In silico ADME, Toxicity Prediction, Pass Analysis, and Molecular Docking of Curcumin derivatives

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Abstract- Curcumin, a bioactive polyphenol from Curcuma longa, has a wide range of pharmacological activities such as antioxidant, anti-inflammatory, anticancer, and antimicrobial activities. Though curcumin has therapeutic benefits, it is hindered by poor bioavailability, fast metabolism, and poor aqueous solubility. To overcome these drawbacks, curcumin derivatives with enhanced pharmacokinetic and pharmacodynamic profiles have been designed. Computational methods, especially in silico tools, have played an important role in the optimization of these derivatives for drug development. Molecular docking analyses, such as CB-Dock, assist in the identification of binding interactions among curcumin derivatives and the target proteins. ADMET prediction assists in analyzing drug-like attributes, while toxicity evaluation by using ProTox analysis and Osiris Property Explorer gives an understanding of possible safety issues. All these in silico approaches streamline the process of screening curcumin derivatives as therapeutic agents. In the current research very few curcumin derivatives were chosen and their ADME, Toxicity parameters, Pass analysis and Molecular docking studies were forecasted by using several in silico tools like Molinspiration, Protox-II, Osiris property explorer, Pass analysis and CB-Dock. The prime objective is to highlight the role of computational tools in improving their pharmacological potential and speeding up drug discovery.

Keywords: Curcumin, *in silico* analysis, toxicity, docking.

1. INTRODUCTION

Curcumin, the major bioactive constituent of the rhizome of Curcuma longa (turmeric), has received widespread interest because of its multifaceted pharmacological activities. Curcumin, being a natural polyphenol, is well known for its anti-inflammatory, antioxidant, antimicrobial, anticancer, and neuroprotective activities [7]. Nevertheless, its clinical use is greatly hampered by poor bioavailability, extensive metabolism, low water solubility, and poor stability.

To address such challenges and improve the therapeutic efficacy of curcumin, scientists have designed and synthesized a large number of curcumin derivatives. The derivatives are structurally engineered to enhance pharmacokinetics, bioavailability, and biological activities while keeping or improving their therapeutic effects.

Curcumin derivatives are prepared by different chemical modifications, such as modifications to its diketone moiety, phenolic hydroxyl groups, or β-diketone structure. Modifications are targeted towards improving solubility, stability, and molecular interactions with biological targets [8]. Examples of notable curcumin derivatives include analogs with increased anti-cancer activity, improved anti-inflammatory activity, and increased cellular uptake.

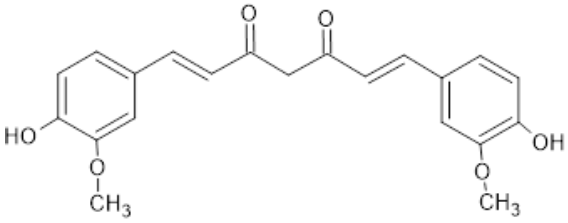


Fig 1 Structure of Curcumin

2. MATERIALS AND METHODS

2.1. Selection of the compounds.

Curcumin and its derivatives were selected to carry out the present work

2.2. *In silico* pharmacokinetic studies

Some of the pharmacokinetic parameters were calculated by molinspiration (www.molinspiration.com) cheminformatics software. Physico-chemical parameters were calculated for the chosen anticancer drugs either by

structure drawing or by typing SMILES notations [1-4]. Molinspiration is also applied in QSAR, molecular modelling and drug design, substructure and similarity searching, bioactivity prediction etc. It even gives 3D structure generator. Drug-likeness screening is performed to ascertain if the novel chemical moiety designed resembles existing known drugs. It depends on how the structural attributes will influence different molecular properties. The properties are, hydrophobicity, hydrogen bonding, electronic distribution, molecule size and flexibility. Besides the above reasons the pharmacophoric properties also affect the behaviour of molecules in a living system, such as bioavailability, transport characteristics, binding capacity to proteins, reactivity, toxicity, metabolic stability and the biological activity. There are several rules explaining the molecular properties relevant for the drugs' pharmacokinetics (absorption, distribution, metabolism and excretion) like Lipinski rule of five, Veber rule, Ghose rule, Ergan rule, Muegge rule, Opera rule of three, Monika rule, Norinder rule of two etc. Lipinski Rule of Five is also referred to as Pfizer's rule of five or the Rule of Five (RO5) and it is the most widely used one that is being followed. The rule is being used for the designed novel molecules and for the prioritization of the synthesis of such drug moieties that are exhibiting high oral bioavailability. Christopher A. Lipinski in 1997, developed rule of five on the basis of the fact that the majority of orally administered drugs are comparatively smaller and moderately lipophilic in character. Based on this rule, the oral absorption of a drug is effective, provided that molecular weight (MW) is below 500 Daltons, hydrophobicity (log P) below 5, number of hydrogen bond donors (HBD) below 5, and number of hydrogen bond acceptors (HBA) below 10. All these numbers are multiples of five, thus it is referred to as Rule of Five (RO5).

2.3. *In silico* bioactivity studies

Bioactivity is predicted by molinspiration and PASS analysis(www.way2drug.com/passonline) software utilities. Bioactivity is a representation of the potency of the drug molecule to act on various receptors like GPCR ligands, Kinase inhibitors, Protease inhibitors, Ion channel modulators, or act on enzymes and nuclear receptors. Greater the bioactivity score, greater is the chance that the suggested molecules are active. Ranks of bioactivity scores are listed in the Table 2. PASS (Prediction of Activity Spectra for Substances) for estimating the bio-medical potential of the drug-like compound. PASS gives time-conscious prediction of diverse kinds of biological activity taking into account the chemical structure of the drug substance. Therefore, conducting PASS calculation is possible to forecast the profiles of bioactivity for putative molecules prior to the chemical synthesis and biological examination. The potential bioactivity profiles of compounds under investigation can be predicted from their structural formulae in MOL file or SD file format. By conducting PASS analysis, one can forecast different potential bioactivities like antidepressant, antineoplastic, antiemetic, antiviral, antidiabetic, antiepileptic, anxiolytic, analgesic etc. PASS prediction relies on the structure-activity relationship knowledge base for over 1,000,000 compounds with documented biological activities. Pa (probability "to be active") assesses the likelihood that the suggested compound is active. Pi (probability "to be inactive") assesses the likelihood that the suggested compound is inactive.

Pa – atom promotes activity (Pa =1, Pi =0)
Pi – atom promotes inactivity (Pa = 0, Pi =0)

Table 1. Bioactivity scores limits

Bioactivity Score	Biological Activity
More than 0.00	Considerably active
Between -0.50 to 0.00	Moderately active
Less than -0.50	Inactive

2.4. *In silico* toxicity studies

Toxicity of the chosen anticancer drugs was predicted by using OSIRIS property explorer and ProTox-II free online software. OSIRIS software assists in pharmacokinetic parameters prediction like cLogP, solubility, molecular weights, drug-likeness, etc and also toxicity parameters like mutagenicity, irritancy, tumorgenicity and reproductivity. Predicted values are appreciated and are color-coded. The high-risk properties like mutagenicity or poor intestinal absorption are marked in red. While drug-like behavior is depicted in green color. ProTox-II is yet another cheminformatics software to predict toxicities of new molecules. ProTox-II supports prediction of various parameters of toxicities like acute toxicity, hepatotoxicity, cytotoxicity, immunotoxicity, carcinogenicity, mutagenicity, adverse results (Tox21)

pathways and toxicity targets [6]. Toxic doses frequently are provided in the form of LD50s in mg/kg body weight. The lethal dose is described by LD50 and refers to when administered to subjects 50% of the test subjects succumb when exposed to a compound. Toxicity classes are specified following the globally harmonized system for the classification labelling of chemicals (GHS).

- Class I: fatal if swallowed (LD50 ≤ 5)
- Class II: fatal if swallowed (5 < LD50 ≤ 50)
- Class III: toxic if swallowed (50 < LD50 ≤ 300)
- Class IV: harmful if swallowed (300 < LD50 ≤ 2000)
- Class V: may be harmful if swallowed (2000 < LD50 ≤ 5000)
- Class VI: non-toxic (LD50 > 5000)

2.5. *In silico* molecular docking studies

CB-Dock is a free online protein-ligand docking method, where the PDB format of the protein and the ligand in SDF format are required. It is very simple to use as one only needs to upload the files and click on docking, with results appearing within minutes. Curcumin and its derivatives were docked using CB-Dock online software with the PDB ID 8FQ7. Curcumin was used as the standard molecule.

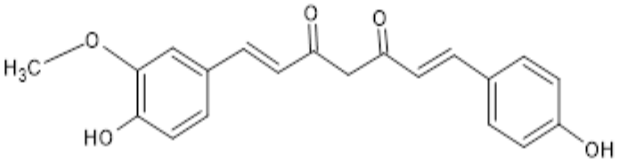
3. RESULTS AND DISCUSSIONS

3.1 Molinspiration

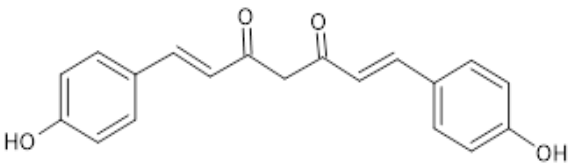
Curcumin derivatives, their compound codes (C-101 to C-110), and molecular descriptors and calculated properties. Interpretation of the values is the focus of the discussion in evaluating the properties, drug-likeness, and biological significance of the derivatives. miLogP quantifies hydrophobicity of the compounds. The values are between -0.34 (C-105) and 5.27 (C-103), reflecting differences in lipophilicity. Compounds with moderate miLogP values, like C-101 (2.68) and C-110 (2.48), could show improved permeability through biological membranes and thus are more desirable in drug development. TPSA, a measure of hydrogen bonding capacity, is quite different across the compounds. Lower TPSA (e.g., C-109 with 74.68 Å²) indicates improved membrane permeability, whereas higher TPSA (e.g., C-105 with 212.47 Å²) may reflect lower permeability but higher solubility in aqueous media. Molecular weights are between 308.33 (C-109) and 634.68 (C-103). Structures with MW under 500 (C-101, C-102, and C-110) are closer to Lipinski's rule of five, and they indicate drug-likeness. The higher-molecular-size molecules, including C-105 and C-106, might suffer from the limitation of absorption and bioavailability. The nOHNH (number of hydrogen bond donors) and nON (number of hydrogen bond acceptors) determine solubility and binding energy. C-105 and C-106, with greater nOHNH values, show greater hydrogen bonding abilities, which might enhance biological target interactions but diminish permeability. Rotatable bonds affect the flexibility of a molecule. C-105 (21 rotatable bonds) and C-106 (17 rotatable bonds) show greater flexibility, which could affect their binding efficiency. However, compounds such as C-109 (6 rotatable bonds) are less flexible and may be more favorable for specific binding. Molecular volume is related to size and steric effects, which impact bioactivity. C-105 and C-106 have greater volumes, which could influence their receptor interactions. Absorption percentages (% ABS) derived from TPSA indicate that compounds with lower TPSA values (e.g., C-109 at 83.23%) are more likely to be absorbed compared to high TPSA compounds such as C-105 (35.69%).

Table 2. ADME properties of Curcumin Derivatives

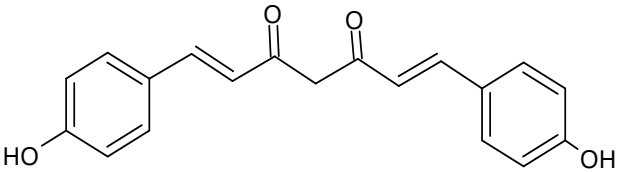
S.NO	Compound code	MI Log P	TPSA	N atoms	MW	n ON	n OHNH	n violations	n rotb	volume	% ABS
1	C-101	2.68	87.07	29	395.45	6	2	0	9	369.34	78.96
2	C-102	2.30	93.07	27	368.38	6	2	0	8	332.18	76.89
3	C-103	5.27	132.43	47	634.68	10	3	2	15	572.96	63.31
4	C-104	2.58	115.05	27	368.38	6	4	0	6	329.95	69.30
5	C-105	-0.34	212.47	45	624.74	12	9	3	21	584.96	35.69
6	C-106	0.93	189.29	43	600.62	12	5	2	17	537.14	43.69
7	C-107	3.03	185.23	27	368.38	6	2	0	5	328.17	79.59
8	C-108	0.85	154.35	35	482.53	9	6	1	13	441.59	55.74
9	C-109	2.67	74.68	23	308.33	4	2	0	6	281.09	83.23
10	C-110	2.48	83.83	25	338.36	5	2	0	7	306.64	80.07



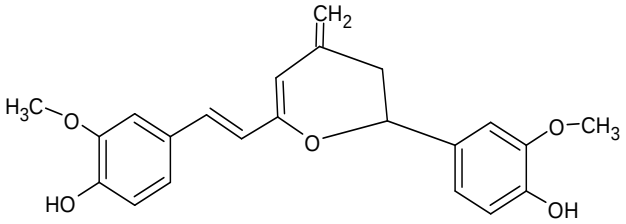
C-101



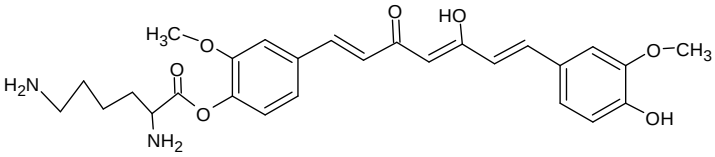
C-102



C-103



C-104



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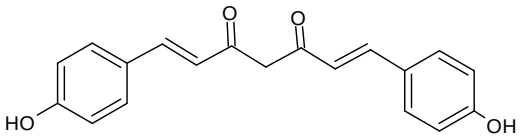
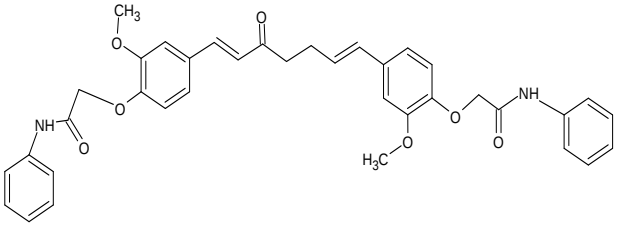
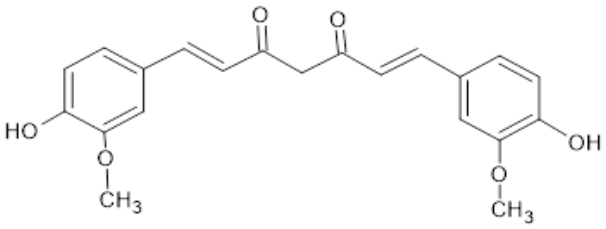


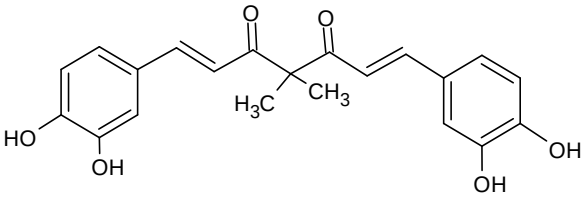
C-106



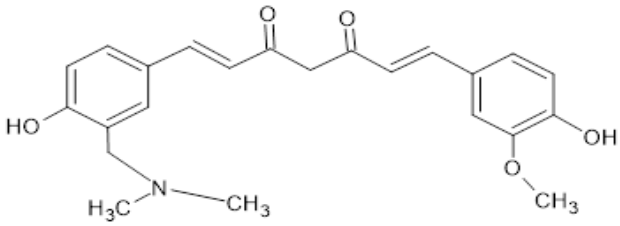
C-107



C-108



C-109



C-110

Fig 2 Curcumin derivatives

Osiris Explorer

The results are color-coded as red, green, and yellow. Green colour indicates compounds that are less toxic, yellow is for mildly toxic, while red is for compounds predicted to be highly toxic. From the prediction in Table 5.2.1, all compounds except C-106 were presumed safe and expected to exhibit little or no toxicity in terms of mutagenicity, tumorigenicity, any irritant effects, and reproductive system effects. All were presented in green for tumorigenicity and mutagenicity. It is found that C-106 may pose some level of risk concerning reproductive toxicity. Mild toxicity was assigned for C-106 concerning its irritant effect and the compounds were declared non-toxic for irritant effect. The other derivatives featured different drug scores for the other drugs, C-101 and C-102 which both scored (0.45).

Table 3. Toxicity Profile of Curcumin Derivatives

S.No	Compound Code	Solubility (mg/mL)	Drug Likeliness	Drug Score	Mutagenicity	Tumorigenicity	Irritant	Reproductive Effect
1	C-101	-3.60	-3.55	0.45	green	green	green	green

2	C-102	-3.59	-4.48	0.45	green	green	green	green
3	C-103	-3.47	1.81	0.80	green	green	green	green
4	C-104	-4.32	-12.30	0.37	green	green	green	green
5	C-105	-5.50	-15.87	0.30	green	green	green	green
6	C-106	-5.24	-9.07	0.10	green	green	yellow	red
7	C-107	-7.76	3.62	0.29	green	green	green	green
8	C-108	-4.24	-0.74	0.41	green	green	green	green
9	C-109	-4.03	-1.42	0.39	green	green	green	green
10	C-110	-4.53	-3.95	0.33	green	green	green	green

Protox-II

The LD50 falls between 1500 mg/kg and 3300 mg/kg, indicating that the compounds displayed low to moderate toxicity. The compounds were classified into two classes of toxicity: Class IV (Potentially Harmful) includes C-101, C-102, C-103, C-106, C-107, and C-110, which may indicate mild toxicity. On the other hand, Class V (Relatively Safe) comprises C-104, C-105, C-108, and C-109, which indicates low toxicity and safer profiles. C-107, the most toxic, had an LD50 of 1500 mg/kg (Class IV). The least toxic were C-105 and C-108, with LD50 values of 3300 mg/kg (Class V). Prediction accuracy ranges from 67.38% to 100%, with C-110 having the highest prediction confidence of 100%. A more rigorous evaluation of Class IV compounds (C-101, C-102, C-103, C-106, C-107, and C-110) seems desirable due to their relatively lower LD50 values, which may suggest potential toxicity concerns. Class V compounds, including C-104, C-105, C-108, and C-109, seem relatively safer for pharmacologic considerations. Each class's safety status suggests that only Class IV should undergo further evaluation; C-110, with a 100% chance of being accurate, stands as a trustworthy prediction. The low probability predictions (67% C-101) should be considered with caution. In conclusion, C-105 and C-108 seem to be the safest options based on their high LD50 and long half-lives, hence Class V.

Hepatotoxicity and Neurotoxicity: All compounds are inactive for hepatotoxicity and neurotoxicity, except C-104 (0.89) and C-109 (0.88), which raise moderate neurotoxic suspicion. Immunotoxicity: The majority are active, meaning they could have an impact on the immune system; C-101, C-102, C-103, C-106, C-107, and C-110 show the highest probabilities of immunotoxicity (> 0.90). Mutagenicity: All compounds except C-109 are inactive, suggesting low risk for genes' mutation. Cytotoxicity: Most assessed compounds are inactive, with the exception of C-101 (0.68 active probability), which would suggest possible cytotoxic activity. Some neurotoxicity risk could be posed by C-104 and C-109, necessitating further assessment for safety. This raises a further topic: the potential risk for immunotoxicity that may be either deleterious or selective, depending on the therapeutic intent. C-109 is the only one that appears to have any potential mutagenic effect, causing great concern for long-term safety. C-101 is notable for possible cytotoxicity, which makes it a candidate for anticancer studies. Candidates with inactive mutagenic potentials that are low in toxicity (C-105 and C-108) may be taken forward for development.

Table 4. Prediction of oral acute toxicity, class and accuracy of Curcumin derivatives.

S.NO	COMPOUND CODE	PREDICTED LD50	PREDICTED TOXICITY CLASS	PREDICTION ACCURACY
1	C-101	2000 mg/kg	CLASS -IV	68.07 %
2	C-102	2000 mg/kg	CLASS -IV	72.9 %
3	C-103	2000 mg/kg	CLASS - IV	67.38 %
4	C-104	2560 mg/kg	CLASS -V	69.26 %
5	C-105	3300 mg/kg	CLASS - V	67.38 %
6	C-106	1772 mg/kg	CLASS -IV	68.07 %
7	C-107	1500 mg/kg	CLASS -IV	67.38 %
8	C-108	3300 mg/kg	CLASS -V	67.38 %
9	C-109	2560 mg/kg	CLASS -V	69.26 %
10	C-110	2000 mg/kg	CLASS -IV	100 %

Table 5. Prediction of hepatotoxicity, neurotoxicity, immunotoxicity and genetic toxicity of anticancer agents.

S.NO	COMPOUND CODE	H	P	N	P	IM	P	M	P	C	P
1	C-101	I	0.70	I	0.57	A	0.99	I	0.74	A	0.68
2	C-102	I	0.61	I	0.81	A	0.98	I	0.88	I	0.88

3	C-103	I	0.66	I	0.52	A	0.91	I	0.55	I	0.62
4	C-104	I	0.68	I	0.89	A	0.70	I	0.85	I	0.74
5	C-105	I	0.85	I	0.61	A	0.99	I	0.68	I	0.68
6	C-106	I	0.76	I	0.83	A	0.92	I	0.78	I	0.67
7	C-107	I	0.60	I	0.79	A	0.98	I	0.72	I	0.85
8	C-108	I	0.79	I	0.62	A	0.99	I	0.64	I	0.70
9	C-109	I	0.65	I	0.88	I	0.90	I	0.82	I	0.93
10	C-110	I	0.61	I	0.83	A	0.94	I	0.79	I	0.85

H-Hepatotoxicity, N-Neurotoxicity, IM- Immunotoxicity, M- Mutagenecity, C-cytotoxicity, P-Probability, I-Inactive, A-Active

3.4. Pass Analysis

PASS analysis of the compounds (C-101-C-110) indicates their probable biological activities with different probabilities of activity (Pa) and inactivity (Pi). The compounds show varied predicted biological activities such as: Feruloyl Esterase Inhibitor: Found in nearly all compounds, indicative of a shared functional attribute in the dataset. Beta-carotene 15,15'-monooxygenase Inhibitor: Also found widespread, reflective of possible activity in modulating carotenoid metabolism. HIF1A and JAK2 Expression Inhibitors: Identified in a number of compounds (e.g., C-102, C-103, C-104), indicating anti-inflammatory or anti-cancer activity. HMOX1 Expression Enhancer: Identified in C-101 and C-104, indicating antioxidant or cytoprotective activity. Prostate Cancer Therapy: Indicated for C-106 and C-108, offering a specific therapeutic target. Mucositis and Preneoplastic Conditions Treatment: Available in C-105 and C-108, with potential for gastrointestinal protection. High Pa Values: Substances like C-102, C-103, C-109, and C-110 have high Pa values (>0.9) for various activities, indicating high predicted efficacy. Diverse Activity Spectrum: Compounds exhibit a broad spectrum of activities ranging from enzyme inhibition to expression modulation and treatment of certain conditions. Therapeutic Potential: The fact that compounds possess anti-inflammatory, antioxidant, and anti-cancer activities renders them worthy candidates for further research. Compound Similarity: Certain compounds (e.g., C-103 and C-109) have the same predicted activities, suggesting structural or functional similarity. This analysis illustrates the wide range of biological activities of these compounds, which suggests their potential for further pharmacological investigation.

Table 6. Data of PASS Prediction

S.NO:	COMPOUND CODE	Pa	Pi	Other predicted biological activities
1	C-101	0.936	0.003	Feruloyl esterase inhibitor
		0.898	0.001	Beta-carotene15,15'-monooxygenase inh
		0.887	0.014	Membrane integrity agonist
		0.826	0.003	HMOX1 expression enhancer
2	C-102	0.927	0003	Feruloyl esterase inhibitor
		0.908	0.001	Beta-carotene15,15'-monooxygenase inh
		0.974	0.002	HIF1A expression inhibitor
		0.978	0.001	JAK2 expression inhibitor
3	C-103	0.894	0.004	Feruloyl esterase inhibitor
		0.884	0.002	Beta-carotene15,15'-monooxygenase inh
		0.980	0.002	HIF1A expression inhibitor
		0.962	0.001	JAK2 expression inhibitor
4	C-104	0.867	0.006	Feruloyl esterase inhibitor
		0.774	0.014	HIF1A expression inhibitor
		0.837	0.005	JAK2 expression inhibitor
		0.771	0.004	HMOX1 expression enhancer
5	C-105	0.686	0.006	Beta-carotene15,15'-monooxygenase inh
		0.951	0.003	Mucositis treatment
		0.911	0.002	Preneoplastic conditions treatment
		0.760	0.004	TNF expression inhibitor
6	C-106	0.880	0.05	Feruloyl esterase inhibitor
		0.714	0.016	JAK2 expression inhibitor
		0.907	0.003	Prostate cancer treatment
		0.880	0.005	Feruloyl esterase inhibitor
7	C-107	0.867	0.006	Feruloyl esterase inhibitor
		0.774	0.014	HIF1A expression inhibitor
		0.837	0.005	JAK2 expression inhibitor

		0.771	0.004	HMOX1 expression enhancer
8	C-108	0.659 0.947 0.906 0.763	0.007 0.004 0.002 0.004	Beta-carotene15,15'-monooxygenase inh Mucositis treatment Preneoplastic conditions treatment JAK2 expression inhibitor
9	C-109	0.894 0.884 0.980 0.962	0.004 0.002 0.002 0.001	Feruloyl esterase inhibitor Beta-carotene15,15'-monooxygenase inh HIF1A expression inhibitor JAK2 expression inhibitor
10	C-110	0.927 0.908 0.974 0.978	0.003 0.001 0.002 0.001	Feruloyl esterase inhibitor Beta-carotene15,15'-monooxygenase inh HIF1A expression inhibitor JAK2 expression inhibitor

inh = inhibitor

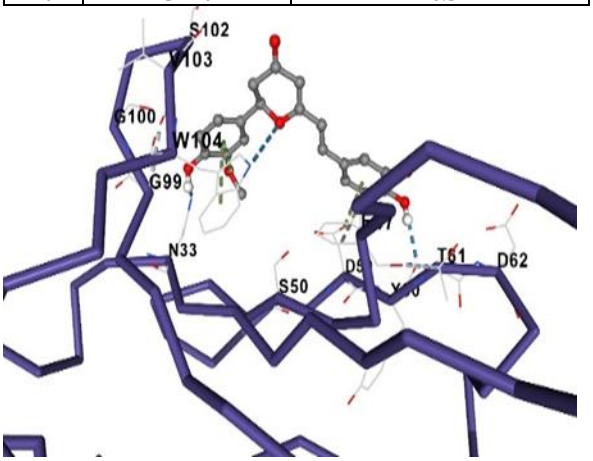
3.5. Docking of Curcumin derivatives towards a protein with PDB id 8fq7 using CB-dock

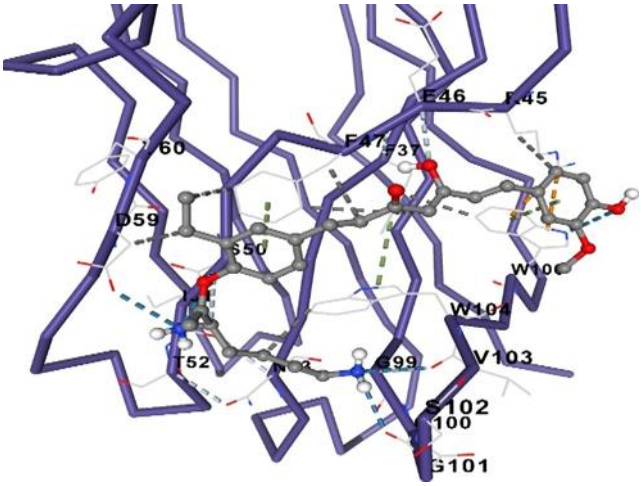
Curcumin derivatives were docked using online software CB DOCK on fibrils having PDB ID 8FQ7. Curcumin was taken as the reference molecule and the outcome was depicted in the table below.

Compound C-104 exhibits the highest binding affinity with a score of -6.9 kcal/mol, denoting the highest interaction with the target protein (8FQ7). This implies that C-104 could possess the greatest possibility of biological activity among the tested compounds. Compounds C-105 (-6.8 kcal/mol) and C-102 (-6.7 kcal/mol) also possess strong binding, hence possible candidates for further investigation. Compound C-106 (-6.0 kcal/mol) had the lowest binding affinity, indicating it can potentially be weaker in binding to the protein target. The scores vary from -6.0 to -6.9 kcal/mol, which means all the derivatives have moderate to strong interactions with 8FQ7. The narrow range of scores indicates that all compounds are structurally weakly compatible with the protein, but minute chemical property differences affect the strength of binding. C-104, C-105, and C-102 have the most promising potential for experimental validation due to their docking scores. Molecular dynamics simulations and experimental validation need to be done to validate these results and determine biological efficacy.

Table 7. Results of docking Curcumin derivatives with proteins (8FQ7) using CB-Dock

S.NO	COMPOUND CODE	DOCKING SCORE WITH 8FQ7
1	C-101	-6.3
2	C-102	-6.7
3	C-103	-6.2
4	C-104	-6.9
5	C-105	-6.8
6	C-106	-6.0
7	C-107	-6.4
8	C-108	-6.6
9	C-109	-6.5
10	C-110	-6.3





Binding of C-104 and C-105 with 8FQ7 receptors respectively using CB dock

4. CONCLUSION

The In-silico investigation of curcumin derivatives was useful in revealing their pharmacokinetics,

toxicity, bioactivity, and binding affinity to the target protein (8FQ7). Based on computational methods like ADME prediction, toxicity prediction, PASS analysis, and molecular docking, we found some promising curcumin derivatives with improved pharmacological potential. Molecular docking analysis found that C-104 (-6.9 kcal/mol) showed the highest binding capacity to the target protein, followed by C-105 (-6.8 kcal/mol) and C-102 (-6.7 kcal/mol), and indicated that these compounds would potentially have improved interaction stability and stronger biological activity. Toxicity testing found that all the derivatives presented low toxicity risk, except C-106, which showed potential reproductive toxicity risks. PASS analysis validated that some of the derivatives have remarkable anti-inflammatory, anticancer, and enzyme-inhibitory activities, suggesting their potential as drugs. In summary, based on our results, C-104, C-105, and C-102 are the topmost compounds to be taken to further biological assessment and experimental confirmation. Additional studies in the form of molecular dynamics simulations and in vitro/in vivo assays are required to validate their effectiveness and safety for therapeutic use. This research highlights the significance of computational drug discovery in speeding up the discovery and optimization of curcumin-derived drugs for diseases.

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