Terbit *online* pada laman web jurnal : https://jes-tm.org/index.php/jestm/index

Journal of Engineering Science and Technology Management

| ISSN (Online) 2828 -7886 |

Article

Molecular Docking Approach to Curcumin Compounds and Its Derivatives as Anticancer Agents: A Literature Review

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DOI: 10.31004/jestm.v6i1.308

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ARTICLE INFORMATION

Volume 6 Issue 1
Received: 11 October 2025
Accepted: 20 March 2026
Publish *Online*: 30 March 2026
Online: at https:JESTM.org

Keywords

Anticancer,
Cancer,
Curcumin,
Derivatives,
Molecular Docking

A B S T R A C T

Cancer remains a major global health challenge, with increasing incidence and mortality rates. This study aims to systematically review the potential of curcumin and its derivatives—particularly bisdemethoxycurcumin and amino acid–curcumin conjugate (H1)—as anticancer agents using molecular docking approaches, with EGFR identified as the most frequently studied protein target in the last five years. A Systematic Literature Review (SLR) was conducted, analyzing ten original articles published between 2020 and 2025 from PubMed and Google Scholar. The population encompassed all full-text studies on molecular docking of curcumin and its derivatives against cancer protein targets, with purposive sampling based on inclusion and exclusion criteria. Data were extracted on ligands, protein targets, docking software, validation parameters, and binding energies, then analyzed using narrative synthesis and comparative methods. The results show that curcumin and its derivatives interact with multiple cancer-related proteins, such as EGFR, HER2, CDK2, and androgen receptors, with derivatives like bisdemethoxycurcumin (−9.0 kcal/mol) and H1 (−9.2 kcal/mol) exhibiting more stable binding energies than natural curcumin. These findings indicate that specific curcumin derivatives have higher anticancer activity and overcome bioavailability limitations. The conclusion highlights the need for standardized molecular docking protocols and integration with biological assays to support clinical development of curcumin-based therapies.

1. Introduction

Cancer remains one of the most significant global health challenges, with incidence and mortality rates continuing to rise each year. According to the World Health Organization (WHO) and the American Cancer Society (ACS), there were over 20 million new cancer cases and nearly 10 million cancer-related deaths in 2022, and these numbers are projected to increase to 35 million cases by 2050 (Sung et al., 2021; Li et al., 2024). Furthermore, the GLOBOCAN 2020 report confirms that cancer is the second leading cause of death worldwide, underscoring the urgent need for the development of more effective and safer therapeutic strategies (Sung et al., 2021; Kusuma et al., 2022).

Standard therapies such as chemotherapy and radiotherapy have proven effective, but they frequently cause toxic side effects in normal cells and trigger drug resistance, prompting the exploration of new therapeutic agents based on natural bioactive compounds (Amin et al., 2025; Sharifi-Rad et al., 2020). One of the most widely studied candidates is curcumin, the principal polyphenol from turmeric (Curcuma longa), which exhibits anti-inflammatory, antioxidant, and anticancer activities through the regulation of key molecular pathways (Amin & Tsani, 2025; Kusuma et al., 2022).

Although curcumin has demonstrated potential as an anticancer agent, its clinical effectiveness is limited by poor bioavailability and low stability (Amin & Amelia, 2025; Sharifi-Rad et al., 2020). Multiple studies have reported that curcumin can interact with several cancer-related protein targets, including EGFR, HER2, CDK2, and androgen receptors, which play crucial roles in cell proliferation, apoptosis, and metastasis (Li et al., 2024; He et al., 2023). However, most research remains limited to in silico affinity predictions without sufficient biological validation, making it difficult to confirm the clinical efficacy of curcumin and its derivatives (Amin, Puspatiara, et al., 2025; Sumirtanurdin et al., 2020).

Advances in computational technology, particularly molecular docking methods, have enabled the virtual evaluation of bioactive compound interactions with cancer protein targets, offering greater efficiency in terms of time and cost compared to in vitro or in vivo approaches (Deshmukh et al., 2025; Sumirtanurdin et al., 2020). These in silico approaches are especially critical for curcumin derivatives because they allow rapid screening of numerous structural modifications such as hybrid conjugates or amino acid analogs to predict binding affinity and specificity against key cancer targets like EGFR or CDK2 before committing to costly chemical synthesis and experimental validation. This preliminary assessment also helps identify potential toxicity risks and optimize pharmacokinetic properties early, addressing curcumin's inherent challenges like poor bioavailability while prioritizing the most promising candidates for further development. Nevertheless, inconsistencies in software platforms, non-standardized validation parameters, and a lack of integration with pharmacokinetic data and biological assays remain major obstacles.

This study aims to systematically review in silico findings on the interactions of curcumin and its derivatives with cancer protein targets using molecular docking approaches, assess the consistency and validity of published data, and identify methodological limitations that need to be addressed in future research. The urgency of this research lies in the need for a comprehensive review that can serve as a scientific foundation for the development of curcumin as a natural product-based anticancer agent, while also providing guidance for researchers in designing more standardized and clinically oriented studies (Amin & Tsani, 2025; Deshmukh et al., 2025). The novelty of this study is reflected in the synthesis of recent evidence from various molecular docking studies of curcumin and its derivatives against cancer protein targets, along with a critical evaluation of methodological quality and clinical development prospects (Li et al., 2024; Kusuma et al., 2022).

2. Literature Review

2.1 Curcumin's Therapeutic Potential and Challenges

Curcumin, extracted from Curcuma longa, has garnered extensive interest as a natural anticancer agent due to its diverse biological activities, including anti-inflammatory, antioxidant, and modulation of multiple signal transduction pathways. The compound exhibits the capability to regulate cell proliferation, induce apoptosis, and modulate critical proteins involved in cancer progression such as EGFR, HER2, CDK2, and p53. Despite this promise, curcumin's clinical efficacy is compromised by poor bioavailability and chemical instability, necessitating optimization strategies such as

chemical modification and advanced drug delivery systems. These challenges highlight why recent research consistently explores curcumin derivatives and hybrids for enhanced stability and potency, as well as multi-targeted anticancer mechanisms.

2.2 Molecular Docking Investigations and Multi-Target Approaches

Molecular docking has become a standard in silico approach, effectively predicting ligand–protein interactions, affinity, and binding orientations for bioactive compounds prior to costly biological validation. Recent studies mapping docking profiles of curcumin and up to 20 derivatives have identified improved binding energy profiles (ΔG ranging -6 to -9 kcal/mol), particularly for compounds such as hexahydro curcumin, tetrahydro curcumin, and various hybrid analogs. For example, docking simulations targeting CDK2, EGFR, HER2, p53, and androgen receptors consistently show that certain curcumin derivatives and hybrids yield more stable complexes and stronger hydrogen bonding than the parent molecule, contributing to both cell cycle inhibition and enhanced apoptosis induction. Besides affinity assessment, advanced protocols now integrate molecular dynamics simulations and QSAR to validate ligand stability and pharmacokinetic profiles, as seen in the work by Nainggolan et al. (2025).

The multitarget mechanism of curcumin derivatives is reinforced by data from network pharmacology and pathway enrichment, implicating pathways such as PI3K-Akt, MAPK, and Ras in therapeutic activity against prostate, breast, colon, and liver cancers. Furthermore, curcumin analogs show the ability to upregulate tumor suppressor pathways (eg, enhancing wild-type p53 function or reactivating mutant p53) and downregulate growth signals, indicating broad-spectrum anticancer potential. This multitarget profile underscores curcumin's advantage in addressing cancer's inherent complexity and resistance mechanisms.

2.3 Structural Optimization and Validation Imperatives

Pharmacophore modeling and further structure–activity relationship analyzes have allowed for the rational design of curcumin derivatives with enhanced interaction profiles, improved pharmacokinetics, and reduced toxicity. For example, interaction with Lys33, Glu81, and Leu83 residues on CDK2 and hydrogen bonding with His273 on mutant p53 have been proposed as key determinants of inhibitor potency in several docking studies. Despite robust in silico evidence, methodological heterogeneity—including software variations, non-standardized validation protocols, and incomplete integration of pharmacokinetic and biological validation—remains a major bottleneck for clinical translation.

Recent studies recommend combining standardized molecular docking workflows with biological and pharmacokinetic assays to confirm predicted interactions and establish therapeutic relevance (Amin et al., 2025; Deshmukh et al., 2025). Such integrated validation is crucial for progressing from affinity prediction to real-world anticancer drug development.

2.4 Summary and Recommendations

The literature establishes that curcumin and its structurally optimized derivatives exert anticancer effects via multi-target, multi-pathway mechanisms, with superior affinity and stability compared to unmodified curcumin. Key efforts moving forward should focus on refining molecular docking protocols, enhancing pharmacokinetic modeling, and conducting rigorous biological validation to enable the clinical application of curcumin-based therapies

3. Research Methodology

3.1 Type and Method of Research

This study employs a Systematic Literature Review (SLR) approach, systematically synthesizing in silico research on curcumin and its derivatives as anticancer agents via molecular docking. The SLR method enables researchers to evaluate and integrate findings from multiple primary studies rigorously and transparently, strengthening the scientific base for subsequent drug development. Reference to SLR is consistent with established guidelines (PRISMA 2020; Page et al., 2021) and methodological recommendations in health and pharmaceutical research (Sugiyono, 2022; Creswell & Creswell, 2022). SLR was chosen due to its efficiency in mapping, critiquing, and synthesizing recent evidence in a way that supports reliable decision-making in research and practice.

3.2 Instruments and Data Analysis Techniques

Data collection used systematic searches (2020–2025) in PubMed and Google Scholar with keywords: ("molecular docking" OR "in silico") AND ("curcumin" OR "curcuminoid") AND ("cancer" OR "anticancer") (March 15, 2026). The 2020+ timeframe captures recent docking software advancements and curcumin analog developments, as pre-2020 studies used outdated AutoDock 4.0 lacking accuracy for modern hybrids (Page et al., 2021; Sugiyono, 2022). Data extraction followed PRISMA with JBI quality assessment (Munn et al., 2019; Emzir, 2024).

3.3 Population and Sample

The population comprised all original full-text articles reporting molecular docking of curcumin and its derivatives against cancer protein targets published in the target time range. The sample was selected through comprehensive identification, screening, and eligibility processes, as prescribed by SLR guidelines (Creswell & Creswell, 2022; Sudaryono, 2021). Inclusion criteria required articles written in English or Indonesian, presenting molecular docking outcomes, and full access to the manuscript. Exclusion criteria filtered out abstracts, editorials, proceedings, non-cancer studies, and unclear methodologies. Sampling in SLR reflects theoretical and purposive sampling concepts, as emphasized by Creswell (2022) and Emzir (2024)

4. Results and Discussion

4.1 Research Procedures

The research procedures comprised four main steps: (1) Identification of relevant articles by systematic database search; (2) Screening titles and abstracts for relevance and duplication; (3) Eligibility assessment based on inclusion and exclusion criteria; (4) Final selection and analysis of articles. These procedures align with the PRISMA 2020 model for SLR and established frameworks for qualitative and mixed methods research described by Sugiyono (2022), Creswell & Creswell (2022), and Sudaryono (2021). Data extraction was performed regularly into a standardized datasheet, followed by analysis through narrative synthesis and Results and Discussion

Based on the review, ten articles were selected according to the inclusion criteria. The results of the Systematic Literature Review are presented in Table 1 below.

Table 1. Results of the Systematic Literature Review

Reference	Ligand	Target Receptor	Docking Software	Validation Parameters	Bond Energy Value	Interpretation of Molecular Mechanisms
(Li et al., 2024)	Curcumin	SRC, STAT3, AKT1, EGFR (prostate cancer)	AutoDock Vina + Cytoscape (network)	Validation of RMSD < 2 Å, PPI interaction	< -1.85 kJ/mol	Inhibits proliferation by modulating the PI3K-Akt & MAPK pathways.
(He et al., 2023)	Curcumin	CDK2, AURKB, TOP2A (colon cancer)	AutoDock Vina	Redocking & RMSD	< -6.0 kcal/mol	Induces apoptosis & inhibits cell cycle via IL-17 and PI3K-Akt.
(Sativa et al., 2024)	Curcumin & Xanthorrhizol	Lck kinase (colorectal cancer)	AutoDock Vina	Validation with native ligand (RMSD < 2 Å)	Curcumin -5.12 kcal/mol, Xanthorrhizol -6.26 kcal/mol	Xanthorrhizol is more effective than curcumin in suppressing cell proliferation signals.
(Nurlaila et al., 2024)	Curcumin, Atlantone, Bisdemethoxycurcumin	Main Protease (breast cancer)	AutoDock 4.2	Remdesivir control	Curcumin -2.81 kcal/mol, Atlantone	Atlantone is more potent, but curcumin still exhibits Mpro

					-6.74 kcal/mol	inhibitory activity.
(Moreno-q et al., 2022)	Curcumin–resveratrol hybrid	MMP7, caspase 3/7, p53 (colorectal cancer)	Auto Dock Vina	Re-docking + RMSD	~ -8.0 kcal/mol	Hybrids suppress cell growth through activation of apoptosis via caspase and p53.
(Aman et al., 2023)	Curcumin & analogues	DYRK2 kinase	Auto Dock Vina + GROMACS (MD)	Pharmacophore validation + redocking	-8.5 to -9.2 kcal/mol	Curcumin analogs inhibit DYRK2 more potently, suppressing cell cycle progression.
(Panda et al., 2022)	Curcumin–DCA hybrids	HER2 & EGFR (breast cancer)	Auto Dock Vina	Validation RMSD < 2 Å	About -8.7 kcal/mol	Hybrids suppress cell growth through activation of apoptosis via caspase and p53.
(Ahsan et al., 2022)	Curcumin analogs (3b & 3c)	EGFR	Auto Dock Vina	Validation with reference ligands	-7.5 to -8.1 kcal/mol	H-bond and π-stacking interactions stabilize binding to EGFR, enhancing antiproliferative activity.
(Cao et al., 2025)	Amino acid–curcumin conjugates (H1)	AKT/FOXO1 (liver cancer)	Auto Dock Vina + SwissADME	In silico pharmacokinetic validation	H1: -9.2 kcal/mol	The conjugate activates apoptosis via the AKT/FOXO1 pathway, more potent than native curcumin.
(Pratama et al., 2021)	Curcumin, Demethoxy, Bisdemethoxy	Androgen receptor (prostate cancer)	Auto Dock 4.2	Redocking RMSD < 2 Å	Bisdemethoxy -9.0 kcal/mol (strongest)	Bisdemethoxy curcumin binds more stably to the androgen receptor, effectively inhibiting proliferation.

This systematic review was designed to address the scientific gap of a lack of comprehensive reviews of curcumin's interactions with various cancer target proteins through a molecular docking approach. Ten articles analyzed demonstrated that curcumin and its derivatives interact with various cancer receptors or target proteins, including tyrosine kinase receptors such as EGFR and HER2 (Li et al., 2024), cell cycle regulatory proteins such as CDK2, DYRK2, and TOP2A (He et al., 2023), and androgen receptors, all of which play crucial roles in proliferation, apoptosis, and cancer development (Pratama et al., 2021).

Key amino acid residues consistently interacting with active derivatives include Lys33, Glu81, and Leu83 on CDK2, as well as His273 on mutant p53, forming stable hydrogen bonds and hydrophobic interactions that enhance binding specificity across multiple studies. Structure-Activity Relationship (SAR) analysis reveals that electron-withdrawing groups and methoxy substitutions improve activity over native curcumin by stabilizing the β-diketo tautomeric form, increasing planarity for better receptor fit, and enhancing hydrogen bonding capacity with critical residues—explaining why bisdemethoxycurcumin (−9.0 kcal/mol) and H1 conjugate (−9.2 kcal/mol) outperform the parent compound.

Narrative synthesis suggests curcumin acts through multitarget and multipathway mechanisms. In prostate cancer, it suppresses PI3K-Akt and MAPK pathways (Li et al., 2024). In colon cancer, CDK2 and AURKB interactions inhibit cell cycle and induce apoptosis (He et al., 2023). Breast cancer studies show atlantone binds more stably to Mpro than curcumin (Nurlaila et al., 2024), while xanthorrhizol from Curcuma xanthorrhiza exhibits higher Lck affinity (Sativa et al., 2024).

5. Conclusion

The main findings of this systematic review demonstrate that curcumin and its derivatives possess significant anticancer activity through multi-target and multi-pathway mechanisms, interacting with key cancer-related proteins such as EGFR, HER2, CDK2, and androgen receptors. Derivative compounds and hybrids consistently exhibit more stable binding energies, typically ranging from -6 to -9 kcal/mol, compared to natural curcumin, which translates to stronger inhibitory effects on cancer cell proliferation and enhanced induction of apoptosis. The review also highlights that structural modifications, such as the addition of methoxy or hydroxy groups, can further improve the specificity and potency of curcumin derivatives against cancer targets. These findings support the potential of curcumin-based compounds as promising candidates for the development of multi-target anticancer therapies.

However, the review identifies several methodological limitations in the current body of research. Most studies rely heavily on in silico affinity predictions without comprehensive biological validation, such as in vitro or in vivo assays, which limits the translation of these findings into clinical applications. Additionally, there is considerable variability in the molecular docking protocols, software platforms, and validation parameters used, which may affect the reliability and comparability of results. Future research should focus on integrating standardized molecular docking procedures with robust pharmacokinetic modeling and biological assays to strengthen the evidence base. Practical implications include the need for collaborative efforts between computational and experimental researchers to accelerate the clinical development of curcumin derivatives, ensuring that promising in silico candidates are rigorously validated and optimized for therapeutic use.

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