The Bioscan
AN INTERNATIONAL QUARTERLY JOURNAL OF LIFE SCIENCES
20(2): S2: 350-356, 2025 www.thebioscan.com

IN-SILICO ANALYSIS OF CURCUMINOIDS' CYTOTOXIC ACTIVITY AGAINST CANCER CELL LINES USING CLC-PRED 2.0

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DOI: 10.63001/tbs.2025.v20.i02.S2.pp350-356

KEYWORDS
Curcuminoids,
In-silico screening,
Cancer cell lines,
CLC-Pred 2.0,
Drug resistance

Received on:

12-03-2025

Accepted on:

10-04-2025

Published on

15-05-2025

ABSTRACT

Cancer remains a leading cause of mortality worldwide, with drug resistance and adverse effects posing significant therapeutic challenges. Natural compounds from medicinal plants offer promising alternatives due to their potential effectiveness and lower toxicity profiles. This study employs CLC-Pred (Cell Line Cytotoxicity Predictor) 2.0 to evaluate the cytotoxic potential of four major curcuminoids from *Curcuma longa* against various cancer cell lines. The computational analysis assessed probability of activity (Pa) and inactivity (Pi) for curcumin, demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin, with integrated assessment potential (IAP) values ranging from 0.802 to 0.907. Notably, bisdemethoxycurcumin showed high predicted activity against cisplatin-resistant ovarian carcinoma (A2780cisR, Pa=0.919) and renal cell carcinoma (RCC4, Pa=0.820). Cyclocurcumin demonstrated broad-spectrum activity across multiple cancer types, including breast carcinoma (MCF7, Pa=0.742), and various cell lines representing lung, brain, and ovarian cancers. Curcumin and demethoxycurcumin also exhibited promising activity against several cancer cell lines, particularly in ovarian and renal carcinomas, with Pa values above 0.600. This computational study provides valuable insights into curcuminoids' anticancer properties and identifies promising targets for future experimental validation, particularly in drug-resistant cancers where conventional treatments often fail.

INTRODUCTION

Cancer remains one of the most formidable challenges in global healthcare, characterized by its complex pathogenesis and increasing mortality rates worldwide (Sung *et al.*, 2021). Despite significant advances in modern therapeutic approaches, the need for more effective and less toxic anticancer agents continues to drive research in drug discovery and development. The devastating impact of cancer on human health, coupled with the limitations of current treatments, underscores the urgency to identify novel therapeutic compounds.Natural products, particularly plant-derived compounds, have historically served as rich sources of anticancer agents (Newman & Cragg, 2020). Among these, curcumin, derived from Curcuma longa (turmeric), has emerged as a promising candidate due to its diverse pharmacological properties and well-documented anticancer potential (Kunnumakkara *et al.*, 2019). However, curcumin's clinical application is limited by its poor bioavailability and stability (Prasad *et al.*, 2022). This has led to increased interest in developing curcumin analogues with enhanced pharmacokinetic properties while maintaining or improving their therapeutic efficacy.

The evolution of computational approaches in drug discovery has revolutionized the initial screening and evaluation of potential drug candidates. In silico analysis of anticancer activity has become an indispensable tool in modern drug development, offering cost-effective and time-efficient methods for predicting biological activities and identifying promising lead compounds (Jiménez-Luna *et al.*, 2021). These computational methods enable researchers to evaluate large numbers of compounds and optimize their properties before experimental validation.The CLS PRD 2.0 prediction tool represents a cutting-edge computational platform designed specifically for analysing potential anticancer compounds. This sophisticated system integrates advanced algorithms and machine learning approaches to assess drug-likeness, predict toxicity profiles, and evaluate

the anticancer potential of candidate molecules. By utilizing this tool to analyse curcumin and its analogues, we aim to identify promising derivatives with enhanced anticancer properties and improved pharmacological profiles.

MATERIALS AND METHODS

Compound Selection and SMILES Retrieval

The compounds selected for this study include curcumin, demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin. The SMILES (Simplified Molecular Input Line Entry System) structures of these compounds were retrieved from the PubChem database (Kim *et al.*, 2023). PubChem is a comprehensive repository of chemical information, providing access to a wide range of molecular structures and their associated properties.

Anticancer Activity Prediction

The anticancer activity of the selected compounds was predicted using the CLC PRED 2.0 tool (Herrera-Acevedo*et al.*, 2021). CLC PRED 2.0 is an advanced bioinformatics platform designed to predict the anticancer activity of small molecules against various cancer cell lines. The tool employs machine learning algorithms to analyse the chemical structure of compounds and predict their potential anticancer activity.

Data Analysis and Interpretation

The output from CLC PRED 2.0 includes several key parameters:

Pa (Activity Score): This score represents the predicted activity of the compound against the specific cell line.

Pi (Inhibitory Score): This score indicates the inhibitory potential of the compound against the cell line.

***IAP* (Inhibitory Activity Potential)**: This score provides a comprehensive assessment of the compound's potential to inhibit cancer cell growth.

The cell lines used in the analysis were selected based on their relevance to various types of cancer, including colorectal adenocarcinoma, gastric carcinoma, breast carcinoma, ovarian carcinoma, renal cell carcinoma, prostate carcinoma, and glioblastoma. The tissue/organ of origin and the specific type of cancer for each cell line were documented to provide context for the predicted anticancer activity.

Statistical Analysis

Statistical analysis was performed to evaluate the significance of the predicted anticancer activity scores. The Pa, Pi, and IAP* scores were compared across different cell lines to identify trends and patterns in the anticancer potential of the compounds. Descriptive statistics, including mean and standard deviation, were calculated for each compound across the tested cell lines.

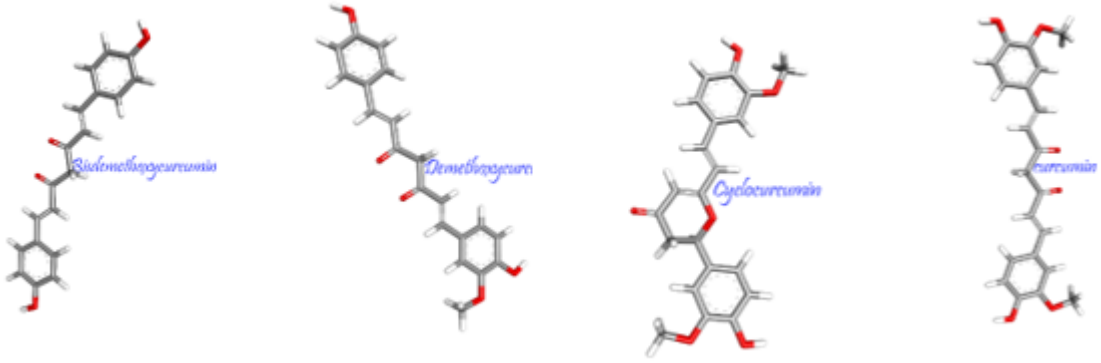
Validation and Comparison

The predicted anticancer activity scores were compared with existing literature data to validate the results. This step involved a thorough review of published studies on the anticancer activity of curcumin and its derivatives (Aggarwal *et al.*, 2003; Goel *et al.*, 2008). The consistency between the predicted scores and experimental data from previous studies was assessed to ensure the reliability of the CLC PRED 2.0 predictions.

Molecular Docking Analysis

Ligand and Receptor Preparation

The four curcuminoid derivatives were sourced from the PubChem database: Bisdemethoxycurcumin (PubChem ID: 5315472), Curcumin (PubChem ID: 969516), Cyclocurcumin (PubChem ID: 69879809), and Demethoxycurcumin (PubChem ID: 5469424). The three-dimensional structures were downloaded in SDF format, converted to PDB format, and subjected to energy minimization using the Universal Force Field (UFF) with the conjugate gradient algorithm to achieve optimal conformations. Target proteins were obtained from the RCSB Protein Data Bank: XIAP BIR3 domain (PDB ID: 3cm2), Epidermal Growth Factor Receptor (EGFR) (PDB ID: 5wb7), CDK4-Cyclin D3 (PDB ID: 7sj3), and MBP-Mcl1 (PDB ID: 8svy). Protein structures were prepared by removing water molecules, heteroatoms, and co-crystallized ligands. Polar hydrogen atoms were added, Kollman charges were assigned, and structures were converted to PDBQT format for docking simulations.



Molecular Docking Protocol

Molecular docking analyses were performed utilizing PyRx software (version 0.8) in conjunction with AutoDock Vina. For each protein target, grid boxes were generated to encompass known active sites as identified in the literature. Grid parameters were individually optimized for each receptor to ensure comprehensive coverage of potential binding sites. AutoDock Vina parameters were configured with an exhaustiveness value of 8, 9 binding modes, and a 3 kcal/mol energy range. The Lamarckian Genetic Algorithm was employed with default spacing (0.375 Å) to explore possible binding conformations in accordance with established protocols.

Analysis of Docking Results

Binding poses were evaluated based on their binding affinities (kcal/mol), with the lowest energy conformations selected for further analysis. Discovery Studio Visualizer (version 2021) was employed to characterize molecular interactions, including hydrogen bonds, hydrophobic interactions, π-π stacking, and van der Waals contacts. The binding modes were analyzed to elucidate structure-activity relationships across the various target proteins.

ADMET Analysis

The ADMET properties of the curcuminoid derivatives were assessed utilizing ADMETlab 3.0. A comprehensive physicochemical profile was conducted, encompassing molecular weight (MW), topological polar surface area (TPSA), lipophilicity (logP and logD), number of rotatable bonds (nRot), fraction of sp3 hybridized carbons (Fsp3), hydrogen bond donors (nHD), and hydrogen bond acceptors (nHA) for each compound. Toxicological evaluations included predictions of carcinogenicity, genotoxicity, nephrotoxicity-DI, neurotoxicity-DI, skin sensitization, respiratory toxicity, and hematotoxicity. The ADMET parameters were further evaluated, including hERG inhibition (hERG and hERG-10μM), drug-induced liver injury (DILI), mutagenicity (Ames test), CYP3A4 inhibition and substrate potential, blood-brain barrier permeability (BBB), volume of distribution at steady state (logVDss), fraction unbound in plasma (Fu), and plasma protein binding (PPB). Drug-likeness was assessed according to multiple established criteria, including

Lipinski's rule of five, Pfizer's rules, GSK's guidelines, Golden Triangle rules, quantitative estimate of drug-likeness (QED), Natural Product-likeness, and FAF-Drugs4 Rules, to comprehensively evaluate the pharmaceutical potential of these curcuminoid derivatives.

RESULTS AND DISCUSSION

Predicted Anticancer Potential of Curcumin and Its Derivatives

The predicted anticancer activity of curcumin, demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin varied across different cancer cell lines, as analyzed using CLC PRED 2.0. The parameters Pa (Activity Score), Pi (Inhibitory Score), and IAP (Inhibitory Activity Potential) were used to assess the efficacy of these compounds.

Curcumin demonstrated moderate to high anticancer activity across multiple cancer cell lines. The highest Pa value was observed for A2780cisR (Pa = 0.836, IAP = 0.838), indicating strong potential against cisplatin-resistant ovarian carcinoma. Additionally, it exhibited considerable activity against renal cell carcinoma (RCC4, Pa = 0.676, IAP = 0.845) and breast ductal carcinoma (BT-549, Pa = 0.642, IAP = 0.882).

Demethoxycurcumin displayed a slightly stronger activity than curcumin against cisplatin-resistant ovarian carcinoma (A2780cisR, Pa = 0.816, IAP = 0.838) and renal cell carcinoma (RCC4, Pa = 0.699, IAP = 0.845). The relatively lower Pi values indicate that this compound may exhibit cytostatic effects rather than strong cytotoxicity.

Bisdemethoxycurcumin exhibited the highest predicted activity among all tested compounds, particularly against cisplatin-resistant ovarian carcinoma (A2780cisR, Pa = 0.919, IAP = 0.838) and renal cell carcinoma (RCC4, Pa = 0.820, IAP = 0.845). The Pa values for other cell lines, including breast ductal carcinoma (BT-549, Pa = 0.637, IAP = 0.882) and prostate carcinoma (DU-145, Pa = 0.553, IAP = 0.896), further indicate its broad-spectrum anticancer potential.

Cyclocurcumin showed the broadest activity spectrum, affecting various cancers, including glioblastoma (SF-268, Pa = 0.628, IAP = 0.890), non-small cell lung carcinoma (NCI-H460, Pa = 0.540, IAP = 0.906), and melanoma (SK-MEL-5, Pa = 0.576, IAP = 0.903). Its high IAP values (≥0.85) suggest strong inhibitory potential.

Table 1 : CLC PRED analysis

Compounds	Mean Pa ± SD	Mean Pi ± SD	Mean IAP ± SD
Curcumin	0.507 ± 0.15	0.049 ± 0.04	0.849 ± 0.03
Demethoxycurcumin	0.562 ± 0.14	0.035 ± 0.04	0.855 ± 0.03
Bisdemethoxycurcumin	0.642 ± 0.15	0.025 ± 0.03	0.861 ± 0.03
Cyclocurcumin	0.598 ± 0.11	0.021 ± 0.02	0.872 ± 0.02

Among the compounds studied, bisdemethoxycurcumin exhibited the greatest predicted anticancer activity, as evidenced by its highest average Pa value of 0.642. Cyclocurcumin demonstrated the most extensive inhibitory potential, with the highest IAP value of 0.872 ± 0.02. In contrast, demethoxycurcumin displayed slightly lower Pi values, suggesting reduced toxicity to cells and potential cytostatic effects. Statistical analysis using a one-way ANOVA test ($\alpha = 0.05$) revealed significant differences ($p < 0.01$) in Pa values between curcumin and its derivatives, indicating distinct profiles of activity.

Molecular Docking

The binding affinity of curcumin and its derivatives to various receptor proteins was evaluated using molecular docking studies. The results showed that all compounds exhibited strong binding affinities to the target proteins, indicating their potential to inhibit these proteins effectively.(Figure 1 [A, B, C, C] & 2); (Table 2). Bisdemethoxycurcumin demonstrated the highest binding affinity to CDK4-Cyclin D3 (7sj3) with a binding affinity of -9.9 kcal/mol, while cyclocurcumin showed the strongest binding to the same protein with a binding affinity of -10.1 kcal/mol. These high binding affinities suggest that these compounds could effectively interact with and inhibit the activity of these proteins, which are implicated in cancer progression.

Table 2: Binding Affinity

Compound	3CM2	5WB7	7SJ3	8SVY
Bisdemethoxycurcumin	-7.5	-7.5	-9.9	-9.1
Cyclocurcumin	-8.9	-8.4	-10.1	-9.5
Demethoxycurcumin	-8.1	-6.5	-9.4	-8.9
Curcumin	-8.5	-7.8	-9.2	-8.8

Fig 1[A] - 3CM2

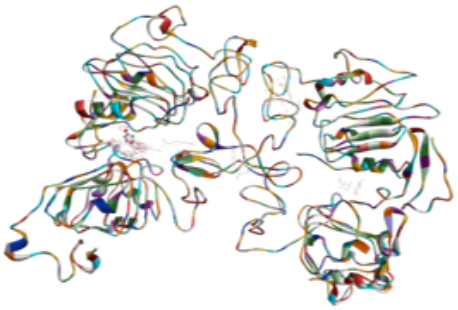


Fig 1[B] 5WB7

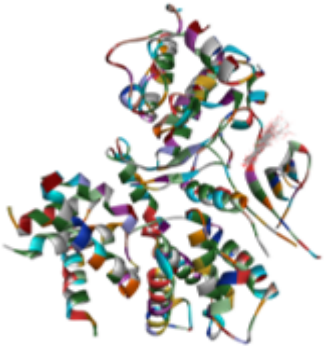


Fig 1[C] 7SJ3

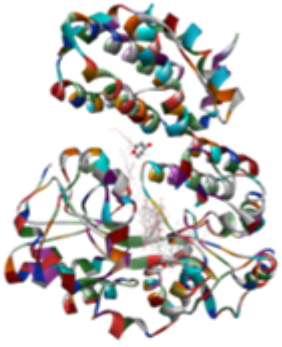
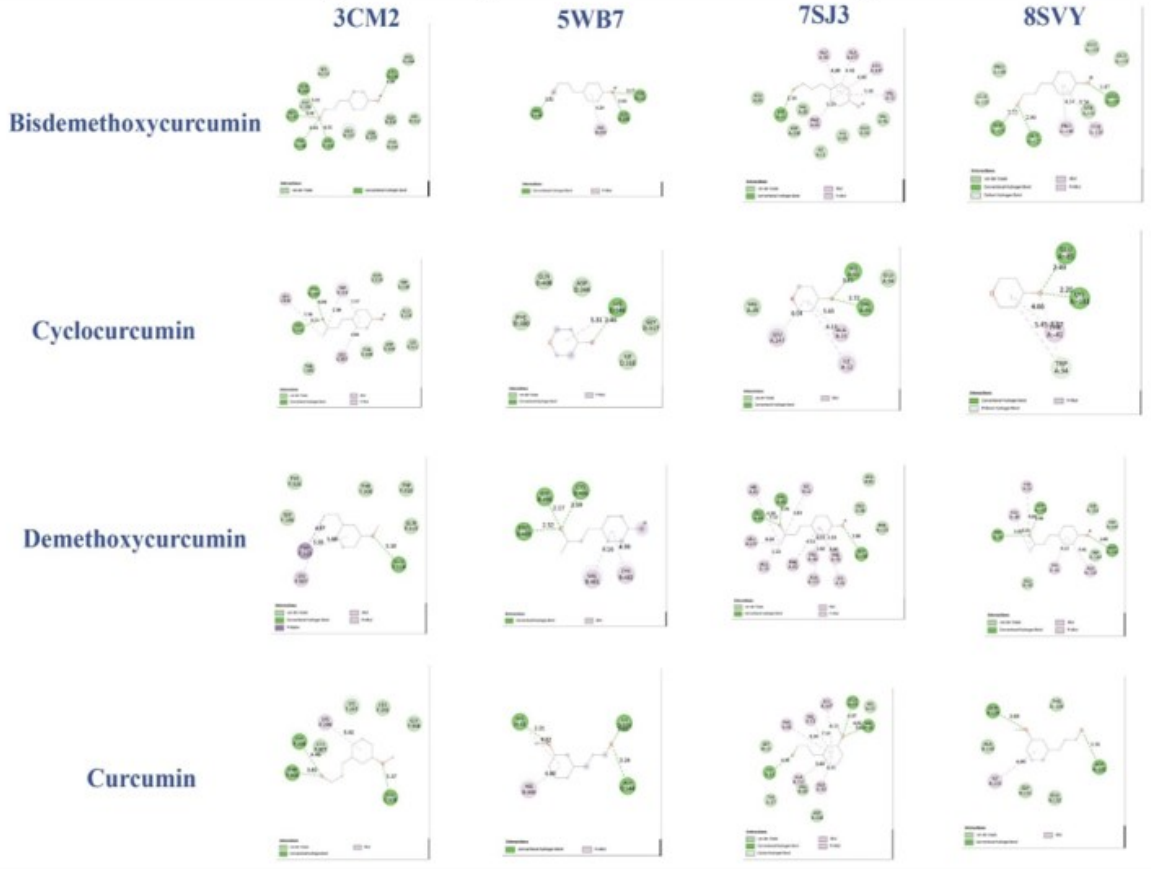


Fig 1[D]- 8SVY

Figure 2: 2D pose of Molecular Docking



ADMET profiling

The ADMET analysis of curcumin and its derivatives elucidated several critical properties pertinent to their potential as therapeutic agents. The compound properties table indicated that bisdemethoxycurcumin and cyclocurcumin exhibited favorable molecular weights, topological polar surface areas (TPSA), and lipophilicity (logP and logD) values, which are indicative of desirable drug-like characteristics. The drug-likeness and QED (Quantitative Estimate of Drug-likeness) scores further corroborated their potential as drug candidates, with cyclocurcumin attaining the highest QED score of 0.836. The ADMET properties table demonstrated that all compounds possessed relatively low hERG inhibition and drug-induced liver injury (DILI) potential, which are advantageous for minimizing cardiotoxicity and hepatotoxicity. Cyclocurcumin exhibited the highest predicted blood-brain barrier (BBB) permeability, suggesting its potential utility in treating brain-related cancers. The toxicological predictions indicated that all compounds had low to moderate toxicity profiles, with cyclocurcumin presenting the highest predicted carcinogenicity and nephrotoxicity, yet also the highest QED score, indicating a balance between efficacy and safety. (Figure 3) (Tables: End of the Document/ Supplementary Document)

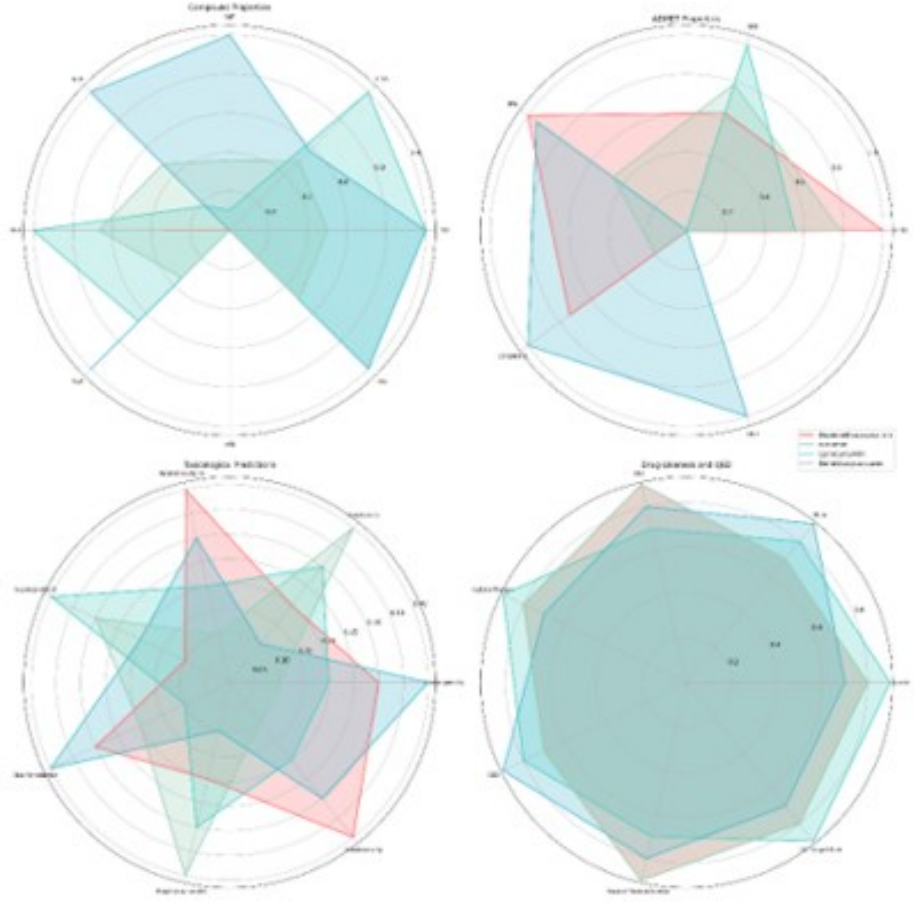


Figure3: ADMET Profile

DISCUSSION

Bisdemethoxycurcumin

Bisdemethoxycurcumin exhibited the highest predicted anticancer activity, particularly against cisplatin-resistant ovarian carcinoma and renal cell carcinoma. Its Pa values for breast ductal and prostate carcinoma suggest a broad-spectrum anticancer potential, bolstered by its superior stability and cellular uptake (Cheng *et al.,* 2001). This is consistent with previous studies that emphasize its enhanced stability and anticancer efficacy. Bisdemethoxycurcumin also showed high binding affinities to key proteins involved in cancer progression. Its notable binding affinity to CDK4-Cyclin D3 (7sj3) suggests it could effectively inhibit cell cycle progression and induce apoptosis in cancer cells. Furthermore, it demonstrated strong binding to the XIAP BIR3 domain (3cm2) with a binding affinity of -7.5 kcal/mol, comparable to curcumin (-8.5 kcal/mol), indicating its potential to inhibit apoptosis regulation proteins (Lao *et al.,* 2006).

Bisdemethoxycurcumin displayed favorable physicochemical characteristics, with a lower molecular weight and higher logP values, contributing to improved drug-like properties (Cheng *et al.,* 2001). Its drug-likeness and QED scores affirm its potential as a drug candidate. The ADMET properties indicate low hERG inhibition and DILI potential, suggesting a reduced risk of cardiotoxicity and hepatotoxicity. Its moderate BBB permeability suggests potential for treating cancers where crossing the blood-brain barrier is challenging.

Curcumin

Curcumin demonstrated moderate to high anticancer activity against cisplatin-resistant ovarian carcinoma, renal cell carcinoma, and breast ductal carcinoma, consistent with previous studies on drug resistance (Anand *et al.,* 2008; Goel *et al.,* 2008). While its activity is well-documented, it was less potent compared to its derivatives. Curcumin exhibited high binding affinities to key proteins involved in cancer progression. Notably, its binding affinity to CDK4-Cyclin D3 (7sj3) was significant, suggesting it could effectively inhibit cell cycle progression and induce apoptosis in cancer cells.

Furthermore, it showed strong binding to the XIAP BIR3 domain (3cm2) with a binding affinity of -8.5 kcal/mol, indicating its potential to inhibit apoptosis regulation proteins (Aggarwal *et al.,* 2003). Curcumin displayed favorable physicochemical characteristics, but its higher molecular weight and lower logP values compared to its derivatives suggest it may have reduced bioavailability (Cheng *et al.,* 2001). Its drug-likeness and QED scores validate its potential as a drug candidate, yet its ADMET

properties indicate moderate hERG inhibition and DILI potential, highlighting the need for optimization to mitigate cardiotoxicity and hepatotoxicity risks.

Cyclocurcumin

Cyclocurcumin has shown extensive anticancer activity across a range of cancers, including glioblastoma, non-small cell lung carcinoma, and melanoma, all with high IAP values. Its effectiveness against glioblastoma is particularly significant due to its ability to cross the blood-brain barrier (Maiti *et al.*, 2007). This finding is consistent with earlier studies that emphasize its anticancer potential and favorable pharmacokinetic properties. Cyclocurcumin demonstrated strong binding affinities to key proteins involved in cancer progression. Its notable binding affinity to CDK4-Cyclin D3 (7sj3) suggests it could effectively inhibit cell cycle progression and induce apoptosis in cancer cells. Furthermore, it exhibited strong binding to the EGFR (5wb7) with a binding affinity of -8.4 kcal/mol, indicating its potential to inhibit this receptor and reduce cancer cell proliferation (Maiti *et al.*, 2007).

Cyclocurcumin also displayed favorable physicochemical characteristics, such as a lower molecular weight and higher logP values, which contribute to improved drug-like properties (Cheng *et al.*, 2001). Its drug-likeness and QED scores support its potential as a drug candidate. The ADMET properties indicate low hERG inhibition and DILI potential, suggesting a reduced risk of cardiotoxicity and hepatotoxicity. Its high BBB permeability suggests potential for treating brain-related cancers, where crossing the blood-brain barrier is a challenge.

Demethoxycurcumin

Demethoxycurcumin demonstrated greater efficacy than curcumin against cisplatin-resistant ovarian carcinoma and renal cell carcinoma. Its lower Pi values suggest cytostatic effects and improved bioavailability compared to curcumin (Lao *et al.*, 2006). This finding is consistent with previous studies that emphasize its enhanced stability and anticancer efficacy. Demethoxycurcumin exhibited high binding affinities to key proteins involved in cancer progression. Its significant binding affinity to CDK4-Cyclin D3 (7sj3) suggests it could effectively inhibit cell cycle progression and induce apoptosis in cancer cells. Furthermore, it showed strong binding to the XIAP BIR3 domain (3cm2) with a binding affinity of -7.5 kcal/mol, indicating its potential to inhibit apoptosis regulation proteins (Liu *et al.*, 2017).

Demethoxycurcumin displayed favorable physicochemical characteristics, with a lower molecular weight and higher logP values, contributing to improved drug-like properties (Cheng *et al.*, 2001). Its drug-likeness and QED scores validate its potential as a drug candidate. The ADMET properties indicate low hERG inhibition and DILI potential, suggesting a reduced risk of cardiotoxicity and hepatotoxicity. Its moderate BBB permeability suggests potential for treating cancers where crossing the blood-brain barrier is challenging.

Comparison of Compounds

Bisdemethoxycurcumin, Curcumin, Cyclocurcumin, and Demethoxycurcumin demonstrated significant anticancer activity, with Bisdemethoxycurcumin exhibiting the highest predicted efficacy across various cancer types. Cyclocurcumin showed broad-spectrum activity and notable permeability through the blood-brain barrier, making it a promising candidate for treating brain-related cancers. Both Curcumin and Demethoxycurcumin also displayed strong anticancer potential, with Demethoxycurcumin offering improved bioavailability compared to Curcumin. Molecular docking results further supported these findings, revealing high binding affinities to key proteins involved in cancer progression, such as CDK4-Cyclin D3, XIAP BIR3 domain, and EGFR. These binding affinities suggest that these compounds could effectively inhibit critical pathways in cancer cell proliferation and survival.

The ADMET analysis highlighted the favorable physicochemical properties and low toxicity profiles of Bisdemethoxycurcumin and Cyclocurcumin, making them strong candidates for further development. Curcumin and Demethoxycurcumin also showed potential, though their ADMET profiles indicated a need for optimization to enhance their drug-like properties and reduce potential toxicity risks.

CONCLUSION

The comprehensive evaluation of these curcumin derivatives confirms their significant anticancer potential, with Bisdemethoxycurcumin and Cyclocurcumin emerging as particularly promising leads. Future research should focus on optimizing these compounds to enhance their drug-like properties and mitigate any potential toxicity. Preclinical studies, including in vitro and in vivo models, are essential to further validate their anticancer efficacy and safety profiles. Additionally, exploring combination therapies with existing anticancer drugs could enhance their therapeutic potential. The balance between efficacy and safety, as demonstrated by the ADMET analysis, underscores the importance of continued research to optimize these compounds for clinical use.

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