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Original article

Confirmation of the potential mechanism of pentagamavunon-0 against temporomandibular arthritis using bioinformatic approaches

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ABSTRACT

Background: *Non-steroidal anti-inflammatory drugs (NSAID) are widely used in temporomandibular joint osteoarthritis management. However, the side effects of NSAIDs on multiple organs need to be anticipated. Curcumin is known for its anti-inflammatory and analgesic potential, comparable to that of NSAIDs. In a previous study, structurally modified curcumin increased the pharmacological effect and simultaneously reduced the toxicity and side effects of curcumin. Pentagamavunon-0 (PGV-0) is one of the active components synthesized by the structure modification of curcumin.* ***Purpose:*** *In this study, we identify the potential target of PGV-0 on the pathogenesis of temporomandibular arthritis characterized by inflammation.* ***Methods:*** *We used a bioinformatics approach to compare the PGV-0 target with curcumin and diclofenac sodium as controls. We identified overlapping gene targets of bioactive compounds (PGV-0, curcumin, or diclofenac sodium) retrieved from the SwissTargetPrediction and GeneCards platforms, specifically for temporomandibular arthritis. An interaction model among targets was developed using the STRING database and Gene Ontology Panther to expound on the bioactive compound's function on the key signaling pathway. Finally, we formulated a molecular docking prediction between the bioactive compound and the target protein marker derived from the previous analysis using Molecular Operating Environment tools.* ***Results:*** *This study found that curcumin and PGV-0 targeted different molecular pathways in temporomandibular arthritis compared to diclofenac sodium. Curcumin and PGV-0 shared a similar pathway to curcumin by modulating metalloproteinases (MMPs), especially MMP-9 and MMP-13. Moreover, diclofenac sodium influenced cyclooxygenase metabolism.* ***Conclusion:*** *In this study, PGV-0 targeted metalloproteinase in temporomandibular arthritis pathogenesis. This finding underlines the PGV-0 advantage in preventing metalloproteinase-related tissue damage in temporomandibular arthritis.*

Keywords: *Anti-inflammatory agent; cyclooxygenase; curcumin; diclofenac sodium; chronic inflammation; metalloproteinase*
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INTRODUCTION

Pain in the oral and maxillofacial area is commonly derived from the tooth or the temporomandibular joint (TMJ). Patients with TMJ disorder report light pain to severe dysfunction that plausibly debilitates wellness. A meta-analysis study indicated the worldwide prevalence of TMJ disorder in adults/elderly (aged 20–75 years) and children/adolescents (aged 7–19 years) as 31.1% and 11.3%, respectively.[1] In Indonesia, pain-related TMJ disorder is found in 23.4% (95% CI = 20–27) of children and 36.9% of adolescents (95% CI = 33–41).[2] A systematic review of 86 clinical and in vivo studies reported a common finding among them on the increase of inflammation cytokines and inflammatory markers—including interleukin (IL)-1β, IL-2, IL-6, IL-8, and IL-10, tumor necrosis factor alpha (TNF-α), and bradykinin—in the synovial fluid of individuals with TMJ disorder.[3]

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The most common TMJ disorder is osteoarthritis (OA), a form of arthritis characterized by a chronic degeneration of joint tissue. Clinically, patients with TMJ-OA report pain, limited movement, and destruction of cartilage tissue that is likely accompanied by bone absorption.[3–5] These pathologic events in TMJ-OA are known to be associated with chronic inflammation of joint tissue.[5,6] Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) that is widely prescribed to reduce pain and inflammation in the temporomandibular disorder. Long-term use of NSAIDs causes side effects on the gastrointestinal, cardiovascular, hepatic, renal, cerebral, and pulmonary organs.[7–11] As an alternative natural ingredient to NSAIDs, curcumin has been proven to have anti-inflammatory potential in TMJ-OA.[10,12] However, the compound is unstable and strongly influenced by environmental pH and light. Furthermore, curcumin has low oral bioavailability because of its low solubility in aqueous solutions, instability in metabolic processes, and difficulty in absorbing.[13]

Pentagamavunon-0 (PGV-0) or 2,5-bis(4'-hydroxy-3-methoxybenzylidine) cyclopentanone is an analog of curcumin (1,7-bis-[4'-hydroxy-3-methoxyphenyl]-hepta-1,6-diene-3,5-dione). The PGV-0 synthesis increases curcumin's water solubility and stability at pH > 6.5. This molecule has vast biological properties, such as anti-inflammatory, antioxidant, and antimicrobial properties. The anti-inflammatory property of PGV-0 is reportedly similar to or better than that of curcumin.[14–16] Therefore, we postulated that PGV-0 would work as an anti-inflammatory agent in temporomandibular arthritis. However, no previous research has reported the potential target of the PGV-0 in temporomandibular arthritis.

This study thus aimed to identify the potential target of PGV-0 on the pathogenesis of temporomandibular arthritis characterized by inflammation. We elucidate the potential target of PGV-0 in temporomandibular arthritis by using a bioinformatics approach to analyze, identify, and interpret biomarkers and therapeutic targets of PGV-0. As a comparison, we also analyze diclofenac sodium ($C_{14}H_{11}Cl_2NO_2$) as a commonly used anti-inflammatory and curcumin as the analog of PGV-0. Based on the bioinformatics findings, we perform molecular docking against several target enzymes involved in TMJ diseases to confirm the target interaction. The information from this in silico study provides a scientific basis for designing future research that involves an in vitro/in vivo approach. An in silico method using the Molegro Virtual Docker program was employed to investigate the anti-inflammatory effects of curcuminoids, turmeric extracts with zinc oxide, and eugenol before an in vivo experiment.[17]

MATERIALS AND METHODS

The chemical structure of PGV-0 was represented using the Simplified Molecular Input Line Entry System (SMILES) code as follows: COC1=CC(\C=C2/CC\C(=C/C3=CC(OC)=C(O)C=C)C2=O)=CC=C1O. The canonical SMILES string was then inputted into SwissTargetPrediction, restricting predictions to human protein targets. Bioactive compounds with similar predicted targets as PGV-0 were identified from the SwissTargetPrediction program (http://www.swisstargetprediction.ch/, 2019 version), along with curcumin and diclofenac sodium as reference compounds.

We identified potential targets by searching for "temporomandibular arthritis" in GeneCards (https://www.genecards.org/), which provides comprehensive molecular information about drugs, targets, disease-related genes, and gene function. We selected the top 321 genes generated in GeneCards. A Venn diagram was created to determine the overlap between the potential targets of each compound and the genes expressed in arthritis. The overlaps were identified as potential targets.

The interaction landscape between the overlapping genes of temporomandibular arthritis and the molecular targets of PGV-0, curcumin, and diclofenac sodium was constructed using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database (version 11.0b). The required confidence score was set at 0.700 (high confidence). Active interaction sources included text mining, experiments, databases, co-expression, neighborhood, gene fusion, and co-occurrence. The molecular action view visualized the predicted associations.

We examined the upstream and downstream genes of the main signaling pathways that link PGV-0, curcumin, and diclofenac sodium to temporomandibular arthritis using the Gene Ontology (GO) Panther Mapper system (https://www.genome.jp/kegg/mapper.html). Furthermore, we used the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database to present our knowledge of the molecular interaction, reaction, and relationship networks for metabolism, genetic information processing, and cellular processes of PGV-0 and temporomandibular arthritis. This was performed to identify the top 10 pathways most influenced. We used WebGestalt[18] (http://www.webgestalt.org/) and selected overrepresentation enrichment analysis (ORA) for the enrichment analysis using the KEGG pathway database and functional annotation terms using GO databases (false discovery rate <0.05 was selected as the threshold).

We used the Molecular Operating Environment (MOE) program (version 2010.12) with default settings to generate the molecular interactions between the ligand and receptor (unless stated otherwise). The structure of diclofenac sodium, curcumin, and PGV-0 was drawn using the program's compound builder. The conformational structure was then explored. Mitogen-activated protein kinase-1 (MAPK-1, PDB-ID: 5BVD), matrix metallopeptidase 13 (MMP-13, PDB-ID: 4JPA), cyclooxygenase-1 (COX-1, PDB-ID: 5WBE), and cyclooxygenase-2 (COX-2, PDB-ID: 3LN1) were chosen as the protein targets in this study. The docking protocol of Hasbiyani et al. (2021) was followed. The ligand conformation with the lowest docking score was analyzed for the binding interaction.[19]

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RESULTS

Initially, we identified a total of 321 genes associated with temporomandibular arthritis from the GeneCards database. Following this, the potential targets of the intended compounds were retrieved from SwissTargetPrediction, resulting in 58 genes related to diclofenac sodium and 100 genes for each of curcumin and PGV-0. From the obtained data, we described the logical relationships between the finite sets of genes associated with temporomandibular arthritis, diclofenac sodium, curcumin, and PGV-0 in Venn diagrams (Figure 1). The Venn diagram intersection ruled out 8 genes as targets of diclofenac sodium and 6 genes as targets of curcumin and PGV-0 in temporomandibular arthritis.

The common target shared by diclofenac sodium, curcumin, and PGV-0 is PTGS1, which encodes the COX-1 enzyme. COX-1 catalyzes the first step in synthesizing prostaglandins from arachidonic acid. Initial perspectives viewed PTGS1 as a constitutively expressed housekeeping gene, in contrast to the inducible PTGS2 (COX-2) enzyme, which mediates pathological inflammatory responses.[20] While PTGS2 has been the therapeutic target for developing anti-inflammatory drugs, emerging evidence suggests PTGS1 also contributes to regulating inflammation.

Our study results showed diclofenac sodium's potential drawbacks due to its influence on genes regulating hormonal function. The HTR2A, ESR2, and DRD4 genes encode the receptors of serotonin, estrogen, and dopamine, respectively (National Library of Medicine – NIH, USA). Moreover, curcumin also targets DRD4 genes, implying the possibility of influencing neurological function. Unlike diclofenac sodium and curcumin, PGV-0 is not shown to be related to hormone-related genes. The molecular targets, such as TNF-α, BLC-2, and LYN genes, are not aimed at diclofenac sodium and curcumin. These genes are related to the innate and adaptive immune response in terms of playing roles in the apoptosis regulation of lymphocytes (BLC-2), mast cell degranulation (LYN), and pro-inflammatory cytokines (TNF-α).

Compared to PGV-0, curcumin dominates in molecular targets involved in extracellular degradation. This is shown by its interaction with MMP-3 and MMP-8, which are not present as targets of PGV-0. On the other hand, PGV-0 also targets TNF genes, which are important for proinflammatory cytokine synthesis. These results indicate that the slight difference in the molecular structure of PGV-0 to curcumin leads to the possibility of distinct targets of PGV-0 for temporomandibular arthritis.

We curated temporomandibular arthritis to determine each gene's interaction with diclofenac sodium, curcumin, and PGV-0 and then visualized the network through STRING web tools. Protein–protein interactions between diclofenac sodium, curcumin, PGV-0, and inflammatory targets were predicted using STRING v11.0. STRING analyzes known and predicted protein–protein associations with direct (physical) and indirect (functional) evidence. We searched for interactions between each gene associated with diclofenac sodium (Drugbank ID: DB01097), curcumin (PubChem CID: 969516), or PGV-0 (no identifier, structure formula provided), and inflammatory targets MMP-3 (P08254), MMP-13 (P45452), IL-1β (P01584), TNF-α (P01375), and NF-kB (P19838).

We outlined three types of gene interaction in diclofenac sodium, curcumin, and PGV-0, including co-expression, co-occurrence, and insignificant association. *Co-expression* indicates that two proteins show similar expression patterns across conditions; they are often involved in similar biological processes and pathways. *Co-occurrence* means two proteins are often mentioned together in scientific literature; they are often studied together and may interact or be part of the same biological processes and pathways. *Insignificant* means there is no significant evidence that the two proteins interact or are functionally associated based on the data sources in STRING.

The interaction network model (Figure 2) indicated that diclofenac sodium targeted inflammatory-related protein synthesis. Meanwhile, curcumin and PGV-0 gene interactions were more related to the matrix extracellular degradation via MMP regulation. MMPs are involved

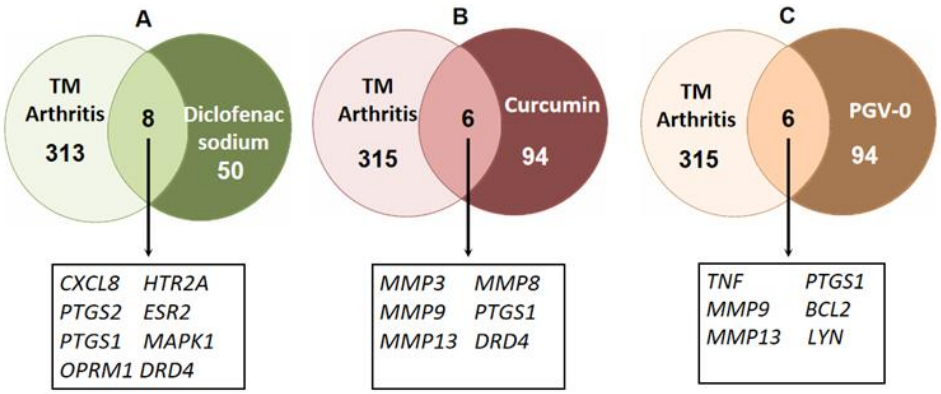

Figure 1. The estimated number of target genes of (A) diclofenac sodium, (B) curcumin, and (C) pentagamavunon-0 (PGV-0) based on the intersection between associated genes in temporomandibular (TM) arthritis collected from GeneCards and prediction targets of each compound from SwissTargetPrediction.

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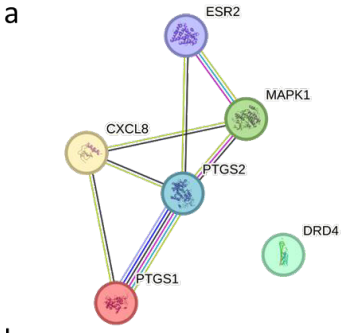
in extracellular matrix degradation, leading to cartilage destruction in arthritis, including temporomandibular arthritis. Specifically, MMP-9 and MMP-13 mediate pathological processes resulting in the degradation of collagen and the onset of inflammatory symptoms in temporomandibular arthritis patients.[21–23]

The results of the GO Panther analysis also support this hypothesis. According to this analysis, the genes associated with diclofenac sodium, curcumin, or PGV-0 that overlap with temporomandibular arthritis contributed to several molecular functions, biological processes, and cellular components (Figure 3).

The GO Panther study showed that in the molecular function category, diclofenac sodium, curcumin, and PGV-0 correlated with 10 molecular functions. The intermolecular binding activity in diclofenac sodium showed the highest percentage, followed by catalytic activity and molecular transducer activity. Curcumin and PGV-0 are dominated by cytoskeletal motor activity, continued by catalytic and molecular transducer activities. In biological process categories, diclofenac sodium predominates cellular processes, biological function, and stimulus response. Curcumin and PGV-0 play a more significant role in immune, cellular, and localization processes. Based on the cellular component category, all three substances work to dominate cellular anatomical entities.

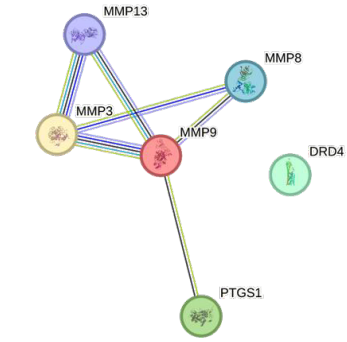
Curcumin and PGV-0 influence identical pathways in temporomandibular arthritis (Figure 4). Both substances were found to have the highest activity in the neuroinflammatory response. Curcumin alleviates neuroinflammation by suppressing TNF-α, IL-1β, nitric oxide, and NF-κB gene expression.[24] However, more evidence is needed to highlight PGV-0 action against neuroinflammation. Unlike diclofenac sodium, curcumin and PGV-0 consistently showed a strong relationship with extracellular matrix metabolism, including collagen processing and binding,

a



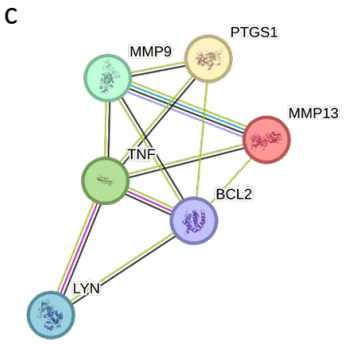
Gene 1	Gene 2	Known Interaction
ESR2	*MAPK1*	insignificant
ESR2	*PTSG2*	co-expression
MAPK1	*PTSG2*	insignificant
MAPK1	*CXCR8*	co-expression
PTSG2	*CXCR8*	co-expression
PTSG2	*PTSG1*	co-expression
CXCR8	*PTSG1*	co-expression

b



Gene 1	Gene 2	Known Interaction
MMP13	*MMP3*	co-expression co-occurence
MMP13	*MMP9*	co-expression
MMP9	*MMP8*	co-expression
MMP9	*MMP3*	co-expression co-occurence
MMP9	*PTGS1*	co-expression
MMP8	*MMP3*	co-occurence

c



Gene 1	Gene 2	Known Interaction
MMP9	*PTGS1*	co-expression
MMP9	*MMP13*	co-expression
MMP9	*BCL2*	co-expression
MMP9	*TNF*	co-expression
PTGS1	*TNF*	co-expression
PTGS1	*BCL2*	insignificant
MMP13	*BCL2*	insignificant
MMP13	*TNF*	co-expression
TNF	*BCL2*	co-expression
LYN	*TNF*	insignificant
LYN	*BCL2*	co-expression

Figure 2. Visualization of the protein–protein interaction from target predictions of (A) diclofenac sodium, (B) curcumin, and (C) pentagamavunon-0 using the STRING tool.

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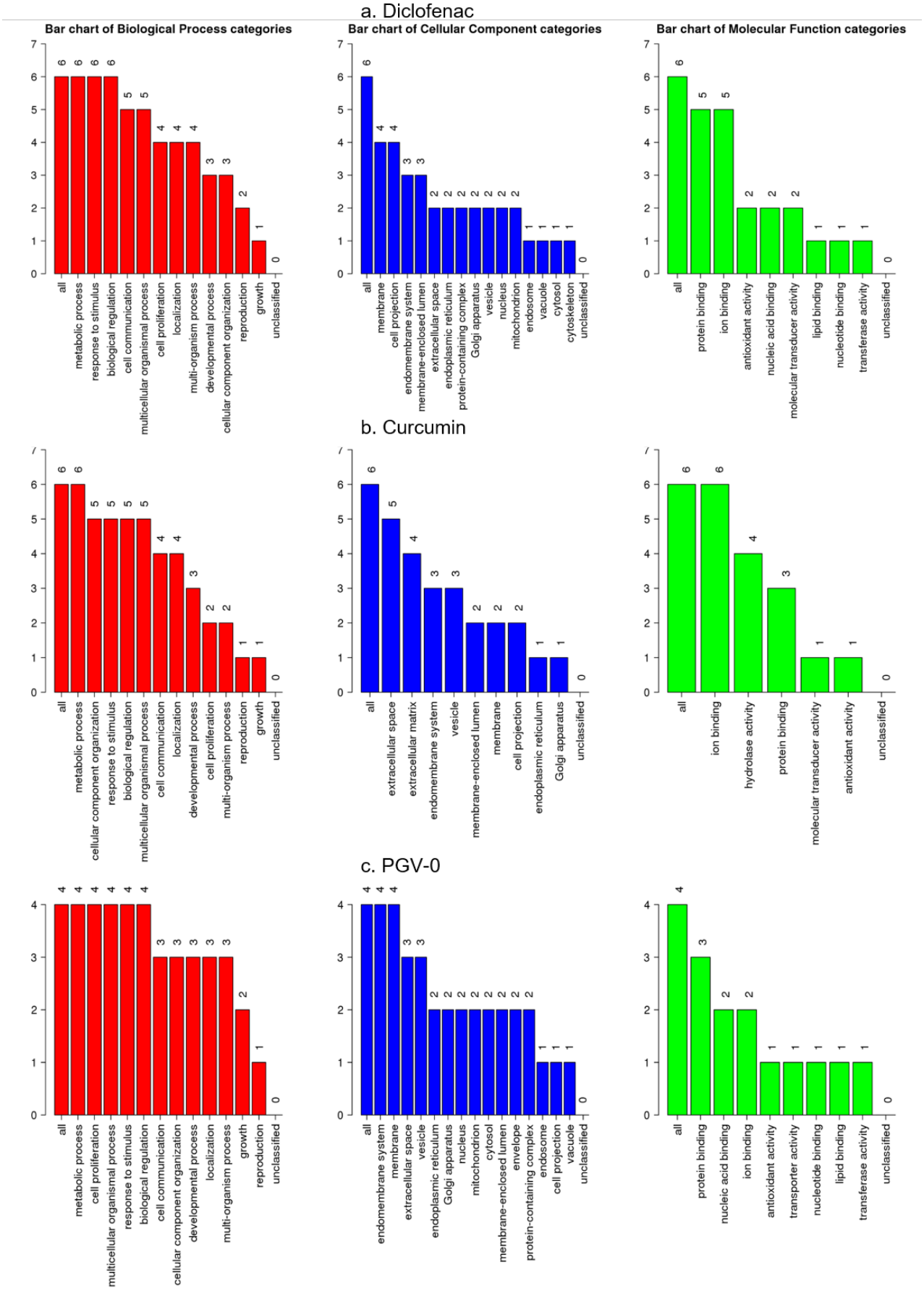

Figure 3. Gene oncology analysis based on the molecular function, biological process, and cellular component categories.

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as well as metallopeptidase activity. This finding indicates that curcumin and PGV-0 have an alternative mechanism for protecting the integrity of the extracellular matrix. This underlined our gene target analysis result that showed curcumin and PGV-0 targeted MMP gene expression.

We hypothesized that both curcumin and PGV-0 provide more protection against cartilage tissue damage due to arthritis in the TMJ compared to diclofenac sodium. We considered simulating the interaction of diclofenac sodium, curcumin, and PGV-0 with inflammatory and tissue destruction markers related to temporomandibular arthritis, PTGS2, MAPK-1, and MMP-13, using the molecular docking approach. To compare the potential collateral impact of the anti-inflammatory activity on platelet and gut protection function, we evaluated the interaction of all agents with PTGS1 (Figures 5). Furthermore, we compared the docking score to describe the binding affinity between ligand and target (Table 1).

The molecular docking results based on analysis in MOE (Table 1) showed a more stable interaction between MAPK-1 and COX-2 with curcumin or PGV-0 than with diclofenac sodium. The free energy of binding between MMP-13 and curcumin or PGV-0 was shown to be more negative than with diclofenac sodium. This indicates that curcumin and PGV-0 might provide better inflammatory control. However, a recent meta-analysis study failed to provide evidence that curcumin has a superior anti-inflammatory effect compared to diclofenac sodium due to a lack of data.[25] This lack calls for future unbiased randomized clinical trials. Regarding this suggestion,

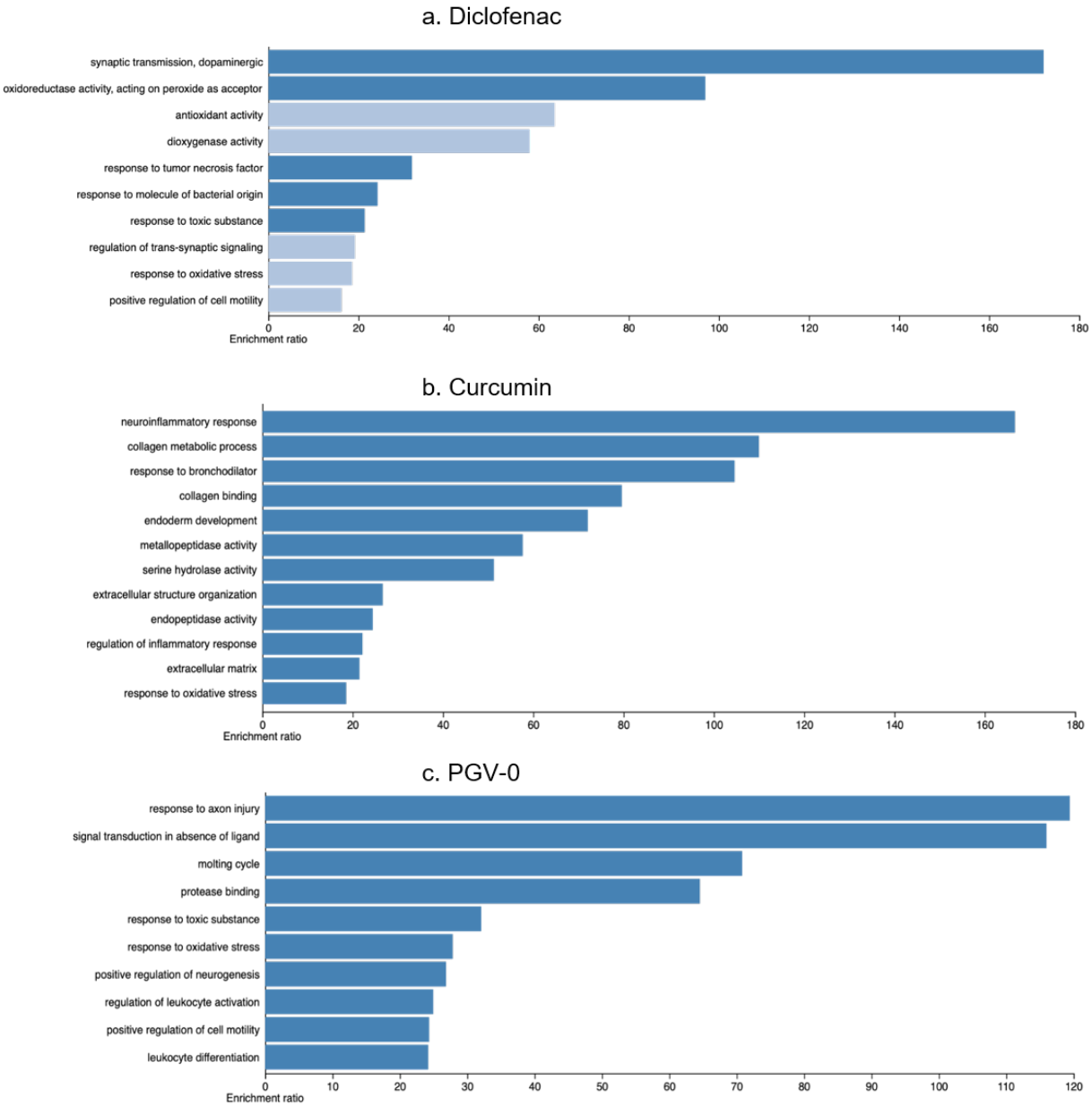

Figure 4. Enrichment analysis based on the KEGG pathway for (a) diclofenac sodium, (b) curcumin, and (c) pentagamavunon-0 (PGV-0).

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Table 1. The molecular docking results based on MOE analysis

Protein	PDB ID	Naltive ligand		Diclofenac	Curcumin	PGV-0
		RMSD (Å)	Docking Score (kcal/mol)	Docking Score (kcal/mol)	Docking Score (kcal/mol)	Docking Score (kcal/mol)
MAPK-1	5BVD	1.29	−15.27	−11.34	−13.61	−13.77
MMP-13	4JPA	1.38	−10.84	−9.88	−13.47	−14.39
COX-1	5WBE	0.34	−14.77	−10.95	−15.12	−16.17
COX-2	3LN1	0.57	−13.90	−12.26	−20.67	−17.46

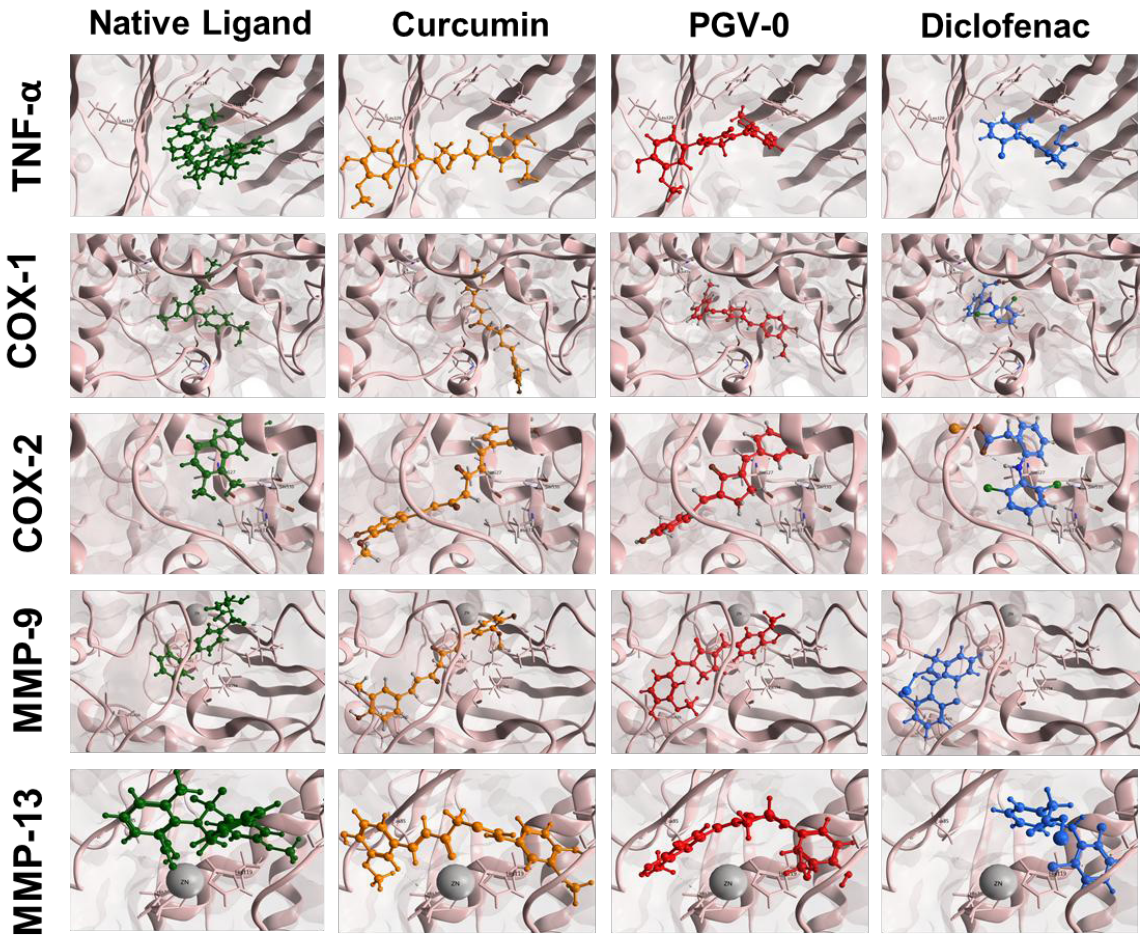

Figure 5. Three-dimensional visualization for molecular docking analysis on diclofenac sodium, curcumin, and PGV-0 activity toward PTGS-1, PTGS-2, MAPK-1, and MMP-13 receptors.

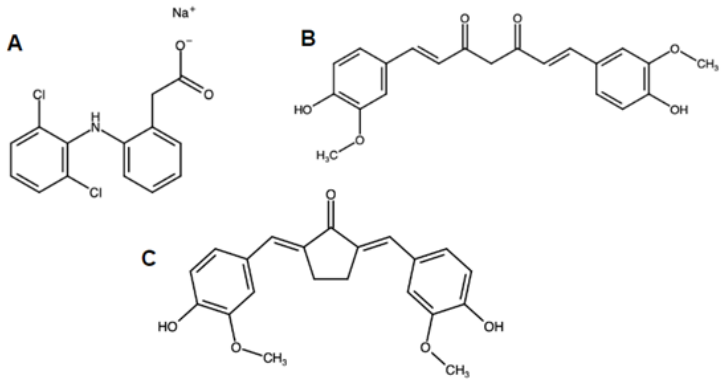

Figure 6. The chemical structures of (A) diclofenac sodium, (B) curcumin, and (C) pentagamavunon-0.

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we also recommended evaluating COX-1 expression parameters, as this study showed that the more negative docking score of the interaction between COX-1 and curcumin, or PGV-0 implies their potential to also influence COX-1 expression.

DISCUSSION

Curcumin's low bioavailability hinders its development as an oral anti-inflammatory agent. Hence, PGV-0 (Figure 6C) was introduced to improve curcumin's physicochemical properties, increase its effectiveness, and reduce its toxicity and adverse effects.[14,15] With higher bioavailability, PGV-0 is expected to provide optimal therapeutic effects at lower doses.

Diclofenac sodium belongs to the family of phenylacetic acid of NSAIDs approved by the Food and Drug Administration of the USA to treat arthritis. It inhibits prostanoid synthesis, thus constraining the COX-2 activity and preventing the progression of inflammation. However, it also halts COX-1 activity, which is needed for homeostasis, especially related to platelet activity and protection of the gastric mucosa from acidity. Although diclofenac sodium is proven to be more specific to COX-2, the side effects—for example, the development of gastritis caused by a decline in the protective effect—remain problematic.[26,27]

Curcumin (Figure 6B), derived from turmeric (*Curcuma longa*) plants, is among the alternative compounds to diclofenac sodium. A randomized, open-label, parallel, active-controlled clinical study of 139 patients with knee OA showed a comparable anti-inflammatory effect of the administration of 500 mg curcumin to 50 mg diclofenac sodium three times a day. However, fewer adverse effects were reported by patients who received curcumin. Although not statistically significant, the number of patients who needed acetaminophen rescue was higher in the curcumin group than in the diclofenac sodium group.[26,28]

This study indicated that diclofenac sodium, curcumin, and PGV-0 might have different mechanisms in temporomandibular arthritis pathogenesis. Unlike diclofenac sodium, curcumin and PGV-0 targeted matrix metalloproteinases (MMP)-related genes, MMP-9 and MMP-13. Moreover, curcumin also targeted MMP-3 and MMP-8. This finding was in line with the previous experimental research on curcumin, as it played an important role in regulating MMP in the pathogenesis of OA. Furthermore, MMP-13 is known to be involved in cartilage degradation in OA.[22] Curcumin has been shown to downregulate the expression of MMP-3 and MMP-13 in chondrocytes, thus exerting a chondroprotective effect.[29] A previous study demonstrated that curcumin inhibits MMP-13 production induced by IL-1β in articular chondrocytes by suppressing the NF-κB pathway.[30] In the case of the predicted target of diclofenac sodium, it was found that the MAPK-1 gene was only being targeted by the diclofenac sodium. However, another study reported that curcumin stimulates the MAPK pathway of human articular chondrocytes.[31]

The overall finding of this study predicts the potential of PGV-0 as an anti-inflammatory and protective agent against cartilage degradation in TMJs. Using the bioinformatics approach, we showed that PGV-0 shared a similar mechanism with curcumin but was different from diclofenac sodium.

Several studies have reported increased levels of MMP-9 and MMP-13 in the synovial fluid of patients with temporomandibular arthritis compared to healthy individuals.[22,32] MMP-9 breaks down collagen types IV and V, allowing for immune cell migration and inflammation in the TMJ. Meanwhile, MMP-13 cleaves key collagen types II and III in cartilage tissue. Developing targeted therapies against MMP-9 and MMP-13 may alleviate TMJ arthritis symptoms and impede further advancement of this debilitating condition. In addition to MMP, co-expression and co-concurrence of innate and adaptive immune function of TNF, LYN, and BCL-2 genes were found in PGV-0. This indicates that PGV-0 orchestrated the inflammatory response, providing an additional effect from curcumin.

A previous study reported that diclofenac sodium, curcumin, and PGV-0 exhibit anti-inflammatory and analgesic properties.[10,15,33] However, according to the KEGG enrichment analysis (Figure 6), diclofenac sodium has a different mechanism from curcumin and PGV-0 in temporomandibular arthritis. Diclofenac sodium is mainly related to synaptic transmission, dopaminergic, and oxidoreductase activity. Both the KEGG enrichment and gene target analyses in this study showed diclofenac sodium's relation with dopamine. As dopaminergic has been reported to influence the analgesic effect of paracetamol,[34] diclofenac sodium has the potential to similarly act as an analgesic through the dopaminergic pathway. In contrast, KEGG enrichment analysis failed to show the relationship of curcumin and PGV-0 with the dopaminergic pathway. Studies demonstrate that curcumin can downregulate matrix MMPs, especially MMP-13, which plays a pivotal role in cartilage degradation.[29,30] An in vitro study revealed that curcumin inhibits IL-1β-induced MMP-13 production in chondrocytes by suppressing the phosphorylation of p38 and JNK-MAPK signaling pathways.[35]

In conclusion, this bioinformatic study showed that, as an analog of curcumin, PGV-0 targeted MMP in temporomandibular arthritis pathogenesis. This finding underlined the advantage of PGV-0 in preventing MMP-related tissue damage in temporomandibular arthritis.

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REFERENCES

1. Valesan LF, Da-Cas CD, Réus JC, Denardin ACS, Garanhani RR, Bonotto D, Januzzi E, de Souza BDM. Prevalence of temporomandibular joint disorders: a systematic review and meta-analysis. Clin Oral Investig. 2021; 25(2): 441–53.
2. Marpaung C, van Selms MKA, Lobbezoo F. Prevalence and risk indicators of pain-related temporomandibular disorders among Indonesian children and adolescents. Community Dent Oral Epidemiol. 2018; 46(4): 400–6.
3. Almeida LE, Doetzer A, Beck ML. Immunohistochemical markers of temporomandibular disorders: a review of the literature. J Clin Med. 2023; 12(3): 789.
4. Monasterio G, Castillo F, Betancur D, Hernández A, Flores G, Díaz W, Hernández M, Vernal R. Osteoarthritis of the temporomandibular joint: clinical and imagenological diagnosis, pathogenic role of the immuno- inflammatory response, and immunotherapeutic strategies based on t regulatory lymphocytes. In: Temporomandibular joint pathology - current approaches and understanding. InTech; 2018. p. 208.
5. Lu K, Ma F, Yi D, Yu H, Tong L, Chen D. Molecular signaling in temporomandibular joint osteoarthritis. J Orthop Transl. 2022; 32: 21–7.
6. Wang XD, Zhang JN, Gan YH, Zhou YH. Current understanding of pathogenesis and treatment of TMJ osteoarthritis. J Dent Res. 2015; 94(5): 666–73.
7. Ouanounou A, Goldberg M, Haas DA. Pharmacotherapy in temporomandibular disorders: a review. J Can Dent Assoc. 2017; 83: h7.
8. Kołodziejska J, Kołodziejczyk M. Diclofenac in the treatment of pain in patients with rheumatic diseases. Reumatologia. 2018; 56(3): 174–83.
9. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 2020; 180: 114147.
10. Boarescu I, Pop RM, Boarescu P-M, Bocșan IC, Gheban D, Râjnoveanu R-M, Râjnoveanu A, Bulboacă AE, Buzoianu AD, Bolboacă SD. Anti-inflammatory and analgesic effects of curcumin nanoparticles associated with diclofenac sodium in experimental acute inflammation. Int J Mol Sci. 2022; 23(19): 11737.
11. Busse JW, Casassus R, Carrasco-Labra A, Durham J, Mock D, Zakrzewska JM, Palmer C, Samer CF, Coen M, Guevremont B, Hoppe T, Guyatt GH, Crandon HN, Yao L, Sadeghirad B, Vandvik PO, Siemieniuk RAC, Lytvyn L, Hunskaar BS, Agoritsas T. Management of chronic pain associated with temporomandibular disorders: a clinical practice guideline. BMJ. 2023; 383: e076227.
12. Amin LE, Gamily M El. Biological impact of curcumin on the healing of tempromandibular joint in experimentally induced arthritis. J Oral Maxillofac Surgery, Med Pathol. 2021; 33(3): 260–6.
13. Phumsuay R, Muangnoi C, Dasuni Wasana PW, Hasriadi, Vajragupta O, Rojsitthisak P, Towiwat P. Molecular insight into the anti-inflammatory effects of the curcumin ester prodrug curcumin diglutaric acid in vitro and in vivo. Int J Mol Sci. 2020; 21(16): 5700.
14. Ritmaleni. Synthesis of pentagamavunon-0 (PGV-0): An improved technique. Int J Pharm Sci Rev Res. 2016; 39(1): 9–11.
15. Astuti IY, Marchaban M, Martien R, Nugroho AE. Design and optimization of self nano-emulsifying drug delivery system containing a new anti-inflamatory agent pentagamavunon-0. Indones J Chem. 2017; 17(3): 365.
16. Marbawati D, Umniyati SR. Effects of curcumin and pentagamavunon-0 against dengue-2 virus infection in vero cells; an in vitro study. Procedia Environ Sci. 2015; 23: 215–21.
17. Meizarini A, Siswandono S, Riawan W, Rahayu RP. In silico and in vivo anti-inflammatory studies of curcuminoids, turmeric extract with zinc oxide, and eugenol. Trop J Pharm Res. 2018; 17(2): 269.
18. Liao Y, Wang J, Jaehnig EJ, Shi Z, Zhang B. WebGestalt 2019: gene set analysis toolkit with revamped UIs and APIs. Nucleic Acids Res. 2019; 47(W1): W199–205.
19. Hasbiyani NAF, Wulandari F, Nugroho EP, Hermawan A, Meiyanto E. Bioinformatics analysis confirms the target protein underlying mitotic catastrophe of 4T1 cells under combinatorial treatment of PGV-1 and galangin. Sci Pharm. 2021; 89(3): 38.
20. GeneCards The Human Gene Database. PTGS2 gene-prostaglandin-endoperoxidase synthase 2: protein coding. 2024. Available from: https://www.genecards.org/cgi-bin/carddisp.pl?gene=PTGS2. Accessed 2024 May 12.
21. Hu Q, Ecker M. Overview of MMP-13 as a promising target for the treatment of osteoarthritis. Int J Mol Sci. 2021; 22(4): 1742.
22. Loreto C, Filetti V, Almeida LE, La Rosa GRM, Leonardi R, Grippaudo C, Lo Giudice A. MMP-7 and MMP-9 are overexpressed in the synovial tissue from severe temporomandibular joint dysfunction. Eur J Histochem. 2020; 64(2): 3113.
23. Suhartini, Narmada IB, Hamzah Z, Joewarini E. NFkB and MMP-13 expression in condylar cartilage of temporomandibular joint with occlusal disharmony in vivo. Dent J. 2024; 57(1): 22–7.
24. Hatami M, Abdolahi M, Soveyd N, Djalali M, Togha M, Honarvar NM. Molecular mechanisms of curcumin in neuroinflammatory disorders: a mini review of current evidences. Endocr Metab Immune Disord Drug Targets. 2019; 19(3): 247–58.
25. Zeng L, Yang T, Yang K, Yu G, Li J, Xiang W, Chen H. Efficacy and safety of curcumin and curcuma longa extract in the treatment of arthritis: a systematic review and meta-analysis of randomized controlled trial. Front Immunol. 2022; 13: 891822.
26. Shep D, Khanwelkar C, Gade P, Karad S. Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. Trials. 2019; 20(1): 214.
27. Alfaro RA, Davis DD. Diclofenac. StatPearls Publishing; 2023.
28. Kotha RR, Luthria DL. Curcumin: biological, pharmaceutical, nutraceutical, and analytical aspects. Molecules. 2019; 24(16): 2930.
29. Henrotin Y, Priem F, Mobasheri A. Curcumin: a new paradigm and therapeutic opportunity for the treatment of osteoarthritis: curcumin for osteoarthritis management. Springerplus. 2013; 2(1): 56.
30. Wang J, Ma J, Gu J-H, Wang F-Y, Shang X-S, Tao H-R, Wang X. Regulation of type II collagen, matrix metalloproteinase-13 and cell proliferation by interleukin-1β is mediated by curcumin via inhibition of NF-κB signaling in rat chondrocytes. Mol Med Rep. 2017; 16(2): 1837–45.
31. Shakibaei M, Mobasheri A, Buhrmann C. Curcumin synergizes with resveratrol to stimulate the MAPK signaling pathway in human articular chondrocytes in vitro. Genes Nutr. 2011; 6(2): 171–9.
32. Perotto JH, Camejo F de A, Doetzer AD, Almeida LE, Azevedo M, Olandoski M, Noronha L, Trevilatto PC. Expression of MMP-13 in human temporomandibular joint disc derangement and osteoarthritis. Cranio®. 2018; 36(3): 161–6.
33. Farmasyanti CA, Kuijpers-Jagtman AM, Susilowati H, Meiyanto E. Effects of pentagamavunon-0 (PGV-0) as alternative analgesics on orthodontic tooth movement in rats. Padjadjaran J Dent. 2019; 31(3): 152.
34. Bhagyashree A, Manikkoth S, Sequeira M, Nayak R, Rao SN. Central dopaminergic system plays a role in the analgesic action of paracetamol: Preclinical evidence. Indian J Pharmacol. 2017; 49(1): 21–5.
35. Lee YT, Yunus MHM, Ugusman A, Yazid MD. Natural compounds affecting inflammatory pathways of osteoarthritis. Antioxidants (Basel, Switzerland). 2022; 11(9): 1722.

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