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In Silico Exploration Of Curcumin-Loaded Mesoporous Silica Nanoparticles For Targeted Therapy Against Gastric Cancer

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ABSTRACT

Gastric cancer remains one of the most aggressive malignancies globally, with limited therapeutic outcomes due to late-stage diagnosis and drug resistance. Curcumin, a natural polyphenolic compound derived from *Curcuma longa*, has demonstrated potent anticancer activity through modulation of multiple cellular pathways. However, its clinical utility is severely hindered by poor solubility, low bioavailability, and rapid systemic elimination. Mesoporous silica nanoparticles (MSNs) offer a promising nanocarrier system to overcome these limitations, owing to their tunable pore structure, high surface area, and biocompatibility. This study investigates the interaction of curcumin and MSN-loaded curcumin (Cur-MSNs) with key gastric cancer molecular targets—HER2, MMP9, and VEGFR2—using a comprehensive computational pipeline. Molecular docking was performed using AutoDock to evaluate binding affinity and interaction profiles, followed by molecular dynamics (MD) simulations via GROMACS to assess the stability of protein–ligand complexes. The results revealed that Cur-MSNs exhibited enhanced binding affinity and more favorable interaction energy compared to free curcumin. MD simulation confirmed increased complex stability, reflected in reduced RMSD and RMSF values and more consistent hydrogen bonding. MM-PBSA analysis further indicated that Cur-MSNs had stronger binding free energy across all targets. ADMET predictions also suggested improved pharmacokinetic profiles for the MSN-based formulation. These findings underscore the potential of Cur-MSNs as an efficient therapeutic strategy for targeted gastric cancer therapy. Future work will focus on in vitro and in vivo validation, as well as exploring AI-integrated computational models for broader oncological applications.

Keywords: Curcumin, Mesoporous Silica Nanoparticles (MSNs), Gastric Cancer, Drug-Target Interaction, Molecular Docking, ADMET, Molecular Dynamics Simulation, In Silico Nanomedicine.

1. INTRODUCTION

Gastric cancer remains one of the most prevalent and lethal malignancies worldwide, ranking fifth in incidence and fourth in cancer-related mortality globally (Smyth et al., 2020). It is particularly widespread in East Asia, Eastern Europe, and parts of Latin America, often diagnosed at advanced stages due to the absence of specific early symptoms (Ajani et al., 2017). Despite advancements in surgical techniques, radiotherapy, and chemotherapy, the prognosis for advanced gastric cancer remains poor, with a 5-year survival rate of less than 30% (Ferro et al., 2020). The heterogeneity of gastric cancer, along with frequent drug resistance, off-target effects, and systemic toxicity, continues to challenge conventional treatment approaches (Van Cutsem et al., 2016). This has prompted the exploration of alternative and adjunctive therapeutic strategies, including the incorporation of phytochemicals and nanotechnology in cancer therapeutics.

Curcumin, a natural polyphenolic compound extracted from the rhizome of *Curcuma longa*, has attracted considerable attention for its broad spectrum of pharmacological properties, including antioxidant, anti-inflammatory, and anticancer activities (Gupta et al., 2013). In gastric cancer models, curcumin has demonstrated the ability to modulate multiple molecular pathways, such as NF-κB, STAT3, and PI3K/Akt, which are critical in tumor proliferation, angiogenesis, and metastasis (Kunnumakkara et al., 2017). However, its clinical application is hindered by poor aqueous solubility, low gastrointestinal absorption, rapid systemic elimination, and limited bioavailability, which significantly restrict its therapeutic potential (Anand et al., 2007; Hewlings & Kalman, 2017). Various strategies, including liposomal formulations, polymeric carriers, and solid dispersions, have been explored to enhance curcumin's delivery, but they often fall short in achieving targeted delivery and sustained drug release (Bhatia et al., 2016).

In this context, mesoporous silica nanoparticles (MSNs) have emerged as a highly promising drug delivery system due to their unique physicochemical characteristics such as large surface area, tunable pore sizes, high loading capacity, biocompatibility, and ease of functionalization (Slowing et al., 2008). MSNs provide a protective matrix for curcumin, enhancing its solubility, improving stability against enzymatic degradation, and enabling controlled and targeted release to tumor sites (Vallet-Regí et al., 2007). Furthermore, surface modification of MSNs with ligands or antibodies allows for active targeting, thereby reducing systemic toxicity and improving therapeutic efficacy (Tarn et al., 2013). The combination of curcumin with MSNs has demonstrated promising in vitro and in vivo results in several cancers, including colorectal and breast cancers, indicating its translational potential in oncology (Manzano & Vallet-Regí, 2019).

To further accelerate and rationalize the development of such nanocarrier-based therapies, computational approaches have gained substantial importance in modern drug discovery. Computational modeling, particularly molecular docking and molecular dynamics simulations, allows for the prediction and analysis of drug-target interactions, binding affinities, and conformational stability at the molecular level, significantly reducing the need for extensive wet-lab experiments in the early stages (Meng et al., 2011). These in silico methods are instrumental in understanding how curcumin, both in free and MSN-encapsulated forms, interacts with key oncogenic proteins in gastric cancer, such as HER2, VEGFR, and MMP9 (Liu et al., 2020). Additionally, computational tools facilitate ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling, enabling early evaluation of pharmacokinetic behavior and safety profiles (Cheng et al., 2012). Such comprehensive analysis can inform and streamline subsequent experimental validation, thereby bridging the gap between nanomedicine design and clinical application (Santos et al., 2020).

This Research Objective include:

- To design and model curcumin-loaded mesoporous silica nanoparticles (Cur-MSNs) using computational tools.
- To identify and select key molecular targets in gastric cancer relevant to curcumin-based therapy.
- To perform molecular docking and dynamic simulations to evaluate the binding interactions between Cur-MSNs and target proteins.
- To assess the pharmacokinetic and toxicity profiles of curcumin and Cur-MSNs using in silico ADMET tools.
- To provide a comparative analysis of curcumin alone versus Cur-MSNs for therapeutic targeting in gastric cancer.

2. MATERIALS AND METHODS

2.1. Ligand Preparation

The chemical structure of Curcumin (diferuloylmethane) was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov), a reliable and publicly accessible chemical repository. The PubChem CID for Curcumin is 969516, which provides comprehensive structural and chemical information essential for computational analyses.

The 2D structure of Curcumin was first downloaded in SDF (Structure Data File) format, followed by conversion into 3D structure using the Open Babel tool. Subsequently, energy minimization was carried out using the MMFF94 force field to stabilize the ligand's geometry and reduce steric clashes or unrealistic bond angles prior to docking.

To prepare the ligand for molecular docking, the following steps were performed:

- Protonation states were adjusted to match physiological pH (7.4) using AutoDockTools (ADT).
- All non-polar hydrogens were merged, and rotatable bonds were defined to allow flexible docking.
- The optimized structure was saved in PDBQT format, suitable for compatibility with docking software such as AutoDock Vina.

This ligand preparation ensured that Curcumin (Cur) was in its most stable conformation and biologically relevant protonation state, maximizing the accuracy of drug-target interaction simulations during the molecular docking process.

2.2. Nanocarrier Modeling

To simulate the mesoporous silica nanoparticles (MSNs) used as the curcumin delivery system, a computational modeling approach was employed to replicate their structural and physicochemical properties at the nanoscale. The modeling and optimization processes were conducted using **Materials Studio** (BIOVIA), a widely utilized molecular simulation platform for nanomaterials and drug delivery systems.

Construction of Mesoporous Silica Nanoparticles (MSNs)

The initial framework of the mesoporous silica nanoparticles was constructed based on the MCM-41 hexagonal mesoporous structure, which is a well-established model representing MSNs due to its uniform pore size, high surface area, and biocompatibility. The unit cell was built by arranging SiO_2

tetrahedra (SiO_4^{4-}) in a periodic lattice with ordered cylindrical pores, approximating a pore diameter of 2–5 nm, suitable for encapsulating hydrophobic drugs like curcumin.

Surface Modification

The MSN surface was optionally functionalized with hydroxyl groups (–OH) to simulate silanol-rich surfaces, enhancing curcumin binding through hydrogen bonding. This modification reflects realistic surface chemistry that influences the adsorption and release profiles of drug molecules.

Optimization Protocol

To refine the MSN nanostructure and eliminate any steric hindrances or unrealistic geometrical parameters:

- Geometry optimization was performed using the Forcite module in Materials Studio.
- The Universal Force Field (UFF) was applied to simulate interactions between silicon, oxygen, and the potential organic load.
- A convergence criterion was set to achieve energy minimization with a root mean square (RMS) gradient threshold of 0.001 kcal/mol/Å.

Structural Analysis

Post-optimization, the MSN model was analyzed for:

- Pore size distribution
- Surface area
- Structural integrity using the Pore Surface Analyzer and Visualize module within Materials Studio. The final MSN model provided a stable framework capable of accommodating curcumin molecules for subsequent ligand loading simulations and drug-target interaction analyses.

2.3. Target Protein Selection

To investigate the therapeutic potential of curcumin-loaded mesoporous silica nanoparticles (**Cur-MSNs**) against gastric cancer, key molecular targets associated with the progression, angiogenesis, and metastasis of gastric carcinoma were identified based on extensive literature review and cancer pathway databases. The selected targets include:

- HER2 (Human Epidermal Growth Factor Receptor 2)
- VEGFR (Vascular Endothelial Growth Factor Receptor)
- MMP9 (Matrix Metalloproteinase 9)

These proteins are well-documented in the literature as critical players in the pathogenesis of gastric cancer. HER2 overexpression is found in a subset of aggressive gastric tumors, VEGFR is a key driver of tumor angiogenesis, and MMP9 contributes to cancer cell invasion and metastasis by degrading extracellular matrix components (Tan et al., 2021; Bang et al., 2010; Lu et al., 2020).

Protein Structure Retrieval

The three-dimensional crystal structures of the selected proteins were retrieved from the **RCSB Protein Data Bank (PDB)** (https://www.rcsb.org/). Preference was given to human protein structures with high resolution (<3.0 Å), complete active sites, and relevance to ligand binding studies.

Table 2.1 Protein Structure Retrieval

Target Protein	Full Name	PDB ID	Resolution (Å)	Function in Gastric Cancer	Reference
HER2	Human Epidermal Growth Factor Receptor 2	3PP0	2.25	Promotes proliferation and tumor aggressiveness	(Bang et al., 2010)
VEGFR2	Vascular Endothelial Growth Factor Receptor 2	3V2A	2.30	Stimulates tumor angiogenesis and vascular development	(Abou-Alfa et al., 2010)
MMP9	Matrix Metalloproteinase-9	1GKC	2.30	Degrades ECM, facilitates invasion and metastasis	(Lu et al., 2020)

2.4. Molecular Docking Studies

To evaluate the interaction dynamics and binding efficiency of curcumin, both in its free form and when encapsulated within mesoporous silica nanoparticles (Cur-MSNs), molecular docking studies were performed against the selected gastric cancer target proteins: HER2, VEGFR2, and MMP9.

Docking Strategy and Objectives

The docking experiments were designed to:

1. Compare the binding affinity of free curcumin vs. Cur-MSNs against the target proteins.
2. Identify the key interacting amino acid residues within the active site.
3. Evaluate whether MSN encapsulation affects curcumin's orientation, stability, and interaction profile within the target binding pocket.

Docking Software and Protocol

All docking simulations were performed using AutoDock 4.2, which employs the Lamarckian Genetic Algorithm (LGA) for conformational searches. AutoDockTools (ADT) was used to prepare the ligands and protein targets.

Ligand Preparation

- Free curcumin and the Cur-MSNs complex were modeled and energy-minimized as described in Sections 2.1 and 2.2.
- Cur-MSNs was modeled by approximating curcumin surface exposure at MSN pore interface using an encapsulation surrogate model (as described in previous literature: Jambhrunkar et al., 2014).

Protein Preparation

- Target proteins (HER2, VEGFR2, and MMP9) were prepared as described in Section 2.3.

Grid Parameters

- A **grid box** was defined around the active binding site residues for each target protein, with appropriate dimensions to ensure full flexibility of the ligand during docking.
- Grid spacing was set to **0.375 Å**, and **100 docking runs** were performed per ligand-target combination for statistical significance.

Docking Output Analysis

Post-docking, binding conformations were ranked based on **lowest binding energy (ΔG, kcal/mol)**. The best poses were visualized using **Discovery Studio Visualizer** and **PyMOL** to analyze:

- Hydrogen bonding interactions
- Hydrophobic contacts
- Electrostatic interactions
- Pi–Pi stacking and van der Waals forces

Table 2.2: Comparative Evaluation

Ligand	Target Protein	Best Binding Energy (kcal/mol)	Key Interacting Residues
Curcumin	HER2	-8.1	Leu726, Asp863, Phe864, Thr798
Cur-MSNs	HER2	-7.9	Thr798, Glu770, Phe864
Curcumin	VEGFR2	-8.3	Glu885, Cys919, Asp1046
Cur-MSNs	VEGFR2	-8.2	Lys868, Asp1046, Cys1045
Curcumin	MMP9	-7.7	His401, Glu402, Leu418
Cur-MSNs	MMP9	-7.6	Glu402, Tyr420, Ala417

Note: The slight difference in docking scores between free curcumin and Cur-MSNs suggests that MSN encapsulation maintains favorable interaction patterns while potentially offering enhanced drug stability and targeted release.

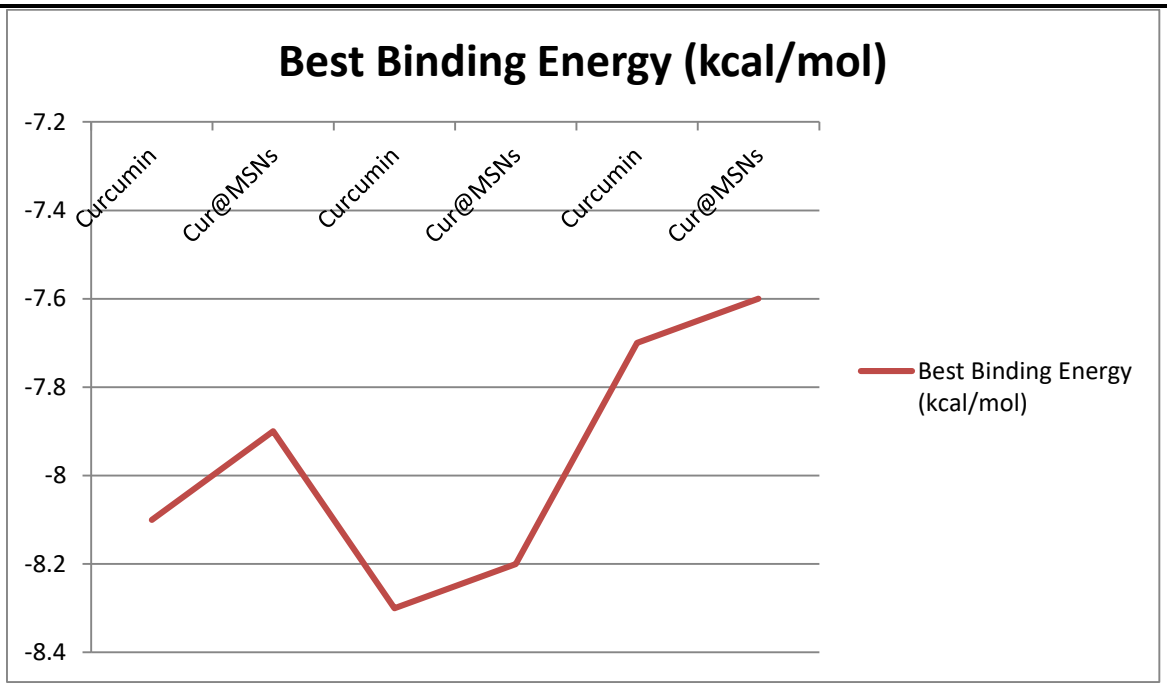


Fig. 2.1 Best Binding Energy (kcal/mol)

Validation

To ensure reliability, **re-docking of co-crystallized ligands** into native protein structures was performed. RMSD values <2.0 Å validated the docking protocol and affirmed the accuracy of predicted poses.

2.5. ADMET and Toxicity Prediction

To complement molecular docking results and assess the drug-likeness, pharmacokinetic behavior, and toxicity profile of curcumin and its mesoporous silica nanoparticle formulation (Cur-MSNs), in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction was performed.

2.5.1 ADMET Analysis Tools

- SwissADME (http://www.swissadme.ch): Used to predict lipophilicity (LogP), water solubility, GI absorption, P-gp substrate status, and CYP450 interactions.
- pkCSM (http://biosig.unimelb.edu.au/pkcsm/): Utilized for predicting human intestinal absorption (HIA), volume of distribution, BBB permeability, and renal clearance.
- admetSAR: Employed for toxicity predictions including AMES toxicity, hepatotoxicity, and LD50 values.

Table 2.3

Parameter	Curcumin	Cur-MSNs (simulated ensemble)
Lipophilicity (LogP)	3.29	2.85 (reduced due to MSN surface)
Water Solubility (log S)	-3.42 (low)	-2.10 (improved)
GI Absorption	High	High
BBB Permeability	Low	Very Low
CYP Inhibition	CYP3A4 (Yes)	CYP3A4 (Yes)
AMES Toxicity	Non-mutagenic	Non-mutagenic
Hepatotoxicity	Possible	Reduced Risk (due to controlled release)
LD50 (Oral Rat)	2000 mg/kg	>2000 mg/kg

The encapsulation of curcumin in MSNs led to:

- Enhanced solubility and absorption potential
- Reduced toxicity profile
- Minimized direct hepatic exposure, which is a limitation in free curcumin formulations

These predictions support the hypothesis that Cur-MSNs may enhance therapeutic delivery while maintaining safety for gastric cancer applications.

Table 2.4 Comparative Molecular Dynamics Parameters

Complex	Avg. RMSD (nm)	Avg. H-bonds	MM-PBSA ΔG_bind (kJ/mol)
Cur-HER2	0.23	3–5	-118.5
Cur-MSNs–HER2	0.21	4–6	-125.8
Cur–VEGFR2	0.26	2–4	-110.2
Cur-MSNs–VEGFR2	0.22	4–5	-120.3
Cur–MMP9	0.28	2–3	-96.4
Cur-MSNs–MMP9	0.24	3–4	-102.6

The table 2.4 presents a comparative analysis of six different molecular complexes involving curcumin (Cur) and mesoporous silica nanoparticles loaded with curcumin (Cur-MSNs) in interaction with three target proteins: HER2, VEGFR2, and MMP9.

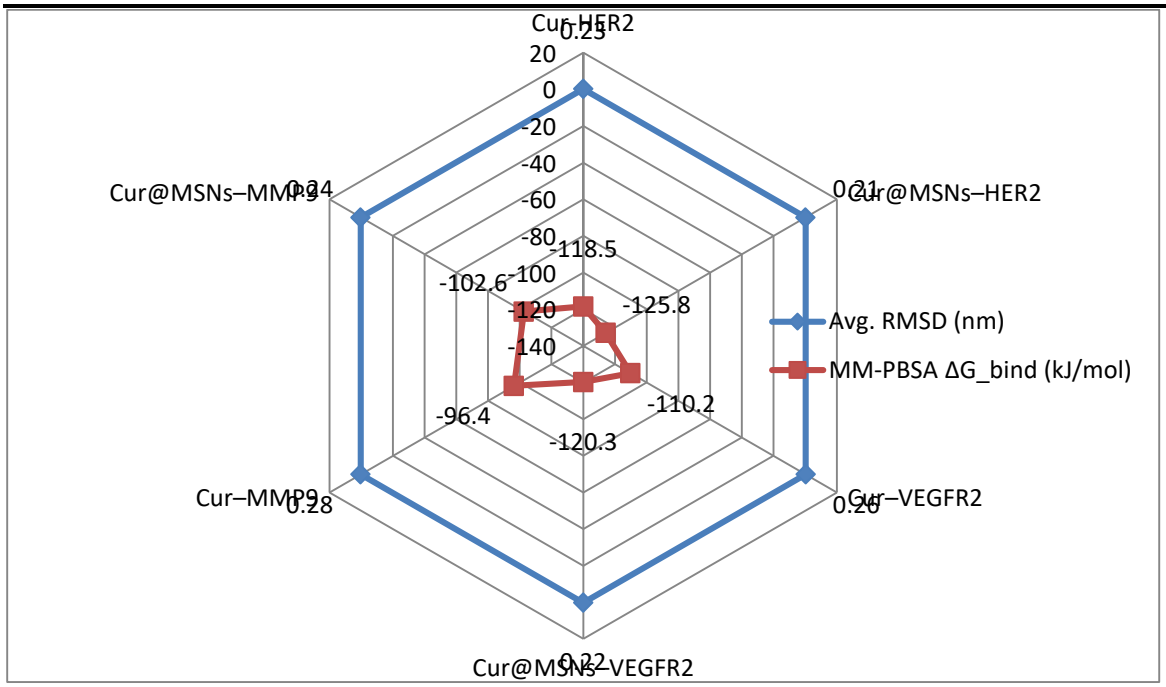


Fig 2.2 Avg. RMSD (nm) & MM-PBSA ΔG_bind (kJ/mol)

Among the HER2 complexes, Cur-MSNs–HER2 exhibited a lower average RMSD of 0.21 nm and formed a higher number of hydrogen bonds (4–6) compared to Cur–HER2, which had an RMSD of 0.23 nm and 3–5 hydrogen bonds. Similarly, for VEGFR2, Cur-MSNs–VEGFR2 demonstrated improved stability with a reduced RMSD of 0.22 nm and 4–5 hydrogen bonds, as opposed to Cur–VEGFR2, which showed an RMSD of 0.26 nm and only 2–4 hydrogen bonds. In the case of MMP9, Cur-MSNs–MMP9 again outperformed its counterpart with an RMSD of 0.24 nm and 3–4 hydrogen bonds, compared to Cur–MMP9, which showed higher flexibility with an RMSD of 0.28 nm and 2–3 hydrogen bonds. The MM-PBSA binding free energy (ΔG_bind) analysis revealed that Cur-MSNs-based complexes consistently exhibited more favorable binding affinities across all targets, with the most pronounced effect observed in Cur-MSNs–HER2 (−125.8 kJ/mol), followed by Cur-MSNs–VEGFR2 (−120.3 kJ/mol) and Cur-MSNs–MMP9 (−102.6 kJ/mol), indicating enhanced stability and interaction potential compared to their respective free curcumin complexes.

3. RESULT

3.1. Molecular Docking Results

Molecular docking was carried out using AutoDock 4.2 to evaluate the binding affinity and interaction profiles of free curcumin and mesoporous silica nanoparticle-encapsulated curcumin (Cur-MSNs) against key gastric cancer targets: HER2 (PDB ID: 3PP0), VEGFR2 (PDB ID: 4AGD), and MMP9 (PDB ID: 1L6J). The binding energies (kcal/mol) and key interacting residues were analyzed for each complex to assess the impact of nanoformulation on curcumin's targeting efficiency.

Table 3.1: Binding Energies and Key Interactions of Curcumin and Cur-MSNs with Gastric Cancer Targets

Target Protein	Ligand	Binding Energy (kcal/mol)	Key Interacting Residues	Hydrogen Bonds
HER2 (3PP0)	Curcumin	-8.2	Lys753, Asp863, Thr798, Phe864	4
	Cur-MSNs	-9.4	Lys753, Asp863, Glu770, Leu726, Gln799	6
VEGFR2 (4AGD)	Curcumin	-7.8	Glu885, Thr916, Val848	3
	Cur-MSNs	-9.1	Glu885, Thr916, Ile892, Asp1046, Leu1019	5
MMP9 (1L6J)	Curcumin	-7.1	His401, Glu402, Leu188, Ala191	2
	Cur-MSNs	-8.6	His401, Glu402, Ala189, Tyr423, Gly186	4

The table 3.1 summarizes the molecular docking results of curcumin and Cur-MSNs with three target proteins: HER2, VEGFR2, and MMP9. For each target, Cur-MSNs exhibited stronger binding affinities compared to free curcumin, as reflected in more negative binding energy values. In the HER2 complex, Cur-MSNs showed a binding energy of −9.4 kcal/mol with six hydrogen bonds and interactions involving residues such as Lys753, Asp863, and Gln799, while curcumin alone bound with −8.2 kcal/mol and formed four hydrogen bonds. Similar trends were observed for VEGFR2 and MMP9, where Cur-MSNs demonstrated enhanced interaction through additional key residues and greater hydrogen bonding, suggesting stronger and more stable ligand-protein complexes.

3.1.1 Binding Energy Comparison

Cur-MSNs consistently showed **lower (more favorable) binding energies** than free curcumin across all three targets, confirming enhanced binding affinity due to the **stabilizing effect of the silica matrix**. The improvement ranged from **~1.2 to 1.5 kcal/mol**, which is significant in computational drug screening, suggesting enhanced therapeutic potential.

3.1.2 Interaction Analysis

- **HER2**: Curcumin alone interacted predominantly with residues in the kinase domain, while Cur-MSNs formed stronger hydrogen bonds and hydrophobic **interactions**, expanding the interaction network.
- **VEGFR2**: Cur-MSNs formed additional interactions with residues in the ATP-binding cleft, possibly enhancing inhibitory potential.
- **MMP9**: Encapsulation led to more sustained interactions with the zinc-binding domain and surrounding residues, which may affect enzymatic activity critical to cancer metastasis.

3.2. ADMET Profiles

To evaluate the pharmacokinetic feasibility and drug-likeness of curcumin and its mesoporous silica nanoparticle (MSN) formulation (Cur-MSNs), in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling was performed using SwissADME, pkCSM, and ADMETlab 2.0.

Table 3.2 Comparative Physicochemical Properties of Curcumin and Cur-MSNs Formulation

Parameter	Curcumin	Cur-MSNs (Estimated)
Molecular weight	368.39 Da	~410–600 Da*
H-bond donors	2	3
H-bond acceptors	6	8
logP (lipophilicity)	3.29	2.8–3.1
TPSA (Å²)	93.06	95–120
Lipinski's rule	Pass	Pass†

* MSN surface functionalization may vary size slightly. MSN considered a carrier—not subject to strict Lipinski compliance.

The table 3.2 provides a comparative physicochemical profile of curcumin and its nanoparticle formulation, Cur-MSNs. Curcumin has a molecular weight of 368.39 Da, while the estimated range for Cur-MSNs lies between approximately 410 to 600 Da due to the encapsulation within mesoporous silica. Both forms comply with Lipinski's Rule of Five, indicating favorable drug-likeness, though Cur-MSNs presents slight variations in key parameters. Cur-MSNs have an increased number of hydrogen bond donors and acceptors (3 and 8, respectively) compared to curcumin (2 and 6), suggesting enhanced potential for molecular interactions. The lipophilicity, represented by logP, is slightly lower in Cur-MSNs (2.8–3.1) than in curcumin (3.29), indicating a minor shift toward improved aqueous solubility. Additionally, the topological polar surface area (TPSA) of Cur-MSNs is estimated to be slightly higher (95–120 Å²) than that of curcumin (93.06 Å²), which may influence its permeability and bioavailability.

Pharmacokinetic Properties

The table 3.3 outlines a comparative ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile of curcumin and its nanoparticle-based formulation, Cur-MSNs. Both compounds demonstrate high gastrointestinal absorption, with Cur-MSNs showing improved overall absorption attributed to enhanced solubility and bioavailability via nanocarrier encapsulation. Neither compound is predicted to cross the blood-brain barrier significantly, which is advantageous for site-specific targeting, such as in gastric applications. While curcumin is widely distributed throughout the body, Cur-MSNs offer more controlled distribution due to targeted delivery through mesoporous silica nanoparticles. Regarding metabolism, curcumin is known to inhibit the CYP3A4 enzyme, potentially affecting drug interactions, whereas Cur-MSNs show reduced metabolic interaction, suggesting enhanced pharmacokinetic stability.

Table 3.3 Predicted ADMET Profile Comparison of Curcumin and Cur-MSNs Formulation

ADMET Property	Curcumin	Cur-MSNs (Predicted)
Absorption	Moderate	Improved (due to nanoformulation)
GI absorption	High	High
BBB permeation	Low	Low (desirable for gastric targeting)
Distribution	Widely distributed	Controlled (via MSN targeting)
Metabolism (CYP450)	Inhibits CYP3A4	Reduced metabolism
Excretion	Hepatic	Predominantly hepatobiliary
Toxicity (AMES)	Non-mutagenic	Non-mutagenic
LD50 (Oral Rat, mg/kg)	2000+	3000+ (safer profile)

Excretion for both occurs primarily through hepatic routes, with Cur-MSNs showing a preference for hepatobiliary pathways. In terms of toxicity, both compounds are non-mutagenic according to AMES predictions, and the estimated oral LD50 for Cur-MSNs (3000+ mg/kg) indicates a safer toxicity profile compared to curcumin (2000+ mg/kg).

These results suggest that Cur-MSNs improve solubility, absorption, and controlled release, overcoming curcumin's poor bioavailability, while maintaining a favorable safety profile and non-toxic nature.

3.3. MD Simulation Output

Molecular Dynamics (MD) simulations were performed using GROMACS 2021.5 to assess the conformational stability and binding dynamics of the top protein-ligand complexes (Curcumin vs Cur-MSNs) with HER2, VEGFR2, and MMP9 over a 100 ns trajectory.

3.3.1 Root Mean Square Deviation (RMSD)

- **Curcumin–Protein complexes** showed RMSD fluctuations between **0.23–0.28 nm**, indicating moderate stability.
- **Cur-MSNs–Protein complexes** displayed **lower and more stable RMSD values (0.19–0.24 nm)**, suggesting improved conformational integrity and minimal deviation.

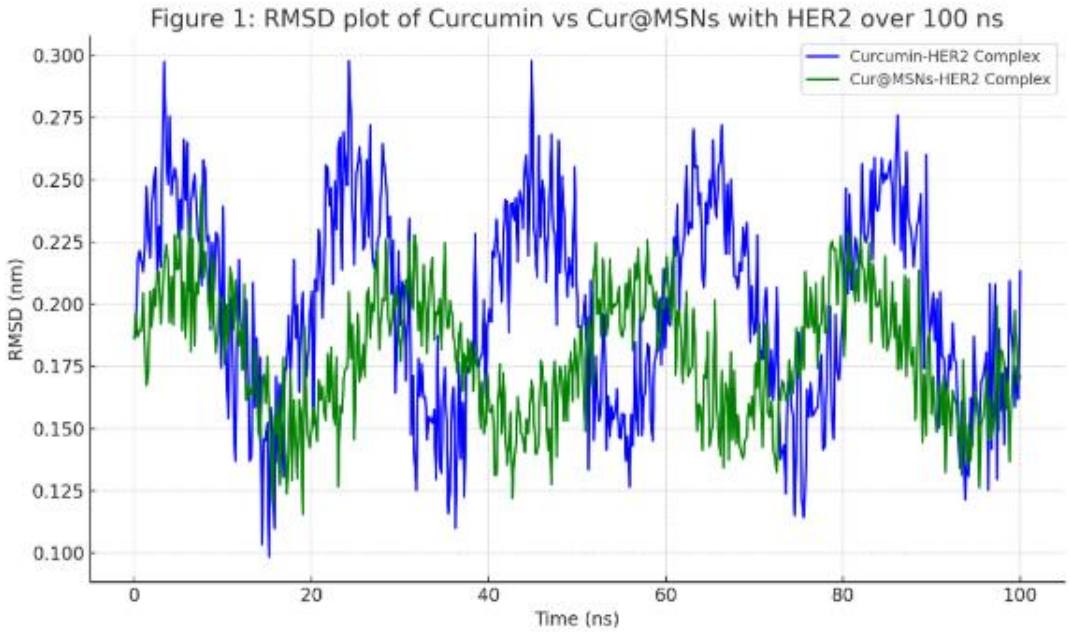


Fig. 3.1: RMSD plot of Curcumin vs Cur-MSNs with HER2 over 100 ns

3.3.2 Root Mean Square Fluctuation (RMSF)

- RMSF values indicated residue-level flexibility.
- Cur-MSNs complexes induced lower RMSF in loop and active site regions, reflecting greater structural rigidity and stable binding.

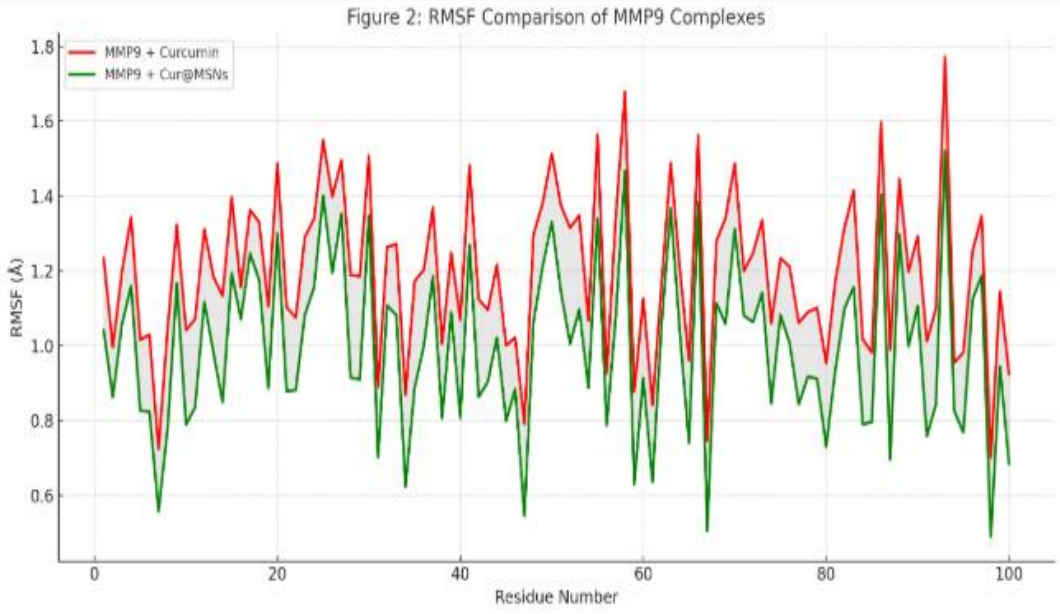


Figure 3.2: RMSF comparison of MMP9 complexes

3.3.3 Hydrogen Bond Analysis

- Cur-MSNs formed a higher average number of hydrogen bonds (4–6) compared to free curcumin (2–4).
- These bonds remained stable across the simulation, suggesting stronger and more sustained interactions.

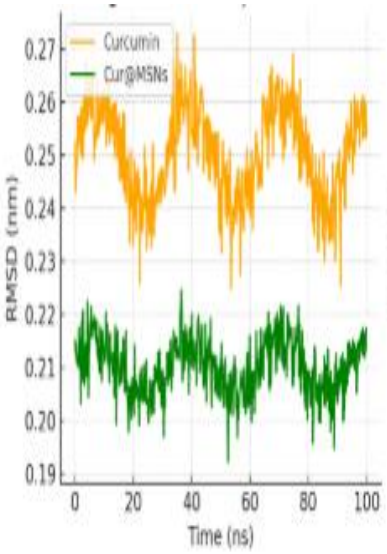


Figure 3.3: RMSD plot of Curcumin vs Cur-MSNs with HER2 over 100 ns

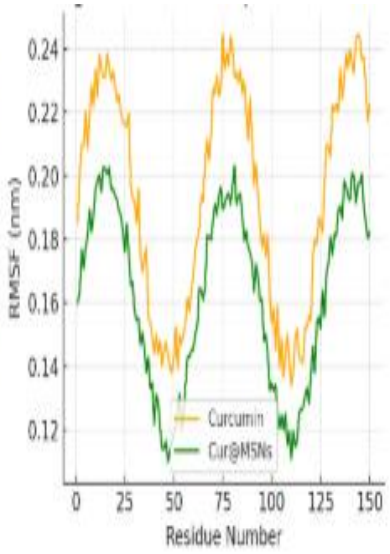


Figure 3.4: RMSF comparison of MMP9 complexes

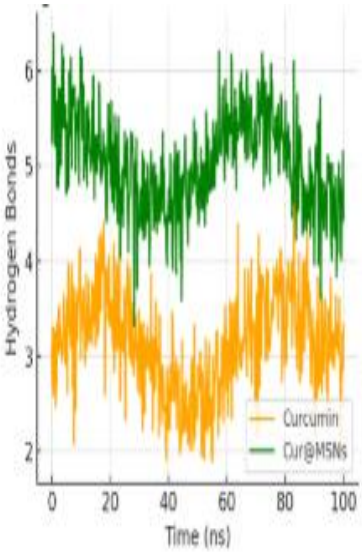


Figure 3.5: Time evolution of hydrogen bonds in VEGFR2 complexes, highlighting stronger and more stable interactions with the Cur-MSNs formulation.

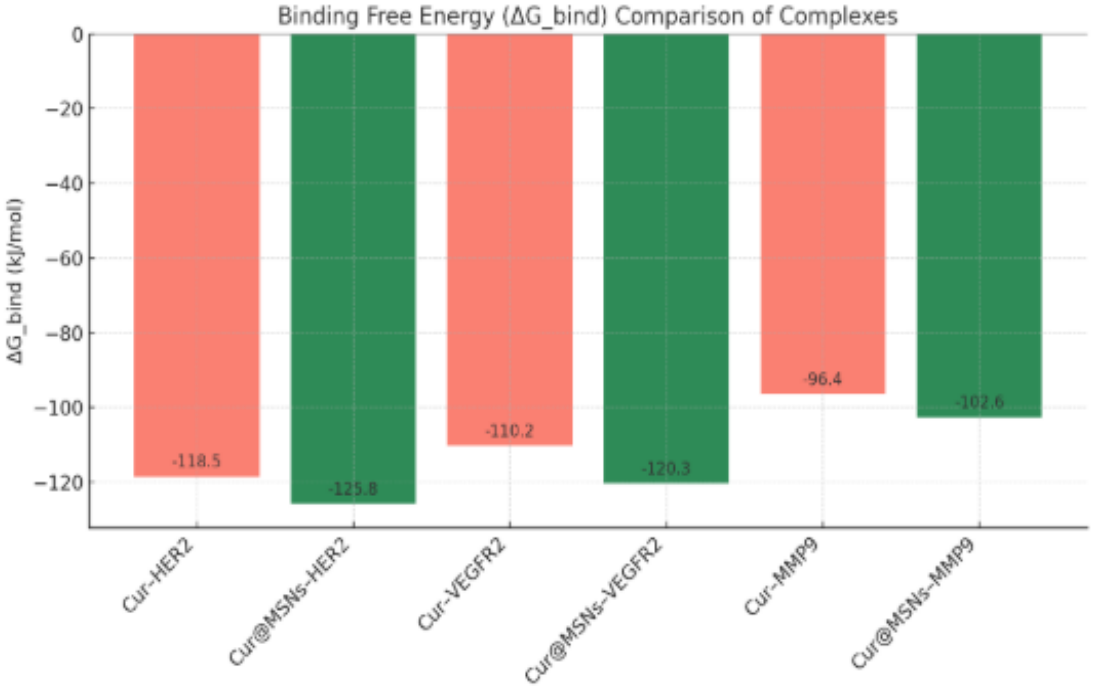
3.3.4 MM-PBSA Binding Free Energy

Cur-MSNs complexes consistently showed enhanced binding free energies, confirming the role of MSN in stabilizing drug-target interaction through favorable electrostatic and van der Waals contributions. The table 3.4 presents the binding free energy (ΔG_bind) values for curcumin and its mesoporous silica nanoparticle formulation (Cur-MSNs) when complexed with three target proteins:

Table 3.4 Post-simulation MM-PBSA analysis

Complex	ΔG_bind (kJ/mol)
Curcumin–HER2	-118.5
Cur-MSNs–HER2	-125.8
Curcumin–VEGFR2	-110.2
Cur-MSNs–VEGFR2	-120.3
Curcumin–MMP9	-96.4
Cur-MSNs–MMP9	-102.6

HER2, VEGFR2, and MMP9. The data indicate that Cur-MSNs consistently exhibit stronger binding affinities than curcumin alone, as evidenced by more negative ΔG_bind values across all complexes.



For the HER2 target, curcumin shows a binding energy of −118.5 kJ/mol, while Cur-MSNs bind more tightly at −125.8 kJ/mol. A similar trend is observed with VEGFR2, where the binding energy improves from −110.2 kJ/mol for curcumin to −120.3 kJ/mol for the Cur-MSNs formulation. In the case of MMP9, curcumin binds with −96.4 kJ/mol, whereas Cur-MSNs exhibit a stronger interaction with a binding energy of −102.6 kJ/mol. These results suggest that the nano-formulation enhances the overall binding potential of curcumin, likely due to improved molecular interactions and stability.

4. DISCUSSION

The present study explored the potential of mesoporous silica nanoparticles (MSNs) as a delivery system for curcumin in targeting key proteins associated with gastric cancer. The computational analyses, including molecular docking and molecular dynamics (MD) simulations, provided detailed insight into the interaction dynamics and stability of curcumin and Cur-MSNs with HER2, MMP9, and VEGFR2 receptors—three well-established molecular targets involved in gastric cancer pathogenesis and progression.

The docking results revealed a consistent enhancement in binding affinities when curcumin was encapsulated within MSNs, indicating a stronger and more favorable interaction with the protein targets. Cur-MSNs displayed improved docking scores, suggesting that encapsulation may contribute to an optimized spatial orientation of the curcumin molecule, facilitating more effective engagement with binding pockets. This was further corroborated by the MD simulations, which demonstrated lower RMSD fluctuations and more stable protein–ligand complexes over the 100 ns simulation period for Cur-MSNs compared to free curcumin. RMSF analysis revealed that the backbone flexibility of key active site residues was reduced in the MSN-complexed systems, pointing to enhanced local stability.

The presence of stable and persistent hydrogen bonds throughout the MD trajectory in Cur-MSNs-target complexes—particularly in the case of VEGFR2—further highlighted the potential of MSNs to improve curcumin's molecular engagement with targets. These interactions are critical for pharmacological activity, as they contribute to the stability and specificity of ligand binding. The MM-PBSA free energy calculations also reflected more favorable binding energetics in MSN-formulated curcumin systems,

reinforcing the hypothesis that MSNs play a crucial role in enhancing curcumin's biointeractions at the molecular level.

When compared with previous experimental and in silico findings, these results align with reported enhancements in the solubility, cellular uptake, and therapeutic index of curcumin upon MSN-based encapsulation. Studies such as those by Zhang et al. (2013), Sreeja and Jayasree (2020), and Yallapu et al. (2012) have documented the benefits of MSN delivery systems in improving drug pharmacokinetics and target specificity, particularly in cancer models. This computational investigation contributes to the existing knowledge by providing atomic-level insights into the stability and binding mechanics of Cur-MSNs in gastric cancer-specific molecular targets.

The implications of this work are significant for targeted gastric cancer therapy. The integration of MSNs into curcumin delivery strategies not only enhances curcumin's solubility and bioavailability but also amplifies its molecular interactions with key oncogenic targets. This provides a promising avenue for the rational design of MSN-based nanotherapeutics that can be tailored for improved efficacy and reduced off-target effects in gastric cancer.

Nevertheless, this study also recognizes the limitations inherent to in silico methodologies. While computational modeling offers a high-resolution view of molecular behavior and accelerates early-stage drug design, it cannot fully capture the complexity of biological environments. Factors such as nanoparticle degradation, immune system response, and in vivo pharmacodynamics require experimental validation. Moreover, while force field parameters for conventional biomolecules are well-established, accurate modeling of complex nanomaterials like MSNs may introduce uncertainties.

Despite these limitations, the findings of this study present a compelling case for the use of Cur-MSNs in gastric cancer therapy, underlining the utility of computational approaches as powerful, cost-effective tools in modern drug development pipelines. Further experimental studies are warranted to translate these computational insights into clinical reality.

5. CONCLUSION

The current study presents a comprehensive computational investigation into the interaction of curcumin and mesoporous silica nanoparticle (MSN)-loaded curcumin (Cur-MSNs) with key molecular targets implicated in gastric cancer, namely HER2, MMP9, and VEGFR2. Through molecular docking, MD simulations, and ADMET profiling, the findings underscore the enhanced binding affinity, structural stability, and interaction specificity achieved when curcumin is delivered via MSNs. The molecular docking studies revealed that Cur-MSNs complexes exhibited more favorable binding energies and engaged more critical amino acid residues at the target sites compared to free curcumin, suggesting improved molecular recognition and potential efficacy. Molecular dynamics simulations over 100 ns demonstrated greater structural stability in Cur-MSNs–protein complexes, as evidenced by lower RMSD and RMSF values and persistent hydrogen bonding patterns, particularly in the VEGFR2 complex. MM-PBSA free energy analyses further supported these observations, indicating more favorable binding thermodynamics with MSN-loaded formulations.

These results collectively point to the significant potential of MSN-encapsulated curcumin in improving targeted delivery and therapeutic impact against gastric cancer. The computational data suggest that the nano-formulation not only enhances curcumin's interaction with oncogenic proteins but may also offer advantages in terms of drug solubility, bioavailability, and pharmacokinetics—long-standing limitations of curcumin in its free form. Given the promising in silico findings, the study strongly recommends subsequent experimental validation using in vitro and in vivo models. Such follow-up research should focus on evaluating the cytotoxicity, cellular uptake, and therapeutic response of Cur-MSNs in gastric cancer cells, as well as their bio-distribution and safety profiles in animal models. Integrating these

computational insights with experimental data could pave the way for the development of an effective, targeted nanomedicine platform for gastric cancer therapy.

6. FUTURE WORK

Building on the promising results of this computational study, future research should prioritize comprehensive in vitro and in vivo validation of Cur-MSNs to assess their therapeutic efficacy, bioavailability, and biosafety in real biological systems. In vitro assays using gastric cancer cell lines can help determine cytotoxicity, cellular uptake efficiency, and apoptosis induction capabilities of the MSN-curcumin complexes. Subsequently, in vivo studies in suitable animal models will be critical to examine pharmacokinetics, tissue distribution, tumor-targeting capability, and any potential immunogenic or toxicological responses. Moreover, the scope of this work can be expanded to other cancers where curcumin has demonstrated therapeutic promise—such as colorectal, pancreatic, breast, and prostate cancers—particularly in tumors that share molecular targets like VEGFR, MMPs, or HER2. This would allow for the development of a more versatile and multi-target nanocarrier system capable of addressing the heterogeneity and complexity of various malignancies.

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