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Scoping Review

Effectiveness of mesoporous silica nanoparticle as drug delivery agents for therapeutic improvement of hepatocellular carcinoma: A systematic review

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Abstract

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, accounting for approximately 75% of all liver cancer cases, and has the worst prognosis. Current therapies for HCC remain suboptimal, with sorafenib therapy only prolonging survival by 2–3 months, combination therapies often cause adverse events (AEs), and drug resistance remains a challenge. To address these issues, mesoporous silica nanoparticles (MSNs) have been investigated as potential drug delivery systems due to their high surface area, tunable pore size, and ability to enhance drug stability and release. The aim of this study was to explore the potential of MSN-based drug delivery systems for improving HCC therapy. This study employed a systematic review design with a computerized search of six databases up to June 15, 2023. Inclusion criteria were: (1) in vivo studies with mouse subjects, (2) subjects with HCC receiving therapy, (3) therapy conjugated with or coated by MSNs, and (4) evaluation of therapeutic effectiveness based on statistical outcomes. Exclusion criteria included irrelevant titles or abstracts, incomplete texts, and non-original research such as reviews, case reports, and conference abstracts. A total of 1,844 studies were screened, and eight studies met the eligibility criteria for analysis. The results indicated that MSN-based drug delivery systems significantly improved therapeutic outcomes in HCC-bearing mice by enhancing drug penetration, reducing tumor size, and minimizing systemic toxicity compared to conventional formulations. These findings suggest that MSNs hold promise as an advanced drug delivery platform for HCC therapy. However, further preclinical and clinical studies are required before translation into clinical practice.

Keywords: Hepatocellular carcinoma, mesoporous silica nanoparticles, drug delivery systems, machine learning, therapeutic efficacy

Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for approximately 75% of all liver cancer cases worldwide, and represents a major global health burden [1]. Despite advances in cancer therapy, the incidence and mortality of HCC continue to rise, making it one of the leading causes of cancer-related death [2,3]. In Indonesia, liver cancer ranks among the top contributors to cancer mortality, reflecting both late-stage diagnosis and limited therapeutic options [2]. Early stages of HCC often present with no clear symptoms, and

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by the time symptoms appear, the disease is usually in an advanced stage, resulting in suboptimal treatment outcomes [4]. The average survival rate for HCC patients is low, with a median survival of only nine months [5]. The difficulty in treating HCC is attributed to its multifactorial triggers and severe clinical effects.

Currently, the first-line systemic therapy for HCC is sorafenib, a multikinase inhibitor that targets the Raf/MEK/ERK pathway and angiogenesis-related receptors [6,7]. While sorafenib modestly improves survival, extending life expectancy by only 2–3 months [6], its clinical benefits are limited by resistance and adverse events such as palmar-plantar erythrodysesthesia, diarrhea, and hypertension [8-10]. Sorafenib resistance has been reported in some cases of HCC [8], often due to interactions with ATP-binding cassette (ABC) transporters, which reduce intracellular drug accumulation [9]. Moreover, its poor aqueous solubility and low bioavailability due to rapid metabolism further compromise its therapeutic efficacy [11].

In addition to sorafenib, several second-line therapies and immunotherapies serve as alternatives. However, many second-line therapies, such as ramucirumab, are effective only for patients with disease progression and not for those resistant to sorafenib [12]. Atezolizumab, combined with antiangiogenesis agent bevacizumab, has shown improved progression-free survival (PFS) compared to sorafenib, achieving 6.8 months with the combination versus 4.3 months with sorafenib. However, atezolizumab combined with bevacizumab resulted in AEs in 98% of patients, with a higher percentage of serious AEs (38%) compared to sorafenib (30.8%) [13]. These side effects can arise from chemotherapy, which not only affects the cells that have malignancy but also affects other cells. For example, chemotherapy can damage the small intestinal mucosal cells, which can lead to diarrhea [14]. Such limitations highlight the need for more targeted and safer therapeutic delivery systems.

Nanoparticles (NPs) have been developed as drug delivery agents to target specific cancer cells. They offer advantages such as good stability, customizable solubility, and the ability to enhance cell-specific targeting [15]. NPs coated with antibodies, carbohydrates, and specific ligands enhance specific and efficient absorption [16]. They can encapsulate poorly soluble drugs, releasing them in a controlled manner to avoid toxicity and side effects. Mesoporous silica nanoparticles (MSN) are particularly promising for cancer therapy due to their non-toxicity, biocompatibility, and provide a uniquely large and tunable pore structure that allows high drug loading and controlled, sustained release over days to weeks [14]. MSN also offers easily modifiable surface chemistry, enabling conjugation with targeting ligands or protective coatings to further enhance delivery efficiency [15]. Collectively, these features distinguish MSNs from other NP platforms and make them an underexplored yet highly promising carrier for anticancer therapy.

Given the challenges in treating HCC and the poor prognosis associated with this disease, the development of novel therapeutic strategies is urgently needed. Conventional systemic agents such as sorafenib are limited by poor solubility, rapid metabolism, adverse effects, and the emergence of drug resistance, which significantly reduce treatment efficacy [1-3]. While various nanoparticle-based systems have been explored to improve drug delivery, many still face challenges such as limited biocompatibility, suboptimal drug loading, and uncontrolled release [4,5]. MSNs offer a unique advantage, as they are highly biocompatible, possess large surface areas and tunable pore sizes for high drug loading, and allow controlled and targeted drug release [6]. These properties make MSNs a promising yet underutilized platform for addressing the current limitations of HCC therapy. Therefore, the aim of this study was to evaluate the potential of MSNs as an effective drug delivery system to enhance therapeutic outcomes in HCC.

Methods

Research design

This study employed a systematic review design conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Eligible studies were identified, screened, and selected based on predefined inclusion and exclusion criteria, and the extracted data were synthesized narratively.

Search strategy

A comprehensive electronic search was conducted across multiple databases, including Scopus, ScienceDirect, PubMed, Taylor & Francis, Wiley, and WorldCat, from June 8 to June 15, 2023. The search strategy used the keywords "Mesoporous silica", "Therapy", and "Hepatocellular carcinoma", combined with Boolean operators (AND, OR) to refine retrieval.

Study selection

Search results from each database were imported into Mendeley and organized in Google Sheets. After removal of duplicates, the remaining articles were screened by title and abstract. Articles that met the inclusion criteria were retained for full-text screening. The selection process adhered to the PRISMA 2020 guidelines, and a PRISMA flow diagram was constructed to report the number of studies identified, screened, excluded, and included in the review. The literature search and study selection process were conducted independently by all authors (NFA, RRM, and UAN).

Eligibility criteria

The eligibility criteria were developed using the Population, Intervention, Comparison, and Outcome (PICO) framework (**Table 1**). Studies were included if they met the following criteria: (1) in vivo experiments conducted in mice, (2) subjects with HCC receiving therapy, (3) therapy conjugated with or coated by MSN, and (4) evaluation of the therapeutic effectiveness of MSN, reported with statistical significance (*p*-value). Studies were excluded if: (1) the title or abstract was not relevant, (2) the full-text was unavailable or data could not be extracted, or (3) the publication type was a review, case series, or conference abstract.

Table 1. PICO framework used to define the eligibility criteria

PICO component	Implementation
Population	Patients with hepatocellular carcinoma (HCC)
Intervention	Mesoporous silica nanoparticle (MSN) anticancer drug delivery
Comparison	No control group
Outcome	Effectiveness of MSN in clinical improvement of patients with HCC

Data extraction

Three researchers (NFA, RRM, and UAN) independently extracted data from each eligible study, beginning with data tabulation in a spreadsheet by UAN. The tabulated data were subsequently checked for accuracy and completeness. Extracted variables included the first author's name and year of publication, study location, study subjects, route of administration, MSN dose, treatment duration, treatment outcome, and *p*-value. To ensure reliability, discrepancies were resolved through discussion; when consensus could not be reached, a fourth reviewer was consulted. A random subset of extracted data was independently verified by a second reviewer to minimize transcription errors and ensure data integrity. The final dataset was synthesized and presented in both narrative and tabular format.

Assessed results

Two reviewers (RRM and UAN) independently assessed the risk of bias for each eligible study using the SYstematic Review Center for Laboratory animal Experimentation (SYRCLE) risk of bias tool. Disagreements were resolved through a group discussion with a third reviewer (NFA). Ten domains of bias were evaluated: (1) random sequence generation; (2) baseline characteristics; (3) allocation concealment; (4) random housing; (5) blinding of interventions and caregivers; (6) random outcome assessment; (7) blinding of outcome assessment; (8) incomplete outcome data; (9) selective outcome reporting; and (10) other source of bias. Each domain was classified as low risk, high risk, or unclear risk of bias.

Results

Overview of literature selection

The initial search across five databases yielded 1,844 records (**Figure 1**). After removing 107 duplicates and excluding 79 non-original research articles (review, case report, case series, or

conference abstract), 1,658 records remained. Of these, 1,611 studies were excluded based on irrelevance to the research topic after title and abstract screening. The full-text of 47 studies were then assessed, of which 32 were excluded for not meeting the inclusion criteria. Of the remaining 15 studies, seven were excluded due to insufficient extractable data (n=4; incomplete outcome reporting, incompatible outcome measures, or lack of methodological detail) or being review articles (n=3). Ultimately, eight studies were included in the final analysis.

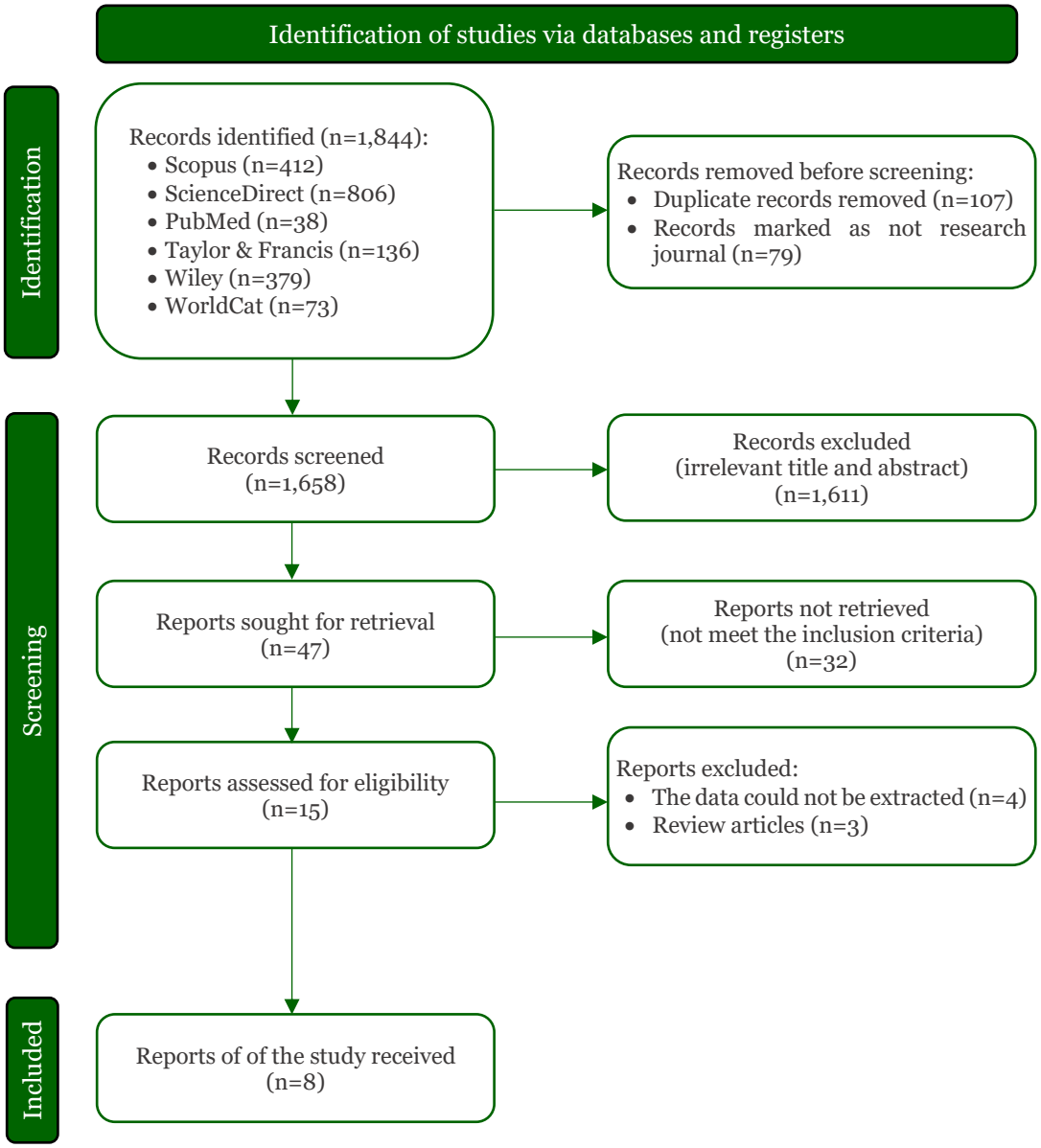


Figure 1. PRISMA flow diagram.

Characteristics and outcomes of research criteria

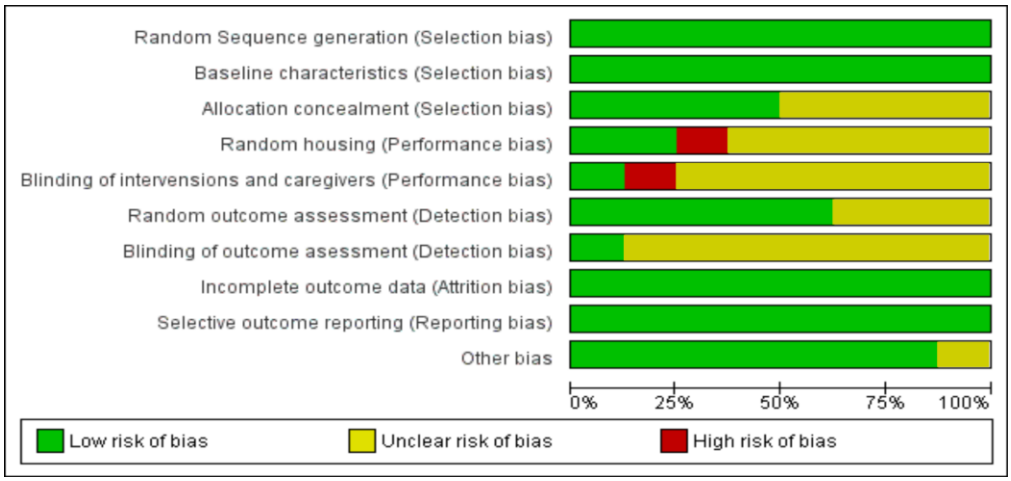
The characteristics of the included studies are summarized in **Table 2**. Most studies were conducted in Asia and utilized female BALB/c type mice, with sample sizes ranging from 25 to 42. The animals were 4–8 weeks old and weighed 18–25 g. MSN-assisted therapies were predominantly administered intravenously at a dose of 10 mg/kg body weight for 7–14 days.

Across all eight studies, administration of MSN-conjugated or MSN-coated therapies was associated with significant improvement in HCC outcomes ($p<0.05$). MSN effectively facilitated targeted delivery of anticancer agents such as doxorubicin and sorafenib, minimizing toxicity and off-target effects. Furthermore, MSN enhanced the efficacy of combination chemotherapy and photodynamic therapy, and demonstrated potential in overcoming multidrug resistance.

Study quality assessment

The overall study quality assessment is presented in **Figure 2A**, and the risk of bias for each study is summarized in **Figure 2B**. Based on the SYRCLE risk of bias tool, it was found that all studies had a low risk of bias in random sequence generation (domain 1), baseline characteristics (domain 2), blinding of outcome assessment (domain 8), and selective outcome reporting (domain 9).

A



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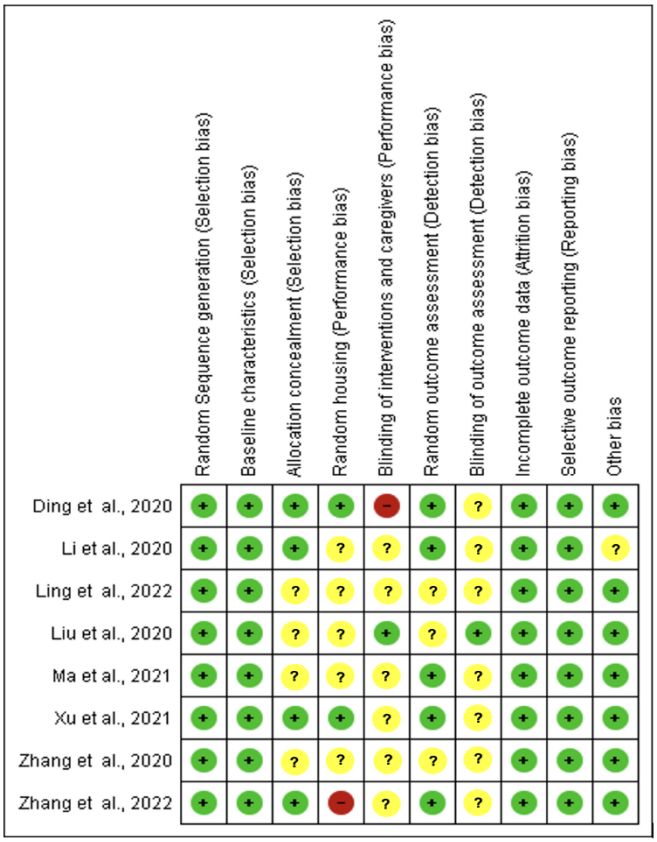

Figure 2. Risk of bias assessment of included studies using the SYRCLE tool. (A) Proportion of studies rated as low, unclear, or high risk of bias across 10 domains. (B) Individual study-level risk of bias assessment. Red (-) = high risk of bias; yellow (?) = unknown risk of bias; green (+) = low risk of bias.

Table 2. Characteristics of included in vivo studies on mesoporous silica nanoparticles (MSN) in hepatocellular carcinoma therapy

Author, year	Research location	Subject	Administration route	Mesoporous silica dosage	Duration	Results	*p*-value
Ding *et al.*, 2020	Asia	42 Female mice of the BALB/c type (age 6–8 weeks)	Intravenous	8 mg/kg/day TATp- MSN DOX	12 days	MSN can efficiently deliver doxorubicin (DOX) to liver cancer cell nuclei well, reduce cytotoxicity and size of HCC cells, and reduce systemic side effects of drugs	$p<0.05$
Li *et al.*, 2020	Asia	36 Female mice of type BAB/c (18–20 gr)	Intravenous	40 mg/kg MSN- SFN and 10 mg/kg FFA	14 days	MSN can significantly improve the effectiveness of anticancer drugs combined with NSAIDs in inhibiting HepG2 tumor growth and decrease cell migration, PGE2 secretion, and enhances the process of cell apoptosis	$p<0.01$
Ling *et al.*, 2022	Asia	25 BALB/c mice (4 weeks old)	Intravenous	5 mg DOX/kg and 1 mg SOR/kg every 2 days	7 days	MSN can effectively help specifically target drugs to tumor cells and remain there for a long time, and assist antitumor drugs such as DOX and SOR without inducing systemic toxicity	$p<0.05$
Liu *et al.*, 2020	Asia	Rats	Intravenous	2 mg/kg/bb MSN	14 days	MSN can effectively induce faster and more significant tumor cell apoptosis and enhance cancer cell uptake of drugs through folate receptor-mediated endocytosis, thereby decreasing cytotoxicity	$p<0.05$
Ma *et al.*, 2021	Asia	30 BALB C/c type female mice (4–5 weeks old) (20 g)	Intravenous	3 mg/kg/2 days MSN-DOX	14 days	MSN can effectively distribute drugs quickly. After being distributed throughout the body, the drug is directly concentrated at the tumor site after circulating for 8 hours, and improve the performance of combined chemo and photodynamic therapy compared to monotherapy	$p<0.05$

In contrast, between five and seven studies (62.5–87.5%) did not adequately report allocation concealment (domain 3), random housing (domain 4), blinding of investigators and caregivers (domain 5), and random outcome assessment (domain 7), and were therefore classified as having an unclear risk of bias. Moreover, two studies (25%) showed a high risk of bias in random housing (domain 4) and blinding of investigators/caregivers (domain 5), respectively. Although most domains indicated a low risk of bias, insufficient reporting in critical domains related to performance and detection bias may affect the robustness of the included studies.

Discussion

HCC remains a major global health burden, with persistently high incidence and mortality documented in epidemiological reports and international cancer registries [1-5]. Despite the availability of various treatment modalities, including loco-regional and systemic approaches, the prognosis for advanced HCC remains poor, largely due to late-stage presentation and the limited effectiveness of current therapies [6,7]. Sorafenib, which has long served as the standard first-line systemic therapy, offers only modest survival benefits and is further constrained by drug resistance, rapid metabolism, poor bioavailability, and frequent adverse effects [8,9]. These challenges highlight the pressing need for novel therapeutic strategies capable of enhancing efficacy while reducing toxicity. Alternative regimens such as immunotherapies (atezolizumab–bevacizumab) and targeted agents (ramucirumab) have demonstrated benefits for certain populations but are still hampered by serious side effects and variable response, particularly in sorafenib-resistant patients [10,12]. These limitations have inspired attention towards nanoparticle-based drug delivery, among which MSN are especially promising due to their tunable properties, safety profile, and ability to be surface-modified for precise targeting [16,17].

MSNs can be customized, modified, and assembled with specific molecules for targeted release at HCC sites (**Figure 4**). They are engineered to exploit tumor microenvironment features such as acidic pH or surface antigens for selective uptake [20,26]. Upon internalization by HCC cells, endosomal release enables cytoplasmic drug delivery [18,20], which can also enhance immune responses and antigen presentation in the tumor microenvironment [25,27]. This dual effect facilitates both direct cytotoxic activity and immunotherapeutic modulation.

Compared to liposomes, polymeric nanoparticles, and PLGA-based implants, MSNs demonstrate higher drug loading capacity and more versatile functionalization [17,23]. For example, sorafenib-loaded MSNs co-administered with flufenamic acid achieved superior tumor inhibition compared to sorafenib alone, indicating synergistic effects in overcoming drug resistance [21]. Similarly, co-delivery of sorafenib with CRISPR/Cas9 via core–shell hollow mesoporous organosilica nanoparticles suppressed tumor growth and multidrug resistance pathways in preclinical HCC models [27]. The ability of MSNs to respond to endogenous tumor microenvironmental stimuli, such as acidic pH and elevated glutathione, enables site-specific release of therapeutics, minimizing systemic toxicity [20,26]. Dual-modality MSN designs combining chemotherapeutics with photodynamic or photothermal agents have also shown synergistic anticancer effects in preclinical models [25]. Thus, MSNs can function not only as carriers but also as multifunctional therapeutic platforms.

Despite these advantages, most evidence remains preclinical, with limited understanding of long-term biosafety, biodegradation, and large-scale manufacturing reproducibility [19,24]. Moreover, no MSN formulation has yet advanced into randomized clinical trials in oncology [23]. Standardization of synthesis protocols and comprehensive toxicological evaluations will be essential for clinical translation. Future studies integrating MSNs with immunotherapy, gene editing, or multimodal regimens may further improve therapeutic outcomes in HCC.

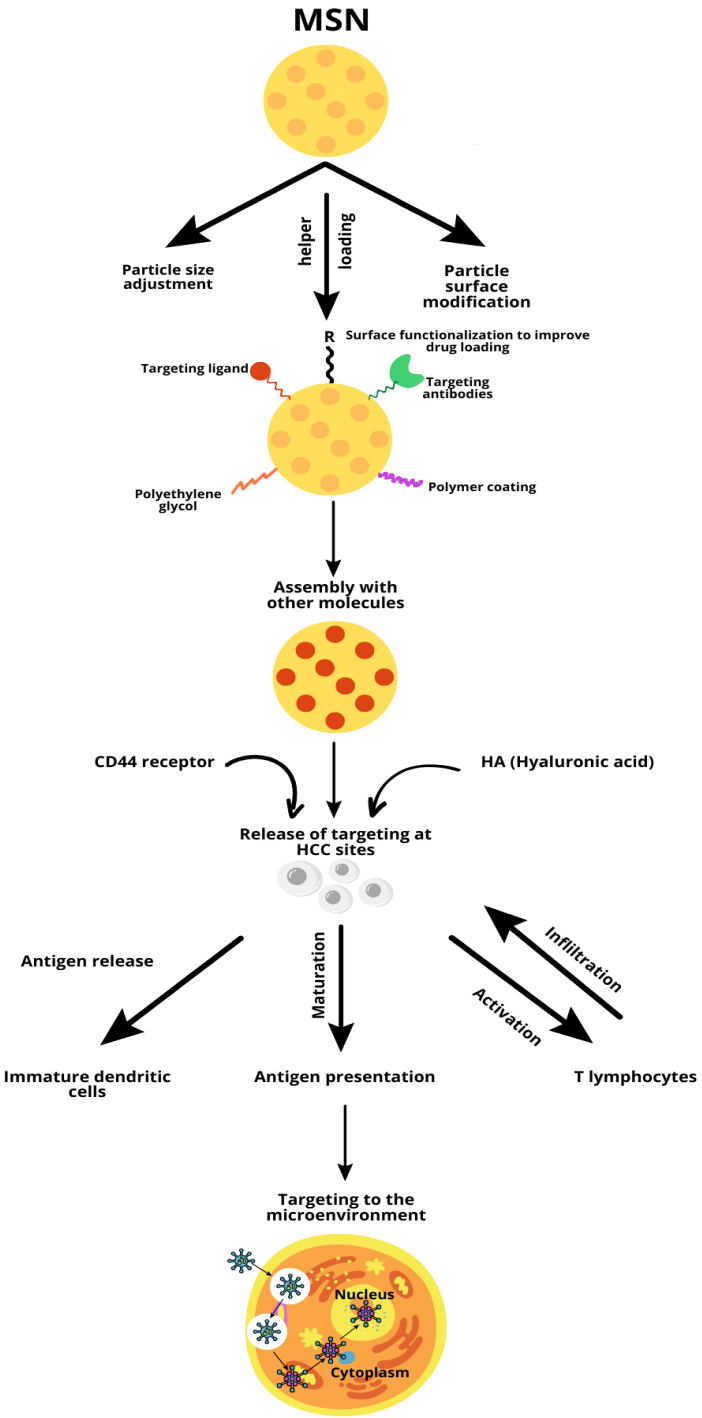

Figure 4. MSN to HCC cells. Before heading to HCC cells, the MSNs will be customized, modified, and assembled accordingly to the molecules used for targeting release at HCC sites. The release of targeting at HCC sites will stimulate immunity, which makes targeting of the microenvironment able to occur.

Conclusion

MSN represents a promising drug-delivery platform for HCC therapy, offering advantages such as high drug-loading capacity, surface functionalization for targeted delivery, and reduced systemic toxicity demonstrated in preclinical studies. Evidence from in vitro and animal experiments indicates that MSNs can enhance drug absorption, prolong retention within tumor tissue, and improve therapeutic selectivity. Nevertheless, these findings remain preliminary, as most studies are limited to experimental models with heterogeneous methodologies and without standardized safety evaluations. Future research should therefore prioritize well-designed clinical trials to determine the optimal dosing, duration, biosafety, and cost-effectiveness of MSN-based

therapies in diverse patient populations. In addition, integrating MSNs with emerging approaches such as immunotherapy and theranostics may broaden their therapeutic potential. Thus, while MSNs hold significant promise in advancing HCC management, rigorous translational and clinical investigations are essential before their clinical utility can be firmly established.

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Competing interests

The author declares that there is no conflict of interest.

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Underlying data

All underlying data have been presented in this article.

Declaration of artificial intelligence use

Artificial intelligence (AI) tools (ChatGPT) were used solely for language refinement, including improving grammar, sentence structure, and readability of the manuscript. All AI-assisted processes were critically reviewed by the authors, and the final decisions and interpretations presented in this article were made exclusively by the authors.

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