ORIGINAL ARTICLE

Natural Bioactive Compounds against Periodontal Matrix Metalloproteinases: A ChEMBL-LOTUS Chemoinformatics Study

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ARTICLE INFO

ARTICLE TYPE
Original Article

ARTICLE HISTORY
Received: November 1, 2025
Accepted: November 30, 2025
Published: December 30, 2025

KEYWORDS
ChEMBL; Chemoinformatics; Matrix metalloproteinases; Natural products; Periodontitis

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DOI
https://doi.org/10.59345/crown.v3i2.330

ABSTRACT

Background: Matrix metalloproteinases (MMPs), particularly MMP-8, MMP-9, and MMP-13, contribute to extracellular matrix degradation in periodontitis, but natural-product bioactivity evidence is dispersed across heterogeneous assays.

Objective: This study aimed to map IC50 and Ki evidence for natural-product-associated compounds against human MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13 and to identify structurally traceable candidates for orthogonal experimental validation.

Methods: Records were extracted from ChEMBL 37 on 5 August 2026 and filtered for positive values with pChEMBL, exact relations, nM units, acceptable validity metadata, no potential-duplicate flag, and direct single-protein assay assignment (confidence score 9). Measurements were summarized by compound-target-endpoint using median pChEMBL. ChEMBL natural-product-flagged candidates were exact-matched by full InChIKey in LOTUS; a study-defined high-support occurrence tier required at least 10 taxa and two reference records.

Results: Of 28,002 raw records, 7,451 met the strict criteria. The 153 flagged candidates yielded 42 LOTUS matches and 35 high-support compounds, forming 81 compound-target-endpoint pairs. Isoliquiritigenin showed IC50 values of 10.0 nM for MMP-9 and 14.13 nM for MMP-13, each from one measurement. Caffeic acid showed a median MMP-9 IC50 of 14.62 nM from two assays in one document. No high-support MMP-8 IC50 record was identified; available Ki values were 4.47 micromolar for pyrogallol and 8.71 micromolar for piceatannol.

Conclusion: These signals prioritize compounds for orthogonal validation but do not establish periodontal selectivity, safety, or efficacy.

1. Introduction

Periodontitis is a chronic inflammatory disease in which a dysregulated host response to a persistent microbial challenge contributes to progressive destruction of the tooth-supporting apparatus. The clinically important tissue changes include degradation of gingival connective tissue, loss of periodontal ligament attachment, and resorption of alveolar bone. These events do not result from a single mediator. They emerge from sustained interactions among microbial products, inflammatory cells, cytokine networks, proteolytic enzymes, and the extracellular matrix. Within this network, matrix metalloproteinases (MMPs) are especially relevant because they can directly cleave structural proteins and modify signaling molecules that regulate inflammation and tissue repair. Excessive MMP activity can therefore convert a normally controlled remodeling process into a mechanism of irreversible periodontal breakdown.[1]

MMPs are zinc-dependent endopeptidases that are synthesized mainly as latent proenzymes and are regulated at transcriptional, activation, localization, and inhibition levels. Their physiological functions include matrix turnover, wound healing, cell migration, and processing of bioactive mediators. Disease develops not merely because an MMP is present, but because the balance among enzyme production, activation, endogenous inhibition, substrate availability, and clearance becomes unfavorable. This distinction matters for inhibitor discovery. A compound that blocks an isolated catalytic domain may not necessarily suppress pathologic proteolysis in a tissue environment, while indiscriminate inhibition may interfere with beneficial remodeling. Molecular potency is consequently an early prioritization variable rather than a surrogate for therapeutic efficacy.[2,3]

Among the periodontal MMPs, MMP-8, MMP-9, and MMP-13 form a biologically compelling core panel. MMP-8, commonly described as neutrophil collagenase, is abundant in neutrophil-rich periodontal inflammation and can contribute to collagen breakdown. MMP-9 is a gelatinase associated with inflammatory cell activity and degradation of denatured collagen and basement-membrane components. MMP-13 has broad collagenolytic activity and may contribute to an amplifying proteolytic environment. MMP-1, MMP-2, and MMP-3 provide an informative extended panel because they represent additional collagenase, gelatinase, and stromelysin activities involved in matrix remodeling. Evaluating compounds across this six-target panel allows an initial distinction between a signal limited to one enzyme and a broader pattern that may warrant selectivity testing.[4,5]

The therapeutic history of MMP inhibition also creates a need for restraint. Catalytic zinc-binding can produce strong biochemical inhibition, yet compounds directed primarily toward a highly conserved catalytic environment may show insufficient selectivity. MMPs also participate in physiological processes, so a broad inhibitor may have effects that are not desirable in long-term periodontal management. The relevant discovery question is therefore not simply which molecule has the lowest reported IC_{50} or K_i. It is which molecular signal remains credible after considering assay identity, endpoint definition, target

assignment, replication depth, structural traceability, potential interference, and the feasibility of achieving local activity without unacceptable off-target effects.[6–9]

Natural products are attractive in this context because they occupy diverse chemical space and include polyphenols, flavonoids, phenolic acids, chalcones, xanthones, and other scaffolds that have been investigated as enzyme modulators. Some natural-product-associated compounds have shown activity against selected MMPs, and the structural diversity of these molecules may support interactions with catalytic or noncatalytic regions. However, the phrase natural product can conceal several different propositions. A structure may be biosynthesized by an organism, reported as a constituent of an organism, derived semisynthetically from a natural scaffold, synthesized for an assay, or merely marked as natural-product-associated in a database. These propositions should not be collapsed into a single claim about provenance or therapeutic suitability.[10–15]

Interpretation is further complicated by the heterogeneity of bioactivity measurements. IC_{50} is the concentration that produces half-maximal inhibition under a defined set of experimental conditions. It may change with substrate concentration, enzyme construct, incubation time, detection method, and inhibition mechanism. K_i is conceptually closer to an equilibrium or kinetic inhibition constant, but its reliability still depends on the model and experimental conditions used to derive it. Two values expressed in nanomolar units are therefore not automatically interchangeable, and IC_{50} and K_i should not be merged into one potency rank. Even within a single endpoint, a median value summarizes reported records but does not eliminate biological and methodological differences among assays. Recent in vivo and translational work on active MMP-8 further illustrates that molecular form, activation state, and analytical context materially affect interpretation.[16]

Curated bioactivity resources make this dispersed evidence searchable. ChEMBL connects standardized chemical structures with targets, assays, documents, activity types, units, and quality-related metadata. Its pChEMBL field places compatible molar activity values on a negative logarithmic scale, enabling descriptive ranking when the underlying activity type and direction are appropriate. ChEMBL nevertheless reflects the literature and deposited data from which its records are curated. A high-quality database field cannot restore assay details that were never reported, and multiple rows may arise from a common experiment or document. Consequently, record-level filtering and retention of assay and document counts are necessary to avoid treating every row as independent confirmation.[17]

LOTUS addresses a different part of the evidence chain by linking natural-product structures to documented organism occurrences and source references. Exact structure matching between ChEMBL candidates and LOTUS can separate a database natural-product flag from documented occurrence evidence. This step strengthens structural traceability but does not prove that the material used in a bioassay was isolated from the reported organism. It also does not measure abundance, extractability, sustainability, purity, stereochemical identity in every source report, or access to sufficient material for development. Occurrence support and bioactivity support must therefore be described as complementary but non-equivalent dimensions.[18]

Existing literature describes periodontal roles of MMPs, natural-product approaches to MMP inhibition, and individual compound series. What remains less clear is how the available molecular records look after applying a uniform, conservative curation strategy across a periodontal target panel and after auditing natural-occurrence support separately from potency. A useful evidence map should reveal both promising signals and negative spaces: targets with few qualifying records, compounds supported only by one assay or document, and apparent natural-product candidates that cannot be exact-matched to a natural-occurrence resource. Such a map can guide efficient experiments without converting database associations into claims of periodontal treatment benefit.

Novelty: The novelty of this study lies in combining strict, endpoint-specific curation of direct human single-protein MMP bioactivities with exact full-InChIKey matching to LOTUS, while preserving measurement, assay, and document depth and explicitly separating molecular potency from natural-occurrence support. Rather than presenting a simple list of low activity values, the framework evaluates evidence strength and identifies the filtered-database gap for MMP-8 alongside candidate signals for MMP-9 and MMP-13.

Aim of the study: This study aimed to map IC_{50} and K_i evidence for natural-product-associated compounds against human MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13; identify structurally traceable candidates for orthogonal experimental validation; compare potency with assay and document depth; and characterize limitations and target-specific gaps in the available molecular bioactivity evidence.

2. Methods

Study design and analytical scope

This was an observational in silico study based on secondary molecular bioactivity records. It was designed as an evidence-mapping and prioritization analysis rather than a clinical study, preclinical efficacy study, systematic review, or quantitative meta-analysis. The study did not estimate a population treatment effect and did not test a causal hypothesis. The primary analytical unit was the compound-target-endpoint combination after parent-molecule normalization. IC_{50} and K_i were maintained as separate endpoints throughout extraction, aggregation, ranking, and interpretation.

The analysis used a tiered target scope. The core periodontal panel comprised MMP-8, MMP-9, and MMP-13 because of their direct relevance to collagen and gelatin turnover in periodontal inflammatory destruction. The extended panel comprised MMP-1, MMP-2, and MMP-3 to provide broader collagenase, gelatinase, and stromelysin context. The six targets and their ChEMBL identifiers are detailed in Table 1. Results emphasized the core panel because it most directly addressed the periodontal prioritization question, whereas the extended panel supported contextual cross-target mapping.

Table 1. Matrix metalloproteinase target panel.

Panel	Target	ChEMBL ID	Analytical role
Core	MMP-8	CHEMBL4588	Principal periodontal collagenase
Core	MMP-9	CHEMBL321	Gelatinase; inflammatory remodeling
Core	MMP-13	CHEMBL280	Broad-spectrum collagenase
Extended	MMP-1	CHEMBL332	Collagenase comparator
Extended	MMP-2	CHEMBL333	Gelatinase comparator
Extended	MMP-3	CHEMBL283	Stromelysin comparator

MMP, matrix metalloproteinase.

Data sources, versions, and access date

ChEMBL 37 was accessed on 5 August 2025. ChEMBL was selected because it provides curated links among compounds, target components, assays, documents, standardized activity values, pChEMBL values, and quality-related annotations. LOTUS was used as the natural-occurrence knowledge source because it links chemical structures to documented biological occurrences and references. Database roles were deliberately separated: ChEMBL supplied bioactivity and assay metadata, whereas LOTUS supplied structure-linked occurrence support.[17,18]

The extraction described in the source manuscript used chembl_webresource_client version 0.10.9 for target resolution and ChEMBL Data Web Services for paginated activity retrieval. The reported execution environment used Python 3.14.3, and the code was described as compatible with Python 3.10 or later. These version statements are reported for transparency. The raw extracts, curated tables, scripts, package manifest, and executed notebook were stated to be retained in the author's research archive, but they were not supplied with the current manuscript case. The present revision therefore reports the source results without claiming an independent rerun.

Target resolution and eligibility

Target records were restricted to human single proteins. Direct single-protein assignment was required in the strict analysis by retaining assays with ChEMBL confidence score 9. This requirement was intended to reduce ambiguity from protein complexes, protein families, nonmolecular targets, or assays for which the relationship between the measured activity and the intended MMP was uncertain. Confidence score was used as a target-assignment criterion, not as a complete indicator of assay design or reporting quality.

Eligible activity types were IC_{50} and K_i. Records were required to have a positive numeric standard_value, an available pChEMBL value, standard_relation equal to '=', and standard_units equal to 'nM'. Exact relations excluded censored values such as greater-than or less-than observations from the primary rank. Requiring an available pChEMBL value ensured that the standardized activity was compatible with the database's logarithmic transformation. Records with a disqualifying data_validity_comment or a potential_duplicate flag were excluded from the strict dataset.

Activity retrieval and retained metadata

For each eligible target, all available IC_{50} and K_i activities were retrieved before applying the strict filters. The retained fields included molecule and parent-molecule identifiers, target identifiers, assay identifiers, document identifiers, standardized endpoint, relation, value, units, pChEMBL value, target-confidence score, validity comment, and potential-duplicate status. Year information was retained when available. These fields supported both numerical summarization and an evidence-depth audit at the compound-target-endpoint level.

Repeated records were not removed merely because they involved the same parent compound and target. Such removal could erase genuinely distinct assays or repeated observations. Instead, potential duplicates identified by the database were excluded, while measurement count, unique assay count, unique document count, and year span were retained after grouping. This approach allowed numerical central tendency to be viewed beside the depth and provenance of the underlying records. It also prevented a compound represented by several rows from being described automatically as independently replicated.

Parent-molecule normalization and grouping

Activities were grouped using the ChEMBL parent-molecule identifier rather than treating every salt, solvate, or other registered form as an unrelated candidate. Parent normalization reduced avoidable fragmentation of evidence across closely related records. The grouped key consisted of parent molecule, target, and endpoint. This key preserved the distinction between targets and between IC_{50} and K_i while allowing records referring to the same parent structure to be summarized together.

For each group, median pChEMBL was used as the descriptive potency summary. The median was chosen because database records can be unevenly distributed and may contain values that differ across protocols. It reduces the influence of an extreme value compared with an arithmetic mean, although it does not resolve assay heterogeneity. The potency corresponding to the median was back-calculated in nanomolar units using the equation shown below. Because pChEMBL is a negative logarithm of molar activity, a higher pChEMBL value represents a lower concentration and hence greater apparent potency.

$$Potency\ (nM) = 10^{9 - median\ pChEMBL}$$

Endpoint separation and interpretation

IC_{50} and K_i were never combined into a single numerical estimate. IC_{50} describes half-maximal inhibition in a particular assay system and can depend on substrate concentration and the mode of inhibition. K_i is more directly related to an inhibition constant but must still be interpreted in relation to the kinetic model and experimental conditions. Ranking was therefore performed within each target-endpoint combination. Comparisons between an IC_{50} and a K_i were descriptive and

explicitly labeled rather than interpreted as if the values were interchangeable.

No conversion was attempted between IC_{50} and K_i because the information required for a valid relationship, including substrate concentration, substrate affinity, and inhibition mechanism, was not consistently available. No value was imputed for missing activity, assay, document, or occurrence fields. Absence of a qualifying record was interpreted as an evidence-availability gap after filtering, not as evidence that a compound lacks biological activity against the target.

Identification of natural-product-associated candidates

The ChEMBL natural_product flag was used as an initial candidate-generation field only. Parent compounds marked by that field in the strict bioactivity dataset were submitted to the occurrence-audit stage. A flag alone was not accepted as proof of natural isolation or biological occurrence because database classification and experimental provenance answer different questions.

Candidate structures were matched to LOTUS using the full InChIKey. Exact full-key matching was selected to minimize ambiguity from names, synonyms, or partial structural identifiers. A match indicated that the same standardized structure was linked to at least one documented natural occurrence in LOTUS. It did not indicate that the specific sample tested in a ChEMBL-linked assay came from the organism or reference listed in LOTUS.

Occurrence-support tiers

The source study applied a study-defined high-support occurrence tier, originally labeled Tier A, requiring documentation in at least 10 taxa and at least two reference records. LOTUS-matched structures below that threshold were labeled Tier B, and ChEMBL-flagged candidates without an exact LOTUS match were labeled Tier C. The threshold was a pragmatic heuristic for prioritization and was not a validated grading system. It measured breadth of database occurrence documentation, not certainty of pharmacological activity.

Taxon and reference counts were interpreted separately from measurement, assay, and document counts. A compound could have extensive occurrence documentation but only one bioactivity measurement, or could have several bioactivity records but limited occurrence documentation. The primary candidate discussion therefore used the phrase high-support occurrence rather than high-quality evidence when referring to the LOTUS tier. Any statement about potency was tied to the ChEMBL assay/document depth.

Descriptive analyses

Data cleaning, grouping, ranking, and tabulation were reportedly performed with pandas. The analysis described the sequential record-selection flow, numbers of compounds and assays, natural-product candidate counts, exact LOTUS matches, occurrence-support tiers, and compound-target-endpoint combinations. For priority compounds, median pChEMBL was translated back to nM or micromolar units for interpretability. Core-panel candidates were evaluated by apparent potency, number of measurements, number of unique assays, number of unique documents, and whether activity extended across more than one core target.

Formal univariate participant summaries, bivariate association tests, multivariable regression, or multivariate models were not appropriate because the corpus consisted of heterogeneous literature-derived assay records rather than a probability sample of people, specimens, or standardized experiments. Treating database rows as independent observations in an inferential model would have produced misleading precision. No significance testing, confidence interval, or pooled effect estimate was generated. The output was intentionally descriptive and hypothesis-generating.

Evidence-depth and cross-target assessment

A compound-target-endpoint signal was described as a single measurement when only one qualifying record remained. Two measurements from a single document were distinguished from measurements distributed across two documents, because multiple assays within one publication do not provide publication-level replication. Document count was treated as a transparent proxy for source breadth, not as proof of independence or reproducibility. Assay descriptions and source links were considered when interpreting unusual or target-sparse findings.

Cross-target assessment was restricted to qualifying records and did not assume that potency values obtained in different assay systems were directly comparable. A compound was considered to have core-panel cross-target coverage when data were present for at least two of MMP-8, MMP-9, and MMP-13. This classification identified compounds suitable for standardized selectivity testing. It did not label broader coverage as inherently beneficial, because inhibition of multiple MMPs may also increase the risk of disrupting physiological remodeling.

Sensitivity analysis status and quality assurance

The source manuscript reported retention of a secondary dataset using confidence score at least 8 for sensitivity work. No numerical results or executable output for that analysis were available in the supplied materials. Accordingly, the confidence-score 9 dataset was the only dataset interpreted in this manuscript, and no robustness claim was made. A future reproducibility package should allow the strict and relaxed-confidence outputs to be compared for candidate membership, rank stability, and target coverage.

Quality assurance included reconciliation of record-flow arithmetic, consistency of compound and combination counts, separation of IC_{50} and K_i, exact relation and unit checks, and verification that every numerical claim in the text matched the corresponding table or source summary. Candidate narratives were written to preserve limitations in measurement and document depth. Citation metadata and DOI values for the final reference list were verified during editorial production, while the underlying numerical dataset remained unavailable for independent recomputation.

Ethics

The study used public molecular bioactivity and natural-occurrence data and involved no human participants, animals, interventions, identifiable personal data, or patient records. Ethical approval was granted by the CMHC Ethics Committee Indonesia (No. 005/CMHC/Ethics/08/2026). Consent to participate was not applicable. The ethics statement does not substitute for

data licensing, database citation, or transparent reporting of computational provenance.

3. Results

Bioactivity retrieval and strict curation

The initial retrieval produced 28,002 IC_{50} or K_i records across the six human MMP targets. These records represented 9,934 unique compounds and 2,175 assays. Requiring a positive standardized value and an available pChEMBL value retained 18,177 records, excluding 9,825 records at that stage. The exact-relation and nM-unit requirements did not further reduce this subset, and no additional record was removed by the disqualifying-validity criterion as summarized in the source flow.

Potential-duplicate exclusion removed 1,755 records, leaving 16,422. Restriction to direct single-protein assays with confidence score 9 excluded a further 8,971 records. The final strict dataset contained 7,451 records from 3,526 compounds and 1,063 assays. Thus, 26.6% of the raw activity rows remained after all strict criteria (7,451/28,002). This percentage is a descriptive calculation from the reported flow and does not represent a biological hit rate. The complete record-selection sequence is detailed in Table 2.

The largest proportional reduction after the pChEMBL requirement occurred when the direct single-protein confidence criterion was applied. This pattern shows that many database records may be numerically standardized while still failing the strict target-assignment requirement used for this study. Conversely, the absence of exclusions at the relation, unit, and validity-warning stages reflects the characteristics of the positive-pChEMBL subset reported by the source pipeline; it should not be generalized to all ChEMBL activities.

Table 2. ChEMBL bioactivity-record curation flow.

Curation stage	Records remaining	Excluded at stage
Raw IC_{50}/K_i records	28,002	0
Positive values with pChEMBL	18,177	9,825
Exact relation and nM units	18,177	0
No disqualifying validity warning	18,177	0
Potential duplicates excluded	16,422	1,755
Direct single-protein assignment (confidence 9)	7,451	8,971

IC_{50}, half-maximal inhibitory concentration; K_i, inhibition constant.

Natural-product candidate audit

Within the strict dataset, 153 parent compounds carried the ChEMBL natural_product flag. Exact matching by full InChIKey found 42 of these structures in LOTUS. Therefore, 111 flagged candidates did not have an exact LOTUS match in the reported audit. The mismatch does not prove that those compounds are synthetic or absent from nature; it indicates that the exact structure was not linked by the matching procedure and database state used in this analysis.

Thirty-five of the 42 LOTUS-matched compounds met the study-defined high-support occurrence threshold of at least 10 taxa and two reference records. These 35 compounds formed 81 compound-target-endpoint combinations across the six-target panel. The counts demonstrate how sequential definitions narrowed the evidence set from a broad database flag to exact structural occurrence support and finally to a heuristic high-support tier. At each step, the filter addressed traceability rather than experimental potency.

Core-panel coverage

The core periodontal panel contained 36 high-support compound-target-endpoint combinations among 24 compounds. MMP-9 accounted for 24 combinations, MMP-13 for 10, and MMP-8 for two. The distribution was therefore strongly concentrated in MMP-9. The sparse MMP-8 representation resulted from the intersection of endpoint availability, strict assay assignment, natural-product flagging, exact LOTUS matching, and the high-support occurrence threshold.

The two qualifying MMP-8 combinations used K_i rather than IC_{50}. No high-support MMP-8 IC_{50} record remained in the strict dataset. This result was treated as a filtered-database gap. It neither rules out MMP-8 activity among the candidate compounds nor estimates the prevalence of such activity in nature. It identifies a specific place where standardized primary experiments could add disproportionate value.

Highest numeric MMP-9 signal

CHEMBL1305393 had the strongest numeric signal reported for MMP-9, with an IC_{50} of approximately 8.13 nM. The ChEMBL summary did not provide an informative preferred name. To avoid assigning an unsupported chemical identity, the candidate was retained under its database identifier and was not promoted as the leading named natural compound. Its numerical rank remains visible in Figure 1, but practical prioritization requires structure and identity review in the underlying ChEMBL record.

Isoliquiritigenin

Isoliquiritigenin showed an MMP-9 IC_{50} of 10.0 nM and an MMP-13 IC_{50} of 14.13 nM. Both signals were high on the apparent potency scale and placed the compound among the strongest named core-panel candidates. Each value was represented by one measurement, one assay, and one document linked to a study of phenolic MMP inhibitors. The cross-target pattern is therefore notable but not independently replicated within the curated corpus.[13]

Because the two endpoint values came from the same publication context, their similarity should not be interpreted as proof of equivalent inhibition under all conditions. It does, however, support a clear experimental priority: compare both enzymes in the same laboratory using matched protein constructs, substrate conditions,

concentration ranges, and counter-screens. Isoliquiritigenin's rank was based on molecular bioactivity and occurrence support, not on evidence of periodontal tissue exposure or efficacy.

Caffeic acid, mangiferin, and quercetin

Caffeic acid showed a median MMP-9 IC_{50} of 14.62 nM. The estimate was supported by two assays but only one document. Relative to a single-row signal, the two measurements provide some within-source consistency, yet they do not constitute independent publication-level replication. The value was therefore described as a strong named molecular signal with limited source breadth.[19]

Mangiferin showed an MMP-9 IC_{50} of 251.19 nM from one assay and one document linked to the phenolic inhibitor study. Its apparent potency was lower than that of isoliquiritigenin and caffeic acid but remained submicromolar. The single-measurement basis means that assay-specific effects could substantially influence its position in the rank.[13]

Quercetin had a median MMP-9 IC_{50} of 530.88 nM derived from two assays and two documents. It also had an MMP-13 IC_{50} of approximately 8.51 micromolar from one assay. Quercetin was therefore less potent in the reported core-panel values than the leading named candidates, but its MMP-9 signal had broader document support. This combination makes it a useful benchmark for replication and selectivity experiments rather than the primary potency lead.[10–12] The candidate-level comparison is summarized in Table 3.

Table 3. Priority natural-product-associated candidates in the core periodontal MMP panel.

Compound	Target	Endpoint	Median potency	Assays/docs	Evidence interpretation
Isoliquiritigenin	MMP-9	IC_{50}	10.00 nM	1/1	High potency; single measurement
Isoliquiritigenin	MMP-13	IC_{50}	14.13 nM	1/1	High potency; single measurement
Caffeic acid	MMP-9	IC_{50}	14.62 nM	2/1	Two assays; one publication
Mangiferin	MMP-9	IC_{50}	251.19 nM	1/1	Single measurement
Quercetin	MMP-9	IC_{50}	530.88 nM	2/2	Two assays and two documents
Pyrogallol	MMP-8	K_i	4.47 µM	1/1	Incomplete assay-origin metadata
Piceatannol	MMP-8	K_i	8.71 µM	1/1	Incomplete assay-origin metadata

docs, source documents; IC_{50}, half-maximal inhibitory concentration; K_i, inhibition constant; MMP, matrix metalloproteinase. Potency ranks should be interpreted with assay/document depth.

MMP-8 Ki signals

Pyrogallol showed an MMP-8 K_i of 4.47 micromolar, and piceatannol showed an MMP-8 K_i of 8.71 micromolar. Each result was represented by one assay and one secondary document. The assay description reported an unknown origin. These values were retained because they met the numerical and target-confidence criteria, but the incomplete provenance reduced interpretive confidence.

The MMP-8 results were not placed on the same rank as core-panel IC_{50} findings. Their endpoint was K_i, their apparent potency was micromolar, and their assay provenance was limited. They are best regarded as prompts for direct retesting. The finding that MMP-8 had only these two qualifying combinations contrasts with the much larger MMP-9 evidence set and is one of the central evidence-gap results of the study.

Cross-target patterns

Twelve high-support compounds had qualifying data for at least two core targets. Isoliquiritigenin combined nanomolar signals for MMP-9 and MMP-13. Quercetin, luteolin, curcumin, isoacteoside, methyl rosmarinate, dimethyl lithospermate, taxifolin, daphnodorin F, and dihydrodaphnodorin B also had data for MMP-9 and MMP-13, although most of the reported MMP-13 values were in the micromolar range. Linked documents included dedicated MMP-13 screening and curcuminoid-MMP investigations.[6–9,13]

Pyrogallol and piceatannol had K_i data for MMP-8 and MMP-9. The cross-target map indicates where a standardized panel assay could distinguish genuine multi-MMP inhibition from assay-specific differences. It does not establish selectivity because the records were generated across heterogeneous protocols and did not cover every relevant MMP or metalloprotease for every compound.

Evidence-depth pattern

The priority table illustrates that apparent potency and evidence depth did not move together. Isoliquiritigenin had stronger reported potency but one measurement per target. Caffeic acid had two assays within one document. Quercetin had weaker apparent MMP-9 potency but two assays across two documents. MMP-8 candidates had sparse records and incomplete assay-origin information. This pattern justified retaining assays and documents as separate reporting fields rather than using the median value alone.

No inferential comparison was made among compounds or targets. The records were not assumed to be independent, and the assay conditions were not sufficiently uniform to support a pooled variance estimate. The complete ranked profile of high-support core-panel IC_{50} candidates is shown in Figure 1. The absence of MMP-8 from the figure reflects the absence of a qualifying IC_{50} record, not a graphical omission or a claim of zero activity.

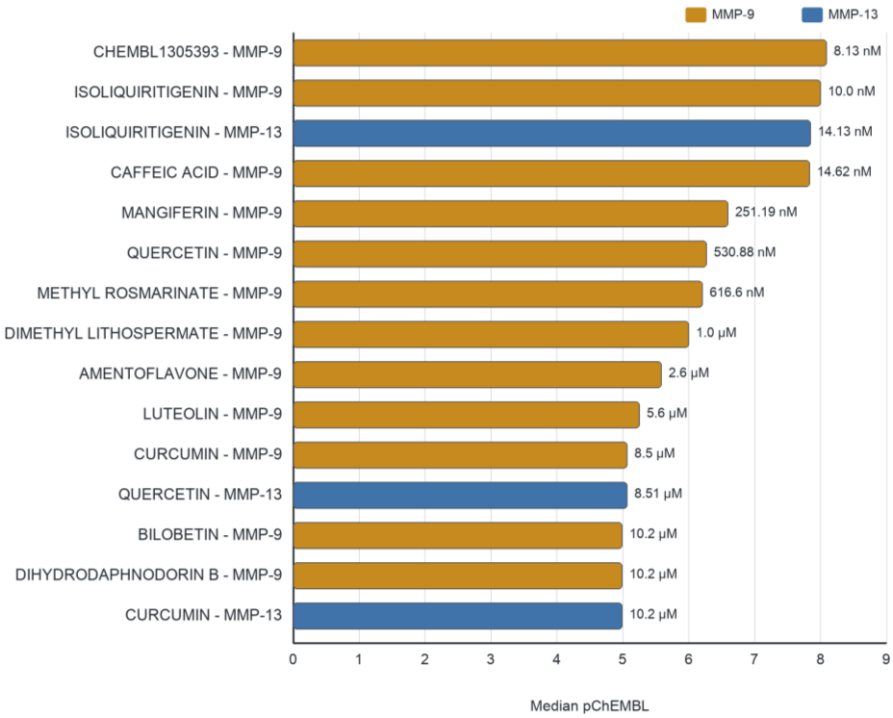

Figure 1. *Ranked median pChEMBL values for high-support IC_{50} candidates in the core periodontal MMP panel. Higher pChEMBL indicates greater apparent potency. MMP-8 is absent because no high-support IC_{50} record met the strict criteria.*

4. Discussion

Principal findings

This study produced a conservative map of natural-product-associated inhibitory signals against a periodontal MMP panel. From 28,002 raw IC_{50}/K_i records, 7,451 met the strict numerical, duplication, and direct-target criteria. Among 153 ChEMBL-flagged parent compounds, 42 exact-matched to LOTUS and 35 met the study-defined high-support occurrence threshold. The resulting evidence emphasized MMP-9, identified a smaller MMP-13 set, and revealed a marked scarcity of qualifying MMP-8 records.

The strongest named signals were isoliquiritigenin against MMP-9 and MMP-13 and caffeic acid against MMP-9. Isoliquiritigenin combined low-nanomolar apparent potency with cross-target coverage, but each value depended on a single measurement from one document. Caffeic acid had two assays, yet both were linked to one document. These compounds merit experimental priority because the signals are strong enough to test, not because the database evidence establishes periodontal efficacy.[13,19]

Quercetin offered a different evidence profile. Its MMP-9 potency was lower than the leading named compounds, but the median was supported by two assays across two documents. Mangiferin had a submicromolar MMP-9 value with one-measurement depth. The comparison demonstrates why a rank based only on a concentration value would be incomplete: potency, replication depth, target coverage, and assay provenance identify different strengths and uncertainties.[10–12]

Interpretation of isoliquiritigenin

The isoliquiritigenin findings are notable because the compound showed nanomolar IC_{50} values against two enzymes in the core periodontal panel. A similar numerical range for MMP-9 and MMP-13 may indicate a reproducible interaction with features shared by the assay targets, but the current evidence cannot distinguish true dual-target potency from protocol-specific behavior. The linked study provides a credible experimental origin for the records, yet one publication cannot establish laboratory-to-laboratory reproducibility.[13]

The next decision for isoliquiritigenin should therefore be empirical. Recombinant human MMP-9 and MMP-13 should be tested side by side, followed by MMP-8 and additional metalloprotease counterscreens. Concentration-response curves should cover the full transition from no inhibition to maximal effect, with sufficient replicates to estimate uncertainty. If activity persists, kinetic experiments can explore inhibition mechanism. Only after orthogonal biochemical confirmation should periodontal cellular relevance be examined.

Interpretation of caffeic acid

Caffeic acid ranked close to isoliquiritigenin for MMP-9 and had two qualifying assays. The underlying publication examined caffeic-acid amide structure-activity relationships, providing a relevant medicinal-chemistry context. Two assays within one document may reduce concern that the value is a single transcription or extraction error, but they can still share reagents, laboratory practices, and detection technology. The evidence is repeat observation rather than independent replication.[14,19]

Caffeic acid is also a chemically reactive phenolic scaffold, so a low reported concentration should trigger careful interference controls. Metal interaction, redox behavior, substrate effects, and detection-system interference can mimic or exaggerate inhibition. A strong follow-up design would test the parent compound and selected analogues using both fluorescence-based and nonfluorescent readouts, include zinc and aggregation controls, and confirm compound identity and purity before interpreting a structure-activity pattern.

Interpretation of quercetin and mangiferin

Quercetin's broader MMP-9 document support makes it valuable as a reference compound even though its apparent potency was lower. Its additional, weaker MMP-13 signal

also creates an opportunity to assess whether potency separation is maintained under matched conditions. A standardized experiment could determine whether the approximately order-of-magnitude differences suggested by the database persist when substrate, enzyme concentration, incubation, and detection are controlled. The result would be more informative than comparing database medians alone.[10–12]

Mangiferin occupied an intermediate position, with submicromolar MMP-9 activity from a single assay. Its signal should be considered provisional. Confirmation may be technically demanding because physicochemical behavior, solubility, and optical properties can affect assay performance. These factors were not evaluated in the evidence map. The compound remains a reasonable secondary candidate, particularly if confirmatory experiments are designed around the limitations of phenolic and highly functionalized molecules.

The MMP-8 evidence gap

MMP-8 is highly relevant to periodontal collagen degradation, yet no high-support MMP-8 IC_{50} record survived the strict workflow. The only qualifying high-support combinations were micromolar K_i records for pyrogallol and piceatannol, each linked to one assay with incomplete origin metadata and one secondary document. The imbalance between biological relevance and database coverage is more important than the individual ranks of those two values.

Several explanations are possible, and the present data cannot distinguish them. MMP-8 may have been screened less frequently than MMP-9; relevant records may lack pChEMBL or exact standardized metadata; compounds may fail the natural-occurrence threshold; or high-confidence target assignment may be unavailable. The correct conclusion is therefore a data gap created by the defined evidence intersection. Describing it as lack of natural MMP-8 inhibitors would exceed the evidence.

A focused MMP-8 campaign could address this gap efficiently. The leading MMP-9/MMP-13 candidates, the two existing MMP-8 K_i candidates, and structurally diverse comparators should be tested in one assay matrix. Reporting should include the enzyme construct, activation state, substrate identity and concentration, buffer composition, zinc and calcium conditions, preincubation, readout, positive control, curve-fitting method, and replicate uncertainty. Such a dataset would be more decision-relevant than adding isolated literature values.

Meaning and limits of pChEMBL aggregation

pChEMBL is valuable because it places compatible standardized activities on a common logarithmic scale. It simplifies ranking and reduces the visual dominance of large unit differences. Nevertheless, the transformation standardizes scale rather than experimental biology. Two assays with the same pChEMBL may use different substrates, protein domains, activation procedures, or detection systems. A median pChEMBL is consequently a robust descriptive center of the retrieved values, not a meta-analytic effect.

The decision to retain measurement, assay, and document counts partially addresses this problem by showing how much evidence contributes to each median. It does not solve dependence among records. Two ChEMBL assays may originate from the same article or laboratory; one article may report several conditions; and database rows may represent related experiments. A future reanalysis with the full extract could stratify values by assay format and document, but such modeling would still require careful assumptions and enough observations within each stratum.

Endpoint separation was equally important. IC_{50} and K_i express related but distinct quantities. Converting one into the other requires mechanistic and kinetic information that was not consistently available. Combining them could have produced an apparently comprehensive rank at the cost of interpretive validity. Reporting the sparse MMP-8 K_i evidence separately from the MMP-9 and MMP-13 IC_{50} signals preserved the meaning of the measurements.

Natural-occurrence evidence and provenance

Exact full-InChIKey matching reduced the risk of false agreement caused by synonyms or common names. The reduction from 153 ChEMBL-flagged candidates to 42 LOTUS matches illustrates that a classification field and a structure-linked occurrence record are not interchangeable. LOTUS adds a transparent connection between a chemical structure, biological taxa, and source references. The study-defined threshold further emphasized compounds with broader occurrence documentation.

Even this strengthened traceability has boundaries. A LOTUS occurrence does not establish the concentration of a compound in an organism, the feasibility of isolation, the identity of the tested material, or the environmental and economic sustainability of sourcing. It cannot determine whether a ChEMBL assay used an isolated natural product, a purchased standard, a synthetic specimen, or a derivative. The manuscript therefore uses natural-product-associated or documented occurrence rather than claiming natural isolation for every assay.

The high-support tier should also not be mistaken for a pharmacological evidence grade. Ten taxa and two references were pragmatic thresholds defined by the source study. They may favor widely investigated compounds and disadvantage rare but genuine metabolites. Sensitivity analyses using alternative occurrence thresholds would be informative if the underlying data become available. Until then, the tier is best used as a prioritization aid and reported with its exact definition.

Assay interference and false-positive risk

Natural-product-associated screening hits require particular attention to assay interference. Polyphenolic molecules may aggregate, chelate metals, undergo redox reactions, quench or enhance fluorescence, absorb at detection wavelengths, or react nonspecifically with proteins. Some of these mechanisms can create concentration-response curves that resemble target inhibition. Structural-alert approaches such as PAINS filters may help identify risk, but an alert is not proof that a compound is inactive, and absence of an alert is not proof of validity.[14,15]

Orthogonal confirmation should therefore be designed around the likely interference mechanisms. A nonfluorescent or differently configured readout can test optical artifacts. Detergent sensitivity and dynamic light scattering can address aggregation. Zinc and other metal controls can help distinguish broad chelation from more

specific binding. Enzyme-free and substrate-only wells can identify direct effects on the signal. Compound stability and purity should be documented, and active concentrations should be compared with solubility limits.

These precautions are especially important when a database rank depends on one measurement. A single strong value is valuable for prioritization but vulnerable to an unrecognized assay artifact. Reproducing the effect with a second method changes the evidential status more than adding another measurement under the same detection principle. The recommended validation sequence therefore emphasizes orthogonality before extensive biological interpretation.

Biological and periodontal translation

Recent primary studies provide a translational context without proving that the database-ranked candidates will treat periodontitis. Propolis flavonoids and a monoterpene glycoside have been evaluated in experimental periodontal models, while resveratrol has been studied in both a mouse model and patients with periodontitis.[20–23] Curcumin formulations have also been tested in experimental periodontitis.[24,25] Beyond the periodontium, recent studies have examined natural-product modulation of MMP-3/MMP-13, computationally prioritized cinnamic-acid derivatives for MMP-9, an in vitro MMP-13-targeted compound, and pharmacologic MMP-8 inhibition.[26–29] A contemporary clinical study further confirmed that salivary MMP-8 activity varies with periodontal and diabetic status, reinforcing the need to distinguish molecular inhibition from biomarker behavior.[30]

Biochemical inhibition is only the first step toward periodontal relevance. An active molecule must remain chemically stable, reach the extracellular or pericellular environment where the target enzyme is active, retain activity in the presence of proteins and ions, and avoid unacceptable toxicity to gingival fibroblasts, periodontal ligament cells, epithelial cells, immune cells, and other local tissues. None of these properties can be inferred from an isolated-enzyme IC_{50} or K_i.

Selectivity is also context dependent. Simultaneous inhibition of MMP-9 and MMP-13 might be attractive if both drive a pathologic proteolytic state, but excessive inhibition of MMPs may disturb normal matrix turnover and repair. A validation panel should extend beyond the three core enzymes to related MMPs and other metalloproteases. Selectivity ratios and cellular target engagement would be more informative than a binary active/inactive designation.

Local periodontal delivery could eventually offer a way to concentrate a validated inhibitor at a diseased site while limiting systemic exposure. However, formulation questions arise only after potency, selectivity, interference, and cellular safety are confirmed. Residence time in the periodontal pocket, dilution by crevicular fluid, interaction with biofilm and host proteins, release kinetics, and tissue tolerability would all need experimental study. The present evidence map does not evaluate these translational variables.

Proposed experimental validation pathway

A rational first validation set would include isoliquiritigenin and caffeic acid as potency leads, quercetin as a broader-document comparator, mangiferin as a secondary submicromolar signal, and pyrogallol and piceatannol as MMP-8 gap candidates. CHEMBL1305393 should be included only after its chemical identity, structure, and provenance are resolved. A known standardized MMP inhibitor should serve as a positive control, and vehicle controls should match each compound's solvent conditions.

The first stage should use recombinant human MMP-8, MMP-9, and MMP-13 with matched assay design. Full curves, biological and technical replicates, prespecified fitting criteria, and uncertainty estimates should be reported. The second stage should use orthogonal detection and counterscreens for aggregation, fluorescence interference, redox behavior, and nonspecific metal chelation. Confirmed hits should then undergo mechanism and selectivity testing across the extended MMP panel.

The third stage should evaluate activity in inflammation-stimulated periodontal cell systems. Measurements could include extracellular proteolytic activity and matrix-related outcomes, accompanied by viability and cytotoxicity assays. These experiments should distinguish direct enzyme inhibition from changes in MMP expression or secretion. Only compounds with reproducible biochemical activity, adequate selectivity, and a cellular safety margin should progress to local-delivery formulation or more complex tissue models. The candidate-specific rationale and validation sequence are detailed in Table 4.

Table 4. Evidence-informed validation priorities.

Candidate	Current molecular signal	Evidence depth	Priority validation
Isoliquiritigenin	MMP-9 IC_{50} 10.00 nM; MMP-13 IC_{50} 14.13 nM	1 assay/1 document per target	Matched MMP-8/-9/-13 panel; orthogonal readout; selectivity
Caffeic acid	MMP-9 median IC_{50} 14.62 nM	2 assays/1 document	Repeat curve; optical, aggregation, redox, and chelation controls
Quercetin	MMP-9 median IC_{50} 530.88 nM; MMP-13 about 8.51 µM	2 assays/2 documents for MMP-9; 1 assay for MMP-13	Cross-target benchmark under identical conditions
Mangiferin	MMP-9 IC_{50} 251.19 nM	1 assay/1 document	Independent biochemical replication and interference testing
Pyrogallol and piceatannol	MMP-8 K_i 4.47 and 8.71 µM	1 assay/1 document each; incomplete origin metadata	Direct MMP-8 retest with complete assay provenance

All listed values reproduce the curated narrative and Table 3; proposed tests are prospective recommendations, not completed experiments.

Strengths

The study has several methodological strengths. It defined a biologically relevant target panel, separated IC_{50} from K_i, required exact relations and standardized units, excluded potential duplicates, and restricted the primary analysis to direct single-protein target assignments. It normalized to parent molecules while retaining repeated observations and reported assay and document counts beside potency. These decisions reduce several common sources of overstatement in database mining.

A second strength was the separation of natural-product flagging from documented occurrence. Exact full-InChIKey matching provided greater structural specificity than name matching, and the occurrence threshold was explicitly labeled as study-defined. The narrative also preserved the distinction between a molecular signal, experimental replication, natural occurrence, selectivity, safety, and clinical efficacy. This layered interpretation is more useful for experiment selection than a simple potency list.

Limitations

First, ChEMBL aggregates literature-derived measurements generated under heterogeneous protocols. Median pChEMBL cannot correct differences in substrate, construct, incubation, detection, or inhibition mechanism. Second, most priority combinations were supported by one measurement, and assay and document counts are imperfect proxies for independent replication. Third, confidence score 9 strengthens target assignment but does not guarantee complete assay metadata, as illustrated by the MMP-8 records.

Fourth, the LOTUS threshold was an author-defined heuristic. Occurrence documentation does not establish the provenance of the assayed material, natural abundance, accessibility, or purity. Exact InChIKey matching may also miss records affected by structure standardization or stereochemical representation. Fifth, candidates lacking a LOTUS match or high-support tier were excluded from the principal natural-occurrence shortlist even though some may be genuine natural products or valuable derivatives.

Sixth, the raw and curated datasets, scripts, notebook, and confidence-score sensitivity output were not supplied for independent reproduction. The record counts and rankings could be checked for internal consistency but not recomputed from source data during this revision. Seventh, no inferential analysis was appropriate, and the descriptive rank should not be read as a statistically estimated superiority order.

Finally, the study did not assess inhibition mechanism, broader metalloprotease selectivity, assay interference, compound purity, solubility, stability, periodontal tissue penetration, local bioavailability, toxicity, formulation performance, animal outcomes, or clinical efficacy. These are not minor missing details; they define the boundary between a database-derived molecular hypothesis and a translational candidate. The conclusions are intentionally limited to prioritization for orthogonal testing.

Future research

Future computational work should release the exact target identifiers, query code, raw activity extracts, curated dataset, software manifest, and executed notebook under a stable repository record. The strict confidence-score 9 analysis should be compared with the reported confidence-score at least 8 dataset, with changes in candidate membership, target coverage, and rank documented. Alternative natural-occurrence thresholds and structure-matching diagnostics could clarify how strongly the shortlist depends on the study-defined heuristic.

Future experimental work should prioritize quality over the number of screened compounds. A small, chemically diverse panel tested across MMP-8, MMP-9, and MMP-13 under standardized and orthogonal conditions would address the largest uncertainties identified here. Transparent reporting of negative results would be especially valuable for MMP-8 and for compounds that show optical or chelation artifacts. Subsequent cellular and formulation studies should be contingent on replicated biochemical evidence.

5. Conclusion

Strict integration of ChEMBL 37 bioactivity records with exact LOTUS occurrence matching produced a focused, evidence-qualified map of natural-product-associated inhibitors for periodontal MMP research. Isoliquiritigenin provided the strongest named cross-target signal, with nanomolar IC_{50} values for MMP-9 and MMP-13, while caffeic acid showed a similarly strong MMP-9 signal supported by two assays within one document. Quercetin was less potent but had broader MMP-9 document support, and mangiferin remained a single-measurement submicromolar candidate. The analysis also identified a major MMP-8 evidence gap: no high-support IC_{50} record met the strict criteria, and only two micromolar K_i records with limited assay provenance were available. Potency ranks, natural-occurrence support, and evidence depth answered different questions and were therefore interpreted separately. The findings support a targeted program of standardized biochemical replication, orthogonal interference testing, selectivity assessment, and periodontal cell validation. They do not establish inhibition in periodontal tissues, safety, local bioavailability, or clinical efficacy.

Declarations

Ethics approval and consent to participate: The study used public molecular bioactivity data and involved no human participants, animals, or personal data. Ethical approval was granted by the CMHC Ethics Committee Indonesia (No. 005/CMHC/Ethics/08/2026). Not applicable because the study did not involve human participants or identifiable personal data.

Data and code availability: The raw extracts, curated datasets, version manifest, extraction and natural-occurrence annotation scripts, and executed analysis notebook are retained in the corresponding author's research archive. A public repository identifier was not available in the supplied materials.

Author contributions (CRediT): AM: Conceptualization, methodology, software, formal analysis, investigation, data curation, visualization, writing - original draft, and project administration. PU: Methodology, validation, investigation, and writing - review and editing. SA: Validation, data curation, visualization, and writing - review and editing. IS: Validation, supervision, and writing - review and editing. All authors reviewed and approved the final manuscript and accept responsibility for the integrity of the work.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this article.

Use of artificial intelligence: None declared. The authors remain responsible for verifying all scientific content and for the final manuscript.

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