RESEARCH PAPER

Structural Insights into Curcumin Interaction with Inflammatory Cytokines and Proliferative Protein Targets in Early Childhood Caries - An In Silico Docking Study

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ABSTRACT

Background:

Early childhood caries (ECC) involves microbial activity and host-mediated inflammatory responses. Cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), along with proliferative markers like minichromosome maintenance protein-2 (MCM-2), play important roles in disease progression. Curcumin is a natural polyphenolic compound with reported anti-inflammatory properties.

Objective:

To evaluate the molecular interaction of curcumin with key inflammatory cytokines and the proliferative marker MCM-2 associated with ECC using an in-silico molecular docking approach.

Materials and Methods:

Three-dimensional crystal structures of IL-6 (PDB ID: 1P9M), IL-1β (PDB ID: 8C3V), TNF-α (PDB ID: 2AZ5), and MCM-2 (PDB ID: 7W68) were retrieved from the RCSB Protein Data Bank. Protein structures were prepared by removing water molecules and heteroatoms followed by addition of polar hydrogens and Kollman charges. Curcumin (PubChem CID: 969516) was obtained from the PubChem database and energy-minimized using the Universal Force Field. Molecular docking was performed using AutoDock Vina integrated within the PyRx virtual screening platform. Multiple docking poses were generated and the lowest-energy conformations were selected. Ligand–protein interactions were analyzed using BIOVIA Discovery Studio to identify hydrogen bonding and hydrophobic contacts.

Results:

Curcumin demonstrated stable binding with all targets. The highest binding affinity was observed with MCM-2 (−7.5 kcal/mol), followed by IL-6 (−6.9 kcal/mol), TNF-α (−6.4 kcal/mol), and IL-1β (−5.8 kcal/mol). Interaction analysis revealed hydrogen bonding and hydrophobic contacts within the protein binding pockets.

Conclusion:

Curcumin demonstrated favorable binding interactions with inflammatory cytokines and the proliferative protein associated with early childhood caries. These findings suggest that curcumin may influence host inflammatory and cellular responses involved in ECC progression. However, further experimental studies are required to validate these molecular interactions and confirm their biological significance.

Keywords: *Early Childhood Caries; Curcumin; Molecular Docking; In-Silico Analysis; Inflammatory Cytokines; Interleukin-6; Tumor Necrosis Factor-alpha; Interleukin-1 beta; MCM-2 Protein; Oral Health Biomarkers*

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INTRODUCTION

Early childhood caries (ECC) is one of the most common chronic diseases affecting young children and continues to be a major public health concern worldwide. It is characterized by rapid destruction of primary tooth structure, often leading to pain, infection, difficulty in eating, and reduced quality of life in affected children.[1] The development of ECC is multifactorial and results from the interaction of cariogenic microorganisms, dietary sugars, host factors, and environmental influences[2]. Among the microbial factors, acidogenic bacteria such as *Streptococcus mutans* play a central role in initiating the carious process through biofilm formation and acid production that promotes enamel demineralization.[3] However, current evidence suggests that microbial activity alone cannot fully explain the severity and progression of the disease. The host immune response within dental tissues plays a significant role in determining the inflammatory environment and the extent of tissue destruction during ECC progression.[4]

Inflammatory cytokines are important mediators of the host response to bacterial invasion in dental caries. Among these, interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) are key regulators of inflammatory signaling pathways and are known to be elevated in inflamed pulpal tissues and carious lesions.[5] These cytokines stimulate immune cell recruitment, promote inflammatory amplification, and activate intracellular signaling cascades such as the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, which contribute to pulpal inflammation and tissue damage.[6] In addition to inflammatory mediators, proliferative proteins also play an important role in the cellular response to tissue injury. The minichromosome maintenance complex (MCM2–7) is a group of proteins involved in DNA replication and cell cycle regulation, and MCM-2 is widely used as a marker of cellular proliferation. Increased expression of MCM proteins has been associated with active cell replication and may reflect proliferative activity within inflamed dental tissues during disease progression.[7]

In recent years, natural bioactive compounds have gained considerable attention for their potential role in modulating inflammatory processes associated with oral diseases. Curcumin, a polyphenolic compound derived from the rhizome of *Curcuma longa*, has been extensively studied for its anti-inflammatory, antioxidant, and antimicrobial properties.[8] Experimental studies have shown that curcumin can suppress inflammatory mediator production and inhibit major signaling pathways such as NF-κB and MAPK, thereby reducing inflammatory responses in various disease conditions. In dental research, curcumin has also demonstrated inhibitory effects against cariogenic microorganisms including *Streptococcus mutans*, suggesting its potential application in preventive and therapeutic dental formulations.[9]

Despite the growing interest in the therapeutic potential of curcumin, the molecular mechanisms through which it may interact with inflammatory and proliferative proteins involved in ECC are not clearly understood. Most previous investigations have focused primarily on its antimicrobial activity or general anti-inflammatory effects, while limited studies have explored the structural interaction between curcumin and specific cytokine targets associated with caries-related inflammation.[10], Furthermore, the potential interaction between curcumin and proliferative markers such as MCM-2, which may play a role in tissue response during ECC progression, has not been extensively investigated.[11]

Computational molecular docking provides a valuable method for predicting ligand–protein interactions and understanding potential mechanisms of drug action at the molecular level.[12],[13],[14] By evaluating binding affinity, interaction residues, and structural compatibility, docking studies can provide insights into how bioactive compounds may influence key biological pathways. Therefore, investigating the docking interactions of curcumin with inflammatory cytokines such as IL-6, IL-1β, TNF-α and the proliferative marker MCM-2 may help to better understand its potential role in modulating host inflammatory responses in ECC.

Based on this rationale, the present study aimed to perform an in-silico molecular docking analysis to evaluate the interaction of curcumin with major inflammatory and proliferative protein targets associated with early childhood caries. Understanding these molecular interactions may provide mechanistic insight

into the potential therapeutic relevance of curcumin in modulating immune-inflammatory pathways involved in ECC.

MATERIALS AND METHODS

Study Design

The present investigation was designed as an in-silico molecular docking study to evaluate the binding interactions between curcumin and selected inflammatory and proliferative protein targets associated with early childhood caries (ECC). Molecular docking was performed to predict the structural compatibility, interaction patterns, and binding affinity of curcumin with key cytokines involved in inflammatory signaling as well as a cellular proliferation marker implicated in tissue response during disease progression. The study aimed to provide mechanistic insights into the potential modulatory role of curcumin on inflammatory pathways associated with ECC.

Retrieval of Protein Structures

Three-dimensional crystallographic structures of the selected target proteins were retrieved from the RCSB Protein Data Bank (https://www.rcsb.org).[11] The proteins were selected based on their established role in inflammatory signaling and cellular proliferation in host immune responses. The retrieved structures included interleukin-6 (IL-6; PDB ID: 1P9M), interleukin-1β (IL-1β; PDB ID: 8C3V), tumor necrosis factor-alpha (TNF-α; PDB ID: 2AZ5), and minichromosome maintenance protein-2 (MCM-2; PDB ID: 7W68). IL-6, IL-1β, and TNF-α are major pro-inflammatory cytokines that regulate immune activation and inflammatory amplification, whereas MCM-2 serves as a proliferative marker involved in DNA replication and cell cycle progression. These proteins collectively represent key molecular pathways associated with inflammatory and proliferative responses during ECC progression.

Protein Preparation

Prior to docking simulations, the retrieved protein structures were prepared to ensure structural stability and accurate ligand interaction. Protein preparation involved removal of co-crystallized ligands, water molecules, and heteroatoms. Polar hydrogen atoms were subsequently added to the protein structures to facilitate proper hydrogen bonding interactions during docking. Kollman charges were assigned to the protein atoms to stabilize electrostatic interactions within the docking environment. The prepared protein structures were then converted into PDBQT format to enable compatibility with the docking software.[11]

Ligand Preparation

Curcumin was selected as the ligand for docking analysis due to its reported anti-inflammatory and antioxidant properties. The three-dimensional structure of curcumin was obtained from the PubChem database (PubChem CID: 969516) in Structure Data File (SDF) format. The ligand structure was subjected to geometry optimization and energy minimization using the Universal Force Field (UFF) to obtain a stable conformation suitable for docking simulations. Following energy minimization, Gasteiger partial charges were assigned and the ligand structure was converted into PDBQT format for docking analysis.[15]

Molecular Docking Procedure

Molecular docking simulations were performed using the AutoDock Vina docking engine integrated within the PyRx virtual screening platform. AutoDock Vina predicts ligand–protein binding affinity using an empirical scoring function that estimates the free energy of binding by evaluating intermolecular interactions such as hydrogen bonding, hydrophobic contacts, steric complementarity, and ligand conformational flexibility within the receptor binding site. During the docking process, the algorithm samples multiple ligand orientations and conformations within a defined search space and calculates their corresponding binding energies. For each protein target, a grid box of approximately 40 Å × 40 Å × 40 Å was defined around the predicted active binding region to allow adequate exploration of possible ligand binding conformations within the protein cavity. The docking simulations generated multiple binding poses for each protein–ligand complex, typically producing nine conformational modes ranked according to predicted binding affinity. The conformation with the lowest binding energy (most negative value) was considered the most stable binding pose and was selected for further evaluation. The resulting ligand–protein complexes were subsequently analyzed to identify key molecular interactions, including hydrogen bonding, hydrophobic interactions, and π-stacking contacts, that contribute to ligand stabilization within the protein binding pocket.

Binding Affinity and RMSD Evaluation

The docking results were analyzed based on predicted binding affinity values expressed in kilocalories per mole (kcal/mol) and root mean square deviation (RMSD)

values. Binding affinity values indicate the predicted strength of ligand–protein interaction, with more negative values suggesting stronger binding. Among the analyzed targets, curcumin demonstrated the highest binding affinity with MCM-2 (−7.5 kcal/mol), followed by IL-6 (−6.9 kcal/mol), TNF-α (−6.4 kcal/mol), and IL-1β (−5.8 kcal/mol). RMSD values were evaluated to determine the stability and reliability of docking conformations. The top-ranked docking poses exhibited RMSD values close to 0 Å, indicating consistent and stable ligand orientation within the protein binding pocket.

Interaction and Visualization Analysis

Detailed ligand–protein interactions were analyzed using BIOVIA Discovery Studio Visualizer. Two-dimensional (2D) interaction maps and three-dimensional (3D) structural representations were generated to identify key amino acid residues involved in ligand binding. The interaction analysis revealed multiple stabilizing forces including conventional hydrogen bonds, carbon hydrogen bonds, π–π stacking interactions, π–alkyl interactions, π–sigma interactions, and hydrophobic contacts. These interactions contribute to ligand stabilization within the protein binding cavity and influence the strength and specificity of ligand–protein binding.

Computational Tools and Software

All computational simulations were performed using PyRx virtual screening software with AutoDock Vina as the docking engine. Structural preparation and interaction visualization were conducted using BIOVIA Discovery Studio Visualizer.[16] These computational tools enabled efficient prediction and analysis of ligand–protein binding interactions and structural compatibility between curcumin and the selected inflammatory and proliferative protein targets. Docking parameters were set with an exhaustiveness value of 8 and grid center coordinates corresponding to the predicted active site residues.

RESULTS

Molecular Docking Analysis of Curcumin with Selected Inflammatory and Proliferative Targets

Molecular docking simulations were performed to evaluate the binding affinity and interaction characteristics of curcumin with key inflammatory cytokines and a proliferative marker implicated in early childhood caries (ECC). The docking analysis revealed that curcumin was able to interact with all selected protein targets, including interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and minichromosome maintenance protein-2 (MCM-2). The predicted binding energies ranged from −5.8 kcal/mol to −7.5 kcal/mol, suggesting stable ligand–protein interactions across the analyzed structures. The top docking poses for each complex showed RMSD values close to 0 Å, indicating a reliable and consistent orientation of the ligand within the predicted binding cavities.

Protein	PDB ID	Binding Energy (kcal/mol)	Key Interacting Residues
MCM-2	7W68	−7.5	Arg446, Gln616, Asp448
IL-6	1P9M	−6.9	Thr130, Asn135, Ser192
TNF-α	2AZ5	−6.4	Gly121, Leu57
IL-1β	8C3V	−5.8	Leu137, Ser192

Table 1: Predicted Binding Affinity and Key Residue Interactions of Curcumin with Selected Inflammatory and Proliferative Protein Targets Associated with Early Childhood Caries

Table 1 summarizes the molecular docking results of curcumin with the selected protein targets involved in inflammatory signaling and cellular proliferation in early childhood caries. The table presents the Protein Data Bank (PDB) identifiers of each target protein along with the predicted binding affinity values obtained from AutoDock Vina. Binding affinity values are expressed in kilocalories per mole (kcal/mol), where more negative values indicate stronger ligand–protein interactions. The table also lists the major amino acid residues involved in ligand binding within the protein cavity, which contribute to the stabilization of the curcumin–protein complex through hydrogen bonding and hydrophobic interactions. Among the evaluated targets, curcumin exhibited the strongest interaction with the proliferative protein MCM-2, followed by IL-6, TNF-α, and IL-1β. These findings highlight the potential structural compatibility of

curcumin with proteins associated with inflammatory and proliferative pathways involved in the progression of early childhood

Interaction of Curcumin with TNF-α (PDB ID: 2AZ5)

Docking analysis revealed that curcumin binds within the TNF-α binding pocket with a predicted binding affinity of −6.4 kcal/mol for the most stable conformation. Several docking poses were generated during the simulation; however, the top-ranked pose showed an RMSD value of 0 Å, suggesting a stable docking configuration. Interaction mapping from the two-dimensional diagram indicated that curcumin forms hydrophobic contacts within the TNF-α binding cavity, involving residues such as Gly121 and Leu57. These interactions were primarily mediated through π-alkyl and hydrophobic interactions between the aromatic rings of curcumin and the surrounding amino acid residues. The three-dimensional docking structure further revealed additional stabilizing interactions, including π–π stacking and hydrophobic contacts within the protein pocket. Such interactions contribute to the stabilization of the ligand within the TNF-α structure and suggest that curcumin may interact with structural regions associated with cytokine activity. These findings support the potential ability of curcumin to interact with TNF-α mediated inflammatory signaling pathways.

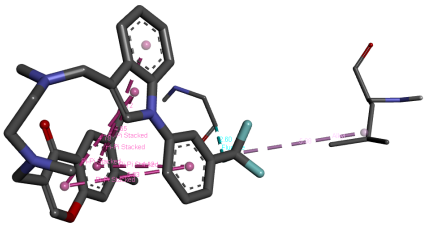

Figure 1(A)

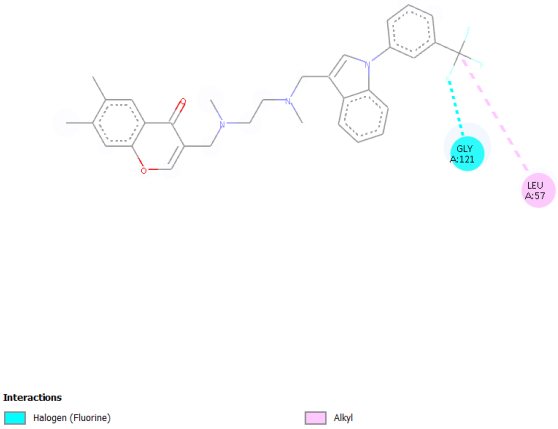

Figure 1(B)

Figure 1: Molecular docking interaction of curcumin with tumor necrosis factor-alpha (PDB ID: 2AZ5). (A) Three-dimensional structure of the docked complex demonstrating the orientation of curcumin within the TNF-α binding pocket. The protein backbone is represented in ribbon form and the ligand is shown in stick representation. The lowest energy docking pose exhibited a binding affinity of −6.4 kcal/mol. (B) Two-dimensional interaction map showing hydrogen bonds, hydrophobic contacts, and π-alkyl interactions between curcumin and amino acid residues in the TNF-α active site.

Interaction of Curcumin with MCM-2 (PDB ID: 7W68)

Among the proteins analyzed in this study, curcumin demonstrated the strongest binding interaction with MCM-2, with a predicted binding affinity of −7.5 kcal/mol for the most stable docking pose. The RMSD value of 0 Å observed for the best docking conformation indicates a stable orientation of the ligand within the protein binding site. Detailed interaction analysis showed that curcumin forms multiple hydrogen bonds with key residues in the MCM-2 protein structure. Conventional hydrogen bonds were observed with residues Arg446, Gln616, and Asp448, which are located within the binding region of the protein. Additional stabilizing interactions included carbon-hydrogen bonds and π-π stacking interactions involving residues Tyr447 and

Val472. These interactions create a stable ligand–protein complex that enhances binding stability within the MCM-2 cavity. The presence of several hydrogen bonding and hydrophobic contacts suggests that curcumin can be accommodated effectively within the MCM-2 binding pocket. Considering the role of MCM proteins in DNA replication and cellular proliferation, the observed interactions may indicate a potential influence of curcumin on proliferative pathways associated with inflammatory responses in dental tissues.

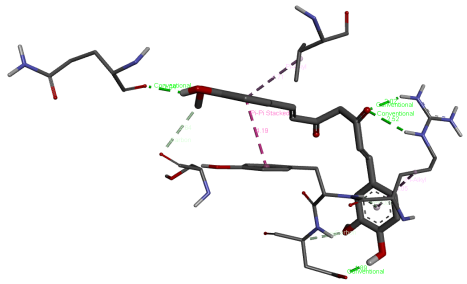

Figure 2(A)

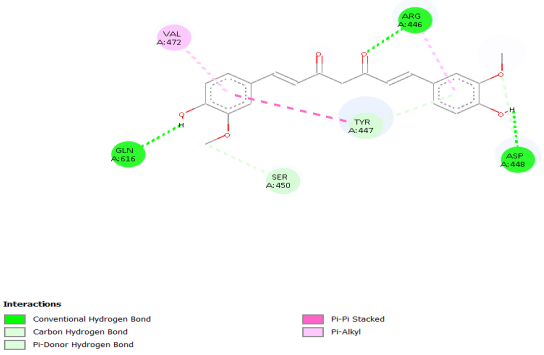

Figure 2(B)

Figure 2: Molecular docking interaction of curcumin with the proliferative marker minichromosome maintenance protein-2 (PDB ID: 7W68) (A) Three-dimensional representation showing curcumin bound within the MCM-2 binding cavity. The docked pose represents the most stable conformation with the lowest predicted binding affinity (−7.5 kcal/mol). (B) Two-dimensional interaction diagram highlighting hydrogen bonds and hydrophobic interactions formed between curcumin and key amino acid residues within the MCM-2 binding pocket, contributing to stabilization of the ligand–protein complex.

Interaction of Curcumin with IL-6 (PDB ID: 1P9M)

Docking simulations between curcumin and IL-6 revealed a binding affinity of −6.9 kcal/mol for the most stable ligand–protein complex. The top docking pose showed an RMSD value of 0 Å, indicating a consistent and reliable binding configuration. The two-dimensional interaction diagram demonstrated that curcumin forms multiple hydrogen bonding interactions with residues Thr130, Asn135, and Ser192 within the IL-6 structure. These hydrogen bonds contribute significantly to the stabilization of the ligand within the cytokine binding cavity. In addition to hydrogen bonding, hydrophobic interactions were also observed between the aromatic rings of curcumin and nearby residues including Phe136. A π-anion interaction involving Glu133 was also detected, which further contributes to ligand stabilization. The combination of hydrogen bonding and hydrophobic contacts suggests a favorable interaction between curcumin and IL-6. Given the critical role of IL-6 in mediating inflammatory signaling and immune activation, these interactions indicate that curcumin may potentially interact with structural regions associated with cytokine signaling.

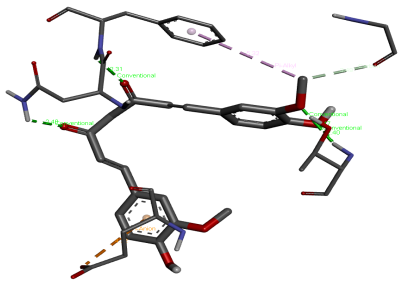

Figure 3(A)

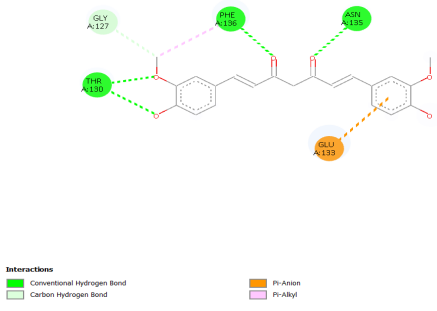

Figure 3(B)

Figure 3: Molecular docking interaction of curcumin with interleukin-6. (PDB ID: 1P9M) (A) Three-dimensional representation of the docked complex showing curcumin positioned within the IL-6 binding cavity. The protein structure is displayed in ribbon format while curcumin is represented in stick form. The docking pose corresponds to the lowest binding energy conformation predicted by AutoDock Vina (−6.9 kcal/mol). (B) Two-dimensional interaction diagram illustrating hydrogen bonding and hydrophobic contacts between curcumin and key amino acid residues within the IL-6 binding pocket.

Interaction of Curcumin with IL-1β (PDB ID: 8C3V)

Curcumin also demonstrated binding interaction with IL-1β, with the most stable docking conformation showing a predicted binding affinity of −5.8 kcal/mol. Although the binding affinity was comparatively lower than that observed with MCM-2 and IL-6, the docking pose remained stable with an RMSD value of 0 Å. Interaction analysis revealed that curcumin forms conventional hydrogen bonds with residues Leu137 and Ser192 within the IL-1β structure. Additional stabilizing interactions were identified through π-sigma and π-alkyl interactions involving residues Val194 and Ala150. These hydrophobic contacts contribute to the stabilization of the ligand within the binding region of IL-1β. Despite the slightly lower binding affinity, the presence of multiple non-covalent interactions indicates that curcumin can still establish stable contact with the IL-1β protein structure. These findings suggest a potential interaction of curcumin with IL-1β-mediated inflammatory pathways.

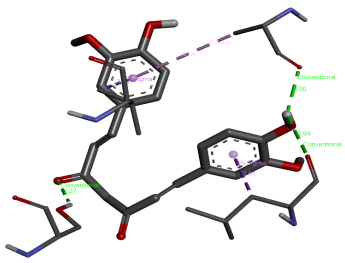

Figure 4(A)

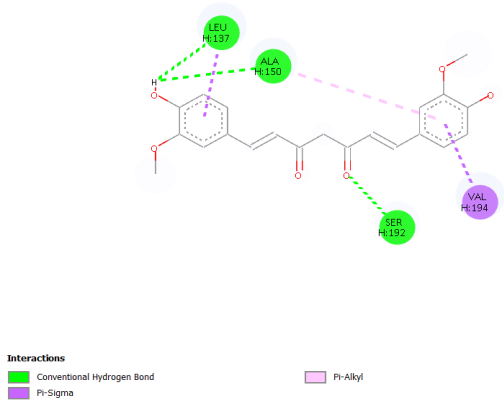

Figure 4(B)

Figure 4. Molecular docking interaction of curcumin with interleukin-1β.(PDB ID: 8C3V) **(A)** Three-dimensional structure showing the docking pose of curcumin within the IL-1β binding cavity. The protein is represented in ribbon format and the ligand in stick form, corresponding to the lowest binding energy conformation (−5.8 kcal/mol). **(B)** Two-dimensional interaction map illustrating hydrogen bonding and hydrophobic interactions between curcumin and surrounding amino acid residues within the IL-1β binding pocket.

Comparative Analysis of Docking Interactions

Comparison of binding affinities among the selected protein targets revealed that curcumin exhibited the strongest interaction with MCM-2 (−7.5 kcal/mol), followed by IL-6 (−6.9 kcal/mol), TNF-α (−6.4 kcal/mol), and IL-1β (−5.8 kcal/mol). The relatively higher binding affinity observed with MCM-2 suggests that curcumin may interact more strongly with proteins associated with cellular proliferation, in addition to inflammatory cytokines.

The docking analysis showed that curcumin forms stable ligands–protein complexes with key inflammatory cytokines (IL-6, IL-1β, TNF-α) and the proliferative marker MCM-2 associated with early childhood caries. The highest binding affinity was observed with MCM-2 (−7.5 kcal/mol), followed by IL-6 (−6.9 kcal/mol), TNF-α (−6.4 kcal/mol), and IL-1β (−5.8 kcal/mol). These interactions were stabilized mainly through hydrogen bonding and hydrophobic contacts within the binding

pockets, indicating good structural compatibility. Overall, the findings suggest that curcumin may potentially influence inflammatory and proliferative pathways involved in ECC progression.

DISCUSSION

Early childhood caries (ECC) is increasingly recognized as a disease involving a complex interplay between microbial biofilm activity and host immune responses. While cariogenic bacteria initiate the demineralization process, inflammatory mediators released within dental tissues significantly influence disease severity and progression. Pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) are known to regulate inflammatory signaling and contribute to pulpal immune activation and tissue destruction. In addition, proliferative markers such as the minichromosome maintenance protein complex (MCM2–7) play a role in cellular replication and repair processes during tissue injury. The present in-silico molecular docking study demonstrated that curcumin interacts favorably with these inflammatory and proliferative proteins, with the strongest binding affinity observed for MCM-2 (−7.5 kcal/mol), followed by IL-6 (−6.9 kcal/mol), TNF-α (−6.4 kcal/mol), and IL-1β (−5.8 kcal/mol). These findings suggest that curcumin may potentially influence both inflammatory and proliferative molecular pathways associated with ECC progression.

The docking interaction observed between curcumin and IL-6 in the present study is consistent with previous experimental findings demonstrating that curcumin suppresses IL-6 mediated inflammatory signaling. Gong et al. reported that curcumin exhibits strong docking affinity toward inflammatory cytokines including IL-6 and significantly reduces IL-6 expression in LPS-stimulated macrophages.[17] Similarly, Lan et al. demonstrated that curcumin attenuates IL-6 production and suppresses activation of the NLRP3 inflammasome in human dental pulp stem cells by inhibiting NF-κB signaling pathways.[18] These findings reinforce the biological relevance of the docking interaction observed in the present study, indicating that curcumin may interact with IL-6 at the molecular level and thereby contribute to the regulation of inflammatory responses within dental tissues.

Curcumin also demonstrated a stable interaction with TNF-α in the present study, with a binding affinity of −6.4 kcal/mol. TNF-α is a major pro-inflammatory cytokine that plays a central role in amplifying inflammatory responses and recruiting immune cells to sites of infection. Previous studies have consistently reported that curcumin reduces TNF-α expression in inflammatory disease models. Justo et al. observed reduced TNF-α immunoreactivity following curcumin supplementation in experimental apical periodontitis, indicating suppression of inflammatory cell infiltration in oral tissues.[19],[20] Similarly, Pimentel et al. demonstrated that curcumin administration significantly reduced TNF-α levels in diabetic rats with periodontitis and improved inflammatory parameters.[21] The docking interaction observed in the present study therefore provides structural support for these experimental observations and suggests that curcumin may exert anti-inflammatory effects through interaction with TNF-α associated signaling pathways

The interaction between curcumin and IL-1β observed in this study further highlights the anti-inflammatory potential of this natural compound. Although the predicted binding affinity for IL-1β was comparatively lower than that for IL-6 and TNF-α, stable ligand–protein interactions involving hydrogen bonds and hydrophobic contacts were identified within the IL-1β binding cavity. Deng et al. demonstrated that curcumin derivatives significantly reduce IL-1β expression and promote anti-inflammatory macrophage polarization in experimental models of periodontitis.[22], [23]Likewise, Jin et al. reported that curcumin suppresses IL-1β production and inhibits NF-κB activation in LPS-stimulated inflammatory cells.[24] These findings suggest that curcumin may interfere with IL-1β mediated inflammatory cascades, and the docking results obtained in the present study provide molecular evidence supporting this mechanism.

Another notable observation in the present study is the relatively strong interaction between curcumin and the proliferative marker MCM-2, which exhibited the highest binding affinity among the analyzed proteins. MCM proteins are essential components of the DNA replication machinery and are widely used as indicators of cellular proliferation. Although previous studies investigating curcumin have largely focused on inflammatory cytokines, emerging evidence suggests that curcumin may also influence cell cycle regulation and proliferation pathways. Selim et al. demonstrated that curcumin modulates inflammatory signaling and cellular proliferation through interaction with MAPK-related

pathways.[25] The strong binding affinity observed between curcumin and MCM-2 in the present study therefore suggests that curcumin may potentially influence proliferative responses within inflamed dental tissues, representing a novel aspect of the present investigation. The stronger interaction observed with MCM-2 may suggest a potential influence of curcumin on proliferative cellular responses associated with inflamed pulp tissue

Several other studies also support the anti-inflammatory properties of curcumin and its interaction with cytokine-mediated signaling pathways. Sadia et al. reported docking interactions between curcumin derivatives and IL-1β with favorable binding energy values, highlighting the structural compatibility of curcumin with inflammatory mediators.[26] Ghany et al. demonstrated that curcumin-based analogs interact with TNF-α and significantly reduce inflammatory cytokine levels in experimental models.[27] Similarly, Li et al. reported that curcumin derivatives inhibit IL-6 and TNF-α signaling through modulation of the JAK/STAT pathway.[28],[29] These findings suggest that curcumin may exert anti-inflammatory effects through multiple molecular mechanisms involving both direct cytokine interaction and upstream signaling pathway modulation.

In addition to molecular and cellular studies, translational and clinical investigations further support the therapeutic potential of curcumin in oral inflammatory diseases. Khalil et al. demonstrated that liposomal curcumin formulations significantly improved periodontal outcomes and reduced inflammatory cytokine levels in diabetic patients with periodontal disease.[30],[31] Similarly, Vergara et al. reported that curcumin-based delivery systems reduce IL-1β and TNF-α expression in models of oral mucositis and promote tissue healing.[32],[33], These studies highlight the translational relevance of curcumin as a potential host-modulatory therapeutic agent for inflammatory oral diseases.

Overall, the findings of the present study are consistent with the existing literature demonstrating the anti-inflammatory properties of curcumin. The stable docking interactions observed with IL-6, TNF-α, and IL-1β support the hypothesis that curcumin may interact with key cytokines involved in inflammatory signaling pathways associated with ECC. Furthermore, the strong interaction observed with MCM-2 suggests that curcumin may also influence proliferative responses within inflamed dental tissues. These observations expand the understanding of curcumin's potential role in modulating both inflammatory and proliferative molecular mechanisms involved in ECC pathogenesis. However, further experimental studies including molecular dynamics simulations, in-vitro cytokine assays, and clinical investigations are required to validate the functional significance of these computational predictions.

The present study is limited by its computational design, as molecular docking alone cannot fully replicate the complex biological environment of dental tissues. Nevertheless, the study provides valuable structural insights into the interaction between curcumin and key inflammatory and proliferative proteins associated with ECC. A major strength of this work is the combined evaluation of inflammatory cytokines and a proliferative marker, offering a broader molecular perspective of ECC pathogenesis. Future studies should incorporate molecular dynamics simulations, in-vitro cytokine assays, and in-vivo models to validate these findings and further explore the therapeutic potential of curcumin in caries-associated inflammation.

CONCLUSION

The present in-silico docking study demonstrated that curcumin exhibits favorable binding interactions with key inflammatory cytokines (IL-6, IL-1β, and TNF-α) and the proliferative marker MCM-2 associated with early childhood caries. Among the analyzed targets, the strongest interaction was observed with MCM-2, followed by IL-6, TNF-α, and IL-1β. These findings suggest that curcumin may potentially modulate both inflammatory and proliferative pathways involved in ECC progression. However, further experimental and clinical studies are required to validate these computational observations and establish the therapeutic relevance of curcumin in ECC management.

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