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Computational insights into Curcumin's modulation of Epithelial-mesenchymal transition in pulmonary fibrosis

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Pulmonary fibrosis (PF) is a progressive interstitial lung disease characterized by excessive production and accumulation of extracellular matrix, resulting in permanent lung damage. The epithelial-mesenchymal transition (EMT) plays a central part in the development of fibrosis; however, therapeutic strategies targeting EMT remain limited. Curcumin, a natural polyphenol with known anti-inflammatory and anti-fibrotic properties, presents a promising candidate for modulating EMT. This study aimed to evaluate the potential of curcumin as an EMT-targeting agent in pulmonary fibrosis using computational approaches. Protein targets of curcumin were predicted using the SwissTargetPrediction and STITCH databases. Protein-protein interaction (PPI) networks were analysed via STRING. Molecular docking studies were performed using AutoDock Vina with EMT-related proteins (TGFBR1, EGFR, MAPK1, and MMP9). Drug-like and pharmacokinetic properties were assessed using SwissADME, while toxicity was evaluated through Protox-II. Curcumin demonstrated strong binding affinity for multiple EMT regulators, suggesting potential inhibitory activity. Network analysis revealed dense interconnectivity among curcumin targets, indicating a co-regulated EMT-related functional cluster. Curcumin also exhibited favourable drug-like parameters and a low predicted toxicity profile (LD_{50}: 2000 mg/kg). This study supports the role of curcumin as a multitarget modulator of epithelial-mesenchymal transition (EMT) with therapeutic relevance in pulmonary fibrosis. The results warrant further experimental validation to confirm its efficacy and safety in preclinical models.

Keywords: *In silico*, Molecular docking, Preclinical validation, Protein-protein interaction, SwissADME, Toxicity prediction

Pulmonary fibrosis (PF) is a chronic interstitial lung disease characterized by the progressive accumulation of extracellular matrix components, primarily collagen, which results in structural alterations and an irreversible decline in pulmonary function[1]. Clinically, PF presents with dyspnoea, impaired gas exchange, and a poor prognosis, coupled with limited effective treatments and high mortality rates. Although we recognize etiological factors such as environmental exposure, autoimmune conditions, and certain medications, Idiopathic Pulmonary Fibrosis (IPF) is the most widespread and severe form, with no known causes[2,3]. Additionally, epithelial-mesenchymal transition (EMT) plays a key role in the development and progression of pulmonary fibrosis[4,5]. EMT is an active cellular reprogramming process in which epithelial cells shed their polarity and adhesion characteristics, adopting mesenchymal features such as enhanced motility and greater resistance to cell death[6-8]. In fibrosis, alveolar epithelial cells undergo epithelial-to-mesenchymal transition (EMT), contributing to the population of activated fibroblasts, as well as myofibroblasts that produce extracellular matrix proteins and fibrotic mediators[9-12]. Key mediators in EMT include transforming growth factor beta 1 (TGF-β1), mitogen-activated protein kinases (MAPKs), epidermal growth factor receptor (EGFR), and matrix metalloproteinases (MMPs)[13,14]. Despite its central role in fibrotic remodelling, EMT remains an under-targeted pathway in current therapeutic strategies for pulmonary fibrosis (PF)[11]. Pharmacological interventions currently approved for PF, such as pirfenidone and nintedanib, mainly target general anti-fibrotic and anti-inflammatory pathways but do not specifically modulate EMT[15]. The lack of EMT-targeted therapeutics is partly due to the complexity and context-dependent nature of EMT signalling pathways, as well as difficulties in identifying selective and safe modulators[16,17]. Therefore, there is an urgent need to identify and validate compounds that can effectively target EMT-associated molecular drivers to

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reverse or attenuate fibrotic progression in the lungs.Curcumin, a bioactive polyphenol derived from the rhizome of Curcuma longa (turmeric), has been extensively researched for its anti-inflammatory, antioxidant, anticancer, and antifibrotic effects[18–23]. Several preclinical studies have demonstrated that curcumin can interfere with signalling cascades involved in EMT, including the TGF-β/Smad, NF-κB, and MAPK pathways[24,25].

Moreover, curcumin exhibits a favourable safety profile and has shown potential in modulating fibrosis in liver, kidney, and lung tissues[26,27]. These properties make curcumin a promising candidate for further investigation as an EMT modulator in the context of pulmonary fibrosis. *In silico* approaches, such as molecular docking, network pharmacology, and target prediction tools, offer cost-effective and rapid methods for exploring drug-target interactions and underlying molecular mechanisms. These computational techniques enable the identification of potential protein targets, assessment of binding affinities, and evaluation of drug-like properties, thereby facilitating the generation of hypotheses prior to experimental validation. Given the multifactorial nature of EMT in PF, an *in silico*-driven exploration of curcumin's interactions with EMT-associated targets could provide valuable mechanistic insights and guide future translational research[29]. This study aims to investigate the molecular interactions between curcumin and EMT-related targets involved in pulmonary fibrosis using a comprehensive *in silico* approach. By integrating target prediction (STITCH, SwissTargetPrediction), protein-protein interaction analysis (STRING), molecular docking, and ADMET profiling, we seek to evaluate the multitarget potential of curcumin and its therapeutic relevance as an EMT modulator in pulmonary fibrosis.

Materials and Methods

Target prediction of curcumin

To identify potential protein targets for curcumin, two large *in silico* platforms were used. Initially, the SwissTargetPrediction tool was employed, with the canonical SMILES structure of curcumin downloaded from the PubChem database (CID: 969516)and uploaded to the site[30,31]. This tool predicted potential protein targets based on similarity scores using 2D and 3D structures of well-known ligands. Additionally, the STITCH 5.0 database was used to analyze actual and proposed interactions between curcumin and its protein targets[32]. This site combined experiment-based, database-based, and computationally predicted data. A cutoff of a confidence score of 0.7 and above was used, and the targets identified were associated with epithelial-mesenchymal transition (EMT) and fibrosis pathways.

Construction of Protein–protein interaction (PPI) networks

In order to comprehend functional relationships between targets of curcumin, protein-protein interaction (PPI) networks were created with the aid of STRING v11.5[33]. The curated targets identified by SwissTargetPrediction and STITCH were explored in the STRING database using a minimum required interaction score of 0.700, which corresponds to a high degree of confidence[31-33]. The resulting network was visualized based on edge confidence and node interconnectivity. Moreover, enrichment analysis of the signal clusters (based on the use of GO terms and KEGG pathways) identified key signalling clusters that were involved in regulating the epithelial-mesenchymal transition (EMT).

Molecular docking studies

Protein and ligand preparation

The preparation of ligands involved obtaining the 3D structure of curcumin from the PubChem database. For protein selection, several EMT-related proteins were identified, including TGFBR1, EGFR, MAPK1, and MMP9, based on their relevance in the literature and through *in silico* methods. The 3D models of these proteins were obtained from the Protein Data Bank at the RCSB. In the preparation process, water molecules and heteroatoms were removed from these structures, followed by the addition of polar hydrogens and Kollman charges using AutoDock Tools, which facilitated subsequent docking studies.

Docking procedure

Molecular docking was conducted using AutoDock Vina[34], which allowed for the evaluation of the binding affinity of ligands to various protein targets. A grid box was meticulously defined around the active site of each protein, ensuring that the spacing was appropriate to accommodate ligand flexibility during the docking process. The binding affinity was measured in kilocalories per mole (kcal/mol), providing a quantitative assessment of the interactions. To further analyze the results, the docked complexes were visualized using PyMOL[35], enabling a detailed examination of hydrogen bonding and the specific interaction residues involved in the binding.

Drug-likeness, ADMET profiling and toxicity prediction

The pharmacokinetic profile and drug-likeness of curcumin were comprehensively evaluated using various tools. SwissADME[36] was utilized to predict key metrics such as Lipinski's Rule of Five, gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, and bioavailability scores[37]. Additionally, an analysis of curcumin's oral bioavailability and synthetic accessibility was conducted. To further assess the safety and toxicity profile of curcumin, the ProTox-II tool was employed, where the compound's SMILES notation was entered to predict the LD_{50}, toxicity class, and organ-specific adverse effects. The predicted LD_{50} value for curcumin was reported to be 2000 mg/kg, categorizing it under toxicity Class 4, classifying it as potentially harmful if swallowed[38].

Results

Target prediction and Protein-protein interaction

The SwissTargetPrediction and STITCH platforms were employed to identify curcumin's interaction with molecular targets implicated in epithelial-mesenchymal transition (EMT) and pulmonary fibrosis. Table 1 shows the predicted targets of curcumin, from which common key proteins of both EMT and pulmonary fibrosis were selected for further studies.The STITCH analysis revealed that curcumin interacts with several core EMT regulators, including TGF-beta receptor 1 (TGFBR1), matrix metalloproteinase 9 (MMP9), epidermal growth factor receptor (EGFR), and MAPK1 (mitogen-activated protein kinase 1)[39,40] (Fig. 1). These proteins are recognized for their roles in fibrosis progression, cell migration, proliferation, and extracellular matrix (ECM) remodelling. Additionally, the protein–protein interaction (PPI) network, constructed using STRING, highlighted a highly interconnected cluster of curcumin-associated targets.

Molecular docking

Docked poses visualised via PyMOL and Discovery Studio[41]confirmed a favourable spatial orientation of curcumin within the active sites of each protein, supporting its potential to inhibit or modulate the activity of these EMT-related proteins (Fig. 2).

Drug-likeness, and ADMET profiling

Furthermore, the boiled-egg diagram from the SwissADME analysis revealed that curcumin meets several criteria of Lipinski's Rule of Five, indicating moderate gastrointestinal (GI) absorption and minimal likelihood of penetrating the blood-brain barrier (BBB) (Fig. 3 & Table 2). This suggests that curcumin has the potential for systemic distribution while minimising central nervous system side effects. Additionally, the compound demonstrated suitable bioavailability scores and acceptable synthetic accessibility, thereby reinforcing its drug-like properties for oral administration.

Table 1 — Predicted Protein Targets of Curcumin

Predicted Protein Name	Gene Symbol	UniProt ID	Prediction Tool Used	Probability / Score	Relevance to EMT / PF
Mitogen-Activated Protein Kinase 1	MAPK1	P28482	SwissTargetPrediction	0.19	Involved in TGF-β and PI3K/Akt signaling in EMT
Epidermal Growth Factor Receptor	EGFR	P00533	SwissTargetPrediction	0.14	Key upstream regulator of EMT and fibroblast activation
Estrogen Receptor Alpha	ESR1	P03372	SwissTargetPrediction	0.13	Modulates gene transcription; role in EMT in lung diseases
Cyclin-Dependent Kinase 2	CDK2	P24941	PharmMapper	Fit Score: 6.85	Regulates cell cycle progression during EMT
Heat Shock Protein HSP 90-alpha	HSP90AA1	P07900	PharmMapper	Fit Score: 6.45	Stabilizes EMT transcription factors
Phosphatidylinositol 3-Kinase	PIK3CA	P42336	SwissTargetPrediction	0.11	PI3K/Akt pathway component; drives EMT
Histone Deacetylase 1	HDAC1	Q13547	SwissTargetPrediction	0.10	Epigenetic regulator; promotes EMT by silencing E-cadherin
Peroxisome Proliferator-Activated Receptor Gamma	PPARG	P37231	BindingDB / SwissTargetPrediction	–	Anti-inflammatory target; curcumin may modulate fibrosis via PPARG
Matrix Metalloproteinase-9	MMP9	P14780	BindingDB	Kd ~ 1.2 μM	Facilitates ECM remodeling and EMT progression
Transforming Growth Factor Beta Receptor I	TGFBR1	P36897	PharmMapper / SwissTP	Fit Score: 5.90	Key EMT signalling receptor; target for fibrosis reversal

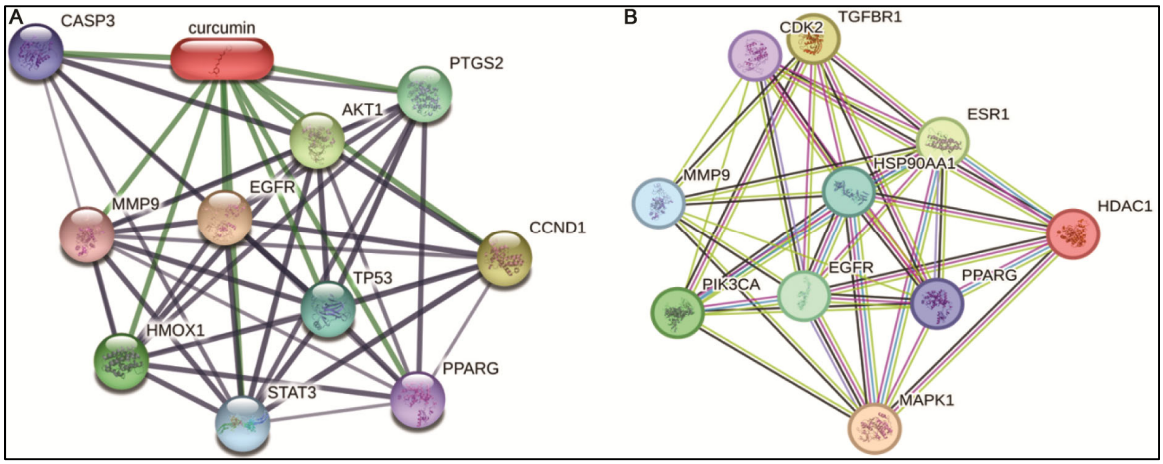

Fig. 1 — STITCH (A); and STRING (B) network visualisations show curcumin's predicted interactions with key EMT- and fibrosis-associated proteins, including EGFR, MMP9, MAPK1, and TGFBR1. These interactions highlight curcumin's multitarget potential in modulating signalling pathways relevant to pulmonary fibrosis

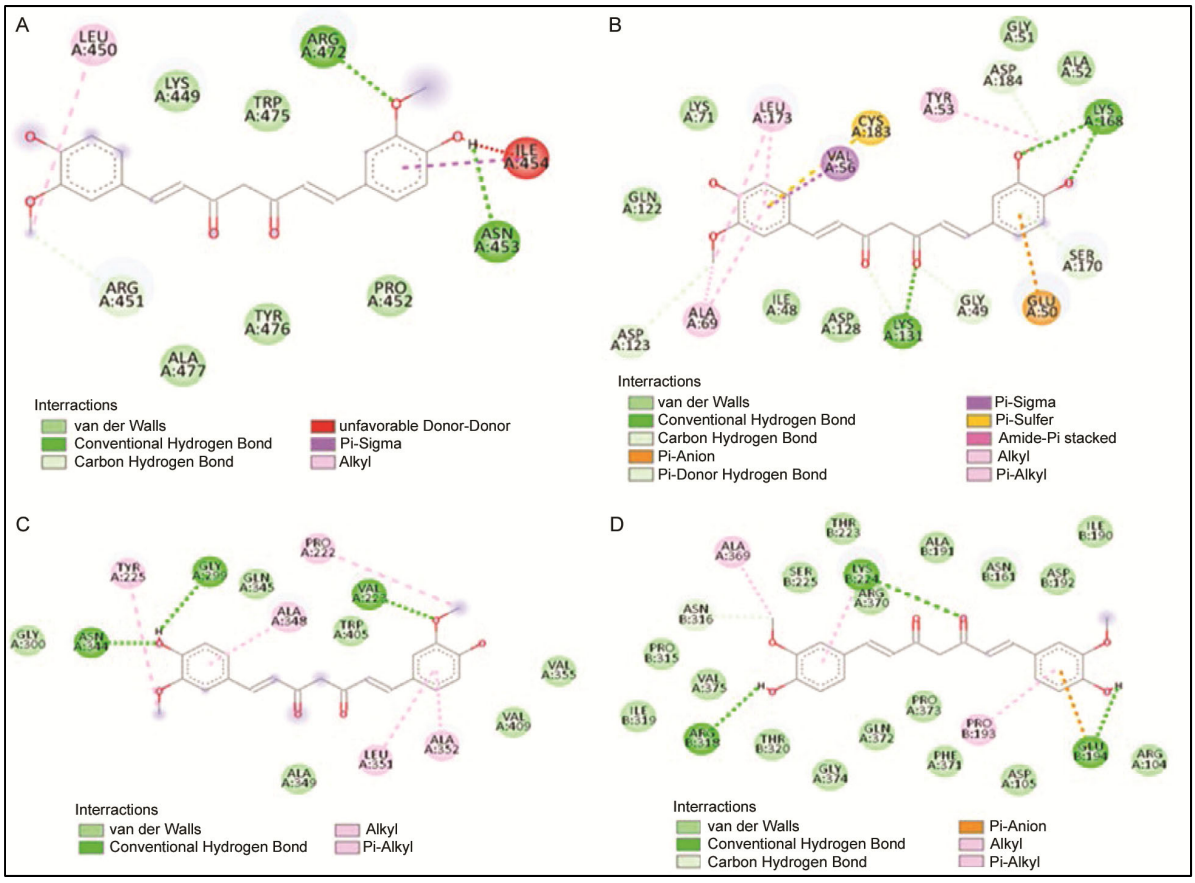

Fig. 2 — 2D interaction diagrams of curcumin with key EMT-associated proteins: (A) TGFBR1; (B) EGFR; (C) MAPK1; and (D) MMP9. Hydrogen bonds, van der Waals forces, and hydrophobic interactions illustrate stable binding, supporting curcumin's potential as a multitarget modulator in pulmonary fibrosis therapy

Toxicity Prediction

Using ProTox-II, the predicted LD_{50} of curcumin was found to be 2000 mg/kg, classifying it as toxicity Class 4, which indicates a low level of acute toxicity. No significant hepatotoxicity, mutagenicity, or carcinogenicity risks were predicted, further supporting the safety profile of curcumin (Fig. 4).

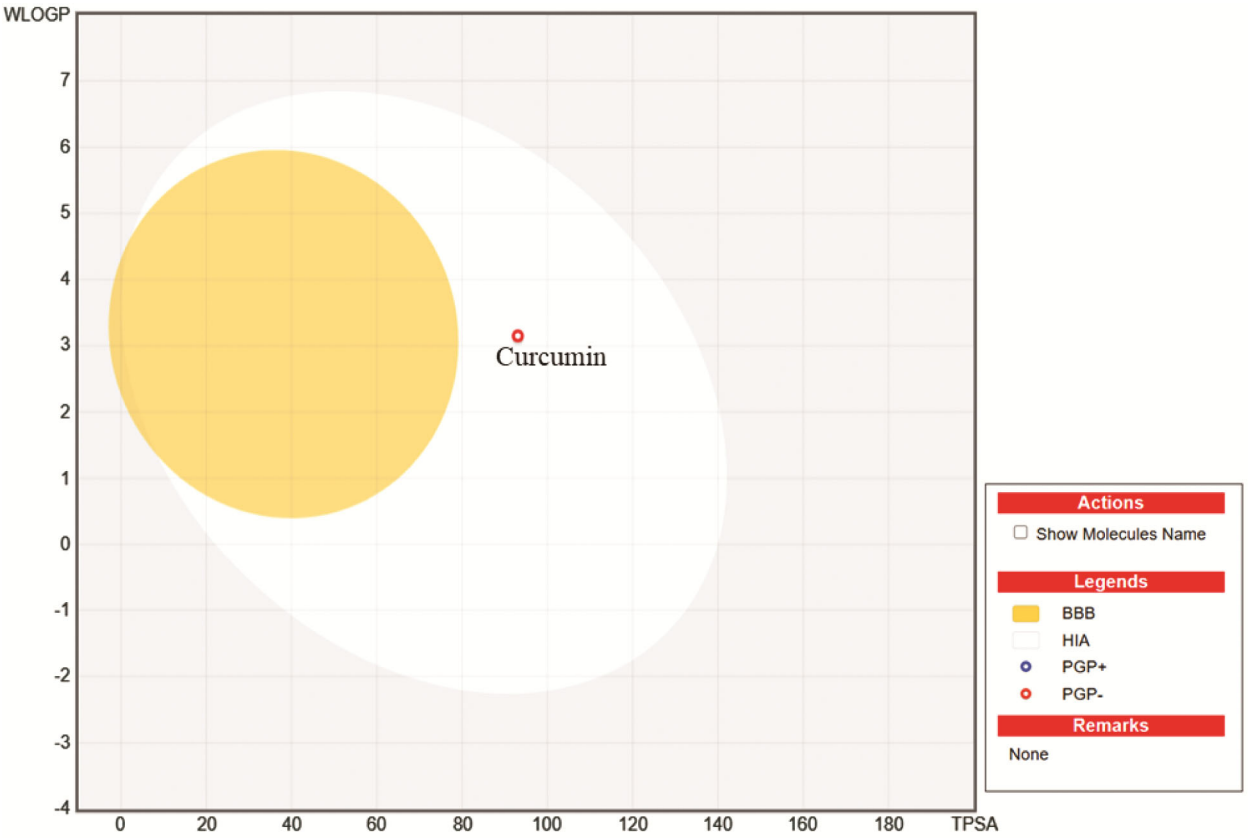

Fig. 3 — The boiled-egg plot of curcumin's pharmacokinetics shows it in the human intestinal absorption (HIA) region but outside the blood–brain barrier (BBB) zone, indicating good oral absorption and limited central nervous system (CNS) penetration.

Table 2 — Drug likeness and toxicity prediction of curcumin

Target Protein	PDB ID	Binding affinity (kcal/mol)	Key Interactions
TGFBR1	1PY5	−8.3	Hydrogen bonding with Asp351, hydrophobic contacts
EGFR	1M17	−8.1	Hydrogen bonds with Met769, π–π interactions
MAPK1	2OJJ	−7.8	Binding at ATP pocket, polar interactions
MMP9	1GKC	−7.6	Zn^{2+} coordination site proximity, H-bonding with Glu402

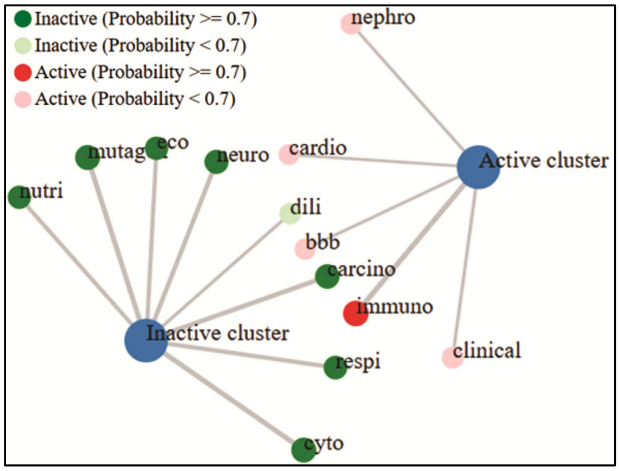

Fig. 4 — ProTox-II's toxicity prediction network indicates curcumin's low toxicity, with most parameters falling within the inactive cluster (green) and minimal predicted immunotoxic and carcinogenic activity.

Discussion

Pulmonary fibrosis is a complex, multi-pathway disease characterised by dysregulated wound healing and persistent fibroblast activation. Identifying compounds that can interact with multiple signalling networks involved in fibrosis is crucial for therapeutic advancement. Recent findings highlight the potential of curcumin as a multitarget modulator within the epithelial-mesenchymal transition (EMT) axis, suggesting its viability as an adjunctive therapy for fibrotic lung diseases. A key observation from the study is the convergence of EMT regulatory proteins within a tightly interconnected protein-protein interaction network, which not only emphasises the biological relevance of identified targets but also highlights the potential for synergistic inhibition

through a single agent. This network coherence strengthens the hypothesis that curcumin influences a cascade of interdependent pathways related to fibrotic remodelling, including signal transduction, cell proliferation, and extracellular matrix turnover[39]. Docking analysis reveals that curcumin may exert its anti-fibrotic effects by hindering receptor activation and blocking downstream kinase signalling, such as through interactions with pivotal EMT drivers. While curcumin's poor systemic bioavailability has presented challenges in clinical contexts, favourable pharmacokinetic predictions support the exploration of nano formulations or targeted delivery systems to enhance its efficacy[42]. This study effectively links computational predictions with a disease-specific context, placing EMT modulation at the forefront of therapeutic exploration and paving the way for rational drug design. However, to validate these promising results, experimental studies in cellular and animal models are essential, alongside rigorous assessments of potential off-target effects and interactions with existing anti-fibrotic agents. In summary, this research supports further investigation of curcumin as a molecularly guided therapeutic agent in pulmonary fibrosis, with the goal of developing more effective, systems-based treatment approaches for complex fibrotic disorders.

Conclusion

This *in silico* study presents compelling evidence for the potential role of curcumin as a multitarget therapeutic agent in the treatment of pulmonary fibrosis through modulation of epithelial-mesenchymal transition (EMT)-associated pathways. By integrating target prediction, network analysis, and molecular docking methodologies, the research demonstrates that curcumin interacts with key fibrogenic regulators, including TGFBR1, EGFR, MAPK1, and MMP9. The dense interconnectivity observed in the protein interaction network indicates functional coordination among these targets, thereby supporting curcumin's systems-level impact on the progression of fibrosis. Additionally, the study highlights favorable pharmacokinetic parameters and low predicted toxicity, underscoring curcumin's suitability for further development and clinical application. While these findings are preliminary, they provide a robust foundation for future *in vitro* and *in vivo* studies to validate curcumin's EMT-modulating effects and optimize its therapeutic delivery. Ultimately, this research contributes to the growing body of evidence advocating for the repositioning of curcumin as a potential adjunctive treatment for pulmonary fibrotic disorders.

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Conflict of interest

All authors declare that no conflict of interest.

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