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Review Article

DIAGNOSTIC AND THERAPEUTIC ROLE OF MESOPOROUS SILICA NANOPARTICLES IN COMBATING CANCER

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ABSTRACT

Cancer is a global health problem of human beings that is growing day by day despite several advancements in the medical field. The main concern of cancer treatment is the timely and proper diagnosis of this disease and the targeting of therapeutic moieties to the cancer site. Nanotechnology has emerged as a boon for the healthcare system in treating various life-threatening diseases. Mesoporous Silica Nanoparticles (MSNs), have drawn interest in the diagnosis and treatment of cancers and various other diseases. MSNs can be easily adjusted to specifically target cancer cells, improve drug targeting and minimize the undesirable effects. In the imaging and diagnosis of cancer, MSNs can be altered with imaging agents or used as contrast agents in imaging techniques like Magnetic Resonance Imaging (MRI) and Computed Tomography (CT). MSNs can be used to deliver different types of therapeutic molecules alone or in combinations to provide a synergistic effect in eradicating cancer. The current review focused on highlighting the role of MSNs in combating cancer. In addition, the biodegradation, clearance and toxicity profile of MSNs is explained to evaluate their suitability for clinical applications.

Keywords: Mesoporous silica nanoparticles, Cancer, Applications, Therapeutics, Diagnostics

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INTRODUCTION

After Cardiovascular disease, cancer is responsible for most deaths in the world. A cancerous condition includes uncontrolled, abnormal cell proliferation that eventually spreads to other tissues and causes metastases [1]. Over 23.6 million new cancer patients are projected to be found globally by 2030, and the number is expected to rise yearly [2]. Cancer is mainly treated by chemotherapy, gene therapy and radiotherapy [3]. These methods are designed to target malignant cells to effectively destroy them while causing the least damage to noncancerous healthy cells [4]. Unfortunately, the only tumor that can be treated with radiotherapy and surgery is the localized one in a particular region of the body [5]. Chemotherapy is used to treat advanced tumors that have spread to the blood circulation or lymphatic system. Most chemotherapeutic agents have negative effects on healthy cells. They are only effective up to a point because cancer cells tend to become multi-drug resistant (MDR) [6, 7]. The drawbacks of the chemotherapy include nausea, reduction in lymphocyte count, MDR, poor aqueous solubility, low therapeutic index, nonspecific tumour targeting, invasive methods, side effects, and poor patient compliance [8, 9]. To release anticancer medications at the target site, and to get rid of side effects from conventional treatments, metastasis, and tumor recurrence, it is crucial to develop innovative treatment approaches [10].

MSNs can be designed to target cancer cells with several therapeutic agents, including medications, peptides, nucleic acids, and imaging agents [11]. They can be utilized in drug delivery applications to target medications to certain cells or tissues [12]. MSNs increase the water solubility and bioavailability of hydrophilic drugs [13]. MSNs can be employed as catalyst support in catalysis applications. Because of their high surface area and homogenous pore size distribution, MSNs provide excellent catalytic activity and selectivity [14]. The features of MSNs can be further tailored by adding functional groups to their surface or by employing various synthesis techniques to control their size, morphology, and pore structure [15]. Numerous encouraging findings have been reported in preclinical and clinical research on applying MSNs for cancer therapy [16, 17]. This review is drafted with the help of papers from the past 20 years (2004-2024) and mostly after 2020 from specialised databases such as Science Direct, Pubmed, and Cambridge using the keywords Mesoporous silica nanoparticles, cancer, applications, therapeutics, diagnostics. Other selections include articles from Springer, Taylor and Francis, MDPI, and Wiley, information from Internet sources, and online published articles from ACS, Bentham etc.

Role of mesoporous silica nanoparticles in cancer

Nanotechnology emerged as a boon for treating cancer [18–20]. Quantum dots, carbon nanotubes, polymeric micelles, carbon dots [21] dendrimers, stimuli-based nanomaterials [22], polymeric nanoparticles, lipid nanoparticles, metal nanoparticles, magnetic nanoparticles, solid lipid nanoparticles [23] and MSNs [24–27] are some widely studied nanotechnology-based drug-delivery systems for cancer [13, 28–30]. The four key ingredients required for the formulation of MSNs are a catalyst, a silica precursor like silane, solvents, and a surfactant. MSNs can be generated with different characteristics, including diameter, pore size, surface area, and shape, even though the synthesis only required four basic components as mentioned above [31, 32]. MSNs have been researched to treat a variety of diseases, including cancer [33], Diabetes [34], inflammation [35], and bone/tendon tissue engineering [36]. The dual application of MSNs in the diagnosis and treatment of cancer is described in this review paper.

Mesoporous silica nanoparticles (MSNs) in the diagnosis of cancer

Nowadays, cancer is diagnosed using several medical procedures like examination of blood, and or urine, imaging methods like Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET), followed by a biopsy. Conventional anatomical imaging methods typically identify tumours when they are a few millimetres using MRI or a few centimetres using PET. However, at this state tumour contains millions of cancer cells [37]. Therefore, the cancer imaging technique should be focused on identifying and/or scanning even a small number of tumour cells as possible in the initial stages, ideally before the angiogenic transition. Specialists who diagnose cancer and identify its stage to treat human cancer can only use various imaging techniques such as X-ray, Computed Tomography (CT) scan, MRI, optical microscopy, PET, Single Photon Emission Computed Tomography (SPECT), and Ultra Sound (US). However, only CT scans, MRI, PET and SPECT techniques can provide Three-Dimensional (3-D) images for cancer detection

throughout the human body [38]. All these methods rely on spotting cancer when it begins to show itself physically, at a thickness of about 1 cm^3, by which time the tumour mass will already have about 1 billion cancer cells in it [39].

For more effective treatment of cancer, early lesion diagnosis is crucial. Early lesions typically have modest biological signals. Due to inadequate sensitivity or lack of specificity, small tumours may go undiagnosed. Therefore, it is crucial to focus on the delivery of imaging agents to the lesion site to improve the signal and increase specificity. MSNs can be coupled to imaging agents appropriate for fluorescence, MRI, and PET imaging [40]. Various nanomaterials, including silica nanoparticles [41], Quantum Dots (QDs) [42], and gold nanoparticles [43], have been used for cancer diagnosis and early detection over the past several years [44]. Small molecules like gadolinium chelates and, calcium and other metal ions [45] are commonly employed as contrast agents for MRI and ultrasound. However, these agents cannot produce high-contrast pictures for early cancer diagnosis because of their limited specificity and intrinsic imaging noise [42]. Silica nanoparticles are also utilized as a contrast agent for ultrasound and MRI. MSNs have selective targeting to the tumour sites, and they also provide high drug loading capacity, robustness in designing various functionalizations, and easy biodegradation. Many imaging techniques have been used for the diagnosis, treatment, and monitoring of cancer. Each technique provides a different level of insight into the disease and its location. There is no ideal imaging approach because each method has its pros and cons [37]. MRI gives the best soft tissue contrast, but this method lacks sensitivity. PET also provides the greatest soft tissue contrast, but it has a limited spatial resolution. CT scan is fast, but it has low soft tissue contrast. IR is rapid and very sensitive but has a shallow depth of penetration.

Mesoporous materials are useful for diagnostic applications because of their improved image contrast and chemical stability. Additionally, the ability of MSNs to conjugate functional molecules within the pores creates new opportunities for numerous measurements and detection. Drugs and dyes can be used to track the position and activity of therapeutic medicines due to the low toxicity of silica-based porous materials and their capacity to contain a range of luminous markers [40]. A detailed description of the diagnostic application of MSNs in cancer has been given in table 1.

Table 1: MSNs in cancer diagnosis

Formulation	Imaging model	Model	Application	Clinical findings	Reference
Gadolinium-MSN (Gd-MSN)	MRI	-	Diagnosis	High proton relaxivity, imaging-capable nanoparticles that can enter the cells easily.	[46]
Gd-Fluorescein Isothiocyanate Msns (Gd-Dye@MSN)	MRI	Mouse brain	Stem cell tracking	These are perfect T1-agent carriers for MRI stem cell tracking due to their benefits of biocompatibility, longevity, high internalizing efficiency, and pore architecture.	[47]
Mesoporous silica-coated hollow manganese oxide $HMnO@mSiO_2$)	MRI	Mouse	T1 MRI contrast agent	Provided T1-weighted images under strong magnetic fields.	[48]
Dox@Gome (Gold/Mesoporous Silica Hybrid Nanoparticle)	PET imaging	Mouse	Diagnosis of lung tumour	It is a good tool for the detection of clinically relevant spontaneous lung tumours.	[49]
MagneticMag-Dye@MSNs	MRI	Mice	Intracellular Labeling and animal MRI studies	MSNs simultaneously serve as bimodal imaging probes and drug carriers.	[50]
Copper sulfide-mesoporous silica-polyethylene glycol ($CuS@mSiO_2$-PEG) nanocomposites	Near-Infrared (NIR) Irradiation	-	Combination of chemotherapy and photothermal therapy.	It demonstrated satisfactory photothermal effectiveness and pH-responsive drug-release behaviour.	[51]
Gold (Au) capped MSNs	TEM Imaging	-	Enzymes and substrate's intracellular codelivery	Tumour growth monitoring the record of treatment responses and determining therapeutic efficacy.	[52]
Camptothecin-loaded Fluorescent MSNs	TEM Imaging	Mice	Can promote the accumulation of anticancer medicines in tumours, enhancing their effectiveness.	They deliver medications to tumours effectively, preferentially accumulate in tumours, and inhibit the growth of tumours.	[53]
Magnetic mesoporous silica nanoparticles-based, polyelectrolyte (poly-ethylenimine, PEI) and fusogenic peptide-functionalized siRNA delivery system (MSN_siRNA@PEI-KALA peptides)	TEM, Confocal laser scanning microscopy	Mice	siRNA delivery for cancer therapy	MSNs are highly protective of siRNA and have a low level of cytotoxicity. An *in vivo* study confirmed the decrease in tumour growth.	[53]
Perfluorohexane-encapsulated MSNs with indocyanine green–polydopamine layer and poly(ethylene glycol)–folic acid coating, (MSNs PFH@PDA-ICG-PEG-FA)	US/NIRF dual-modal imaging	Mice	Cancer phototherapy	Showed tremendous potential to be used as a flexible multifunctional nanocarrier for cancer imaging and treatment.	[54]
Doxorubicin Chitosan-Folate conjugate (DOX-MSN-SS-CH-FA) MSNs	TEM	Mice	A targeted drug delivery system for breast cancer that responds to both pH and redox stimuli	MSNs showed excellent tumor-suppressing action against Ehrlich Ascites Carcinoma (EAC) in mice. MSNs cured the tumour locally and prevented it from spreading.	[55]
Doxorubicin@Gd doped-MSNs, conjugating with indocyanine green loaded thermosensitive liposomes (DOX@GdMSNs-ICG-TSLs)	Near-Infrared Fluorescence (NIRF), Photo acoustic (PA), magnetic resonance (MR) triple-modal imaging.	Mice	Multimodel imaging-guided chemotherapy and phototherapy for cancer eradication.	The good anticancer effectiveness of the MSNs and satisfactory NIRF, PA, and MRI imaging effects.	[56]
Anastrozole-Chitosan-Folic acid loaded MSNs (MSN-ATZ-CH-FA)	TEM, Fourier transform Infrared (FTIR)	Mice	pH-responsive MSNs that target breast cancer	Breast cancer caused by EAC was more effectively treated with MSN-ATZ-CH-FA.	[57]
polyethyleneimine-polyethylene glycol epirubicin HCl MSNs (MSN-PEI-PEG-EPI)	TEM, FTIR	Mice	Cancer treatment.	MSN-PEI-PEG-EPI had a larger tumour accumulation than free epirubicin hydrochloride (EPI).	[58]
MSNs of Arsenic Trioxide (ATO) grafted with Polyacrylic Acid (PAA)	TEM	Mice	pH-triggered MSNs for poor pharmacokinetics or dose-limited toxicity in the treatment of solid tumours.	Significantly improved anticancer efficacy *in vitro* and *in vivo* studies	[59]
Paclitaxel (PTX)-loaded MSNs	SEM	Mouse	Pore size controllable drug delivery system for chemotherapy	MSNs containing PTX-increased all MCF-7 cells' rates of early and late apoptosis compared to free PTX	[60]

Table 2: Application of MSNs in cancer

Drug	Application	Route of administration	Key findings	Reference
Doxorubicin (DOX)MSNs	Mesothelioma therapy	Intraperitoneal administration	Improved therapeutic efficacy and increased intracellular absorption of DOX by DOX-loaded MSNs.	[69]
Docetaxel (Dtxl) PEGylated silica nano rattles	Liver cancer	Intravenous administration	Enhanced anticancer medicines' bioavailability, boost their effectiveness and lessen their side effects.	[70]
Mannose-Multi functionalized MSNs	Two-photon photodynamic therapy of solid tumour	Subcutaneous administration.	MSNs are effective in two-photon excitation (TPE) Photodynamic therapy in breast and colon cancer cell lines.	[71]
Oxaliplatin MSNs	Pancreatic cancer	Direct tumour injection, I. V. administration	Significant reduction or eradication of tumours.	[72]
Mesoporous Silica Microrod (MSR)-Polyethyleneimine (PEI) vaccine	Cancer Vaccination	Subcutaneous administration in intrascapular region.	Improved dendritic activation and T cell response of host cells. The vaccine eliminated lung metastases that had already formed, inhibited cancer growth, and worked in conjunction with anti-CTLA4 therapy.	[73]
Enzyme (Catalase) encapsulated photosensitizer-loaded hollow silica nanoparticles	Photodynamic Therapy (PDT) in cancer	Intravenous administration	Effective PDT by the generation of reactive oxygen species (ROS) by mitochondria targeting and catalase.	[74]
Lipid-coated biodegradable hollow MSNs	Chemo-immunotherapy using All-Trans-Retinoic Acid (ATRA), doxorubicin and Inter Leukin-2 (IL-2)	Intravenous administration	IFN-γ and IL-12 secretion is encouraged, tumour-infiltrating T lymphocytes and natural killer cells become active, and IL-10, TGF-β, and immunosuppressive myeloid-derived suppressor cells become less active.	[75]
Mesoporous nano vehicle loaded with photosensitizer and Dabrafenib, Trametinib	Microneedle-assisted photodynamic therapy of Deep-seated melanoma	Subcutaneous administration	Skin cancer cells are killed synergistically by reactive oxygen species and caspase-activated apoptosis.	[76]
large-pore silica-coated upconversion nanoparticles	Cancer photodynamic immunotherapy	Subcutaneous administration	Stimulation of effector memory T cells, CD4+, and CD8+ cells.	[77]
Pegylated lipid bilayer supported MSNs of Axitinib Celastrol	Multitargeted cancer therapy	Intravenous administration	Enhancement of the antitumor efficacy by suppression of mitochondrial activity and angiogenesis.	[78]
Poly (L-histidine) and polyethylene glycol-coated MSNs of sorafenib	Antitumor effect	Intravenous administration	Antiproliferation and tumour growth inhibition without any significant toxicity and negligible hemolysis.	[79]
Hollow MSNs containing photosensitizers	Photodynamic and starvation therapy against tumour metastasis	Intravenous administration	Enhancement of PDT and starvation therapy to prevent the spread of tumors.	[80]
Bioinspired diselenide bridged MSNs loaded with cytotoxic ribonuclease A (RNase A)	Dual responsive protein delivery on cancer	Intravenous administration	Homologous targeting and immune invasion characteristics.	[81]
CX-5461loaded MSNs	Cancer therapy	Intravenous administration	Inhibition of cancer cells without causing toxic effects on main organs.	[82]
Mesoporous silica/organosilica nanosystem encapsulating doxorubicin and si-RNA	Multidrug Resistant (MDR) cancer	Intratumoral administration	The first big siRNA molecules released from the organosilica shell improved the anticancer effect of later released small DOX molecules from the silica core by reversing the MDR of cancer cells and downregulating P-gp expression in the cell membrane.	[83]
Glutathione-depletion dendritic mesoporous organosilica nanoparticles containing ovalbumin and toll-like receptor-9	Cancer immunotherapy	Subcutaneous administration	Decreasing the development of tumours and promoting the production of Cytotoxic T Lymphocytes (CTLs).	[84]
Mesoporous silica-coated gold nanorods	Photodynamic and photothermal tumour therapy (PTT)	Subcutaneous administration	Antitumor activity with fewer side effects and extension of tumour-bearing mice survival time.	[85]
Hollow and nonhollow mesoporous silica nanospheres	Cancer vaccine adjuvant	-	Hollow nanospheres enhanced anti-cancer immunity, CD4+ and CD8+T cell populations in mouse splenocytes.	[86]
Asymmetric Head-Tail (HT) MSNs	Vaccine development and Immunotherapy	-	Asymmetrical HTMSN showed a greater level of intake and *in vitro* maturation of dendritic cells and macrophages.	[87]
Multi-shelled dendritic mesoporous organosilica hollow spheres	Cancer immunotherapy	-	Immuno-adjuvant effect of MSNs	[88]
Hollow MSNscontaining $HGP100_{25-33}$, and $TPR2_{180-188}$,	Antitumor immune response	Subcutaneous administration	Tumour suppression without compromising safety.	[89]
Mesoporous Silica Micro Rods-Supported Lipid Bilayers (MSRs-SLBs)	T-cell receptor stimulation	Intravenous administration	Improved ex vivo growth of human and murine T cells using polyclonal and antigen-specific methods compared to commercial beads.	[90]

Mesoporous silica nanoparticles (MSNs) in cancer therapy

MSNs can be categorized into many families based on their pore size, particle diameter, surface area, and manufacturing technique. These families have been explored extensively for drug delivery, including the Santa Barbara Amorphous (SBA), Movable Crystalline Material (MCM), and Michigan State University Materials (MSU) families [61].

MSNs can resolve the insolubility issue of various poorly soluble drugs. Although having outstanding anticancer activity *in vitro*, Paclitaxel (PTX) and Camptothecin (CPT) have little anticancer effects *in vivo* due to their poor aqueous solubility. The pore size and the shape of MSNs are adjustable therefore, they significantly boost the solubility of the medications when used as a carrier. Additionally, the MSN carrier raises the drugs' cytotoxic effects by 86% for CPT against human pancreatic cancer Capan-1 cells and HepG2 human liver cancer cells by 4.3-fold for PTX[62,63]. To treat mice harbouring the C26 tumor, Babaei *et al.* [64] formulated PEGylated MSNs (PEG@MSNR-CPT). The MSNs were loaded with CPT and assessed their effectiveness in comparison to CPT. MSNs can be multi-functionalized to regulate the release of medications. [65] To create redox and pH-responsive nanoparticles that may actively target breast cancer cells, Bhavsar *et al.* [66] formulated Doxorubicin (DOX)-loaded MSNs nanoparticles. The formulation was functionalized with cystamine dihydrochloride and then capped with chitosan-folate. After being exposed to acidic redox conditions (cancer environment; pH 5.5; 10 mmol reduced glutathione (GSH)), the drug was liberated from the particles. Intravenous administration of the formulation was determined to be safe [67].

MSNs have a high degree of stability, which helps to safeguard and stabilize loaded drugs. To create single-and multimodal anticancer treatments, numerous co-therapeutic treatments, including photosensitizers, photothermal reagents, and chemotherapeutic drugs, can also functionalize MSNs [4, 68]. Table 2 provides an overview of MSNs' therapeutic use in cancer.

Toxicity of MSNs

All inorganic materials like gold, silver, iron oxide, silica, and zinc oxide nanoparticles on chronic exposure can cause inflammation, fibrosis, impaired renal clearance, and oxidative stress [91]. The toxicity of these NPs depends on dose, frequency, route of administration, composition, and physicochemical properties [92]. The toxicity of nanoparticles is an important parameter to govern their safety for clinical applications. Acute and subacute toxicity studies are usually conducted to evaluate different parameters like haematological, neurological, and cardiac effects safety. Clinical manifestations of NPs on cardiovascular, respiratory, gastrointestinal effects, dermatological effects, necroscopy, and histopathological investigations and mortality have been used to assess their safety [93]. MSNs are mostly studied for their acute toxicities [94]. MSNs may interact with blood components after administration; hence it is critical to study their hemotoxicity for possible intravenous uses [95]. Indeed, amorphous silica compounds have been demonstrated to induce hemolysis in mammalian Red Blood Cells (RBCs), posing serious biosafety concern.

Biodegradability and clearance of MSNs

Degradation of inorganic materials is difficult. Therefore, it can be assumed that MSNs are not degraded easily and accumulate in the Reticuloendothelial System (RES) organs like the liver and spleen. This can lead to accumulation for a few weeks to some months. The slow degradation of MSNs in the body may cause severe tissue toxicity [30, 96, 97]. The degradation rate of MSNs is affected by their physical properties e. g., size, shape, surface area, aggregation state, surface coatings or surface modification. The degradation of MSNs is affected by the pH and temperature of the site, protein content and their concentration. The degradation of MSNs in the physiological fluids should be studied while evaluating their cytotoxicity [98, 99].

The clearance of MSNs is an important parameter regarding their clinical safety. It has been found that MSNs can be metabolized and excreted through urine by the kidney and thus don't accumulate in the body. Various studies have reported that the MSN scaffold is degraded into orthosilicic acid a tolerable water-soluble compound and excreted by the kidney [100, 101].

CONCLUSION

MSNs have great potential for nanocarrier-based cancer therapy. In this review, we discussed mesoporous materials and their use as MSNs. The potential of MSNs to detect and treat cancer is reviewed in this paper. To deliver therapeutic drugs with high specificity and to selectively aggregate at the tumour site, MSNs can be functionalized with targeting moieties, such as antibodies or peptides. However, there is a need for more advancement that may offer an interesting possibility for the enhancement of the characteristics of MSNs. The eradication of incurable diseases like cancer is only possible after understanding this disease and targeting the molecules to combat the cancer cells without affecting healthy cells. It is expected that MSNs will remain an important area of cancer research in future.

AUTHORS CONTRIBUTIONS

Ms Nupur Katariya and Dr Nidhi Nainwal drafted the manuscript. Dr Ganesh Kumar revised and edited the manuscript. Dr Arvind S. Farswan formatted the manuscript as per journal guidelines.

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CONFLICT OF INTERESTS

None

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