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Original Article

Molecular mechanism of curcumin on periodontitis: A pharmacological network study

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ABSTRACT

Objective: This study aimed to identify the molecular mechanism of curcumin on periodontitis based on a pharmacological network strategy.
Methods: The potential therapeutic targets of curcumin and differentially expressed genes in periodontitis were identified. Subsequently, we extracted the molecules in common and analyzed them. A metabolic pathway enrichment and gene ontology analysis were performed and the protein−protein interaction network was inferred. These analyses allowed the identification of key proteins. Finally, a molecular docking of the main key proteins was performed with curcumin.
Results: Our results showed that 55 genes are differentially expressed in periodontitis and are potential targets of curcumin. In addition, we observed that these genes participate in cell motility and immune response and are related to chemokine receptors (CXCRs) and enzymatic activity, such as arachidonate 5-lipoxygenase (ALOX5). We identified six key proteins, IL1B, CXCL8, CD44, MMP2, EGFR, and ITGAM; molecular docking revealed that these six proteins spontaneously bind to curcumin.
Conclusion: The results of this study helps us understand the molecular mechanism of curcumin in periodontitis. We propose that curcumin affects proinflammatory cytokines, ALOX5, and cell migration through chemokine receptors and acts on the cell membrane. Additionally, we identified six key proteins that are essential in this mechanism, all of which spontaneously bind to curcumin.

1. Introduction

Periodontitis comprises a wide range of inflammatory conditions affecting the supporting structures of the teeth (gingiva, bone, and periodontal ligament) [1]. Periodontitis is a public health problem affecting many of the world's population. In 2017 an estimated 796 million people worldwide suffered from severe periodontitis [2]. The etiology of this disease is multifactorial, and the factors involved are environmental, genetic, and microbial. Genetic factors are mainly involved in the onset of periodontitis but are influenced by environmental factors and vary according to ethnic group. Microbial infections are essential for the onset and progression of periodontitis but are modulated by the host's immune response [3].

The treatment of periodontitis can be divided into two main groups: non-surgical and surgical periodontal treatment. Scaling and root planning are considered the gold standard non-surgical treatment for periodontitis. However, when this treatment is insufficient, adjunctive therapies, such as amoxicillin and metronidazole, may be necessary [4]. Nevertheless, new adjuvant therapies have been proposed in recent years, such as antimicrobial photodynamic therapy, probiotics, prebiotics, statins, and omega-3 and 6 fatty acids, among others [5].

Another type of adjuvant therapy for the treatment of periodontitis is herbal medicine. Herbs have high overall safety and

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possess a multitude of pharmacological actions. Curcumin is a bioactive polyphenol extracted from *Curcuma longa*, which has antioxidant, antimicrobial, anti-inflammatory, analgesic, and anticancer properties [6]. The results of previous studies analyzing the effect of curcumin on periodontitis have been positive, and it has been suggested that curcumin could be used as an alternative to conventional adjuvant therapies [7,8].

The proposed mechanisms of curcumin on periodontitis are mainly antimicrobial and anti-inflammatory effects. It has been proposed that curcumin regulates inflammation by inhibiting NF-κB, JAK/STAT, and mitogen-activated protein kinase signaling pathways [9]. However, the mechanism of action of curcumin in periodontitis has not been fully elucidated; moreover, the molecular targets of curcumin have been poorly studied.

The pharmacological network is a novel strategy to identify mechanisms of action of molecules with pharmacological properties based on the idea that several effective drugs act on numerous targets instead of just one. Network pharmacology is integrative, in *silico* approach to establishing a "protein-compound/disease-gene" network [10,11]. The pharmacological network research methodology begins by identifying therapeutic targets of a given molecule, and these targets are then matched with genes or proteins differentially expressed in a given disease. A protein−protein network is constructed from these key molecules, which is analyzed to find key genes. Finally, *in vivo*, *in vitro*, or *in silico* validation is performed, for example, molecular docking [10].

Therefore, this work aimed to identify the molecular mechanism of curcumin on periodontitis based on a pharmacological network strategy.

2. Material and methods

2.1. Data acquisition

The chemical structure and SMILES (simplified molecular input line entry specification) of curcumin were obtained from the PubChem website (https://pubchem.ncbi.nlm.nih.gov/compound/969516) [12]. We then searched the interactions of curcumin in three different databases, the Swiss Target Prediction database (http://www.swisstargetprediction.ch/) [13], the Comparative Toxicogenomics Database (http://ctdbase.org/) [14], and the STITCH database (http://stitch.embl.de/) [15]. We limited the search for targets to the species "*homo sapiens*."

The target genes for periodontitis were obtained from the Gene Expression Omnibus dataset in the National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/geo/) [16]. We found three datasets related to periodontitis. The first study (GSE10334) was conducted on a total of 247 samples (from 183 diseased and 64 healthy sites) [17]. In the second study (GSE16134), gingival tissue RNA was extracted, reverse-transcribed, labeled, and hybridized with whole-genome microarrays (310 in total) [18]. In the third study (GSE23586), healthy and periodontitis-affected gingival tissues were taken from three patients with severe chronic periodontitis [19].

We identified the differentially expressed genes (DEGs) in the three datasets using the GEO2R analysis tool [16]. The cut-off criteria in this analysis were set as $p < 0.05$ and $|\log FC| > 0.5$. The intersection between curcumin targets and DEGs from the periodontitis datasets was obtained and visualized using the Venny 2.1.0 platform (https://bioinfogp.cnb.csic.es/tools/venny/).

2.2. Gene ontology (GO) and pathway enrichment analyses

The 55 common genes between the DEGs and curcumin therapeutic targets were analyzed with Shiny GO 0.76.3 (http://bioinformatics.sdstate.edu/go/) to determine applicable term enrichment [20]. Gene ontology (GO) enrichment analysis includes a biological process (BP), molecular function (MF), and cellular component (CC) analysis. Metabolic pathway enrichment was performed with the Topp Gene Suite, specifically Topp Fun (https://toppgene.cchmc.org/) [21]. The FDR (False Discovery Rate) adjustment of p-values was performed using the Benjamini-Hochberg method.

2.3. Protein−protein interaction (PPI) network analysis

The protein−protein interaction (PPI) network of target genes was obtained from the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING 11.5; https://string-db.org/) database, with the minimum required interaction score ≥ 0.4 [22]. We then visualized the network with the Cytoscape platform v3.9.1 [23], widely applied to construct and visualize the network, especially in network pharmacology analysis. In the PPI network, the nodes represent the target proteins, while the edges represent the predicted or validated interaction between the proteins. The molecular complex detection (MCODE) plugin was used to determine closely connected network components in the networks [24]. The MCODE plugin of Cytoscape with specifics containing degree cut-off = 4, node score cut-off = 0.2, haircut-off, k-core = 2, and maximum depth = 100 was performed. In addition, we identified the top 10 key genes based on their degree of connectivity.

2.4. Molecular docking simulation

We performed molecular docking studies on curcumin and potential periodontitis targets to verify the reliability of these targets. The PDB (Protein Data Bank) files of potential target proteins were downloaded from the Research Collaboratory for Structural Bioinformatics Protein Data Bank Protein Structure Database (https://www.rcsb.org/) [25]. Non-protein molecules and ligands were removed, and polar hydrogen was added and loaded. From the PubChem Organic Small Molecule Biological Dynamic Database (https://pubchem.ncbi.nlm.nih.gov/compound/969516) [12], the SDF (Spatial Data File) files of the curcumin structure were downloaded and converted into mol2 format with OpenBabel software. Finally, UCSF Chimera software, with the Autodock Vina tool, was used to perform interaction simulations between the target key proteins and curcumin [26].

3. Results

3.1. Analysis of curcumin targets and periodontitis

We obtained the structure of curcumin from PubChem (Fig. 1A). There were 675 curcumin target genes identified, while the DEGs of the datasets were 3078 for GSE10334, 3175 for GSE16134, and 4967 for GSE23586. Matching the DEGs with the curcumin targets (Fig. 1B), 55 genes were selected as potential targets for the therapeutic effect of curcumin in periodontitis.

3.2. Enrichment analysis of overlapping targets

GO enrichment analysis of the 55 target genes showed that the main enriched biological processes were related to cell motility and immune response (Fig. 2A). The main cellular components were related to the cell surface, membrane domains, receptors, and Golgi apparatus (Fig. 2B). Finally, the molecular functions enriched were related to binding to different cell receptors and enzymatic activity (Fig. 2C).

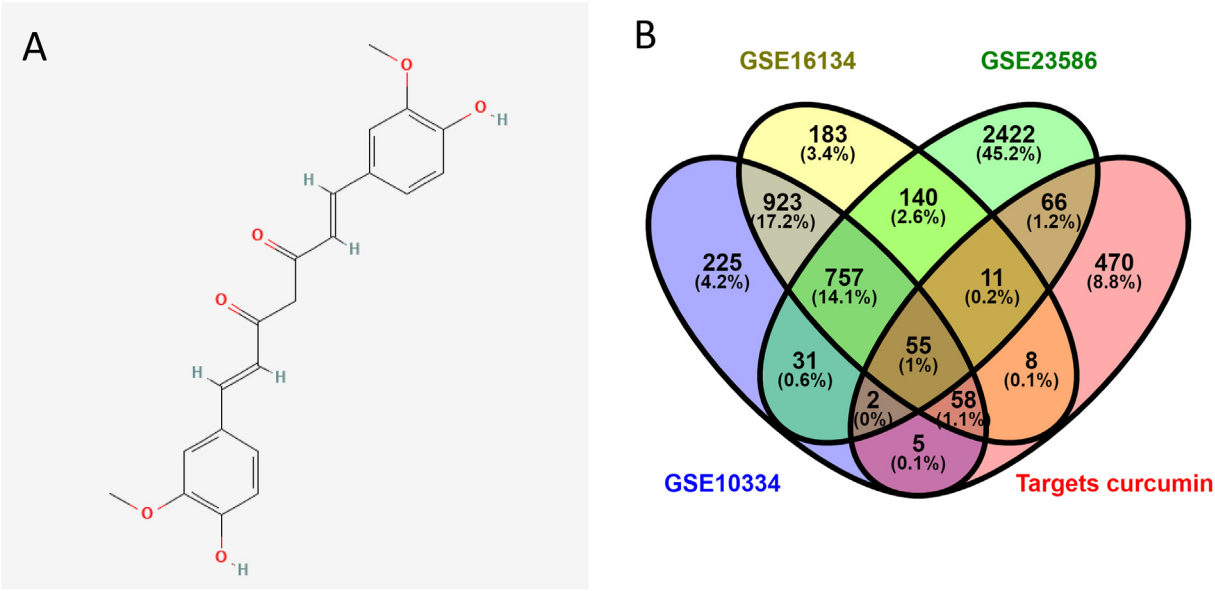

Fig. 1. Curcumin and DEGs. (A) Chemical structure of curcumin in 2D; (B) Venn diagram of the matched genes between DEGs and curcumin targets.

In the metabolic pathway enrichment analysis, most were related to the immune system, mainly cytokines and NF-kappa B. We also found the metabolic pathways of photodynamic therapy, burn wound healing, and lung fibrosis (Table 1).

3.3. PPI network and key target predictions

The PPI network was constructed by the STRING database and imported into Cytoscape. This network's nodes represent proteins, and the edges represent PPIs. The principal network presented 207 interactions among the proteins; the proteins with the most interactions were IL1B, CXCL8, CD44, MMP2, EGFR, and ITGAM, with 28, 23, 23, 20, 20, and 20 interactions of each molecule, respectively (Fig. 3A). A cluster was inferred from the principal network with the MCODE plugin. Interestingly, all six key molecules were part of this cluster (Fig. 3B).

3.4. Validation of key proteins using molecular docking

We performed a molecular docking simulation from the PPI network analysis between curcumin and the six key proteins with the most interactions (Fig. 4). The PDB IDs used in molecular docking were 1IOB, 5D14, 1POZ, 1CK7, 1M14, and 1IDN. The estimate of $\Delta G < 0$ suggests the possibility of spontaneous binding of curcumin to receptor proteins. The results showed that the ΔG of all six proteins were less than 0, indicating that they all spontaneously bind to curcumin.

4. Discussion

Periodontitis is present in a large proportion of the world's population. Although this disease has different treatments, it is not always easy to treat. Therefore, searching for new molecules and their mechanism of action to treat this disease is a growing field of study. In this work, we investigated the molecular mechanism of curcumin on periodontitis through a network pharmacology approach. Our results confirm that curcumin regulates the immune system by inhibiting inflammation, but we also found six key genes through which curcumin exerts its action. In addition, we found that the product of these genes, proteins, have a high probability of spontaneously binding to curcumin.

In this research, we found 55 genes differentially expressed in periodontitis that were also targets of curcumin. When we performed enrichment of these DEGs, we found that the primary biological processes were related to inflammation and cytokine response. The anti-inflammatory effect of curcumin and the intervention of cytokines in this process has been reported in previous research [9,27]. Similarly, a US research group previously reported that a curcuminoid compound regulates the migration of fibroblasts obtained from periodontal tissue [28].

The enrichment of cellular components showed that curcumin acts mainly on the cell surface. This result was experimentally verified when it was observed that curcumin inhibits the entry and adhesion of *Porphyromonas gingivalis* outer membrane vesicles, obtained by confocal laser scanning microscopy [29].

The DEGs in periodontitis were enriched in the molecular function of immune response-related receptors. Among these receptors is the chemokine family CXCRs, which attract immune cells to the site of infection. Curcumin has been reported to block neutrophil chemotaxis through CXCR1 and CXCR2, inhibiting IL-8 signaling [30]. Similarly, another study that employed molecular docking reported that the chemokine receptors CXCR4 and CXCR7 showed a high affinity for curcumin [31]. Arachidonate 5-lipoxygenase (ALOX5) is an enzyme involved in inflammatory processes. Some researchers have linked ALOX5 to periodontitis and the regulation of this molecule by curcumin [32–34]. However, we inferred that ALOX5 participates in the molecular mechanism of curcumin in periodontitis. Therefore, our results show that curcumin inhibits proinflammatory cytokines, ALOX5, and cell migration through chemokine receptors acting on the cell membrane.

We also inferred that DEGs bind insulin-like growth factor II (IGF2) to curcumin. Other studies have shown that curcumin regulates IGF2 in cancer [35,36]. However, what is most interesting is that IGF2 is involved in the development of the periodontal ligament, as well as in the formation of dentin [37,38]. Consequently, curcumin, through IGF2, may regulate periodontal ligament development and dentin formation. Metalloendopeptidases are metalloproteinases (MMPs) that are most active in the progression of periodontitis. We found that curcumin regulates these enzymes'

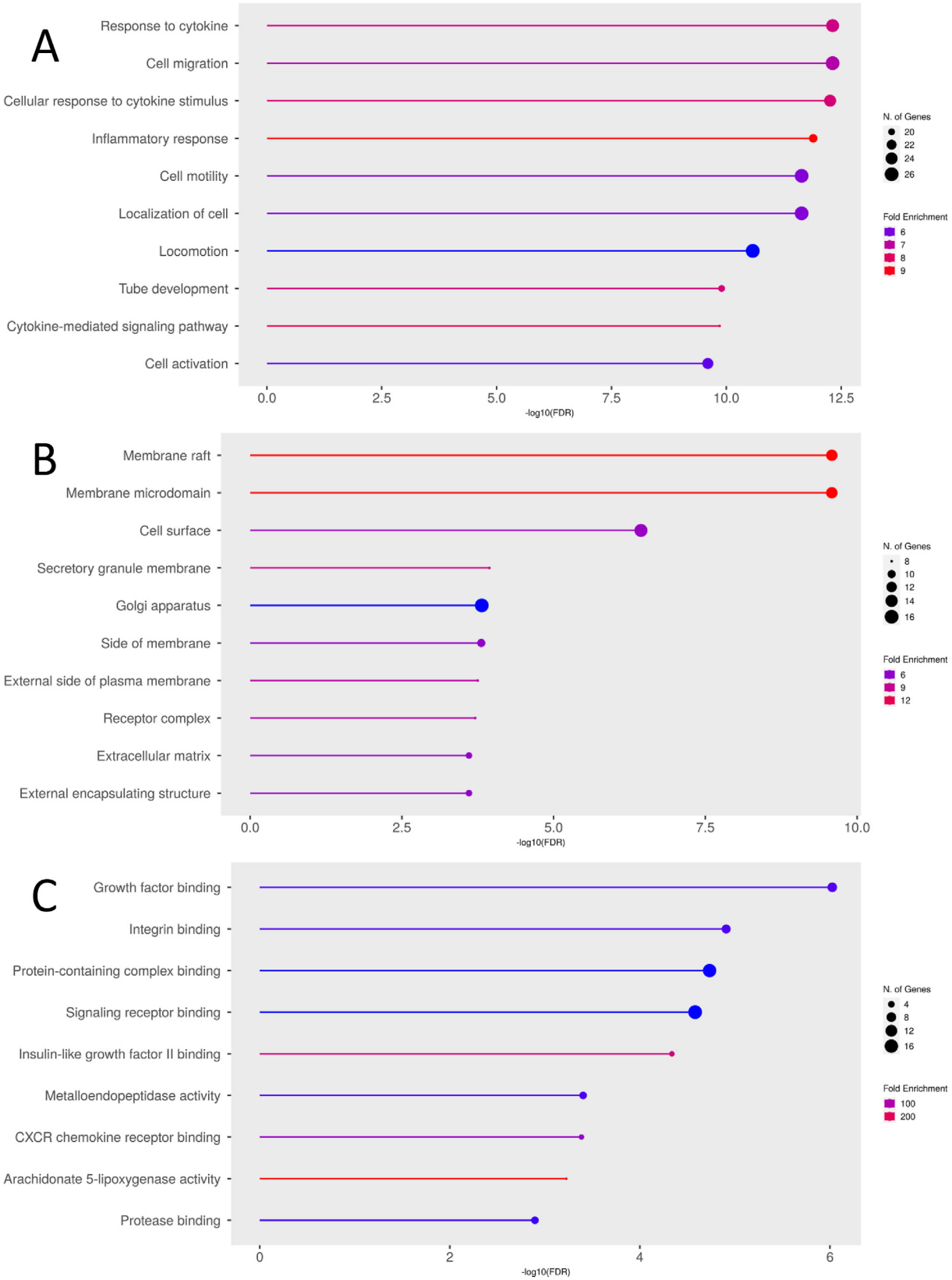

Fig. 2. Gene ontology (GO) enrichment analysis for target genes (top 10). (A) Biological process; (B) Cellular component; (C) Molecular function.

Table 1
Top 10 results for the pathway enrichment analysis of key targets.

Metabolic pathway name	ID	Source	p-value FDR B&H	Hit in Query List
Interleukin-4 and 13 signaling	1,470,923	BioSystems: REACTOME	1.767E-11	VIM, IL18, TIMP1, CD36, MMP2, TNFRSF1B, MMP9, IL1B, ITGAM, ALOX5, VCAM1, CXCL8
Photodynamic therapy-induced NF-kB survival signaling	M39529	MSigDB C2 BIOCARTA (v7.5.1)	4.058E-10	BIRC3, BCL2A1, MMP2, MMP9, IL1B, CXCL2, VCAM1, CXCL8
Burn wound healing	M42571	MSigDB C2 BIOCARTA (v7.5.1)	4.872E-09	VIM, TIMP1, PDGFRB, CXCR4, KDR, MMP2, MMP9, IL1B, CXCL12, CXCL8
Signaling by Interleukins	1,269,318	BioSystems: REACTOME	2.966E-08	VIM, IL18, EGFR, TIMP1, PDGFRB, CD36, MMP2, TNFRSF1B, MMP9, IL1B, ITGAM, CXCL2, HCK, ALOX5, VCAM1, CXCL8
Cytokine Signaling in Immune System	1,269,310	BioSystems: REACTOME	6.935E-08	VIM, IL18, EGFR, TIMP1, PDGFRB, CD36, CD44, BIRC3, MMP2, TNFRSF1B, MMP9, IL1B, ITGAM, CXCL2, HCK, ALOX5, VCAM1, CXCL8
NF-kappa B signaling pathway	634,527	BioSystems: KEGG	5.83E-07	CD14, BIRC3, BCL2A1, IL1B, CXCL2, CXCL12, VCAM1, CXCL8
Lung fibrosis	M39477	MSigDB C2 BIOCARTA (v7.5.1)	7.222E-07	TIMP1, NFE2L2, MMP2, MMP9, IL1B, CXCL2, CXCL8
Cytokine–cytokine receptor interaction	M9809	MSigDB C2 BIOCARTA (v7.5.1)	7.409E-07	IL18, EGFR, PDGFRB, CXCR4, KDR, TNFRSF10C, TNFRSF1B, IL1B, CXCL2, CXCL12, CXCL8
Cytokine–cytokine receptor interaction	83,051	BioSystems: KEGG	8.003E-07	IL18, EGFR, PDGFRB, CXCR4, KDR, TNFRSF10C, TNFRSF1B, IL1B, CXCL2, CXCL12, CXCL8
IL-18 signaling pathway	M39818	MSigDB C2 BIOCARTA (v7.5.1)	1.013E-06	PTPN7, IL18, TIMP1, CD36, BIRC3, MMP2, MMP9, IL1B, MMP14, CXCL2, CXCL8

activity, a result reported experimentally in previous studies [39,40].

Enrichment of the signaling pathways confirmed that the molecular mechanism of curcumin on periodontitis involves cytokines acting through NF-kappa B. The effect of curcumin on IL-4 and IL-8 cytokines in periodontitis has been previously reported [30,41]. Regarding IL-13 studies show that curcumin increases IL-13 expression, and this cytokine is associated with periodontitis [42,43].

After gene enrichment, we inferred the PPI network, and from this network, we identified key genes based on the degree of connectivity. The cutoff point was 20 interactions or more. In addition, we verified these key molecules through molecular docking. We found six key molecules: IL1B, CXCL8, CD44, MMP2, EGFR, and ITGAM.

IL1B is a proinflammatory cytokine widely associated with periodontitis. Two previous studies in which curcumin was used in a gel form showed that curcumin treatment decreased serum and salivary IL1B levels. IL-8 and CD44 are other molecules associated with periodontitis and regulated by curcumin. However, in a study performed in osteoblasts and stimulated with a *P. gingivalis* protein, curcumin could not regulate IL-8 [44]. To the best of our knowledge, no work has been reported investigating the effect of curcumin on CD44 in periodontitis. However, the idea that curcumin

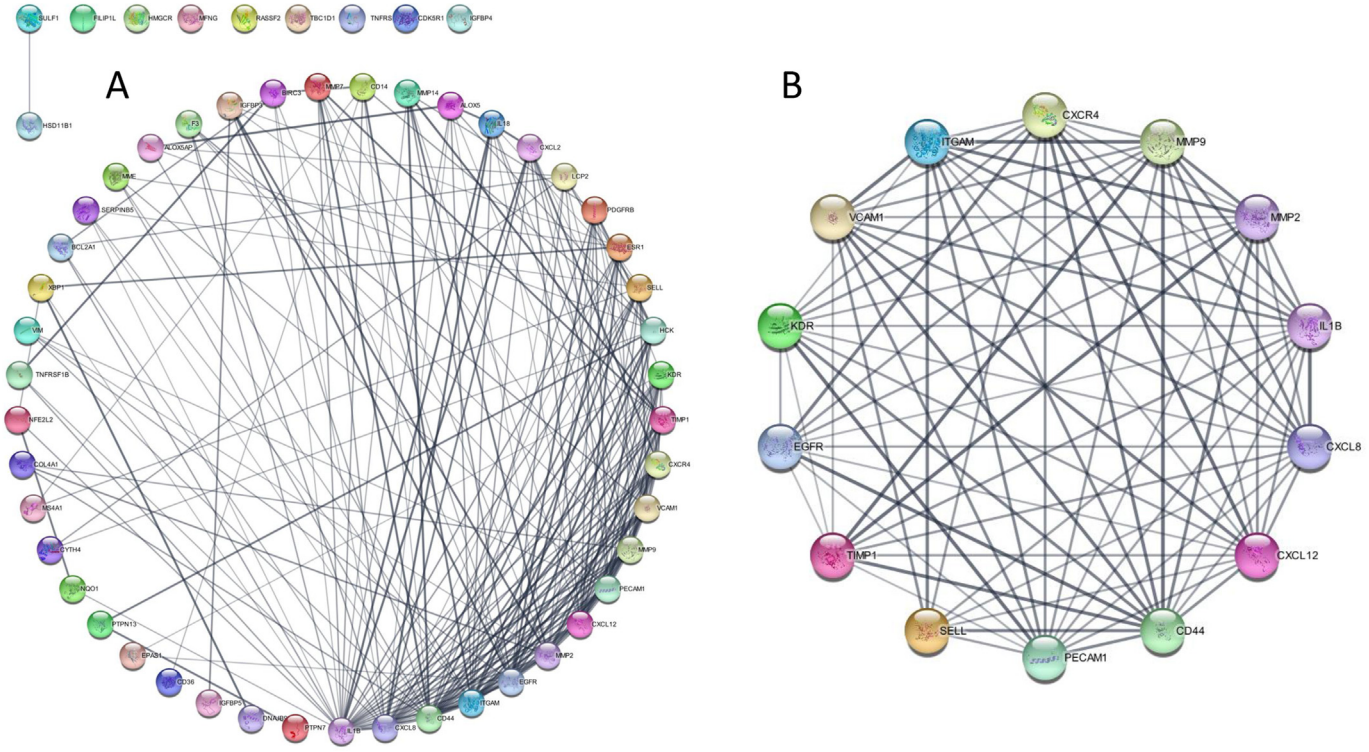

Fig. 3. PPI network. (A) PPI principal network constructed with the match targets; (B) Cluster obtained with the MCODE plugin.

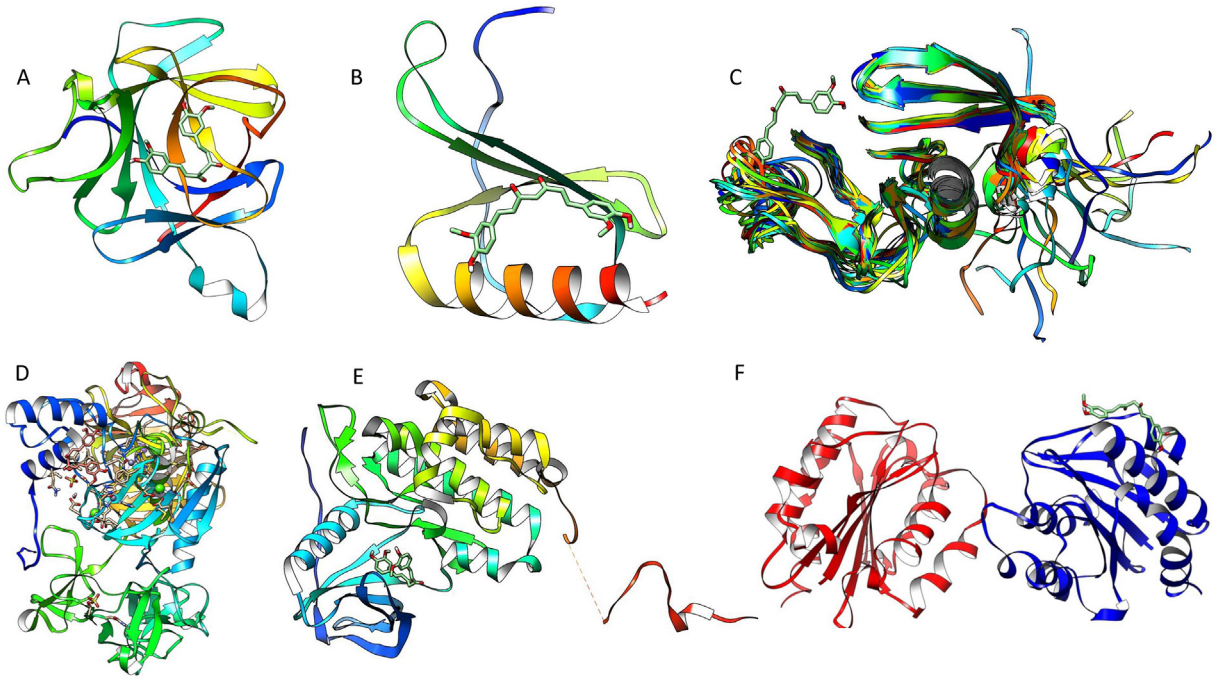

Fig. 4. Schematic diagram of the interaction of curcumin and related targets. (A) IL1B, ΔG = −6.9 kcal/mol; (B) CXCL8, ΔG = −6.6 kcal/mol; (C) CD44, ΔG = −6.6 kcal/mol; (D) MMP2, ΔG = −7.1 kcal/mol; (E) EGFR, ΔG = −7.1 kcal/mol; (F) ITGAM, ΔG = −6.8 kcal/mol.

regulates inflammation in periodontitis through IL-8 and CD44 is feasible. Therefore, testing this hypothesis experimentally is very interesting.

MMP2 is an enzyme that plays an essential role in developing periodontitis. Several reports show that molecules modified from curcumin decrease MMP2 levels in different models of periodontitis [39,45,46]. In contrast, curcumin increased the expression of integrin alpha M (ITGAM) in a murine model of periodontitis; and with respect to EGFR, curcumin inhibited its phosphorylation causing the inhibition of the signaling pathway, in human gingival fibroblasts [47,48].

This research shows valuable information on the molecular mechanism of curcumin on periodontitis. However, like most studies based on bioinformatics analysis, it has several limitations. The first is because the databases in this work infer the mechanisms in which the analyzed molecules participate; therefore, it is necessary to verify the results experimentally. Other points to be analyzed are the dose-response relationship and the route of administration of curcumin. Finally, it is also necessary to consider the pharmacokinetics of curcumin and its possible interactions with other molecules, such as drugs and food.

5. Conclusion

In conclusion, our work helps to understand the molecular mechanism of curcumin on periodontitis. We propose that curcumin inhibits proinflammatory cytokines, the enzyme ALOX5, and the process of cell migration through chemokine receptors on the cell membrane. In addition, six key proteins (IL1B, CXCL8, CD44, MMP2, EGFR, and ITGAM) are essential in this mechanism, all of which spontaneously bind curcumin.

Data availability statement

The data used to support the conclusions of this study can be found in the article itself.

Ethics approval statement

No humans/animals were used for studies that are the basis of this research.

Funding statement

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CRediT authorship contribution statement

JM Guzmán-Flores: Conceptualization, Methodology, Software. **JM Guzmán-Flores, CM Arevalo-Caro, F Martínez-Esquivias, MA Isiordia-Espinoza, L Franco-de la Torre**: Data curation, Writing-Original draft preparation. **JM Guzmán-Flores, CM Arevalo-Caro, F Martínez-Esquivias, MA Isiordia-Espinoza, L Franco-de la Torre:** Writing- Reviewing and Editing.

Conflict of interest

The authors declared that they had no conflict of interests.

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References

[1] Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Prim 2017;3:17038.
[2] Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B, Almas K. Global prevalence of periodontal disease and lack of its surveillance. Sci World J 2020;2020:2146160.

[3] Becerra-Ruiz JS, Guerrero-Velazquez C, Martinez-Esquivias F, Martinez-Perez LA, Guzman-Flores JM. Innate and adaptive immunity of periodontal disease. From etiology to alveolar bone loss. Oral Dis 2022;28:1441–7.
[4] Fischer RG, Lira Junior R, Retamal-Valdes B, Figueiredo LC, Malheiros Z, Stewart B, et al. Periodontal disease and its impact on general health in Latin America. Section V: treatment of periodontitis. Braz Oral Res 2020;34:e026.
[5] Haas AN, Furlaneto F, Gaio EJ, Gomes SC, Palioto DB, Castilho RM, et al. New tendencies in non-surgical periodontal therapy. Braz Oral Res 2021;35:e095.
[6] Giordano A, Tommonaro G. Curcumin and cancer. Nutrients 2019;11.
[7] Terby S, Shereef M, Ramanarayanan V, Balakrishnan B. The effect of curcumin as an adjunct in the treatment of chronic periodontitis: a systematic review and meta-analysis. Saudi Dent J 2021;33:375–85.
[8] Forouzanfar F, Forouzanfar A, Sathyapalan T, Orafai HM, Sahebkar A. Curcumin for the management of periodontal diseases: a review. Curr Pharmaceut Des 2020;26:4277–84.
[9] Li Y, Jiao J, Qi Y, Yu W, Yang S, Zhang J, et al. Curcumin: a review of experimental studies and mechanisms related to periodontitis treatment. J Periodontal Res 2021;56:837–47.
[10] Noor F, Tahir Ul Qamar M, Ashfaq UA, Albutti A, Alwashmi ASS, Aljasir MA. Network pharmacology approach for medicinal plants: review and assessment. Pharmaceuticals 2022;15.
[11] Yuan Z, Pan Y, Leng T, Chu Y, Zhang H, Ma J, et al. Progress and prospects of research ideas and methods in the network pharmacology of traditional Chinese medicine. J Pharm Pharmaceut Sci 2022;25:218–26.
[12] Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Res 2021;49:D1388–95.
[13] Daina A, Michielin O, Zoete V. Swiss Target Prediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res 2019;47:W357–64.
[14] Davis AP, Wiegers TC, Johnson RJ, Sciaky D, Wiegers J, Mattingly CJ. Comparative Toxicogenomics database (CTD): update 2023. Nucleic Acids Res 2022;51:D1257–62.
[15] Szklarczyk D, Santos A, von Mering C, Jensen LJ, Bork P, Kuhn M. Stitch 5: augmenting protein-chemical interaction networks with tissue and affinity data. Nucleic Acids Res 2016;44:D380–4.
[16] Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, et al. NCBI GEO: archive for functional genomics data sets–update. Nucleic Acids Res 2013;41:D991–5.
[17] Demmer RT, Behle JH, Wolf DL, Handfield M, Kebschull M, Celenti R, et al. Transcriptomes in healthy and diseased gingival tissues. J Periodontol 2008;79:2112–24.
[18] Kebschull M, Demmer RT, Grun B, Guarnieri P, Pavlidis P, Papapanou PN. Gingival tissue transcriptomes identify distinct periodontitis phenotypes. J Dent Res 2014;93:459–68.
[19] Abe D, Kubota T, Morozumi T, Shimizu T, Nakasone N, Itagaki M, et al. Altered gene expression in leukocyte transendothelial migration and cell communication pathways in periodontitis-affected gingival tissues. J Periodontal Res 2011;46:345–53.
[20] Ge SX, Jung D, Yao R. ShinyGO: a graphical gene-set enrichment tool for animals and plants. Bioinformatics 2020;36:2628–9.
[21] Chen J, Bardes EE, Aronow BJ, Jegga AG. ToppGene Suite for gene list enrichment analysis and candidate gene prioritization. Nucleic Acids Res 2009;37:W305–11.
[22] Szklarczyk D, Gable AL, Nastou KC, Lyon D, Kirsch R, Pyysalo S, et al. The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Res 2021;49:D605–12.
[23] Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003;13:2498–504.
[24] Bader GD, Hogue CW. An automated method for finding molecular complexes in large protein interaction networks. BMC Bioinf 2003;4:2.
[25] Burley SK, Bhikadiya C, Bi C, Bittrich S, Chen L, Crichlow GV, et al. RCSB Protein Data Bank: powerful new tools for exploring 3D structures of biological macromolecules for basic and applied research and education in fundamental biology, biomedicine, biotechnology, bioengineering and energy sciences. Nucleic Acids Res 2021;49:D437–51.
[26] Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, et al. UCSF Chimera–a visualization system for exploratory research and analysis. J Comput Chem 2004;25:1605–12.
[27] Justo MP, Cardoso CBM, Cantiga-Silva C, de Oliveira PHC, Sivieri-Araujo G, Azuma MM, et al. Curcumin reduces inflammation in rat apical periodontitis. Int Endod J 2022;55:1241–51.
[28] San Miguel SM, Opperman LA, Allen EP, Zielinski J, Svoboda KK. Bioactive antioxidant mixtures promote proliferation and migration on human oral fibroblasts. Arch Oral Biol 2011;56:812–22.
[29] Izui S, Sekine S, Murai H, Takeuchi H, Amano A. Inhibitory effects of curcumin against cytotoxicity of Porphyromonas gingivalis outer membrane vesicles. Arch Oral Biol 2021;124:105058.
[30] Takahashi M, Ishiko T, Kamohara H, Hidaka H, Ikeda O, Ogawa M, et al. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) blocks the chemotaxis of neutrophils by inhibiting signal transduction through IL-8 receptors. Mediat Inflamm 2007;2007:10767.
[31] Murad HAS, Alqurashi TMA, Hussien MA. Interactions of selected cardiovascular active natural compounds with CXCR4 and CXCR7 receptors: a molecular docking, molecular dynamics, and pharmacokinetic/toxicity prediction study. BMC Complement Med Ther 2022;22:35.
[32] Paula-Silva FWG, Arnez MFM, Petean IBF, Almeida-Junior LA, da Silva RAB, da Silva LAB, et al. Effects of 5-lipoxygenase gene disruption on inflammation, osteoclastogenesis and bone resorption in polymicrobial apical periodontitis. Arch Oral Biol 2020;112:104670.
[33] Lin L, Yu W, Zhang W, Li S, Hu S, Jiang B, et al. Expression profile of lipoxygenases in gingival tissues of human periodontitis. Oral Dis 2021;27:567–76.
[34] Hong J, Bose M, Ju J, Ryu JH, Chen X, Sang S, et al. Modulation of arachidonic acid metabolism by curcumin and related beta-diketone derivatives: effects on cytosolic phospholipase A(2), cyclooxygenases and 5-lipoxygenase. Carcinogenesis 2004;25:1671–9.
[35] Xue L, Tao Y, Yuan Y, Qu W, Wang W. Curcumin suppresses renal carcinoma tumorigenesis by regulating circ-FNDC3B/miR-138-5p/IGF2 axis. Anti Cancer Drugs 2021;32:734–44.
[36] Tian B, Zhao Y, Liang T, Ye X, Li Z, Yan D, et al. Curcumin inhibits urothelial tumor development by suppressing IGF2 and IGF2-mediated PI3K/AKT/mTOR signaling pathway. J Drug Target 2017;25:626–36.
[37] Konermann A, Lossdorfer S, Jager A, Chen Y, Gotz W. Autoregulation of insulin-like growth factor 2 and insulin-like growth factor-binding protein 6 in periodontal ligament cells in vitro. Ann Anat 2013;195:527–32.
[38] He P, Zheng L, Zhou X. IGFs in dentin formation and regeneration: progress and remaining challenges. Stem Cell Int 2022;2022:3737346.
[39] Bosca AB, Ilea A, Soritau O, Tatomir C, Miklasova N, Parvu AE, et al. Modulatory effect of curcumin analogs on the activation of metalloproteinases in human periodontal stem cells. Eur J Oral Sci 2019;127:304–12.
[40] Guru SR, Kothiwale SV, Saroch N, Guru RC. Comparative evaluation of inhibitory effect of curcumin and doxycycline on matrix metalloproteinase-9 activity in chronic periodontitis. Indian J Dent Res 2017;28:560–5.
[41] Correa MG, Pires PR, Ribeiro FV, Pimentel SZ, Casarin RC, Cirano FR, et al. Systemic treatment with resveratrol and/or curcumin reduces the progression of experimental periodontitis in rats. J Periodontal Res 2017;52:201–9.
[42] Gao S, Zhou J, Liu N, Wang L, Gao Q, Wu Y, et al. Curcumin induces M2 macrophage polarization by secretion IL-4 and/or IL-13. J Mol Cell Cardiol 2015;85:131–9.
[43] Majumder P, Panda SK, Ghosh S, Dey SK. Interleukin gene polymorphisms in chronic periodontitis: a case-control study in the Indian population. Arch Oral Biol 2019;101:156–64.
[44] Lin HH, Lin YW, Wu CY, Hsiao FP, Lai YL, Hung SL. Stimulatory effects of Porphyromonas gingivalis GroEL protein on interleukin-6 and interleukin-8 in human osteoblasts. J Formos Med Assoc 2021;120:150–6.
[45] Elburki MS, Moore DD, Terezakis NG, Zhang Y, Lee HM, Johnson F, et al. A novel chemically modified curcumin reduces inflammation-mediated connective tissue breakdown in a rat model of diabetes: periodontal and systemic effects. J Periodontal Res 2017;52:186–200.
[46] Deng J, Golub LM, Lee HM, Lin MC, Bhatt HD, Hong HL, et al. Chemically-modified curcumin 2.24: a novel systemic therapy for natural periodontitis in dogs. J Exp Pharmacol 2020;12:47–60.
[47] Perez-Pacheco CG, Fernandes NAR, Camilli AC, Ferrarezi DP, Silva AF, Zunareli MC, et al. Local administration of curcumin-loaded nanoparticles enhances periodontal repair in vivo. Naunyn-Schmiedeberg's Arch Pharmacol 2022;396:311–21.
[48] Smith PC, Santibanez JF, Morales JP, Martinez J. Epidermal growth factor stimulates urokinase-type plasminogen activator expression in human gingival fibroblasts. Possible modulation by genistein and curcumin. J Periodontal Res 2004;39:380–7.