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Unlocking the Anticancer Potential of Metal-Curcumin Complexes: Docking Insights with EGFR

Research Article

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Abstract

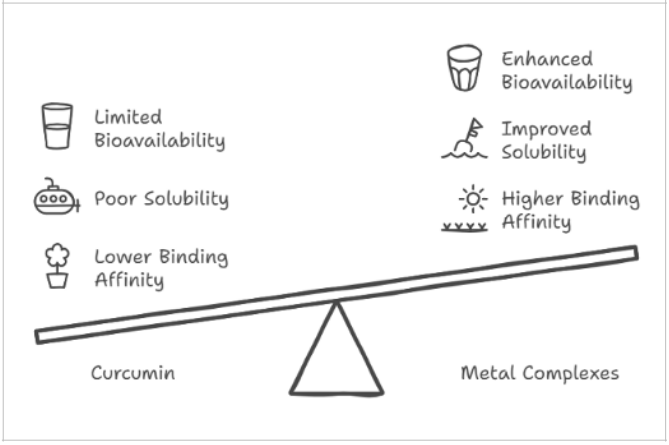
The Epidermal Growth Factor Receptor (EGFR) plays a pivotal role in cervical cancer progression by driving uncontrolled cell proliferation and survival. Given its oncogenic significance, EGFR remains a prime therapeutic target for cancer drug development. Curcumin, a bioactive polyphenol, exhibits promising anticancer properties but suffers from poor solubility and bioavailability, limiting its clinical application. To enhance its pharmacological potential, metal complexation has been explored as a strategy to improve its pharmacokinetics and bioactivity. This study employed molecular docking to assess the binding affinities of curcumin and its metal complexes (Ca, Cu, Mg, Na, Zn) with two EGFR conformations: the active kinase domain (PDB ID: 1M17) and the extracellular ligand-binding domain (PDB ID: 4ZSE). Docking analyses revealed that Ca-Bicurcumin (-11.1 kcal/mol), Na-Bicurcumin (-11.0 kcal/mol), and Cu, Mg, and Zn-Bicurcumin complexes (-10.8 kcal/mol each) exhibited strong binding affinities toward 1M17, outperforming the reference ligand AQ4 (-7.0 kcal/mol) and native curcumin (-7.3 kcal/mol). Similarly, Cu-Bicurcumin (-11.0 kcal/mol), along with Ca, Mg, and Na-Bicurcumin complexes (-10.9 kcal/mol each), displayed superior interactions with 4ZSE, exceeding the binding of ANP (-9.4 kcal/mol) and curcumin (-7.2 kcal/mol). These enhanced interactions resulted from strong hydrogen bonding, hydrophobic interactions, and electrostatic forces, improving receptor complementarity. The findings suggest that metal-curcumin complexes hold promise as EGFR-targeted therapeutics, potentially overcoming curcumin's pharmacokinetic limitations while enhancing its anticancer efficacy. Further, in vitro kinase inhibition assays and in vivo tumor regression studies are necessary to validate their therapeutic potential in EGFR-driven cancers.

Keywords: EGFR, Molecular Docking, Metal-Curcumin Complexes, Kinase Inhibition, Targeted Anticancer Therapy.

Introduction

Cancer remains among the most difficult problems in modern healthcare, with its multifactorial etiology and intricate molecular pathways making things complicated to combat effectively. (1) It remains one of the most challenging diseases in modern medicine, and significant efforts are directed toward discovering novel and effective therapeutic agents.(2) Among various molecular targets, the Epidermal Growth Factor Receptor (EGFR) has garnered substantial attention because it encourages tumor proliferation, angiogenesis, and metastasis.(3) EGFR is a transmembrane tyrosine kinase receptor that, upon ligand binding, triggers downstream signaling pathways, namely the PI3K-AKT, RAS-RAF-MEK-ERK, and JAK-STAT pathways, that leads to uncontrolled cell proliferation, angiogenesis, and metastasis.(4,5) Overexpression and abnormal activation of EGFR have been linked to various malignancies, including lung, breast, and colorectal cancers, making it a prime target for anticancer drugs development. (6)

Figure 1: Compairing Curcumin and its metal Complexes in EGFR Targeting



Curcumin, a bioactive polyphenol extracted from Curcuma longa's rhizome, has long been studied for its multifaceted pharmacological properties, including anti-inflammatory, antioxidant, and anticancer activities. (7,8) However, poor bioavailability, rapid metabolism, and limited solubility have hindered its clinical

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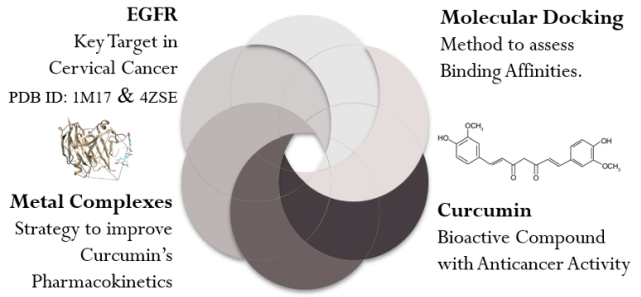
translation.(9) With the ultimate goal to get beyond these restrictions, researchers have looked into the potential of curcumin-metal complexes, which exhibit enhanced stability, solubility and bioactivity.(10,11) In recent years, the integration of bioactive natural compounds with metal ions has gained considerable attention for enhancing therapeutic efficacy in cancer treatment. Curcumin's coordination with transition metal ions, like copper (Cu), zinc (Zn), and platinum (Pt) has shown promising improvements in its anticancer efficacy. (10,12)

Figure 2: Strategy to Overcome Curcumins Limitation



Molecular docking analyses have provided valuable insights into the binding interactions between these complexes and the EGFR tyrosine kinase domain, revealing greater affinity for binding than free curcumin.(13) These findings suggest that metal coordination stabilizes the curcumin structure and facilitates stronger interactions for their anticancer potential. They also propose novel therapeutic candidates for EGFR-targeted cancer treatment. The insights gained from this study may pave the way to rationally develop metal-curcumin compounds as effective anticancer agents, offering new avenues in targeted cancer therapy.(14)

Materials and Methods

Platform for molecular docking

The computational docking assessment of native curcumin and metal-curcumin complexes was conducted using Chimera (version 1.17.3) integrated with AutoDock Vina (version 1.5.7). (15)

Selection of Target Protein Structure

The molecular docking study was conducted using two crystallized structures of the EGFR: **PDB ID: 1M17** and **PDB ID: 4ZSE**. (16,17) These structures are sourced from the Protein Data Bank (PDB).

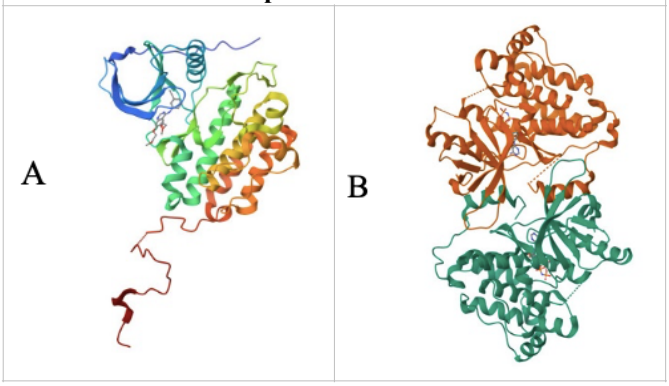
- **PDB ID: 1M17** represents EGFR tyrosine kinase bound [S1] with 4-anilinoquinazoline inhibitor erlotinib.(18)
- **PDB ID: 4ZSE**[S2] [SS3] represents the EGFR 696-1022 T790M/V948R Crystal structure form II. (19)

Both structures were chosen to evaluate the selectivity and binding affinity of **native curcumin and metal-curcumin complexes** against different forms of EGFR, allowing for a comprehensive assessment of their potential as EGFR inhibitors

Preparation of Protein Structures

To assure appropriate docking simulation conditions, the selected EGFR protein structures (1M17 and 4ZSE) were preprocessed using AutoDockTools. This included eliminating water molecules, incorporating polar hydrogens, assigning charges to optimize electrostatic interactions, and defining a grid box to ensure that the ligand was positioned at the functionally relevant location. (20)

Figure 3: Ribbon Representations of EGFR Structures – (A) 1M17 Complexed with AQ4 and (B) 4ZSE Complexed with ANP.



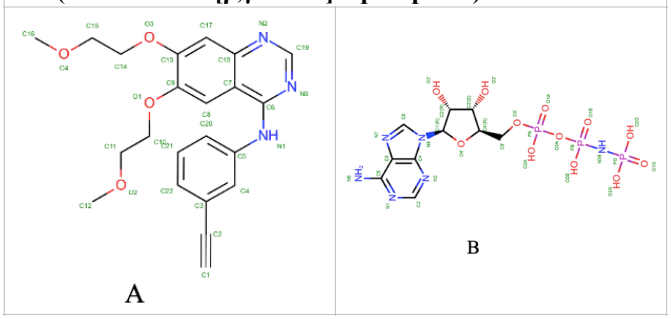
Ligand Preparation

The ligands were made by adding partial charges and polar hydrogens to the compounds to bring them to the necessary protonation state at physiological pH.

Native Ligands: AQ4 and ANP

The native ligands AQ4 and ANP, which are co-crystallized inhibitors of EGFR (PDB IDs: 1M17 and 4ZSE, respectively), were extracted directly from their respective crystal structures. These ligands were pre-processed by eliminating water molecules, allocating Gasteiger charges, and adding polar hydrogens to maintain their biologically active form. Energy minimization was performed using UCSF Chimera with the Amber ff14SB force field to ensure an optimal starting geometry before docking analysis.(21)

Figure 4: Chemical Structures of Native Ligands – (A) AQ4 (4-Anilinoquinazoline Derivative) from 1M17 and (B) ANP (Adenosine-5'-[β,γ-imido]triphosphate) from 4ZSE.



Native Curcumin

We used the PubChem database to obtain Curcumin's 3-D structure (CID: 969516).(22) The ligand was optimized using the Amber ff14SB force

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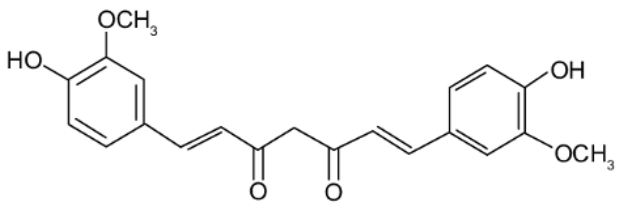
field UCSF Chimera software to ensure an accurate conformational state.

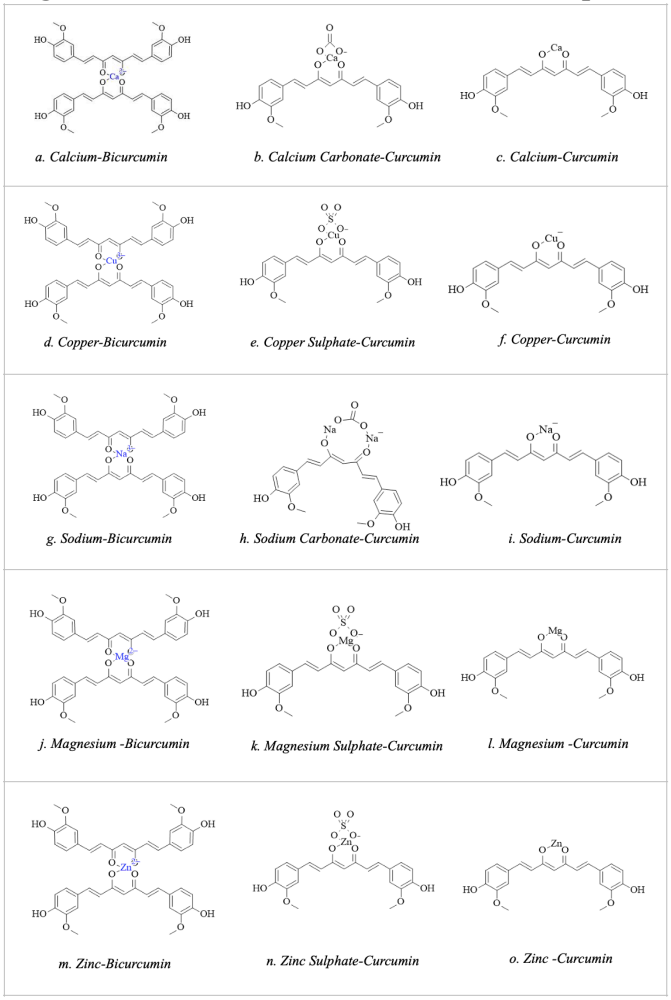
Figure 5: Structure of Curcumin



Metal-Curcumin Complexes

To investigate the role of metal coordination in EGFR inhibition, curcumin-metal complexes were modeled using Chemsketch, optimized using Avagadaro, and transformed into 3D structures with Open Babel. (23) The following metal-curcumin complexes were considered:

Figure 6: Structures of Metal Curcumin Complexes



The optimized geometries were converted into PDBQT format using AutoDock Tools for docking.

Molecular Docking Studies

Docking studies used the EGFR, (PDB IDs: 1M17 and 4ZSE) as target proteins, with each ligand appropriately prepared. Based on complex geometry and binding interactions, the predicted binding energy was analyzed using AutoDock Vina integrated with UCSF Chimera (v1.17.3). Default parameter values were applied for all docking simulations. The grid box coordinates were defined based on the binding site of the co-crystallised ligand AQ4 in PDB ID: 1M17 and ANP in PDB ID: 4ZSE. This ensures that all docking simulations were focused on the experimentally validated active site, allowing for more accurate and meaningful predictions of ligand–receptor interactions. The docking grid box for 1M17 was set to (25 × 25 × 25) Å, centered at (22.014, 0.253, 52.794) Å, while for 4ZSE, the grid box was set to (25 × 25 × 25) Å, centered at (2.367, 20.251, -33.251) Å. The docking results were examined using the "View Dock" tab for further analysis.(24)

Results

Analysis of Molecular Docking of Curcumin and Metal-Curcumin Complexes with EGFR

Figure 7: Color Scale for Docking Scores – Green (strongest binding) to Red (weakest binding)

Table 1: Docking Scores of Native ligand, Curcumin and Metal-Curcumin Complexes Against EGFR (PDB IDs: 1M17 & 4ZSE).

PDBID		1M17	4ZSE
Ligand		AQ4	ANP
Docking Score		-7.0	-9.4
Curcumin	Cur	-7.3	-7.2
Ca BICURCUMIN	Ca-1	-11.1	-10.9
$CaCO_3$	Ca-2	-9.4	-9.4
Ca. Curcumin	Ca-3	-8.5	-8.8
Cu BICURCUMIN	Cu-1	-10.8	-11.0
CuSO4	Cu-2	-9.8	-9.7
Cu. Curcumin	Cu-3	-8.7	-8.9
Mg BICURCUMIN	Mg-1	-10.8	-10.9
MgSo4	Mg-2	-9.7	-9.4
Mg. Curcumin	Mg-3	-8.4	-8.8
Na. BICURCUMIN	Na-1	-11.0	-10.9
Na2Co3	Na-2	-10.0	-9.1
Na. Curcumin	Na-3	-8.4	-8.9
Zn BICURCUMIN	Zn-1	-10.8	-10.8
ZnSO4	Zn-2	-9.6	-10.1
Zn. Curcumin	Zn-3	-8.5	-8.8

Molecular docking studies have been performed to assess the binding interactions of native curcumin and metal-curcumin complexes with EGFR using the crystal structures 1M17 (wild-type EGFR) and 4ZSE (mutant EGFR). The binding affinities, represented as docking scores (kcal/mol), are summarized in the Table 1. Lower docking scores indicate stronger binding interactions between the ligand and the receptor.

Discussion

Comparing the Binding Affinity of Curcumin and Native Ligands (AQ4 and ANP)

The reference ligands AQ4 (for 1M17) and ANP (for 4ZSE) exhibited docking scores of -7.0 kcal/mol and -9.4 kcal/mol, respectively. These values serve as benchmarks for Assessing the efficacy of f curcumin and its metal complexes in EGFR binding.

Native curcumin showed binding scores of -7.3 kcal/mol (1M17) and -7.2 kcal/mol (4ZSE), which are comparable to AQ4 but significantly weaker than ANP. This suggests that while curcumin has some affinity for EGFR, it is not as potent as the native ligand ANP in targeting the mutant EGFR (4ZSE).

Enhanced Binding of Metal-Curcumin Complexes Compared to Curcumin and Native Ligands

The introduction of metal ions significantly enhanced the binding affinity of curcumin derivatives,

with several metal-curcumin complexes outperforming both AQ4 and ANP. The most notable improvements were observed in metallic bicurcumin complexes (BICURCUMIN derivatives), particularly those containing calcium (Ca-1: -11.1 kcal/mol for 1M17, -10.9 kcal/mol for 4ZSE), sodium (Na-1: -11 kcal/mol for 1M17, -10.9 kcal/mol for 4ZSE), copper (Cu-1: -10.8 kcal/mol for 1M17, -11 kcal/mol for 4ZSE), magnesium (Mg-1: -10.8 kcal/mol for 1M17, -10.9 kcal/mol for 4ZSE), and zinc (Zn-1: -10.8 kcal/mol for both 1M17 and 4ZSE).

Among all complexes, all BICURCUMIN Complexes exhibited the strongest binding affinity for 1M17 and 4ZSE, surpassing both AQ4 and ANP. This indicates that BICURCUMIN complexes may serve as a more potent EGFR inhibitor than the native ligand.

Effect of Metal Salts on Binding Affinity

Curcumin complexes with metal salts ($CaCO_3$, $CuSO_4$, $MgSO_4$, Na_2CO_3, $ZnSO_4$) exhibited moderate binding affinities, with scores ranging between -9.4 and -10.1 kcal/mol. These values are still significantly lower (better binding) than native curcumin (-7.3 kcal/mol) and AQ4 (-7 kcal/mol), but slightly weaker than ANP (-9.4 kcal/mol).

For instance, while Cu-BICURCUMIN (Cu-1) demonstrated -10.8 kcal/mol (1M17) and -11 kcal/mol (4ZSE), $CuSO_4$-Curcumin (Cu-2) exhibited slightly weaker binding scores of -9.8 kcal/mol (1M17) and -9.7 kcal/mol (4ZSE). A comparable pattern was noted for $MgSO_4$-Curcumin (-9.7 kcal/mol for 1M17, -9.4 kcal/mol for 4ZSE) compared to Mg-BICURCUMIN (-10.8 kcal/mol for 1M17, -10.9 kcal/mol for 4ZSE). This indicates that free metal ions contribute more effectively to EGFR binding than metal salts.

Comparison of Binding Affinities Across EGFR Variants

Overall, all metal-curcumin complexes exhibited stronger binding to EGFR than both native curcumin and AQ4. Interestingly, the docking scores for mutant EGFR (4ZSE) were slightly better than those for wild-type EGFR (1M17) across most complexes, suggesting that metal-curcumin derivatives may be particularly effective against EGFR-driven drug resistance.

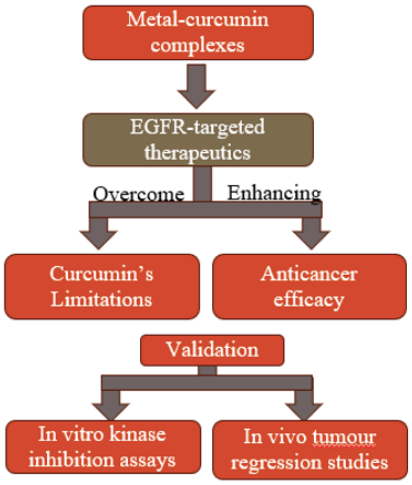
For instance, Cu-BICURCUMIN (-11 kcal/mol) and $ZnSO_4$-Curcumin (-10.1 kcal/mol) showed higher affinity for 4ZSE than ANP (-9.4 kcal/mol), indicating their potential as superior inhibitors for mutant EGFR.

Role of Individual Metal Ions in Binding Strength

- **Copper (Cu)**: Exhibited the strongest interactions, particularly in Cu-BICURCUMIN (10.8 kcal/mol for 1M17, -11 kcal/mol for 4ZSE), highlighting its strong chelation effects with EGFR active site residues.
- **Calcium (Ca)** and **Sodium (Na)**: Also demonstrated high docking scores (-11.1 kcal/mol for Ca-1 and -11.0 kcal/mol for Na-1) for 1M17 and (-10.9 kcal/mol for both Ca-1 and Na-1) for 4ZSE, suggesting significant contributions from electrostatic and coordination interactions.
- **Magnesium (Mg)** and **Zinc (Zn)**: Showed similar trends, with Mg-BICURCUMIN (-10.8 kcal/mol for 1M17, -10.9 kcal/mol for 4ZSE) and Zn-BICURCUMIN (-10.8 kcal/mol for both 1M17 and 4ZSE), reinforcing the importance of metal incorporation in curcumin derivatives.

Conclusion

Figure 8: Flowchart Representation of the Conclusion and Validation Strategy for Metal-Curcumin Complexes as EGFR-Targeted Therapeutics.



The molecular docking studies of curcumin and metal-curcumin complexes with the EGFR provide compelling evidence that metal coordination significantly enhances binding affinity when compared to native curcumin. Among the tested complexes, Cu-BICURCUMIN (-11 kcal/mol for 4ZSE) exhibited the strongest binding affinity, outperforming the native ligand ANP (-9.4 kcal/mol), indicating its potential as a more potent EGFR inhibitor. Additionally, Ca-BICURCUMIN and Na-BICURCUMIN also demonstrated exceptional binding interactions, reinforcing the role of metallic coordination in improving curcumin's anticancer properties.

A comparative analysis of docking scores between wild-type EGFR (1M17) and mutant EGFR (4ZSE) suggests that metal-curcumin complexes may be particularly effective against EGFR mutations associated with drug resistance. This finding is crucial, as EGFR mutations are a major cause of resistance to conventional tyrosine kinase inhibitors (TKIs) used in cancer therapy.

Overall, this study highlights the therapeutic potential of metal-curcumin complexes as novel EGFR inhibitors, with Cu, Ca, Na, Mg, and Zn-based curcumin derivatives exhibiting significantly improved binding affinities over native curcumin. These results provide a strong basis for further preclinical and experimental studies aimed at developing metal-curcumin-based anticancer drugs.

The promising docking results of metal-curcumin complexes against EGFR highlight their potential as next-generation anticancer agents. Additional validation by molecular dynamics simulations, in vitro as well as

vivo research, and mechanistic investigations is necessary. Structural modifications, QSAR modeling, and combination therapy with TKIs could enhance efficacy and overcome resistance. Additionally, Nanoparticle-based delivery methods may improve bioavailability and targeted action. With continued research, these complexes hold significant promise for clinical translation as novel EGFR inhibitors.

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