification of infectious diseases and biothreats. *Adv. Mater.,* 25, 3490−3496.

Lin, Y. S., and Haynes, C. L. (2010), Impacts of mesoporous silica nanoparticle size, pore ordering, and pore integrity on hemolytic

activity. *J. Am. Chem. Soc.,* 132,4834−4842.

Lin, Y. S., Abadeer, N., and Haynes, C. L. (2011). Stability of small mesoporous silica nanoparticles in biological media. *Chem. Commun,* 47, 532−534.

Liu, J., Liu, T., Pan, J., Liu, S., and Lu, G.Q.M. (2018), Advances in multicompartment mesoporous silica micro/nanoparticles for theranostic applications. *Annu Rev. Chem. Biomol. Eng.,* 9,389–411.

Liu, X., Chen, X., Yang, L., Chen, H., Tian, Y., and Wang, Z. (2016), A review on recent advances in the comprehensive application of rice husk ash. *Res Chem Intermed,* 42(2),893–913.

Lu, F., Wu, S. H., Hung, Y., and Mou, C. Y. (2009), Size effect on cell uptake in well-suspended. uniform mesoporous silica nanoparticles. *Small,* 5, 1408−1413.

Lu, J., Liong, M., Zink, J.I., and Tamanoi, F. (2007), Mesoporous silica nanoparticles as a delivery system for hydrophobic anticancer drugs. *Small,* 3 (8),1341–1346.

Madajewski, B., Chen, F., Yoo, B., Turker, M.Z., Ma, K., Zhang, L., Chen, P.M., Juthani, R., Aragon-Sanabria, V., Gonen, M., Rudin, C.M., Wiesner, U., Bradbury, M. S., and Brennan, C. (2020), Molecular engineering of ultrasmall silica nanoparticle-drug conjugates as lung cancer therapeutics. *Clin. Cancer Res,* 26(20),5424–5437.

Mahato, K., Baranwal, A., Srivastava, A., Maurya, P. K., and Chandra, P. (2016), Smart materials for biosensing applications. *In Techno-Societal, International Conference on Advanced Technologies for Societal Applications,* 421−431.

Mahato, K., Nagpal, S., Shah, M. A., Srivastava, A., Maurya, P. K., Roy, S., Jaiswal, A., Singh, R., and Chandra, P. (2019), Gold nanoparticle surface engineering strategies and their applications in biomedicine and diagnostics. *Biotech,* 9:57.

Maity, A., and Polshettiwar, V. (2017), Dendritic fibrous nanosilica for catalysis, energy harvesting, carbon dioxide mitigation, drug delivery, and sensing. *ChemSusChem,* *10*(20), 3866–3913.

Mandal, R., Baranwal, A., Srivastava, A., and Chandra, P. (2018), Evolving trends in bio/chemical sensors fabrication incorporating bimetallic nanoparticles. *Biosens. Bioelectron,* 117,546−56.

Mao, N.D., Lee, S.Y., Shin, H.J., Kwac, L.K., Ko, S.C., Kim, H.G., and Jeong, H. (2018), Biomass fly ash as an alternative approach for synthesis of amorphous silica nanoparticles with high surface area. *J. Nanosci. Nanotechnol.* 18 (5), 3329–3334.

Mebert, A.M., Baglole, C.J., Desimone, M.F., and Maysinger, D. (2017), Nanoengineered silica: properties, applications and toxicity. *Food Chem. Toxicol.* 109 (Pt 1),753–770.

Melde, B. J., and Johnson, B. J. (2010), Mesoporous materials in sensing: morphology and functionality at the meso-interface. *Anal. Bioanal. Chem.,* 398,1565−1573.

Na, M., Chen, Y., Han, Y., Ma, S., Liu, J., and Chen, X. (2019), Determination of potassium ferrocyanide in table salt and salted food using a water-soluble fluorescent silicon quantum dots. *Food Chemistry,* 288, 248–255.

Nozawa, K., Gailhanou, H., Raison, L., Panizza, P., Ushiki, H., Sellier, E., Delville, M. H., and Delville, J. P. (2005), Smart control of monodisperse stöber silica particles: effect of reactant addition rate on growth process. *Langmuir,* 21,1516−1523.

Okoturo-Evans, O., Dybowska, A., Valsami-Jones, E., Cupitt, J., Gierula, M., Boobis, A. R., and Edwards, R.J. (2013), Elucidation of toxicity pathways in lung epithelial cells induced by silicon dioxide nanoparticles. *PLoS One,* 8 (9), e72363.

Pandey, S., Mewada, A., Thakur, M., Pillai, S., Dharmatti, R., Phadke, C., and Sharon, M. (2014), Synthesis of mesoporous silica oxide/C-dot complex (meso-SiO 2/C-dots) using pyrolysed rice husk and its application in bioimaging. *RSC Adv.,* 4(3),1174–1179.

Parul, K., Sudheer, L., and Sheenam, T. (2023), Synthesis of silica spherical to y-shape nanoparticles: a review with surface modifications and its characterization. *Analytical Chemistry Letters,* 13(2),106-126.

Prabha, S., Durgalakshmi, D., Rajendran, S., and Lichtfouse, E. (2021), Plant-derived silica nanoparticles and composites for biosensors, bioimaging, drug delivery and supercapacitors: a review. *Environmental Chemistry Letters,* 19,1667–1691

Prieto-Montero, R., Katsumiti, A., Cajaraville, M.P., Lopez-Arbeloa, I., Martinez-Martinez, V. (2020), Functionalized fluorescent silica nanoparticles for bioimaging of cancer cells. *Sensors,* 20 (19).

Priti, S., Sameer, S., and Sunil, K.S. (2019), Nanosilica: recent progress in synthesis, functionalization, biocompatibility, and

biomedical applications. *ACS Biomater. Sci. Eng.*, 5,4882−4898.

Qin, X., Yin, Y., Yu, H., Guo, W., and Pei, M. (2016), A novel signal amplification strategy of an electrochemical aptasensor for kanamycin, based on thionine functionalized graphene and hierarchical nanoporous PtCu, *Biosens Bioelectron*, 77,752-758.

Qu, W., Meng, B., Yu, Y., and Wang, S. (2017), EpCAM antibody-conjugated mesoporous silica nanoparticles to enhance the anticancer efficacy of carboplatin in retinoblastoma, *Mater. Sci. Eng. C Mater. Biol. Appl.*, 76,646–651.

Rao, V.R. N., Han, H.S., Lee, H., Nguyen, V.Q., Jeon, S., Jung, D.W., Lee, J., Yi, G.R., and Park, J. H. (2018), ROS-responsive mesoporous silica nanoparticles for MR imaging-guided photodynamically maneuvered chemotherapy. *Nanoscale*, 10 (20),9616–9627,

Ren, D., Xu, J., Chen, N., Ye, Z., Li, X., Chen, Q., and Ma, S. (2021), Controlled synthesis of mesoporous silica nanoparticles with tunable architectures via oil-water microemulsion assembly process. *Colloids Surf. A: Physicochem. Eng. Asp.*, 6:11

Rosu, C., Gorman, A. J., Cueto, R., Dooley, K. M., and Russo, P. S. (2016), Sculpting the internal architecture of fluorescent silica particles via a template-free approach, *J. Colloid Interface Sci.*, 467,321−334.

Saei, A.A., Dolatabadi, J.E.N., Najafi-Marandi, P., Abhari, A., and de la Guardia, M. (2013). Electrochemical biosensors for glucose based on metal nanoparticles. *Trends Anal Chem* 42,216–227.

Shimura, N., and Ogawa, M. (2007), Preparation of surfactant template nanoporous silica spherical particles by the stöber method, effect of solvent composition on the particle size. *J. Mater. Sci.*, 42,5299−5306.

Shirshahi, V., and Soltani M. (2014), Solid silica nanoparticles: applications in molecular imaging. *Contrast Media Mol. Imaging*, 20:35

Slowing, I.; Trewyn, B. G.; Lin, V. S. Y. (2006), Effect of surface functionalization of mcm-41-type mesoporous silica nanoparticles on the endocytosis by human cancer cells. *J. Am. Chem. Soc.*, 128, 14792−14793.

Suzuki, K., Ikari, K., and Imai, H. (2004), Synthesis of silica nanoparticles having a well-ordered mesostructureusing a double surfactant system. *J Am Chem Soc*, 126(2),462–463.

Tan, S.Y., Teh, C., Ang, C.Y., Li, M., Li, P., Korzh, V., and Zhao, Y. (2017), Responsive mesoporous silica nanoparticles for sensing of hydrogen peroxide and simultaneous treatment toward heart failure. *Nanoscale*, 9(6),2253–2261.

Tang L., and Cheng J. (2013), Nonporous silica nanoparticles for nanomedicine application. *Nano Today*, 8(3):290–312.

Trewyn, B. G.; Slowing, I. I.; Giri, S.; Chen, H. T.; Lin, V. S. Y. (2007), Synthesis and functionalization of a mesoporous silica nanoparticle based on the sol-gel process and applications in controlled release. *Acc. Chem. Res.*, 40, 846−853.

Tu, J., Boyle, A. L., Friedrich, H., Bomans, P. H., Bussmann, J., Sommerdijk, N. A., Jiskoot, W., and Kros, A. (2016), Mesoporous silica nanoparticles with large pores for the encapsulation and release of proteins. *ACS Appl. Mater. Interfaces*, 8,32211−32219.

Tzankov, B., Yoncheva, K., and Lambov, N. (2014), Mesoporous silica nanoparticles as drug carriers. *Pharmacia,* 61(1),27–37

Vallet-Regí, M., Colilla, M., and González, B. (2011), Medical applications of organic–inorganic hybrid materials within the field of silicabased bioceramics. *Chem Soc Rev,* 40(2),596–607.

Vallhov, H.; Gabrielsson, S.; Strømme, M.; Scheynius, A.; Garcia-Bennett, A. E. (2007), Mesoporous silica particles induce size dependent effects on human dendritic cells. *Nano Lett.*, 7, 3576−3582.

Verma, M.L.J.E.C.L. (2017), Nanobiotechnology advances in enzymatic biosensors for the agri-food industry. *Environ Chem Lett,* 15(4), 555–560.

Wang, W., Wang, P., Tang, X., Elzatahry, A. A., Wang, S., Al- Dahyan, D., Zhao, M., Yao, C., Hung, C. T., Zhu, X., Zhao, T. *et al.* (2017), Facile synthesis of uniform virus-like mesoporous silica nanoparticles for enhanced cellular internalization. *ACS Cent. Sci.*, 3,839−846.

Yang, R., Miao, D., Liang, Y., Qu, L., Li, J., and Harrington, P.D.B. (2015), Ultrasensitive electrochemical sensor based on CdTe quantum dotsdecorated poly (diallyldimethylammonium chloride)-functionalized graphene nanocomposite modified glassy carbon electrode for the determination of puerarin in biological samples. *Electrochim. Acta*, 173,839−846.

Yang, Y.X., Song, Z.M., Cheng, B., Xiang, K., Chen, X.X., Liu, J.H., Cao, A., Wang, Y., Liu, Y., and Wang, H. (2014), Evaluation

of the toxicity of food additive silica nanoparticles on gastrointestinal cells. *J. Appl. Toxicol*. 34, (4)424–435

Yang, Y., Zhang, M., Song, H., and Yu, C. (2020), Silica-based nanoparticles for biomedical applications: from nanocarriers to biomodulators. *Accounts of Chemical Research*, *53*(8), 1545–1556.

Yogeswaran, U., and Chen, S-M. (2008), A review on the electrochemical sensors and biosensors composed of nanowires as sensing material. *Sensors,* 8(1), 290–313.

Younes, M., Aggett, P., Aguilar, F., Crebelli, R., Dusemund, B., Filipic, M., Frutos, M.J., Galtier, P., Gott, D., Gundert- Remy, U., Kuhnle, G.G., Leblanc, J.C., Lillegaard, I.T, Moldeus, P., Mortensen, A., Oskarsson, A., Stankovic, I., Waalkens-Berendsen, I., Woutersen, R.A., Wright, P. Boon, D. Chrysafidis, R. Gurtler, P. Mosesso, D. Parent-Massin, P. Tobback, N. Kovalkovicova, M., Rincon, A.M., Tard, A., and Lambre, C. (2018), Re-evaluation of silicon dioxide (E 551) as a food additive. *EFSA J.* 16 (1), e05088.

Yu, Q., Wang, P., Hu, S., Hui, J., Zhuang, J., and Wang, X. (2011), Hydrothermal synthesis of hollow silica spheres under acidic conditions. *Langmuir,* 27,7185−7191.

Yu, T., Malugin, A., and Ghandehari, H. (2012), Impact of Silica Nanoparticle Design on Cellular Toxicity and Hemolytic Activity.

Zhao, T., Wu, H., Yao, S. Q., Xu, Q. H., and Xu, G. Q. (2010), Nanocomposites containing gold nanorods and porphyrin-doped mesoporous silica with dual capability of two-photon imaging and photosensitization. *Langmuir*, 26, 14937−14942.

Zhou, X., He, X., Shi, K., Yuan, L., Yang, Y., Liu, Q., Ming, Y., Yi, C., and Qian, Z. (2020), Injectable thermosensitive hydrogel containing erlotinib-loaded hollow mesoporous silica nanoparticles as a localized drug delivery system for NSCLC therapy, *Adv. Sci.* 7(23),2001442.